Public Abstract

Estrogen receptor-positive (ER+), HER2-negative (HER2-) breast cancer represents about two-thirds of breast cancers. Most ER+ breast tumors need estrogen to activate the estrogen receptor to be able to grow. For over a century the mainstay of treatment has been to stop that activation, initially with removal of the ovaries and now with medications that manipulate estrogen receptor signaling. After a diagnosis of metastatic ER+, HER2- breast cancer, people receive these medications as their first set of treatments, and for some people they can be very effective for a long time. However, eventually all metastatic ER+, HER2- breast cancer stops responding to estrogen receptor-targeting treatments and begins to grow and metastasize again. We have identified two molecular groups of ER+, HER2- breast cancer that do not respond as well to treatments that stop estrogen receptor activation, even from the very beginning. These two sets of tumors are each defined by distinct gene changes and together account for about ten percent of all ER+/HER2- breast cancer. In this project, we seek to deeply characterize these two sets of tumors to try to find new ways to thwart them. One possible reason why these tumors may be resistant to our standard treatments could be that, in addition to activating the estrogen receptor pathway, they activate the fibroblast growth factor receptor (FGFR) pathway. We think the FGFR pathway may be important for these tumors because the distinct gene changes that define them are members of that pathway. In activating both the estrogen receptor pathway and another receptor pathway, these tumors might be like ER+, HER2+ tumors, where the ER and HER2 pathways interact with each other to help the cancer cells grow and spread. Blocking HER2 activation has revolutionized the treatment of ER+, HER2+ breast cancer, greatly improving outcomes. Blocking FGFR activation has been tried for breast cancer, but, so far, with less success. In this project, we will study metastatic tumors from these two molecular groups using state-of-the-art technologies in order to understand the role of the FGFR, estrogen receptor, and other pathways, as well as the role of the immune system and nearby normal (“stromal”) cells, in allowing these tumors to resist estrogen receptor-targeting treatments. We will collect tumor tissue samples from patients with metastatic breast cancer that classifies as one of these two molecular groups; for comparison, we will also collect tumor tissue samples from patients with metastatic breast cancer that classifies as one of the other molecular groups, which we hypothesize to have activation of the ER pathway but not the FGFR pathway. We will select many different proteins from the FGFR, estrogen receptor, and other important cancer cell pathways, as well as from the immune and stromal cells that enter and surround the tumor. Using new technologies, we will learn where in the tumors and their surroundings these proteins are found, as well as how much of the proteins are there. These studies will identify potential pathways that could be targeted with medications, including both cancer cell pathways and immune pathways, because they are overactive in these tumors. They may also help us understand why small molecule FGFR inhibitors, as have been tried, are not as effective as HER2 inhibitors, and suggest ways to improve their efficacy. Overall, the project will reveal a new perspective on FGFR signaling and immune activation in these resistant, metastatic breast tumors, one we hope will open avenues to developing treatments that can improve the outcomes of people with metastatic breast cancer.