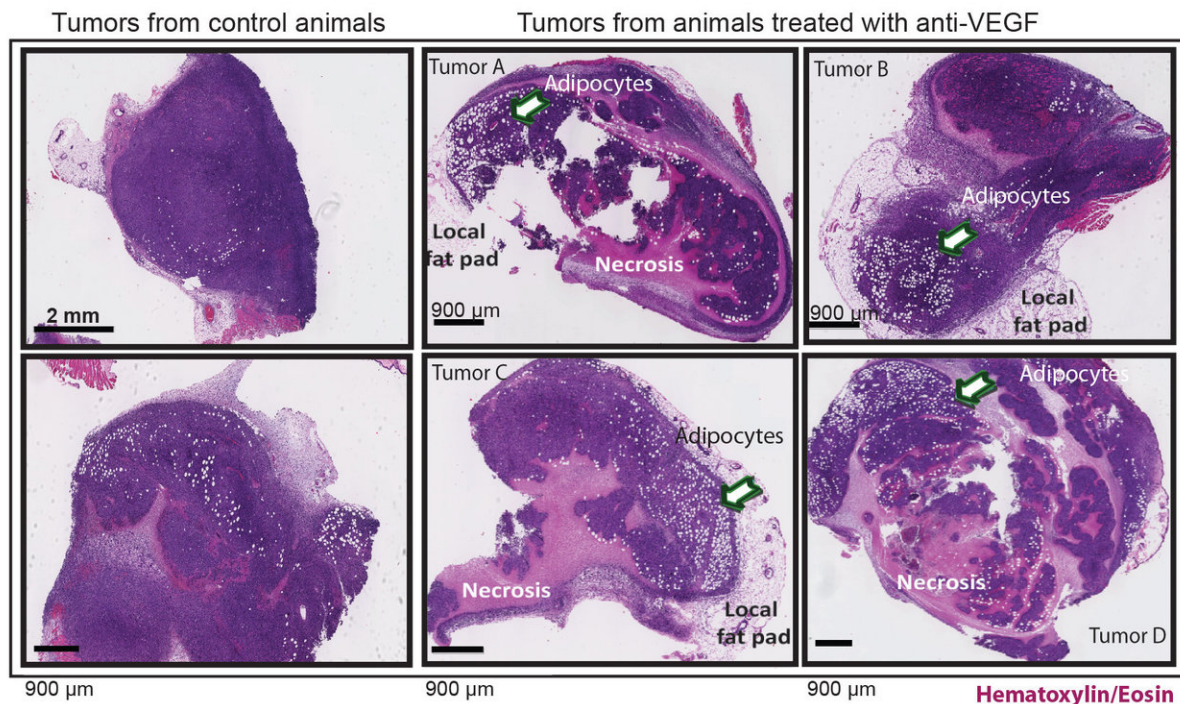


# Obesity may promote resistance to antiangiogenic therapy for breast cancer

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Tissue sections of mouse breast cancer cell tumors before and after anti-VEGF therapy. Right: Adipocyte-rich regions of tumors from animals treated with anti-VEGF. The adipocyte-rich tumor microenvironment in obese mice associates with sustained tumor progression, despite antiVEGF therapy. Credit: J. Incio et al., Science Translational Medicine (2018)

Obesity—which is already known to reduce survival in several types of cancer—may explain the ineffectiveness of angiogenesis inhibitors in

the treatment of breast cancer. A research team led by Massachusetts General Hospital (MGH) investigators describes finding, for the first time, that obesity and obesity-related molecular factors appear to induce resistance to antiangiogenic therapy in breast cancer patients and in two mouse models of the disease. Their report in *Science Translational Medicine* also details specific obesity-related factors underlying that resistance and outlines potential therapeutic strategies that may overcome it.

"Collectively, our clinical and preclinical results indicate that obesity fuels resistance to anti-vascular endothelial growth factor therapy in [breast cancer](#) via production of several inflammatory and pro-angiogenic factors, depending on the subtype of cancer," says Joao Incio, MD, Ph.D., of the Edwin L. Steele Laboratories for Tumor Biology in the MGH Department of Radiation Oncology, lead author of the report. "Targeting these resistance factors may rejuvenate the use of antiangiogenic therapy in [breast cancer treatment](#)."

While promising early studies led to accelerated FDA approval of the anti-vascular endothelial growth factor (VEGF) drug bevacizumab for treatment of [metastatic breast cancer](#), a lack of long-term survival benefit in several subsequent studies led to the withdrawal of approval. Several studies have associated obesity with reduced survival in colon cancer, particularly in patients receiving antiangiogenic therapy, but its role in other cancers has been uncertain.

Nearly 70 percent of breast cancer patients are overweight or obese upon diagnosis, and breast tumors are known to contain a significant proportion of adipose (fatty) tissue. Obesity is also associated with increased levels of inflammatory and angiogenic factors in addition to VEGF, which can contribute to anti-VEGF resistance. The current study was designed to investigate the hypothesis that obesity promotes resistance to anti-VEGF therapy for breast cancer through increased

production of those factors.

The research team first analyzed data from a clinical trial of 99 breast cancer patients treated with bevacizumab, first alone and then with chemotherapy, which showed that the anti-VEGF treatment only benefited a small fraction of patients. The investigators found that participants with [body mass index](#) (BMI) measurements of 25 or more—classifying them as overweight or obese—had tumors that averaged 33 percent larger upon diagnosis than did patients with BMIs less than 25. Furthermore, samples of tumors from patients with higher levels of body fat had a reduced vascular supply, which can interfere with the response to chemotherapy. Circulating levels of interleukin 6 (IL-6), a pro-inflammatory molecule, and fibroblast growth factor 2 (FGF-2), a pro-angiogenic molecule, were elevated in patients with higher BMIs, and these factors were expressed in adipocytes (fat cells) and in other nearby cells within tumors.

Several experiments in two mouse models of breast cancer—one of estrogen receptor (ER)-positive cancer and one of triple-negative cancer—supported the implications of those clinical research findings.

- The microenvironment of tumors from obese mice, which featured many adipocytes and reduced oxygen levels, was associated with reduced response to an anti-VEGF drug.
- In the ER-positive model, adipocytes and certain immune cells within the tumors of obese animals overexpressed several inflammatory and angiogenic molecules, including IL-6. Blocking IL-6 in those mice increased the response to anti-VEGF therapy to that seen in lean animals.
- In the triple-negative model, obese animals had increased levels of FGF-2 but not IL-6, and inhibition of FGF-2 increased treatment response to levels seen in lean animals.
- In both models, blockade of either molecule did not improve

treatment response in lean animals.

"This is the first study to propose that markers such as body mass index could help personalize anti-VEGF therapy, with blockade of molecules like IL-6 or FGF-2 for overweight or obese cancer patients," says Incio. "Identifying and validating predictive biomarkers of treatment response and gaining the ability to classify [patients](#) regarding which of the more than a dozen currently available antiangiogenic therapies would be most beneficial remain major priorities in oncology." He also notes that their results regarding the effects of IL-6 and FGF-2 blockade on obesity-related anti-VEGF resistance could be clinically tested soon, since several inhibitors of those pathways are available. One of the drugs they used to inhibit FGF-2 was metformin, a widely used type 2 diabetes drug that can also suppress the growth of certain cancers.

Co-senior author Dai Fukumura, MD, Ph.D., deputy director of the Steele Labs, says, "Although the role of systemic adipokines—signaling molecules derived from adipose tissues—has been studied in multiple obesity-associated diseases, studies dissecting their role in cancer have been limited. Our studies are the first to demonstrate the role of the adipokines IL-6 and FGF-2 in both [breast cancer patients](#) and clinically relevant animal models and that these adipokines are derived from adipocytes within tumors. There are many different adipokines, and we found that different factors mediate anti-VEGF resistance in different subsets of breast cancers. Investigations of the crosstalk between cancer-associated adipocytes and the tumor microenvironment are needed to develop novel strategies to overcome obesity-induced aggravation of [breast cancer](#)."

**More information:** J. Incio et al., "Obesity promotes resistance to anti-VEGF therapy in breast cancer by up-regulating IL-6 and potentially FGF-2," *Science Translational Medicine* (2018).

[stm.sciencemag.org/lookup/doi/.../scitranslmed.aag0945](http://stm.sciencemag.org/lookup/doi/.../scitranslmed.aag0945)

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