Sylvester Researchers Link Obesity, Postmenopausal Estrogens and Breast Cancer Risk

The findings of a new study could explain a longstanding paradox. Despite the well-known association between estrogens and breast cancer risk, in general women have a higher risk for breast cancer after menopause, a time when overall estrogen levels in the body drop off.

Rehana Qureshi, Ph.D.

Different estrogens predominate before and after menopause,
and this shift could elevate breast cancer risk, according to investigators at Sylvester Comprehensive Cancer Center at the University of Miami Miller School of Medicine.

In the first study to compare the potential contribution of pre- and postmenopausal estrogens, researchers found 17b-estradiol was protective in mice. Younger women tend to have higher levels of this estrogen. In contrast, estrone levels rise after menopause, which could elevate risk on its own — and particularly in combination with obesity.

The study was published in the journal Cell Metabolism.

The results also carry potential implications for diagnosis.

“One of the most interesting translational takeaways is that estrone levels could be a biomarker of a woman's risk for developing breast cancer after menopause,” said Rehana Qureshi, Ph.D., lead author of the study and assistant scientist at Sylvester.

The research offers an explanation why overweight and obese postmenopausal women tend to carry more risk for developing breast cancer. Extra adipose or fat tissue, in premenopausal women leads to high estradiol which provide protection against inflammation.

Furthermore, an estimated 40% of postmenopausal women are obese, placing them at elevated risk for developing breast cancer. Although preliminary, data also suggests obese postmenopausal women who develop breast cancer are at higher risk of dying from metastatic breast cancer.

Inflammation is a bad player that appears to connect estrone,
obesity, and heightened breast cancer risk. Higher levels of estrone were associated with more inflammation among obese mice in the study.

Estrone was also associated with faster tumor growth.

“We found how estrone promotes faster tumor formation in estrogen receptor-positive breast cancer than 17b-estradiol,” Dr. Qureshi said. “This could explain why the number of estrogen receptor-positive breast cancers increase after menopause.”

The findings raise the promise of identifying future therapeutic targets for breast cancer drug development. One possibility is blocking or reducing activity of an enzyme called HSD17B14 that converts 17b estradiol to estrone.

“Higher levels of HSD17b14 were prognostic of poor survival in women with estrogen-receptor positive breast cancer,” Dr. Qureshi said. “Thus, blocking the conversion of 17-b-estradiol to estrone should result in lower risk for ER+ breast cancer after menopause.”

Dr. Qureshi and her colleagues also evaluated mechanisms behind what they found. This analysis showed that estradiol is anti-inflammatory and turns off the genes associated with inflammation, whereas estrone increases the expression of genes that drive inflammation.

Determining whether estrone promotes breast cancer metastasis is a possible avenue of future research. In addition, the researchers might assess whether higher levels of this particular estrogen make it easier for cancer to elude
detection by the body’s immune system.