

Curbing hormones' effects in obese patients could aid against breast cancer

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Once-promising drugs that were abandoned in the fight against breast cancer still could be effective in obese patients, new research suggests.

In laboratory tests, hormones produced by fat cells stimulate breast cancer cells to migrate and invade surrounding tissues, scientists at Emory University School of Medicine found. A class of drugs called epithelial growth factor receptor (EGFR) inhibitors could block the stimulatory effects of the hormones.

The researchers' results are published online and are scheduled for publication in the December issue of the journal *Cancer Research*.

"This group of compounds was basically written off as far as breast cancer goes," says senior author Dipali Sharma, PhD, assistant professor of oncology/hematology at Emory University School of Medicine and Emory Winship Cancer Institute.

Sharma and her colleagues have been studying the effects of leptin, a hormone produced by adipocytes (fat cells), on breast cancer cells. One of leptin's functions is to send "had enough" signals to the hypothalamus, part of the brain that controls appetite, and it also regulates bone formation, reproductive functions and the growth of blood vessels.

Most obese people appear to produce an abundance of leptin but for them, leptin's appetite-controlling effects are muted in ways that are poorly understood. In addition to leptin, obese people also have high

levels of insulin-like growth factor-1 (IGF-1), which is produced primarily by the liver.

"The influence of obesity on breast cancer is more pronounced because most of the breast tissue is made of adipocytes," Sharma says. "There is an increasing amount of evidence for the importance of the environment surrounding the tumor in spurring its growth."

She and first author Neeraj Saxena, PhD, assistant professor of medicine/digestive diseases, found that together leptin and IGF-1 stimulate breast cancer cells to grow more than either does by itself. Together, they activate the EGFR molecule, the target of several anti-cancer drugs.

"Inhibiting either leptin or IGF-1 by itself would only take care of one," Sharma says. "Instead, we thought it would be better to look downstream and see where the two pathways converge."

Various EGFR inhibitors, such as erlotinib and cetuximab, have been approved by the FDA to treat head and neck cancer, lung cancer, colon cancer and pancreatic cancer. One, lapatinib, was approved in 2007 for women with advanced breast cancer who had already received other therapies.

However, clinical studies did not find most EGFR inhibitors effective against breast cancer for a large enough proportion of patients. Some oncologists believe it may be possible to select a fraction of patients, either through genetics or the characteristics of their tumors, who have a better chance of having the drugs work.

In the laboratory, EGFR inhibitors blocked the stimulatory effects of leptin and IGF-1 and had more of an effect on breast cancer cells' ability to migrate and invade other tissues than on proliferation. This suggests

they could blunt aggressive, metastatic tumor behavior, Sharma says.

She says her team's finding could be especially important for "triple negative" breast cancer, a form that does not respond to tamoxifen or the drug trastuzumab. Recent studies have shown a high prevalence of triple negative breast cancer in African-American women.

To strengthen the finding, Sharma is planning more tests in animals that model cancer growth in obese individuals and careful study of leptin and IGF-1 levels in human tumor samples.

Source: Emory University

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