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## Unraveling How Obesity Fuels Cancer FREE

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“We are getting more and more precise about the different risk factors for the various subtypes of cancer,” said Stephen Hursting, Ph.D., M.P.H., professor in the department of nutrition at the University of North Carolina at Chapel Hill. One established factor is obesity, now well linked to at least ten cancers, including pancreatic, colorectal, endometrial, and hormone receptor–positive, postmenopausal breast cancer. “The connections between [cancer and obesity] seem to be getting stronger in part because the quality and quantity of data has increased, particularly data from large, prospective, epidemiological studies,” Hursting said.

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Stephen Hursting, Ph.D., M.P.H.

Cancer Research UK and the UK Health Forum recently issued a report, *Tipping the Scales: Why Preventing Obesity Makes Economic Sense*, that estimates 72% of adults in the United Kingdom are predicted to be overweight or obese by 2035—including 45% of those in the lowest-income quintile projected to become obese. The uptick in obesity is predicted to increase the number of new cancer cases in the next 20 years by 670,000 along with an increase in other chronic diseases. According to Nicola Smith, a senior health information officer at Cancer Research UK, if these numbers are reduced by 1%

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every year from the predicted trend, about 64,200 cancer cases could be avoided over the next 20 years.

## The Body's Fat Deposit Memories

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Avoiding substantial weight gain while maintaining physical fitness is a likely way to avoid metabolic imbalances such as insulin resistance and high circulating levels of hormones. Avoiding such imbalances, in turn, can decrease risk of type II diabetes, cardiovascular disease, and endometrial, postmenopausal breast and colon cancer according to observational studies. Yet, whether losing weight can decrease one's risk of obesity-related cancers is trickier to study in part because monitoring such individuals takes a long time and because of potentially confounding factors that may distinguish those who remain overweight from those who can achieve and maintain weight loss.

As a window into understanding whether some obesity-associated markers remain even after weight loss and how this may affect cancer development, Hursting's lab induced mammary tumors—a model of basal-like breast cancer—in mice that were obese, normal weight, and formerly obese (*Cancer Prev. Res.* ; doi:10.1158/1940-6207.CAPR-15-0348). Despite a normalization in weight (a 10% reduction) and a normalization of insulin and leptin levels, both the formerly obese mice and the obese mice had similar tumor growth and similar circulating inflammatory markers in the mammary tissue. DNA methylation in the mammary tissue of both groups of mice was similar and higher than the normal-weight control animals, suggesting an epigenetic memory of the obese state in the mice that were obese but lost weight. The work implies that weight loss alone may not be enough to overcome some of the negative effects of obesity.

Hursting is analyzing samples from formerly obese women to see whether the observations in mice also hold true in people. “From the mouse study, we think there is an epigenetic reprogramming that occurs with chronic obesity,” Hursting said. “We are also testing if the amount of weight loss, and how the weight is lost, such as diet alone, diet plus exercise, or bariatric surgery, impacts cancer risk,” he added.

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A few human studies show dramatic weight loss to be beneficial for reducing the risk of obesity-related cancers. Some patients who undergo bariatric surgery can decrease the

risk of certain tumors including breast and endometrial. In a retrospective observation study, Susan C. Modesitt, M.D., a gynecological oncologist and researcher at the University of Virginia Health System in Charlottesville, and colleagues found that of 1,482 women who had bariatric surgery, 3.6% developed cancer—mostly breast, cervical, and endometrial—compared with 5.8% of the 3,495 morbidly obese women who had not had bariatric surgery ( $p = 0.002$ ) (*J. Am. Coll. Surg.* 2009;208:1093–8). In another retrospective cohort analysis, bariatric surgery reduced relative risk for developing uterine cancer by 71% and by 81% if the patient maintained a normal weight after the surgery (*Gynecol. Oncol.* 2014;133:63–6).

## Which Metabolic Factors?

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“The next question is, what changes with bariatric surgery in these patients?” said Modesitt, who is focusing on the metabolic factors that can fluctuate with weight loss.

“We’ve seen a big jump in the number of endometrial cancers in the last 25 years partly because of obesity, and the assumption in the past has been that the main link was the conversion of extra androgens to estrogens in fat tissue by the aromatase enzyme.”

Yet hormones alone are not likely enough to explain the link. “There are so many intertwining pathways of growth factors, insulin, inflammation, and hormones that makes this really difficult to sort out the attributable risk to any single factor,” Modesitt said.

Recently, Modesitt and colleagues measured the metabolite changes of 68 women at high risk for obesity-related cancer who had bariatric surgery, reducing their weight by an average of 45kg (or 99 pounds; about 34.5% of their weight). After surgery, the women had improved glucose, insulin, and free fatty acid levels as well as decreased inflammation. “We found, perhaps not surprisingly, that once women lost weight, their insulin and glucose homeostasis improved. But whether improvements will make the difference for no cancer versus cancer for these women in the future, we don’t know yet.”

To better tease out the metabolic factors that may be causally related to cancer, larger studies are needed. [Skip to Main Content](#) “In my ideal world, I would do a study of 5,000 obese women, of whom 50% undergo bariatric surgery, and then look at the differences in cancer rates

and potential obesity related carcinogenic factors between the two groups. But that study, spanning a decade or two, would be difficult to fund because of the high cost,” Modesitt said.

## Where

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Besides the amount of fat, researchers have recognized that visceral obesity—the fat around the midsection that surrounds organs, including the pancreas and liver—is a risk factor for heart disease, type II diabetes, and some types of cancer ( *Proc. Nutr. Soc.* 2012;71:181–9). Visceral fat appears to secrete more hormones and other molecules that affect glucose metabolism and tends to have higher levels of inflammation, according to Rachel A. Murphy, Ph.D., of the School of Population and Public Health at the University of British Columbia in Vancouver.

In a study under review, Murphy’s lab has dissected the pathways that link specific adipose depots and metabolic deregulation. Her team looked for metabolites in the blood in relation to subcutaneous, visceral fat and to overall body mass index to try to identify causal metabolic factors.

One fat depot that has been carefully dissected is the white adipose tissue of the breast. Andrew Dannenberg, M.D., associate director of cancer prevention at the Sandra and Edward Meyer Cancer Center at Weill Cornell Medical College in New York, and colleagues found that inflamed white adipose tissue of the breast occurs in most obese women with breast cancer and is associated with increased levels of aromatase, the rate-limiting enzyme for estrogen biosynthesis ( *Cancer Prev. Res.* 2011;4:1021–9). That local effect of inflammation and aromatase expression in fat tissue is thought to promote cancer progression in women with breast cancer and may be a marker of breast cancer risk. “Aromatase is as well-vetted a target in breast cancer as one can imagine. Large trials have shown women at high risk of breast cancer who take an aromatase inhibitor have as much as a 50% reduction in risk,” Dannenberg said.

Systemic metabolic syndrome also has been linked to increased breast cancer risk, but “exactly why is unclear,” Dannenberg said. Tying the initial demonstration of local breast tissue inflammation to systemic metabolic factors, Dannenberg’s lab showed that about half of the 100 women with early-stage breast cancer who have white adipose inflammation in the breast also had elevated insulin, glucose, triglycerides,

and other markers of metabolic syndrome. In a second cohort of 127 women, inflammation was associated with a worse course of disease for women who go on to develop metastatic breast cancer ( *Clin. Cancer Res.* ; doi:10.1158/1078-0432.CCR-15-2239). “This leads us to postulate that inflammation may be critical for understanding the established link between metabolic syndrome and breast cancer risk,” Dannenberg said. “However, if inflammation has multiple effects including contributing to insulin resistance, then anti-inflammatory strategies to reduce risk may be more effective than simply targeting insulin.”

Because the cause of breast cancer in normal-sized women is uncertain, Dannenberg is investigating both adipose inflammation and aromatase levels in metabolically obese but normal-sized women because he believes occult breast adipose inflammation may be a key driver of breast cancer risk in those normal-sized women. His lab also has begun an effort to develop metabolic markers that could reflect both inflammation and aromatase levels to noninvasively gauge breast cancer risk.

Many others are following suit to find both markers of risk and ways to reduce that risk. “I think we have well established the connection between obesity and cancer. We are now moving away from proving the connection to asking, ‘How do we disconnect the link?’” Hursting said.

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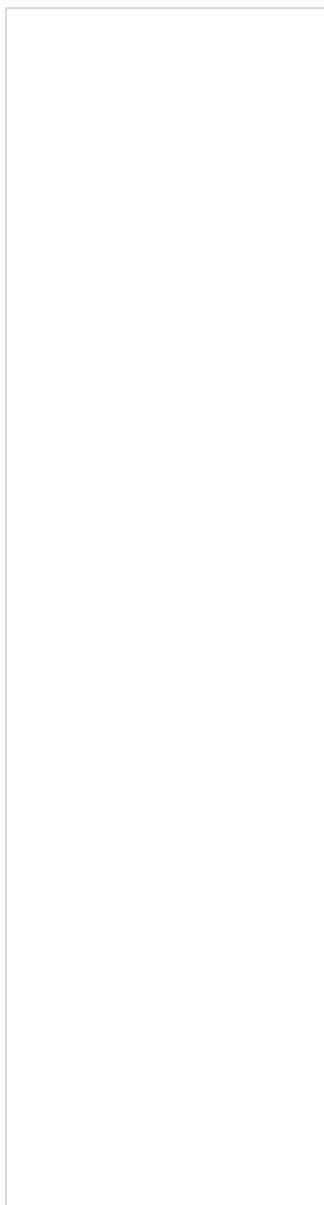
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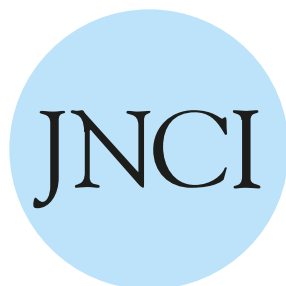
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