Obesity and overeating during menopause together promote breast tumor growth and progression

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Obese women might be able to eliminate their increased risk for postmenopausal breast cancer by taking measures during perimenopause to prevent weight gain and to therapeutically control the metabolic effects of their obesity, according to the results of a preclinical study published in *Cancer Research*, a journal of the American Association for Cancer Research.

"Obese postmenopausal women have increased risk for breast cancer and poorer clinical outcomes compared with postmenopausal women who are lean," said Paul S. MacLean, Ph.D., associate professor of medicine at the University of Colorado Anschutz Health and Wellness Center in Aurora, Colo. "The reasons for this are not fully understood.

"Unfortunately you cannot do the studies needed to address this issue in humans. So, we merged rat models of obesity, breast cancer and menopause to best mimic the events that link premenopausal obesity to an increased rate of postmenopausal breast cancer."

During menopause, women often gain weight because they consume more food than their body needs. In a previous study, MacLean and colleagues used their rat model to show that weight gain following surgical ovariectomy, which models menopause, helped promote breast tumor development in obese rats.

In this study, they confirmed that obesity and overfeeding after surgical ovariectomy together drove aggressive tumor growth and progression.

One reason was that obese rats were unable to appropriately handle the excess sources of energy, in the form of glucose and dietary fat, which accumulated as a result of overfeeding after surgical ovariectomy. Lean rats stored the excess glucose and dietary fat from overfeeding in liver, fat, muscle and healthy breast tissue, a normal metabolic response to overfeeding. In contrast, the healthy tissues in obese rats failed to increase uptake of glucose and dietary fat, but the breast tumors dramatically increased uptake of glucose.

A second reason for the enhanced tumor growth and progression in obese rats compared with lean rats was that tumors from the two groups of animals had different molecular profiles. Tumors from obese rats had higher levels of expression of the progesterone receptor (PR), which was related to higher expression of genes involved in energy use and proliferation.

A similar pattern of increased expression of genes involved in energy use and cell growth was seen in human PR-positive breast tumors from postmenopausal women. According to MacLean, a final piece of evidence indicating that obesity and overfeeding during the menopausal transition converge to promote tumor growth and progression was that the antidiabetic drug metformin reduced tumor burden in obese rats after surgical ovariectomy.

"If our findings in rats translate to humans, it means that the perimenopausal period is a critical window of time for determining breast cancer risk later in life," said MacLean. "This, in turn, means that an obese woman's risk for postmenopausal breast cancer and poor clinical outcome could be reduced by perimenopausal lifestyle modifications, such as restricting food consumption and increasing

exercise, and/or perimenopausal use of drugs, such as metformin, to improve metabolic control."

MacLean and colleagues are now testing this hypothesis in the rat model.

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