[ News * Analysis * Commentary * Controversy ]

May 25, 2011 * Vol. 33 * No. 10

oncology-times.com

# ONCOLOGY TIMES

Publishing for 33 Years

Lippincott Williams & Wilkins
Wolters Kluwer Health

The Independent Hem/Onc News Source


Images: ASCO 2010/Todd Buchanan

## All about ASCO11!

- Plenary Focus on Less Common Tumors, as Great Examples of Science of Clinical Practice.
- First-Ever 'Clinical Trials Day.'
- Electronic, Educational Enhancements.
- What's Back, What's Not from Last Year.
- Increased Emphasis on Supportive/Palliative/Survivorship Issues.
- Preview scoops from Allen Lichter, George Sledge, Michael Link, Sandra Swain, Kathy Miller, Charles Blanke.

MARGARET TEMPERO: How I Treat Patients with Pancreatic Ductal Adenocarinoma p.56


- Hedgehog Pathway Disrupter for Advanced Basal-Cell Cancers.
- Breast Cancer & Obesity Inflammation.
- Advanced Colorectal Cancer: Gemcitabine+FOLFOX.
- Tolerating Risk to Find Efficacy Surrogates.
- Mesothelioma Detection with Proteomic Technology.
- Lung Cancer Chemoprevention.
- Telomere Research Updates.

PERIODICALS

[ ALSO ]



@OncologyTimes

Facebook.com/OncologyTimesNews

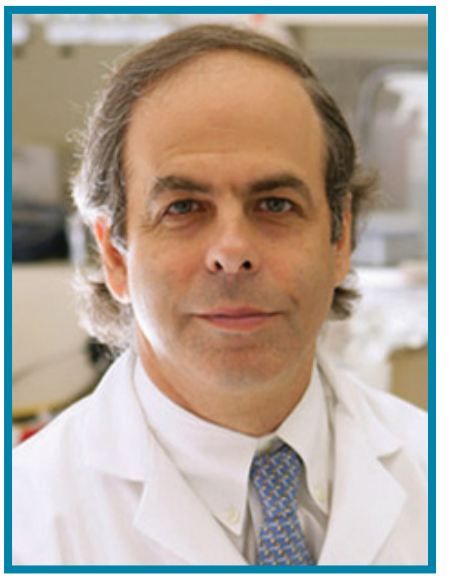
## Joint AACR/ASCO Presidential Forum

# Breast Cancer Linked to Obesity-Induced Inflammation

BY RABIYA S. TUMA, PHD

Obesity is a well-known risk factor for postmenopausal breast cancer, but the molecular mechanisms behind obesity and an increased risk have been obscure. That situation may now be changing, according to Andrew Dannenberg, MD, speaking during the Joint AACR/ASCO Presidential Forum at the American Association for Cancer Research Annual Meeting.

His team has found, he said, that obesity and excess weight lead to inflammatory lesions in the breast tissue of mice and humans. Macrophages are a major component of these lesions, producing pro-inflammatory cytokines and triggering aromatase activity in mouse models of obesity.



ANDREW DANNENBERG, MD: "We have the first evidence that inflammation occurs in the human breast and correlates with being overweight or obese, which are known risk factors for the development of postmenopausal breast cancer and also known to be terribly important in terms of negative prognosis for anyone with breast cancer. This discovery is likely to be important for our current understanding and for developing rational interventions to try to attenuate this process. It may have profound public health implications."

The mechanistic link between excess weight, inflammation, and aromatase reveals potential therapeutic and prevention targets for breast cancer, particularly for hormone-receptor positive tumors. The data may also help explain the link between obesity and triple-negative breast cancer.

"There are many, many examples of chronic inflammatory states predisposing cancer," Dr. Dannenberg, the Henry R. Erle, MD-Roberts Family Professor of Medicine and Director of the Weill Cornell Cancer Center, said in a telephone interview after the meeting. "We have the first evidence that inflammation occurs in the human breast, and it correlates with being overweight or obese, which are known risk factors for the development of postmenopausal breast cancer and also known to be terribly important in terms of negative prognosis for anyone afflicted with breast cancer.

"This discovery is likely to be important for our current understanding and for developing rational interventions to

try to attenuate this process," he said. "I think it may have profound public health implications."

## Following the Trail

Over the last 10 years, scientists have demonstrated that obesity triggers smoldering inflammation in visceral and subcutaneous fat. (Unlike someone with an arthritic joint, who is likely to report swelling and pain, obese individuals are unlikely to report abdominal pain, despite molecular evidence of inflammation, such as expression of proinflammatory cytokines.)

Based on that observation and the fact that breast tissue is largely composed of fat, Dr. Dannenberg hypothesized that inflammation might be contributing to the increased breast cancer risk in overweight post-menopausal women.

"If you read the tea leaves, as I was reading the tea leaves, if inflammation occurs in visceral and subcutaneous fat, why not the breast?" he said. The difference, of course, is that the breast also has an epithelium, which could respond to the inflammatory signals.

To test the hypothesis, Dr. Dannenberg's team compared the mammary tissue from obese mice that had been fed a high-fat diet with tissue from lean mice fed a low-fat diet. As he predicted, the mammary tissue and visceral fat from obese animals included evidence of inflammation, with the presence of crown-like structures, that were nearly absent in lean animals. The crown-like structures include necrotic adipocytes surrounded by macrophages.

The presence of crown-like structures correlated with increased expression of proinflammatory mediators in the visceral fat and mammary gland, including TNF-α, IL-1β, and COX-2. Aromatase expression also increased in the visceral fat and mammary glands from obese animals compared with lean animals, as did aromatase enzymatic activity. Similar results were seen in a genetic mouse model of obesity that does not rely on a high-fat diet.

> Dr. Dannenberg's research group is actively exploring ways to either reduce the number of crown-like structures or render them functionally inert. Either outcome, he said, could lead to an improvement for breast cancer prevention or treatment.

When the team separated the stromal-vascular fraction of the mammary tissue from the adipose fraction, they found evidence of communication between the two compartments. On the one side, obesity was associated with increased NF-κB activity in the stromal-vascular fraction, which contains macrophages, leading to increased production of proinflammatory cytokines. Those cytokines then signaled back to the adipose and possibly other cells where they induced aromatase expression and activity. The elevation in aromatase leads to excess estrogen production.

> "If inflammation occurs in visceral and subcutaneous fat, why not the breast? The difference, of course, is that the breast also has an epithelium, which could respond to the inflammatory signals.

"From our standpoint this is very interesting, because it gives us a number of different molecular hubs that might be targeted through lifestyle, dietary, or pharmacologic strategies to attenuate this phenomenon," Dr. Dannenberg said.

## Inflammation in Human Breast Samples

Of course, that strategy will work only if similar inflammatory lesions and molecular signaling occur in women. To find out, Dr. Dannenberg and colleagues examined breast tissue from 30 women who had undergone breast surgery at Memorial Sloan-Kettering Cancer Center. Crown-like structures in breast tissue were detected in seven of 10 overweight women and six of eight obese women, compared with only one of 12 normal weight women. (Dr. Dannenberg said he thinks one reason such structures have not been reported previously is that they are easily missed when tissues are stained with hematoxylin and eosin. By contrast, they are easy to see when the tissue is probed with an antibody against the macrophage-specific marker CD68.)

The percentage of tissue blocks containing crown-like structures also tended to increase with increasing body mass index. However, the correlation is not perfect. Therefore one cannot always predict whether a woman's breast tissue will carry evidence of inflammation based solely on her body mass index.

The team is continuing to work out the molecular aspects of inflammation in human breast tissue, but Dr. Dannenberg said he is pretty convinced that the presence of the crown-like structures indicates that the molecular signaling process will be resemble what was seen in mice.

And given the numerous examples in which chronic inflammation is associated with tumor formation in humans, the chances are good that the breast tissue inflammation is affecting breast cancer risk, he said. "It is my contention that obesity causes an inflammatory process in the breast and will increase the likelihood of human breast cancer and potentially drives progression too."

And there is circumstantial evidence, already, that reducing that inflammation reduces the risk of disease. Dr. Dannenberg and others reported in a 2004 article in the *Journal of the American Medical Association* that regular aspirin use was associated with a reduction in breast cancer, particularly hormone-receptor positive breast cancer.

At the time, the authors speculated that the effect of aspirin was mediated by inhibiting the production of prostaglandin $E_2$, a known inducer of aromatase. Consistent with this hypothesis, Dr. Dannenberg found both elevated levels of prostaglandin $E_2$ and aromatase in the mammary glands of obese mice.

## Ray Dubois: Work Very Intriguing

Asked for his opinion for this article, Ray Dubois, MD, PhD, Provost and Executive Vice President at the University of Texas MD Anderson Cancer Center, and an expert on COX-2, inflammation, and colon cancer prevention, said, "This might be an explanation for how obesity contributes to cancer progression. I have always been intrigued by the fact that obesity is a chronic inflammatory disease.

> "It is my contention that obesity causes an inflammatory process in the breast and will increase the likelihood of human breast cancer and potentially drives progression too."

"If you look at inflammatory cytokines and other markers of inflammation, they go up in the blood stream of people with a higher BMI. So obesity does put a stress on the system and sort of revs up the inflammatory response. And we certainly know that obesity increases the risk for some cancers, and breast is certainly one of those.

"Now we need to understand the mechanisms by which obesity does that," Dr. Dubois continued. "If obesity does lead to these local inflammatory lesions, that certainly could set up a situation in the tumor microenvironment that promotes cancer progression. [Dr. Dannenberg's work] is very intriguing, and it could explain how a systemic disease, obesity, contributes to something going on locally in breast tissue."

Dr. Dubois cautions, however, that the number of women studied by Dr. Dannenberg's team, thus far, remains small and so the observations need to be

*continued on page 64*

# Big Concerns about Inadvertent Use of Morcellation in Previously Undiagnosed Uterine Leiomyosarcoma

BY ED SUSMAN

"[At gynecologic surgical meetings], you can't go to a session without seeing a morcellator for a fibroid or uterus or a new technique. It is so widely accepted, and you get away with it most of the time, but it doesn't make it right."

ORLANDO, FL—Women who have among the rarest of cancers—leiomyosarcoma—have far better outcomes when the tumors are excised en bloc than when the cancer undergoes morcellation, usually as part of a laparoscopic procedure. That was the conclusion of a report here at the Meeting on Women's Cancer of the Society of Gyncologic Oncology.

The mortality rate among women whose tumors were removed en bloc during a complete hysterectomy was 19.4% after a mean of 63 months of follow-up while in cases where morcellation—i.e., piecemeal removal of lesions and organs—occurred the mortality rate was 44% after a mean follow-up of 39 months, Jeong-Yeol Park, MD, Clinical Assistant Professor of Medicine at Asan Medical Center in Seoul, said in his plenary talk. "Tumor morcellation and spillage during surgery may adversely affect treatment outcomes in patients with these highly malignant tumors."

Ed Susman

PETER LIM, MD: "We have to identify these patients, and as we do more and more robotic and minimally invasive surgery, I think we are going to see a bigger population. We have to better refine our tests."

In the retrospective study, Dr. Park and colleagues identified 56 patients who underwent surgery that involved removal of leiomyosarcomas: 31 of the women were treated with non-morcellation hysterectomy while morcellation occurred in 25 other women.

The non-morcellation group underwent total abdominal hysterectomy as initial surgery without morcellation; the other women underwent surgery that included abdominal, vaginal, or laparoscopic morcellation.

The researchers narrowed their study population to include just women with early leiomyosarcoma confined to the uterus during surgical management. Also included were patients who were referred to the institution after initial surgery had been performed, and the researchers reviewed the medical records of patients treated between 1989 and 2010.

"We sought to compare treatment outcomes and patterns of recurrence in patients with apparently early uterine leiomyosarcoma who did and did not undergo tumor morcellation during surgery," Dr. Park said.

The surgery often begins as treatment for uterine leiomyoma—fibroids—and advances in minimally invasive surgery may involve morcellation to eliminate the fibroids or perform a hysterectomy with less scarring. There are few symptoms or diagnostic tests that can alert the physician that the "benign lesion" is actually a rare but deadly tumor, Dr. Park explained.

"As a result, many patients with early uterine leiomyosarcoma are diagnosed only after surgical management, which may include tumor morcellation."

Ed Susman

NADEEN ABU-RUSTUM, MD: "Most of us would agree that if you knew there is a leiomyosarcoma you would not do a morcellation dissection for this tumor. The problem is that with increasing minimally invasive approaches and the benefits of removing big tumors with morcellation, this has become very popular as the majority of patients will do well and will not have a problem."

When the treating surgeon recognizes that a leiomyosarcoma has been morcellated during surgery, the surgeon often reaches out for help to the gynecologic oncology specialist, but by then fatal damage may have been done. "Once or twice a year we get these phone calls: 'We morcellated a leiomyosarcoma—what should we do next?,'" said Nadeen Abu-Rustum, MD, Director of Minimally Invasive Surgery in the Gynecology Service at Memorial Sloan-Kettering Cancer Center, the Discussant for the study.

*continued on page 66*

## →OBESITY/ INFLAMMATION

*continued from page 63*

confirmed in a substantially larger population of women.

### New Targets & Biomarker Studies

Although Dr. Dannenberg agrees the results need to be confirmed and extended in a larger group of women, he also thinks the observations could be incorporated into ongoing trials as a biomarker for risk. For example, he hypothesizes that studies that examine the impact of adjuvant exercise or weight loss on recurrence risk might find greater benefit in overweight or obese women whose tissue have crown-like structures, relative to women with similar BMI whose tissues don't carry evidence of inflammation.

"Wouldn't you like to know at time zero, if a person has inflammation and how severe it might be, so you can see if they derive bigger benefit?" he said.

"I think the discovery has potentially important implications for future trials and, ultimately, for personalizing therapy, be it behavioral or pharmacologic interventions." Additionally, he notes that the insights might go part way to explaining why aromatase inhibitors appear to be less effective in overweight and obese women, relative to lean women.

Perhaps, most important, though might be the identification of potential targets for intervention, given the growing number of overweight and obese individuals in the population. In addition to the non-steroidal anti-inflammatory drugs that block the COX-2 pathway, there are numerous small molecules and dietary substances that impact the activation of NF-κB, which resides at the top of a signaling cascade in mammary tissue.

Dr. Dannenberg declined to talk about specifics, because the studies are ongoing, but said that his research group is actively exploring ways to either reduce the number of crown-like structures or render them functionally inert. He predicts either outcome could lead to an improvement for breast cancer prevention or treatment.

"You might say there is cause for optimism," he concluded.