# Specific Aims

Body size, alcohol use, physical activity, diet, and tobacco use count among the leading risk factors of mortality in the United States, yet less than ten percent of NIH-funded prevention research projects examine more than one of these indicators. These lifestyle risk factors are also associated with breast cancer, the second most common cancer for women in the United States, who experience a 1 in 8 risk of being diagnosed across their lifetime. What remains unclear is how correlated individual lifestyle indicators comprise a co-existing entity, i.e. a healthy lifestyle factor, and if change in this healthy lifestyle construct is associated with breast cancer incidence. Furthermore, it is unknown if people with extreme lifestyle measures carry a disproportionate breast cancer burden — also characterized as risk inequality. Defining risk inequality measures that involve modifiable behaviors remains an important and underdeveloped area of research in public health and health-promoting lifestyle constructs can also interact with genetic risk factors. With better knowledge of this association, we could do better at identifying subgroups providing optimal targets for breast cancer prevention.

To better understand the role of healthy lifestyle trajectories as they relate to breast cancer incidence and all-cause mortality and their interplay with genetic factors, we plan a three-pronged analytic approach using data from a contemporary large U.S. cohort of women. First, we will use factor analysis to estimate a healthy lifestyle construct and determine if this construct varies across age and racial/ethnic groups. Second, we will assess patterns of change over time in this construct that could influence breast cancer risk and all-cause mortality, through joint modeling of longitudinal effects using time-to-event models. Lastly, we will use risk inequality methods to characterize the concentration of disease burden across the range of lifestyle indicators and use this inequality assessment to determine if it modifies genetic risk of breast cancer through gene-environment models. Postmenopausal women with an unfavorable lifestyle profile and carry a disproportionate disease burden may demonstrate stronger genetic associations with breast cancer risk than those in lower disease-burden groups. Characterizing a constellation of lifestyle indicators as a unified construct and understanding how their changes over time, not just static baseline values, impact cancer and all-cause mortality outcomes can help clarify carcinogenesis and also highlight critical areas of intervention in midlife, providing important insight into avenues of prevention.

**Aim 1**: Characterize a lifestyle construct from indicators in a contemporary cohort of women and assess trajectories across age. *Hypothesis 1*: Correlated lifestyle indicators will fit within a factor and will be consistently defined as age increases.

**Aim 2**: Assess the relationships between the lifestyle factor changes and incident breast cancer and all-cause mortality outcomes. *Hypothesis 2*: Groups with improving lifestyle trajectories are at lower risk for breast cancer and all-cause mortality.

**Aim 3**: Assess associations between polygenic risk scores and breast cancer risk for lifestyle groups with highest disease burden compared to groups with lowest burden. *Hypothesis 3*: Groups carrying a disproportionately higher lifestyle-based disease burden will display stronger genetic associations with cancer incidence compared to those with a lower burden.

Evidence from this research can provide knowledge in an understudied area of breast cancer and mortality prevention to help understand how groups of related modifiable lifestyle indicators: 1) form a construct, 2) change over time and influence breast cancer incidence, and 3) modify genetic risk. This knowledge can help target the most impactful domains within lifestyle indicators to reduce the growing burden of disease that occurs with age in the population of postmenopausal women.