American Cancer Society – Institutional Research Grants 2014

"Prospective metabolite biomarkers of human breast cancer"

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Breast cancer continues to be a major contributor to morbidity and mortality among women in the U.S. Genetic factors alone account for a small fraction of total risk for developing breast cancer, with the vast majority of breast cancer risk remaining acquired exposures that accumulate over the course of a woman's life, including exposures related to host state and physiology such as obesity, environment, diet and even microbiota. These exposures all alter small molecule chemical mediators, or metabolites, within the circulation that directly impact the pathogenesis of breast cancer and serve as biological markers for exposure related risk of disease. We hypothesize that such exposure related metabolite biomarkers will enable prospective assessment of breast cancer risk with far greater precision than afforded by traditional risk factors, and may even allow for sub-stratification of patients at elevated risk for cancer related outcomes (metastasis and death) or even specific drug responsiveness. Identification of such robust small molecule biomarkers have the potential to transform our understanding and clinical care of patients with breast cancer. While the use of massive parallel sequencing has revolutionized the assessment of genetic markers, technologies and approaches capable of capturing exposure related biomarkers of disease across large-scale clinical cohorts have remained absent. Work from our group has recently established innovative, high throughput mass spectrometry based analytical approaches for the assessment of thousands of small molecule metabolites in plasma, including those originating from host physiology, as well metabolites originating from environmental exposures, diet, and microbiota. These tools enable the comprehensive assessment of plasma small molecule metabolites as *prospective biomarkers* associated with the development of breast cancer, even years prior to formal diagnosis, onset of clinically relevant disease or cancer related outcomes. In this American Cancer Society Institutional Research Grant application, we aim to leverage our novel mass spectrometry approaches within the context of one of the largest epidemiological studies of women's health in the U.S. to date. In the Women's Health Study (WHS) of 27,495 healthy women enrolled in 1993, we will apply our mass spectrometry approaches to quantify small molecule metabolites in plasma samples obtained at baseline, focusing on 1586 WHS cases in which a diagnoses of incident breast cancer was made over the greater than 20 year follow up study period and 2000 age-matched, clinically-matched control WHS participants. From these studies, we will identify specific small molecules positively or negatively associated with the development of incident breast cancer and breast cancer related outcomes. Future work will validate prioritized metabolites associated with breast cancers in independent clinical cohorts, as well as use statistical genetics and experimental approaches to assess the causal contribution of prioritized metabolites in promoting or protecting against the development of breast cancer transformation.

This proposed work represents the most comprehensive assessment of small molecule mediators of human breast cancer to date, and will greatly advance our understanding of circulating factors that contribute to the pathogenesis of breast cancer.