

The Impact of Obesity and Obesity Treatments on Breast Cancer

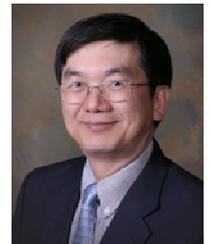
PROJECT SUMMARY AND PROGRESS REPORT

Given the current epidemic of obesity in the United States, understanding its effects on breast cancer is increasingly important. For postmenopausal women, obesity increases the risk of developing breast cancer. In addition, obesity is associated with a worse prognosis after the onset of breast cancer in both pre- and post-menopausal women. Obesity indirectly promotes the growth of breast cancer cells through three pathways: insulin growth factor (IGF-1), estrogen, and adipokines (hormones secreted by fat cells). Research suggests that drugs used to treat obesity or diabetes may inhibit the growth of estrogen-receptor positive (ER+) breast cancer cells. Therefore, these drugs may delay the onset of breast cancer in overweight and obese patients and the combination of anti-obesity or diabetes drugs with anti-estrogen therapies, such as aromatase inhibitors, may be an important treatment strategy for overweight and obese, postmenopausal breast cancer patients.

This Susan G. Komen for the Cure Promise Grant supports a 5-year, \$7.2 million research project to investigate the impact of obesity on breast cancer and evaluate anti-obesity/anti-diabetes treatments for the prevention and/or treatment of breast cancer.

THE RESEARCH TEAM

Dr. Sai-Ching “Jim” Yeung is an Associate Professor in the Department of Emergency Medicine and the Department of Endocrine Neoplasia & Hormonal Disorders at the University of Texas M.D. Anderson Cancer Center in Houston, TX. He earned his PhD from the University of Houston and his medical degree from St. Louis University, after which he completed an internship and residency in internal medicine, then a fellowship in Endocrinology and Metabolism at Baylor College of Medicine.



Dr. Francisco J. Esteva is a Professor in the Departments of Breast Medical Oncology and Molecular & Cellular Oncology at the University of Texas M.D. Anderson Cancer Center in Houston, TX. Dr. Esteva received his MD and PhD degrees from the University of Zaragoza School of Medicine in Spain. He completed an internship and residency in internal medicine at Cooper Hospital/University Medical Center in Camden, NJ and continued on to Georgetown University Medical Center where he completed a clinical fellowship in medical oncology.



Dr. Mong-Hong Lee is a Professor in the Department of Molecular and Cellular Oncology at the University of Texas M.D. Anderson Cancer Center. Dr. Lee received his PhD from the University of Pittsburgh. He then completed postdoctoral training at Memorial-Sloan-Kettering Cancer Center, after which he joined the University of Texas M.D. Anderson Cancer Center in Houston, TX.



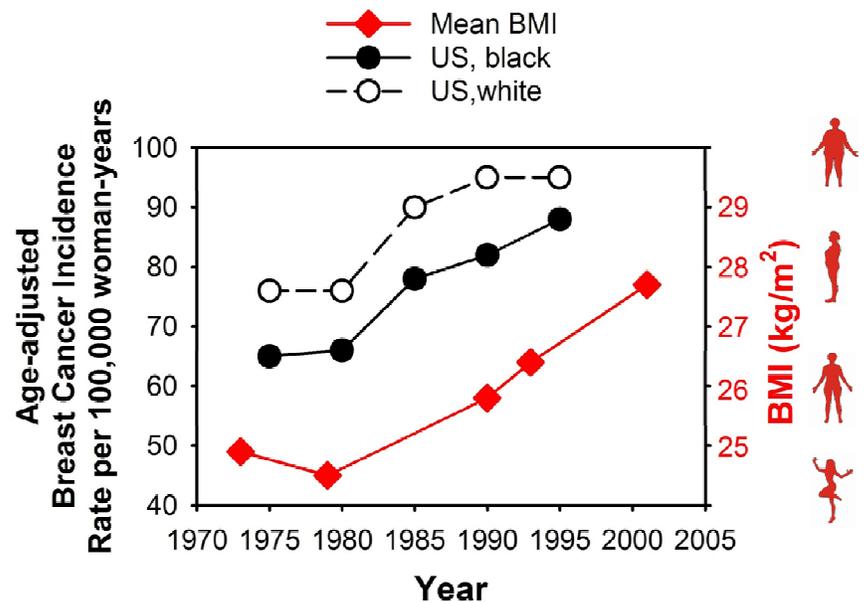
The Co-Investigators have assembled a unique team of experienced clinicians and research scientists with expertise in medical oncology, endocrinology, molecular biology, pathology, transgenic mouse models, and statistics, who are working together with patient advocates to determine the role obesity plays in breast cancer progression and investigate the use of anti-obesity treatments for the prevention and treatment of breast cancer.

RESEARCH GOALS AND PROGRESS

Through this Promise Grant, the investigators will conduct preclinical studies to identify the biological links between obesity and breast cancer. In addition, they will perform a clinical trial of insulin-sensitizing drugs (typically used to treat diabetes) with the aromatase inhibitor exemestane to see if the addition of insulin-sensitizing drugs will improve outcomes for overweight and obese postmenopausal women with metastatic ER+ breast cancer. Additional studies will investigate the mechanism of action for this drug combination. Specifically, the project has two primary goals:

1. Develop animal models of obesity in ER+ breast cancer, identify the hormones and signaling pathways that link obesity to the development of breast cancer and assess whether treatments for obesity delay tumor formation or improve survival. These studies will provide information about how obesity may contribute to breast cancer progression. Various anti-obesity treatments, including caloric restriction as well as drugs that suppress the appetite, inhibit fat absorption, or combat insulin resistance, will be tested in these preclinical animal models for their potential to prevent or delay the development of breast cancer and/or treat breast cancer once it has developed.

The Epidemic of Obesity and Rising Incidence of Breast Cancer



The body mass index of the US population has been rising over the last 30 years, creating an epidemic of obesity. The age-adjusted incidence of breast cancer in both the white and black populations in the US has been increasing over the same period, suggesting a link between breast cancer and obesity.

2. Investigate the effects of insulin-sensitizing drugs on tumor progression and overall survival in obese postmenopausal breast cancer patients being treated with aromatase inhibitors. This trial will

identify the optimal doses of these drugs to use and will determine whether the combination of diabetes drugs and aromatase inhibitors is more effective than aromatase inhibitors alone for treating obese, postmenopausal breast cancer patients. In addition, the effects of these drugs on insulin, estrogen, and adipokines will be assessed to identify molecules that may serve as biomarkers to help identify which patients are most likely to respond to this combination therapy.

During their first two years of funding, the research team has developed two preclinical mouse models of obesity in ER+ breast cancer and initiated studies to identify the hormones and signaling pathways that are affected by obesity and contribute to breast cancer progression. These animal studies have shown the following:

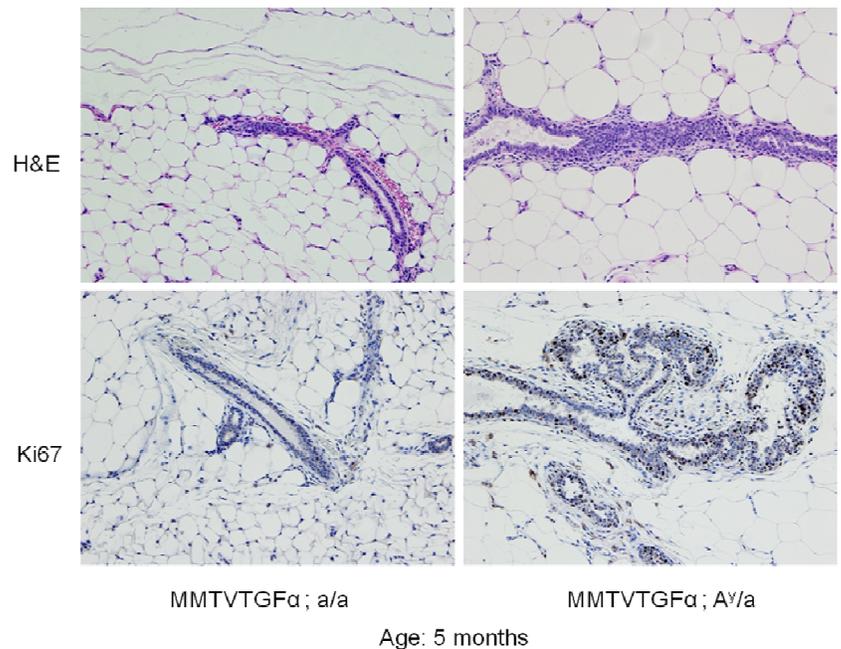
- Higher circulating levels of several molecules, including insulin, IGF-1, estrogen, and adipokines, were detected in the mouse model of obesity and diabetes in ER+ breast cancer compared to their

non-obese counterparts. In addition, the obese mice showed early signs of breast cancer (ductal hyperplasia and increased cell proliferation) at a younger age than their non-obese counterparts.

- There was a higher incidence of mammary tumors and more rapid tumor progression in the mouse model of obesity with metabolic syndrome in ER+ breast cancer than the control group. In addition, preliminary data suggest that the obese mice with metabolic syndrome may have more cases of invasive carcinoma.

Other studies showed that leptin (an adipokine) stimulates growth of ER+ breast cancer cells, regardless of whether or not the cells express HER2. (Breast cancer cells that express HER2 are generally more aggressive than those that do not express HER2.) The presence of estrogen further enhanced the leptin-stimulated breast cancer cell growth, providing a link between adipokines and breast cancer progression.

In addition, a Phase I study of an aromatase inhibitor plus the anti-obesity drug, Avandamet® (rosiglitazone plus metformin) was initiated. A total of 15 women were enrolled in the Phase I trial. No toxicity has been observed in the highest doses to be tested. A Phase II trial is planned using an aromatase inhibitor plus the diabetes drug, metformin, in obese, postmenopausal patients with ER+ breast cancer.



Through this Promise Grant, the investigators developed a mouse model of obesity and diabetes with ER+ breast cancer. This figure shows that, at the age of 5 months, mammary fat pads from the obese female mice with diabetes had ductal hyperplasia (upper right panel) while those of their non-obese female littermates were normal (upper left panel). In addition, mammary cells from the obese female mice showed a significant increase in cell growth (lower right panel) as compared to their non-obese littermates (lower left panel).

HOW WILL THIS RESEARCH BRING US CLOSER TO THE CURES?

It has been estimated that up to 50% of postmenopausal breast cancer deaths in the United States can be attributed to obesity, and studies indicate that as many as 18,000 breast cancer deaths in the United States could be avoided each year if body mass index (BMI) was kept below 25 throughout adulthood. There is currently an obesity epidemic in the United States, and it is crucially important to find ways to lessen the impact of obesity on breast cancer progression.

The multidisciplinary research team funded by this Promise Grant is collectively focused on the goals of understanding the biological links between obesity and breast cancer and finding treatments that will reduce or eliminate the contributions of obesity to the development and progression of breast cancer. If successful, these studies will improve the clinical outcome for overweight or obese postmenopausal patients with ER+ breast cancer, leading to reduction in incidence and mortality from this disease.

Susan G. Komen for the Cure® is proud to fund research that will provide insight into the link between obesity and breast cancer and improve outcomes for overweight and obese breast cancer patients.

June 2011