Proposed for an NCI Cohort Consortium Study
Date Proposed: June 2008
Date Approved: July 2008
Proposed By: Louise Brinton
Cohort Consortium Information: Geoffrey Tobias (Executive Secretary)

Male Breast Cancer in the Cohort Consortium

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Male breast cancer is uncommon, accounting for only 0.7% of all breast cancers (1). Although it shares some similarities with female breast cancer, there are some marked differences, including an older average age at onset and higher overall incidence rates among blacks than whites (2, 3). Recent reports of rising incidence (4, 5) have raised concern, although it is unclear the extent to which this may merely represent earlier detection.

The rarity of male breast cancer has posed difficulties for identifying etiologic factors. Most studies have been of a case-control design, leading to questions regarding whether identified risk factors reflect selective recall after disease onset. Although genetic factors have been shown to be important, they appear to explain only a small proportion of disease occurrence, as is also true for female breast cancers. Most environmental factors have received scant attention (6).

In one of the few prospective studies to date, conducted within the NIH-AARP Diet and Health Study, we recently identified important relationships with obesity and physical inactivity, suggesting the importance of hormonal factors (7). In addition, we found an increased risk associated with bone fractures, which was unexpected given that females show the opposite relationship. Although low estrogen levels have been hypothesized as the underlying mechanism for low breast cancer risk in women with fractures (8), in men both estrogens and androgens are important for bone maintenance (9). Thus, given decreasing testosterone levels with age, bone fractures may relate to male breast cancer through alterations in the bioavailable estrogen/testosterone ratio.

To more fully understand the etiology of male breast cancers, we are proposing to examine risk factors across multiple studies involved in the Cohort Consortium. This will allow accrual of sufficient number of cases of this rare tumor to evaluate multiple exposures, some of which could not be fully evaluated in the AARP study (e.g., excessive alcohol consumption, gynecomastia, liver and thyroid diseases, infertility history, usage of exogenous hormones, certain occupational exposures).

The cohorts that have collected biologic samples will be especially valuable contributors as there are a number of biomarkers that could be measured and provide important clues to etiologic mechanisms. The assessment of hormones is especially exciting given recently developed liquid chromatography mass spectrometry techniques at NCI's Frederick hormone laboratory for measuring estrogens and metabolites and androgens that require only small sample amounts (10, 11). Assessment of ratios of bioavailable estrogens to androgens is of particular interest.

This study would be the first to prospectively evaluate the role of endogenous hormones, as well as other possible biomarkers, including genetic markers that have not been assessed in previous epidemiologic investigations. It is clear that *BRCA2* has unique influences on male breast cancers (12), but whether other markers are predictive has yet to be determined. If there are a sufficient number of samples available for DNA

extraction, collaborators from DCEG's Core Genotyping Facility would be sought to assure the most appropriate approaches for evaluating genetic markers for this rare cancer.

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