



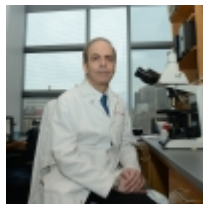
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# The Inflamed Fat-Cancer Connection

With prevention as an objective, Andrew Dannenberg studies how reducing inflammation in the body—caused by obesity for example—may lessen cancer risk.

## Featured



**Andrew J. Dannenberg**

Joan and Sanford I. Weill Department of Medicine, Weill Cornell Medicine

by Caitlin Hayes

We hear a lot about breakthroughs in cancer treatment: therapies that trigger the immune system to attack the disease; designer drugs that can target precise molecules on a tumor's

surface. “That’s critically important work,” says Andrew J. Dannenberg, Medicine at Weill Cornell Medicine. Dannenberg, however, comes at the problem from a different angle.

“I’ve always been a big believer in trying to reduce disease risk as opposed to simply treating it,” he explains. “And lifestyle factors are extremely important for the development and progression of cancer.” Dannenberg asks: what lifestyle changes can we make to reduce the risk of cancer from the get-go?

Increasingly, inflammation has been linked to numerous diseases, from diabetes to neurodegenerative diseases to cancer. It follows that reducing inflammation may lower cancer risk. For many years, Dannenberg has studied the preventative effects of anti-inflammatory drugs on cancer. More recently, he has focused on the link between obesity, inflammation, and cancer, as well as the role diet plays, with results that have significant implications for public health.

## Obesity and Breast Cancer

In 2003, researchers found that obesity caused fat tissue to become inflamed, triggering many studies on how inflamed fat could play a role in diabetes and cardiovascular disease. When Dannenberg initiated his research in this area in 2009, no one had yet studied if or how inflamed fat was associated with cancer.

Dannenberg had already been studying breast cancer and the role of prostaglandins, fatty acid-derived compounds that are key players in inflammation. “I knew the breast was comprised of significant amounts of adipose or fat tissue, and I reasoned that obesity could be causing the fat to become chronically inflamed, just as others had shown for fat in other parts of the body,” Dannenberg says. “I then hypothesized that if such inflammation were to happen in the breast, it could alter the risk for cancer.”

Dannenberg quickly found, in obese mouse models and in women, that the breast fat manifested this inflammatory state and that it was accompanied by molecular changes. The inflammation was associated with an increase in the expression of aromatase, a key enzyme that regulates the production of estrogen—a hormone that drives the development and growth of most breast cancers in postmenopausal women. In 2011, Dannenberg and his group brought attention to this obesity-associated inflammatory condition in the breast.

Since 2011, they’ve made a series of groundbreaking observations. Studying human breast tissue after mastectomy, they found a link between inflammation in the breast fat and worse cancer prognosis. “This was a significant finding because it credentialed the observation we had made with something clinically important,” Dannenberg says.

In human studies, Dannenberg’s group then found that breast fat inflammation was associated with altered metabolism. “We discovered that what was going on in the breast

was actually a sentinel for what was going on more diffusely in other fat depots in the body," Dannenberg says. "And if a third of a woman's body is made up of fat, and that fat has a low-grade, painless inflammatory process, you can imagine that leading to changes in the blood."

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From blood tests, Dannenberg found that leptin, a protein derived from fat cells, and insulin—both of which are linked to increased breast cancer risk—were elevated in women with inflamed breast fat. Building on Dannenberg's findings, a group from the Mayo Clinic recently reported that inflamed breast fat is associated with an increased risk of breast cancer.

### Healthy Weight Women and Breast Cancer

It wasn't just obese women who had this inflammatory condition. "Fully a third of women who have a normal body mass index, as defined by the World Health Organization, have the same subclinical inflammatory process," Dannenberg says.

He calls this group the walking wounded. They have a body mass index (BMI) of less than 25, considered healthy, but still have inflamed breast fat and the resulting molecular changes. "This is potentially very important because we have a poor understanding as to why a woman with a normal BMI, who doesn't have a hereditary cause for breast cancer, develops the disease," Dannenberg says.

The results also suggested that women with a normal BMI and occult breast inflammation have excess body fat. "The results raised the intriguing possibility that excess body fat in these normal-BMI women contributed to inflammation and increased cancer risk," Dannenberg explains.

In a recent study, Dannenberg and colleagues from Albert Einstein College of Medicine and Memorial Sloan Kettering Cancer Center used data from the Women's Health Initiative to further elucidate the relationship between body fat and estrogen-dependent breast cancer in postmenopausal women with a normal BMI. Remarkably, the normal-BMI women with excess body fat had double the risk of estrogen-dependent breast cancer.

This finding is significant because it can explain why thousands of postmenopausal women who are thought to have a healthy weight develop breast cancer each year. "One potential implication of this work relates to screening. If postmenopausal women who have a normal BMI undergo formal testing of body composition and are found to have excess body fat, there may still be time to reduce risk," Dannenberg says. "A major challenge is developing reliable, evidence-based interventions that will reduce body fat."

## More Questions about Obesity, Inflammation, and Disease Prevention

Moving forward, Dannenberg has lots more questions that he's exploring. He wants to know how obesity and inflammation are related to DNA damage in the breast epithelium, and the relationship between obesity, inflammation, and breast cancer risk across various ethnicities. He is also interested in the role diet and exercise play in this inflammatory process and to what extent losing excess body fat reduces inflammation and lowers cancer risk in those who already exhibit this inflammatory state.

"We're also hoping to look at whether or not normal-BMI women who have excess body fat are also at increased risk for cardiovascular disease. It's unlikely that it's a breast cancer-only issue," he says. "You might argue that a failure to recognize excess body fat in someone who has a normal BMI could lead to a range of significant medical problems. It's a big issue that medicine has yet to adequately address."

And women aren't the only ones affected by these breakthroughs. Dannenberg has also reported that inflamed fat is associated with high grade prostate cancer as well as worse outcomes for tongue cancer patients. "It appears that inflamed fat is playing a role in the pathogenesis of multiple types of cancer," he says.

## Sugar and Colon Cancer

Dannenberg was medically trained as a gastroenterologist and has recently returned to this area of expertise to tackle the rapid rise in inflammatory bowel disease (IBD) in the United States. Both forms of IBD, ulcerative colitis and Crohn's disease, are associated with higher risks of colon cancer. "The increased incidence of IBD has happened too quickly for it to be genetic," Dannenberg says. "That strongly suggests something environmental is going on."

The spike in IBD has coincided with an increase in the consumption of the kind of sugar in soda, candy, and many other processed foods. Dannenberg and his group are testing the effects of specific sugars on colitis.

"We found that feeding a specific type of sugar leads to worsening of experimental colitis," Dannenberg says. "Since that time, we've demonstrated that a diet containing this widely-consumed sweetener also leads to a change in the microbiota in the colon, which contributes to the worsening of colitis and potentially a heightened cancer risk."

Always with an eye toward prevention, Dannenberg is also studying whether other dietary factors can block or mitigate the harmful effects of sugar. Preliminary data are promising, and Dannenberg hopes to make significant contributions that will reduce cancer risk and improve overall health.

“With obesity such an epidemic, it’s been very rewarding to spend the last eight or nine years working on the link between obesity, inflammation, and cancer, and now we’re poised to think hard about ways to reduce risk based on our findings,” Dannenberg says. “And the work on dietary sugar and the colitis-colon cancer connection dovetails nicely with this effort to reduce disease risk—all of which comes from my belief that lifestyle research, from bench to bedside, is very important to complement our genomic efforts to enhance precision medicine and improve patient care.”

Dannenberg is a scientific adviser for SynDevRx, Inc., a company dedicated to developing treatments for patients whose cancer is associated with metabolic dysfunction.

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