



**Susan G. Komen
Research Grants – Fiscal Year 2014**

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Using breast tissue expression patterns to inform our understanding of breast cancer risk factors

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Lead Organization: Brigham and Women's Hospital and Harvard Medical School

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Public Abstract:

Breast cancer results from the interaction of lifestyle, genetic, environmental and tissue-specific factors. This complex process is multi-step and takes years to develop. A number of lifestyle factors have been consistently linked to increases (e.g., alcohol intake, postmenopausal obesity) or decreases (e.g., physical activity, premenopausal obesity) in risk of breast cancer. However, how these increases (or decreases) occur at the cellular level is largely unknown. Several primary pathways have been identified (for example, obesity increases estrogen exposure, which in turn increases breast cancer risk) but there are likely multiple other pathways also playing a role. We believe that by looking at the correlation between breast cancer risk factors, and gene expression in breast tissue, we may learn what some of these other pathways are. In the current project, we propose to examine detailed RNA expression profiles in both breast tumors and normal breast tissue collected from a subset of premenopausal women in the Nurses' Health Study II, as well as similar profiles derived from a subset of postmenopausal women from the Nurses' Health Study. We will link these expression profiles to several lifestyle exposures assessed prior to cancer diagnosis. For all samples, the NuGen/Affymetrix Human Transcriptome Array platform will be utilized; in total we expect to have 600-650 matched pairs (tumor plus adjacent normal). All women have provided repeated and detailed data on a range of breast cancer risk factors. Specifically, we propose to assess physical activity, vitamin D, obesity in premenopausal and postmenopausal women, and alcohol intake. Studies conducted to date suggest that physical activity reduces the risk of both premenopausal and postmenopausal breast cancer, and improves survival in women with breast cancer. Our project should help us identify why this happens. Studies also indicate that vitamin D may play a role in breast cancer risk, with the most convincing evidence coming from animal and laboratory studies; evidence from studies in humans is inconsistent. Increased postmenopausal obesity have consistently been shown to be associated with both increased risk of postmenopausal breast cancer as well as decreased breast cancer survival. This increased risk is likely in part through weight gain increasing estrogen levels, a well-established cause of breast cancer, but other factors (e.g., increased inflammation) also may play a role. Interestingly, premenopausal BMI consistently shows an inverse association with breast cancer risk. The reason for this association is unknown, but will be explored as part of this project. Finally, alcohol is wellconfirmed to increased risk of breast cancer, and although multiple mechanisms have been proposed (e.g., increased estrogen or androgens, increases in oxidation), none have been confirmed. By identifying differences in RNA expression profiles in breast cancer as well as normal breast tissue associated with these breast cancer risk factors, we will provide new insight into biologic mechanisms underlying these exposures. Further, the identified expression signatures in normal breast and breast cancer may represent new therapeutic targets for breast cancer prevention and treatment.