Susan G. Komen for the Cure
Research Grants – Fiscal Year 2011

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Immune and Collagen Basis of Breast Cancer Risk

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Awarded: $599,996
Grant Mechanism: Investigator Initiated Research
Research Focus: Etiology

Public Abstract:
In 1998, the cooperative group NSABP released the results of a large randomized trial comparing tamoxifen to placebo which showed a 49% reduction of invasive cancer in those women who received tamoxifen. However almost 10 years later, less than 52,000 women (an estimated<1% of those eligible) reported use of tamoxifen for breast cancer risk reduction. The low uptake of tamoxifen chemoprevention can in part be attributed to poor risk stratification algorithms which, although generally accurate in predicting population-level risk for breast cancer, do not reliably discriminate between low and high risk in a given individual. Faced with weighing known side effects with an unknown personal benefit, it is not surprising that most women decide against chemoprevention. Among individual known breast cancer risk factors, epidemiological studies have found that breast density is one of the strongest predictors of breast cancer, second only to a BRCA mutation. However, the molecular changes that underlie the risk conferred by BD remain largely unknown. One obvious biomarker to study in this regard is collagen, which makes up 90% of the proteins in the breast and forms the structural support for all the glands in the breast tissue. There are exciting emerging data that have demonstrated a complex communication between collagen and the immune system, and suggests that this interplay may form the basis of the increased breast cancer risk seen in women with dense breast tissue. Breast density is most commonly assessed on mammography, but measured in this way, it does not accurately predict risk for breast cancer in an individual since many women with low density still develop breast cancer while others with high breast density do not. MRI has been used to evaluate breast cancers, but its utility in measuring breast density is still unknown. Preliminary studies suggest that density measured by mammography and MRI are not the same, so it is possible that MRI breast density may be as good or even better in discriminating breast cancer risk.

In this study, we seek to identify which immune and collagen characteristics confer the increased breast cancer risk seen in women with high breast density. To accomplish this goal, we will examine the tissue of women undergoing mastectomy for cancer, and compare the immune and collagen properties around the cancer, in the same breast but distant from the cancer, and in other patients who had breast reduction but did not have cancer. By doing this, we will gain a better understanding how immune and collagen features are associated with development of cancer. We will also evaluate whether different immune and collagen states give rise to different types of cancer, showing again the relationship between properties of the breast tissue and cancer. We will then determine whether mammograms in these women taken before surgery showed a high breast density. Moreover, we will study whether MRI

characteristics such as quantitative density measurement and density patterns (these are difficult to discern on mammography) track with these high risk immune and collagen characteristics even more closely than mammographic density does. These MRI patterns will be evaluated on preoperative studies, and many of the MRI measures will be automated.

The overarching goal of this study is to improve risk stratification for individuals based on a better understanding of how the immune system and the structural proteins of the breast act together to determine breast density and increase breast cancer risk. If successful, this project will improve the utility of breast density as a risk factor by identifying which breast density characteristics on mammography or MRI are most closely related to the immune and collagen features found in breasts harboring tumor. Currently, imaging findings will be the surrogate for the changes occurring in the tissue. However, if we identify those immune or collagen properties that are highly predictive of cancer, it would be possible to explore whether this information could be obtained directly from the a breast core biopsy or from the blood. Ultimately, we seek this information to enable women to make better choices regarding their own breast cancer risk, based on an individualized test. It is hoped that these studies will help determine whether an individual has very low risk or whether chemoprevention is strongly recommended. This increased clarity about the tradeoffs will allow women to make truly informed decisions about their breast health.

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