Public release date: 9-Jan-2009

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High insulin levels raise risk of breast cancer in postmenopausal women

Elevated insulin may play a key role in the link between obesity and breast cancer

January 9, 2009 – (BRONX, NY) — Higher-than-normal levels of insulin place postmenopausal women at increased risk of breast cancer, researchers at Albert Einstein College of Medicine of Yeshiva University report. Their findings, published in the January 7 issue of the *Journal of the National Cancer Institute*, suggest that interventions that target insulin and its signaling pathways may decrease breast cancer risk in these women.

Breast cancer is the most common cancer among women in the United States. Last year, approximately 182,000 women were diagnosed with breast cancer and more than 40,000 died from the disease. The majority of breast cancers arise in women past the age of menopause.

Obesity is a well-established risk factor for postmenopausal breast cancer, but just how obesity and breast cancer are connected is unclear. Many researchers have assumed that the link is estrogen—a hormone that is known to increase breast-cancer risk and is found at higher-than-average levels in obese women. But obese women also have other hormonal imbalances that may play a role in triggering breast cancer. One such imbalance is elevated levels of insulin, which stimulates the growth of breast cells in tissue culture. The Einstein study is the first to prospectively identify insulin's role in breast cancer while controlling for estrogen levels.

The multi-year Women's Health Initiative (WHI)—the largest study of postmenopausal women ever funded by the National Institutes of Health—followed health outcomes in more than 93,000 postmenopausal women. At enrollment, each participant donated blood samples that were stored for later analysis.

In 2004, the Einstein researchers selected a subset of more than 1,600 of these participants: 835 who had developed breast cancer during the study, and a random sample of 816 women

representative of the WHI as a whole. Using the blood samples and other measurements taken when the women enrolled, the researchers assessed their fasting insulin level, naturally occurring levels of estradiol (a form of estrogen), and body mass index, or BMI (a measure of obesity). After dividing the women into four groups based on their fasting insulin levels and controlling for estrogen levels, the researchers found that women with the highest insulin levels were nearly 50 percent more likely to have developed breast cancer compared with women who had the lowest insulin levels.

Most of this effect was observed in the large subset of women from the WHI study who did not use hormone-replacement therapy. HRT has a strong effect on insulin and other hormonal factors, so eliminating this variable gives a clearer picture of insulin's effect on breast cancer. "Among these women, the influence of insulin on breast cancer risk was quite high," says lead author Marc Gunter, Ph.D., assistant professor of epidemiology & population health at Einstein. "Women with the highest insulin levels in their blood were more than two times more likely to develop breast cancer than women with the lowest insulin levels." Moreover, "when we controlled for insulin, the association between obesity and breast cancer became much weaker," adds Dr. Gunter. "This means that a large component of that obesity-cancer relationship may be mediated by insulin levels."

The findings have important implications for prevention, and possibly treatment, of postmenopausal breast cancer, according to Howard Strickler, M.D., M.P.H, who was senior author of the paper and a professor of epidemiology & population health at Einstein. "Research now needs to focus on ways to reduce insulin's effects on cell growth and replication in the breast while preserving its positive metabolic effects.

There are several possibilities and working with our laboratory collaborators we hope to make fast progress," said Dr. Strickler.

"It is also possible that screening non-diabetic postmenopausal women for high insulin levels could prove useful in identifying individuals at high risk for breast cancer," says Dr. Strickler.

The current study is part of a broader research program at Einstein. Researchers are focusing on how the effects of insulin and insulin-like growth factors on cell replication and survival influence a variety of conditions. "Every cell in the body carries insulin receptors and most carry IGF-1 receptors, so it makes sense that this biologic pathway could play a major role in health and disease across a broad range of conditions and we have to do much more to understand these relationships,"notes Dr. Strickler. So far, studies by Dr. Strickler and his colleagues have

shown that insulin and/or IGFs also play a role in endometrial and colorectal cancer, as well as the progression of certain viral diseases, including HIV, hepatitis C virus in the liver and human papillomavirus (the cause of cervical cancer).

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