Title: OLDER BREAST CANCER PATIENTS: RISK FOR
COGNITIVE DECLINE

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OLDER BREAST CANCER PATIENTS: RISK FOR COGNITIVE DECLINE

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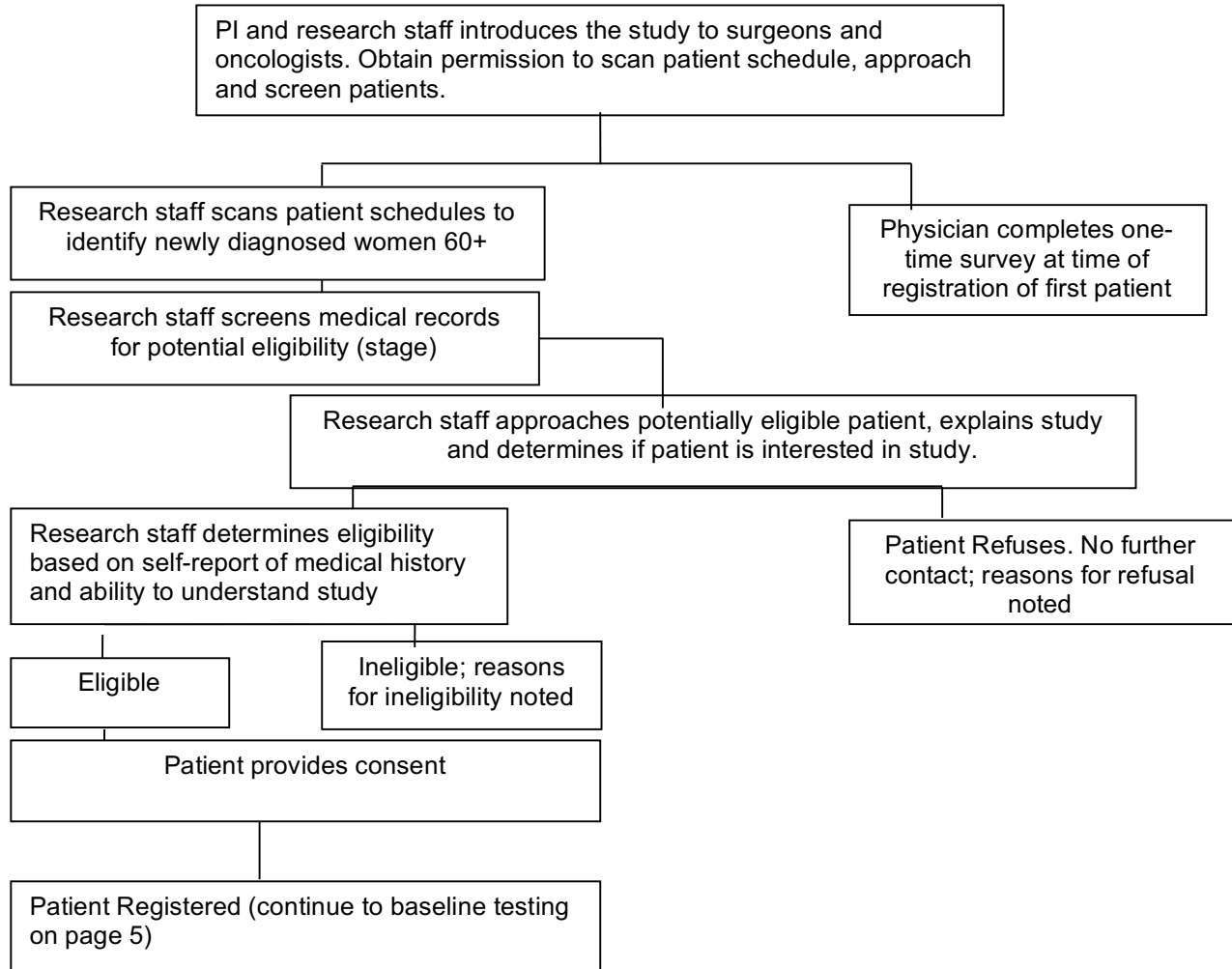202-687-3770
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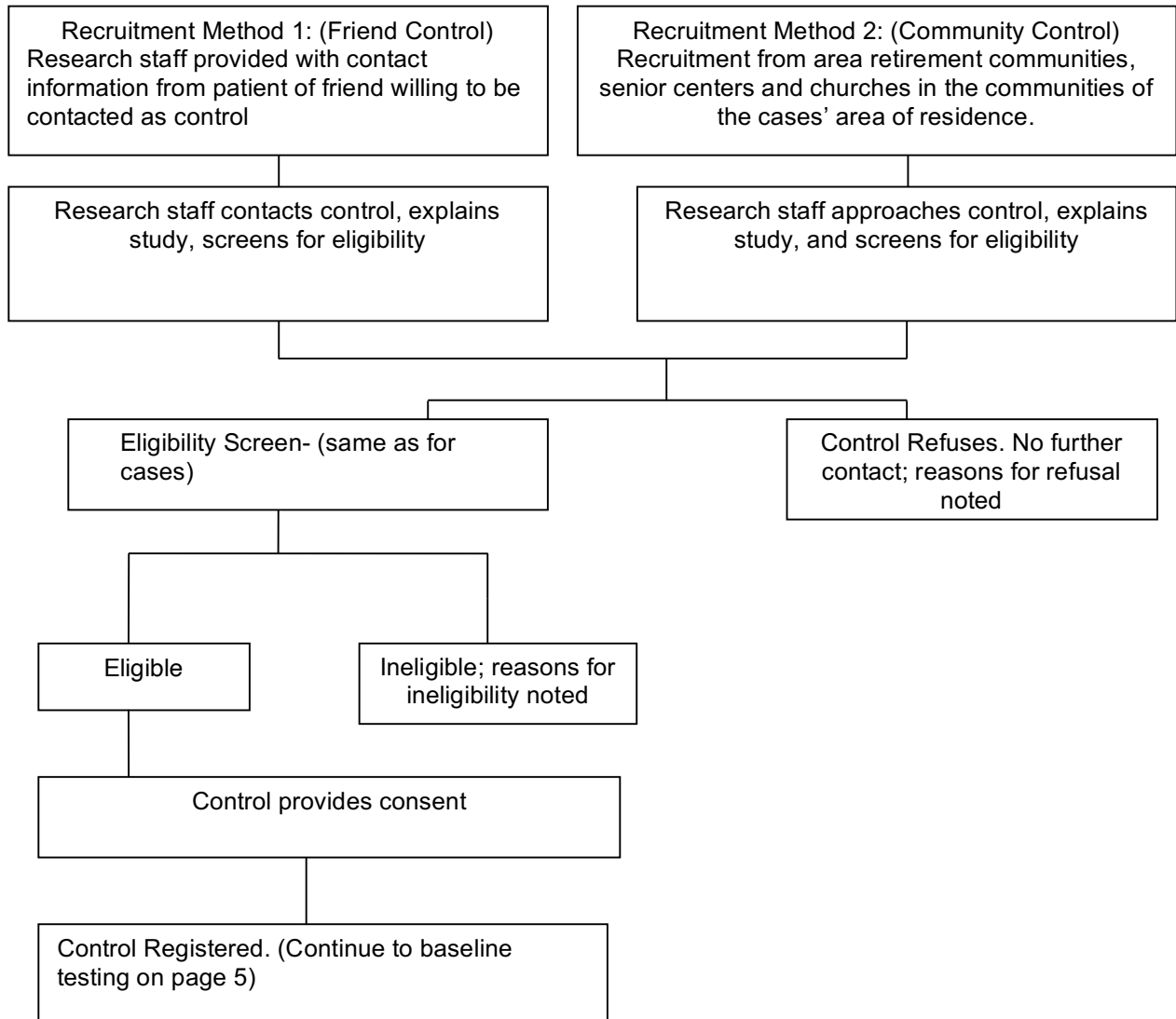 National Institutes of Health
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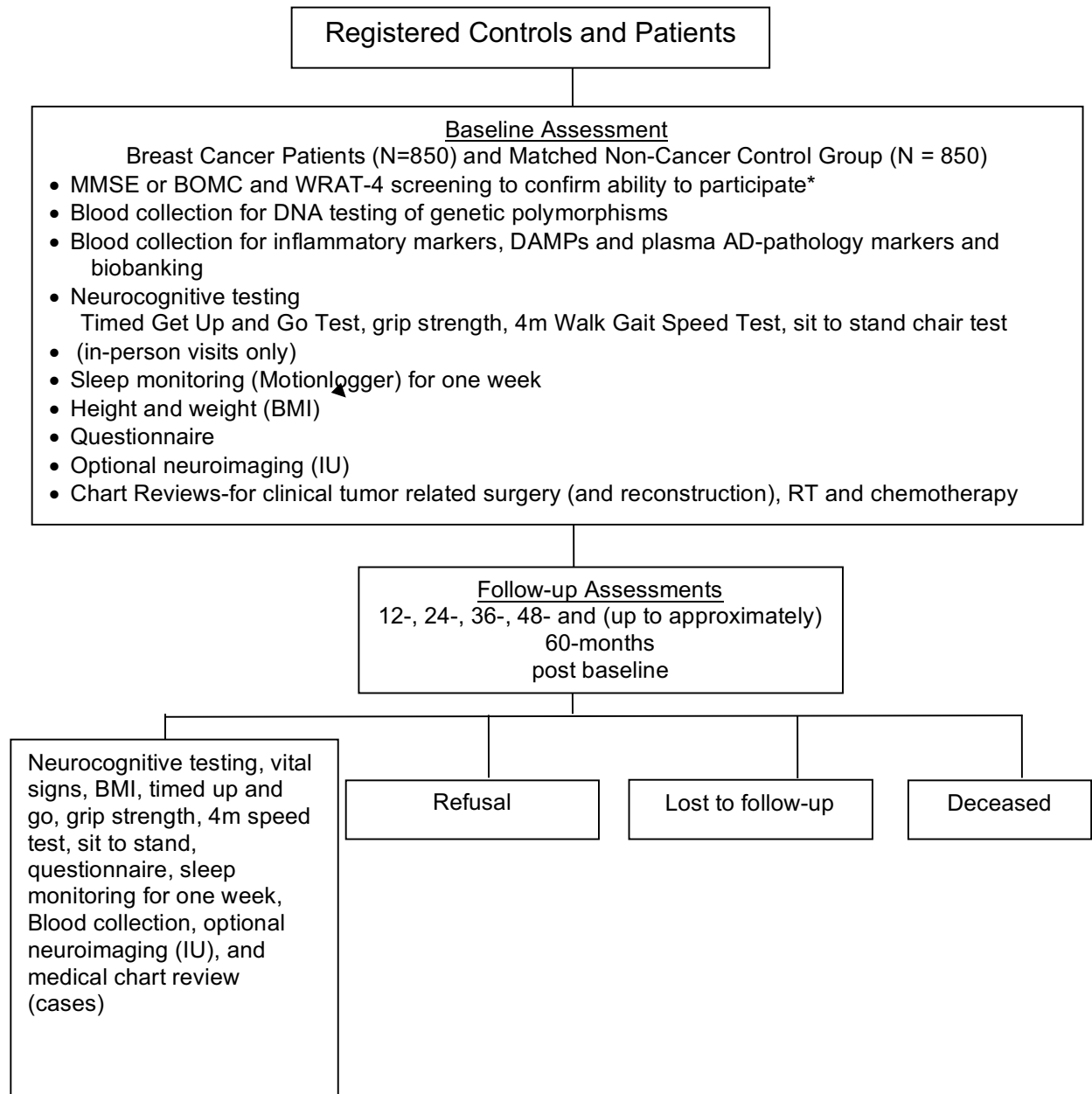# OLDER BREAST CANCER PATIENTS: RISK FOR COGNITIVE DECLINE

Schema for Patients:

PI and research staff introduces the study to surgeons and oncologists. Obtain permission to scan patient schedule, approach and screen patients.

Research staff scans patient schedules to identify newly diagnosed women 60+

Physician completes one-time survey at time of registration of first patient

Research staff screens medical records for potential eligibility (stage)

Research staff approaches potentially eligible patient, explains study and determines if patient is interested in study.

Research staff determines eligibility based on self-report of medical history and ability to understand study

Patient Refuses. No further contact; reasons for refusal noted

Eligible

Ineligible; reasons for ineligibility noted

Patient provides consent

Patient Registered (continue to baseline testing on page 5)

OLDER BREAST CANCER PATIENTS: RISK FOR COGNITIVE DECLINE

Schema for Controls:

```
┌─────────────────────────────────┐   ┌─────────────────────────────────┐
│ Recruitment Method 1: (Friend   │   │ Recruitment Method 2: (Community│
│ Control)                        │   │ Control)                        │
│ Research staff provided with    │   │ Recruitment from area retirement│
│ contact information from patient│   │ communities, senior centers and │
│ of friend willing to be         │   │ churches in the communities of  │
│ contacted as control            │   │ the cases' area of residence.   │
└─────────────────────────────────┘   └─────────────────────────────────┘
              │                                      │
┌─────────────────────────────────┐   ┌─────────────────────────────────┐
│ Research staff contacts control,│   │ Research staff approaches control,│
│ explains study, screens for     │   │ explains study, and screens for │
│ eligibility                     │   │ eligibility                     │
└─────────────────────────────────┘   └─────────────────────────────────┘
```

┌─────────────────────────────────┐   ┌─────────────────────────────────┐
│ Eligibility Screen- (same as for│   │ Control Refuses. No further   │
│ cases)   │   │ contact; reasons for refusal   │
│   │   │ noted   │
└─────────────────────────────────┘   └─────────────────────────────────┘

┌──────────────┐   ┌─────────────────────────┐
│ Eligible   │   │ Ineligible; reasons for │
│   │   │ ineligibility noted   │
└──────────────┘   └─────────────────────────┘

┌─────────────────────────────────┐
│ Control provides consent   │
└─────────────────────────────────┘

┌─────────────────────────────────┐
│ Control Registered. (Continue to│
│ baseline testing on page 5)   │
└─────────────────────────────────┘

```
                    ┌─────────────────────────────────────┐
                    │   Registered Controls and Patients   │
                    └─────────────────────────────────────┘
                                      │
┌──────────────────────────────────────────────────────────────────────┐
│                        Baseline Assessment                             │
│   Breast Cancer Patients (N=850) and Matched Non-Cancer Control        │
│                         Group (N = 850)                                │
│  • MMSE or BOMC and WRAT-4 screening to confirm ability to participate*│
│  • Blood collection for DNA testing of genetic polymorphisms           │
│  • Blood collection for inflammatory markers, DAMPs and plasma         │
│      AD-pathology markers and biobanking                               │
│  • Neurocognitive testing                                              │
│      Timed Get Up and Go Test, grip strength, 4m Walk Gait Speed       │
│      Test, sit to stand chair test                                     │
│  •  (in-person visits only)                                            │
│  • Sleep monitoring (Motionlogger) for one week                        │
│  • Height and weight (BMI)                                             │
│  • Questionnaire                                                       │
│  • Optional neuroimaging (IU)                                          │
│  • Chart Reviews-for clinical tumor related surgery (and               │
│      reconstruction), RT and chemotherapy                              │
└──────────────────────────────────────────────────────────────────────┘
                                      │
                    ┌─────────────────────────────────────┐
                    │      Follow-up Assessments          │
                    │ 12-, 24-, 36-, 48- and (up to       │
                    │ approximately) 60-months            │
                    │        post baseline                │
                    └─────────────────────────────────────┘
```

| Neurocognitive testing, vital signs, BMI, timed up and go, grip strength, 4m speed test, sit to stand, questionnaire, sleep monitoring for one week, Blood collection, optional neuroimaging (IU), and medical chart review (cases) | Refusal | Lost to follow-up | Deceased |

Cognitive impairment on MMSE or BOMC or less than 3rd grade reading level on WRAT, she will be thanked and participation will end.

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1.0 PROTOCOL SUMMARY

We will use the vulnerability model of cancer survivorship to prospectively describe the magnitude of systemic therapy effects on cognition in older (age $\geq$60 years) breast cancer patients over up to approximately a 60 month period, test associations between cognition and quality of life (QOL) and evaluate whether APOE and COMT polymorphisms and inflammatory biomarkers, moderate cognitive outcomes. To achieve our objectives, we have assembled a multi-disciplinary team of oncologists, geriatricians, neurologists, neuro- and cognitive psychologists, behavioral scientists, and consumers from Lombardi Comprehensive Cancer Center (LCCC), Memorial Sloan-Kettering Cancer Center (MSKCC), Moffitt Cancer Center, City of Hope Cancer Center (COH) (discontinued study visits 11/2021), Hackensack University Medical Center (HUMC) (discontinued study visits 1/2020), Indiana University School of Medicine (IU), University of California, Los Angeles (UCLA) and University of South Florida (USF). This team will work together to prospectively enroll 850 newly diagnosed older breast cancer patients from LCCC, MSKCC, Moffitt, COH, HUMC and IU, all of which are tertiary referral centers with high volumes. A prospective referent group from the same source population as the patients who are not exposed to cancer or its treatments is critical for inference regarding the longitudinal trajectory of cognitive decline. Therefore, we will match an equal number of non-cancer friend controls. Friend controls reduce confounding by design, maximize internal validity, and enhance the efficiency of control recruitment (e.g., friends will be more motivated to participate than random community controls). If friends are not available, we will recruit controls from community settings who are frequency matched to patients on age, education, race and area.

We will administer baseline neuropsychological testing *prior* to any systemic treatment (or at enrollment for controls), survey women about subjective cognitive function, psychosocial factors, QOL, physical measures and activities of daily living (IADLS). Women will always be tested prior to systemic treatment. We will avoid giving a baseline assessment on the same day that a woman will have chemo unless it is otherwise not possible. We will abstract cancer-related treatment data from medical records for cases. Since it is not feasible to obtain all medical records from cases and controls on general health issues that could affect cognition, cases and controls will provide self-reported medical history. At enrollment we will measure vital signs when possible, body mass index and obtain blood samples to test for APOE and COMT polymorphisms and examine inflammatory biomarkers; some DNA will be stored for future testing. If women are unable to provide blood, saliva samples will be used for DNA. APOE, COMT, future DNA testing and inflammatory biomarker analysis are for research purposes only; results will not be shared with participants. Participants will wear an actigraph to measure sleep for one week. Eligible participants at GU and IU will have the option to participate in state-of-the-art imaging assessments to elucidate structural and functional brain changes associated with cognitive decline. We will conduct follow-up interviews, measure vital signs if possible, BMI and repeat the neuropsychological testing, surveys and physical measures every 12 months up to approximately 60-months after baseline assessment. The 12-month time point corresponds to approximately 3-6 months post-treatment among women who receive chemotherapy. Since work by our team and

others suggests that pre-frontal and frontal systems are the most affected by cancer therapy,[1] our primary cognitive outcome will be change in summary score on tests included in the Executive Functioning, Working Memory, and Psychomotor Speed Domain (referred to as "EWP"). In secondary analyses, we will assess broader cognitive effects and consider questions of differential impact by examining changes in scores on four additional domains: Language, Attention, Learning and Memory, and Visuospatial. Neuroimaging will look at the corresponding gray matter atrophy, white matter diffusivity and brain functioning during the performance of selected tests of working and episodic memory, default mode activity during resting state and white matter hyper-intensities.

Since cognition decreases with age, treatment effects could have a greater impact on older than on younger breast cancer patients. However, most prior studies have focused on younger patients, omitted baseline assessments, had small samples of older women, or depended on patient self-report of memory.[2] This study will be the first to rigorously examine risks for targeted cognitive decline in older cancer patients, and the first to include genetic vulnerability, inflammatory markers, the role of physical activity and impact on QOL. The results of this research will contribute to designing appropriate regimens for older women, developing preventive interventions, informing clinical decision-making about treatment in this growing population, and guiding second generation studies.[3-5]

2.0   OBJECTIVES AND SCIENTIFIC AIMS

2.1 Conduct assessments every 12 months up to approximately 60-month to identify trajectories of longitudinal cognitive function (normal, phase shift, or accelerated aging).

2.2 Identify risk factors for decline in cognitive function in the period up to approximately 60 months post-enrollment.

2.3 Assess inflammation as a potential mechanism for cognitive decline.

2.4 To use neuroimaging to assess structural and functional effects of cancer treatment.

2.5 Compare longitudinal biological aging in older breast cancer survivors vs. non-cancer controls and test the effects of exposure to more intensive cytotoxic cancer treatments (e.g., chemotherapy, repeated radiation) vs. endocrine therapy only or being a control on biological aging.

2.6 Determine whether longitudinal physical and cognitive functional decline in older survivors is greater than in controls and test if differences are mediated by biological aging.

2.7 Evaluate the impact of sleep on longitudinal function and biological aging in survivors vs. controls.

3.0   INTRODUCTION

Breast cancer is the leading cancer among women in the US.[6] Half of the new cases each year occur among the population that is 60 years or older (hereinafter referred to as "older").[6-8] These numbers will double over the coming decades as the population ages and life expectancy lengthens[9] so that by 2030 the number of new cases among older women will double. Thus, over the coming decades there will be a large increase in the absolute number of older women diagnosed with and seeking therapy for breast cancer.[10,11] Systemic adjuvant chemotherapy (and hormonal regimens for estrogen receptor [ER] positive cases) is presently standard treatment to decrease the risk of relapse and mortality.[12] Decisions about systemic therapy are based on patient and provider assessments of the balance between benefits and risks of

treatment. For several reasons, decisions about systemic therapy are more complex for older women than younger women, especially for chemotherapy. First, the benefits from chemotherapy may decrease with increasing age, although this conclusion is limited by the small number of older women in the original trials.[13] Second, the risks of major chemotherapy toxicity increase with age. For example, Muss et. al. found that older breast cancer patients experienced a 1.5% rate of chemotherapy-related mortality compared to 0.2% for younger patients.[14] Third, many older women have medical conditions that can impact the ability to tolerate chemotherapy. Despite the increased risk, data from our research shows that many older women would be willing to undergo chemotherapy for as little as a 12-month gain in life (C.1). Despite their large numbers, we know little about how systemic therapy affects cognition in older patients. Since cognitive side effects are among the most feared symptoms in older adults,[15,16] these data will help inform decisions about treatment risks and benefits in this growing population. The addition of novel imaging data will be able to advance our understanding of how brain structural and functional changes translate into clinically relevant cognitive changes in the rapidly expanding population of aging cancer patients. The insights from this research are intended to inform future mechanistic research and contribute to informed systemic treatment decision making.

3.1 Conceptual Framework

Our depiction of how systemic therapy produces cognitive decline (and decrements in QOL) in older breast cancer patients builds on our prior work.[17,18] and the vulnerability model of survivorship.[19] We define cognitive decline as failure to show practice effects on neuropsychological testing over time and/or decreases in scores.[20] We postulate that systemic treatments lead to poor cognitive outcomes through several pathways, including direct toxic effects on the brain and indirect side effects, such as fatigue.[21-23] Other outcomes (e.g., satisfaction and mortality), may also be affected by treatment, but are not the focus of this study. Our model highlights the fact that the impact of systemic treatment on cognition in older women takes place against the backdrop of aging, one of the strongest predictors of cognitive decline. We include a friend-matched control group to capture this trajectory. Since there is credible evidence that APOE genotype affects the risk of cognitive decline after systemic therapy, we include this gene in our model.[20,24-26] The model acknowledges that other factors, such as cognitive reserve, frailty, activity and vascular status, may also be independent risks for cognitive impairment, and must be considered as potential confounders if not equally distributed among patients and controls. Cognitive "reserve" is based on factors such as intelligence, education, literacy and occupation. Reserve has been shown to protect against decline.[2,27-32] Like cognitive reserve, "frailty" reflects a loss of physiological reserve and regulation. Frailty may affect treatment received and increase risk of cognitive decline.[33-38] Factors that impair the vascular integrity of the brain and increase in prevalence with age are also potential causes of cognitive decline, including hypertension, elevated cholesterol, and cardiac disease. Treatment side effects such as persistent fatigue and inactivity may also affect cognitive (and QOL) outcomes.[39,40] We focus on the variables shown in Figure 1 since they can be easily measured, are modifiable and/or can be targeted by interventions.[41]

Figure 1. Vulnerability Model of Cognitive Impairment in Cancer   **Survivors**

Aging

Physician
- Age, gender
- Attitudes
- Propensities

Risk Factors
- APOE genotype
- Cognitive reserve
- Vascular status
- Frailty

Chemo and/or Hormonal Rx

Side Effects
- Fatigue

Cognition

Survivorship Outcomes
- Quality of Life
- (Satisfaction)
- (Recurrence)
- (Death)

Clinical
- Stage
- ER Status
- Comorbidity
- Frailty

Patient
- Age, race
- Education
- Insurance
- Social support
- Mood

Physician, patient and clinical factors also affect treatment and outcomes that follow from therapy.[4,42-52] Of these, comorbidity is likely to be particularly important, since half of older individuals have 3 or more conditions, and many are increasingly frail.[34,53-55] Other individual factors, such has mood, are related to self-reported cognition,[56-58] and can also be part of QOL outcomes. Obesity is another factor that can affect QOL and cognition via its impact on comorbidities, hormonal levels and as an indirect marker of activity. In addition, there is a circular relationship, or endogeneity, between some covariates in our model. For instance, as noted above, comorbidity and frailty will influence the selection of chemotherapy, so that women who receive chemotherapy may be healthier than average.[59] Healthier women are less likely to develop cognitive (and QOL) declines than women with comorbidities and frailty.[60] Therefore, it might appear that women who undergo chemotherapy have better cognitive (and QOL) outcomes than women who are not treated with chemotherapy, if one does not consider these selection factors. We will conduct propensity score approach to "correct" for this selection bias when estimating the impact of systemic treatment on cognitive and QOL outcomes.

3.2 Systemic Therapy and Cognition

Breast cancer systemic therapy has been associated with self-reported and objectively measured cognitive declines in 17% to 75% of younger cancer patients,[3,47,61,62,62-72] even after controlling for depression, anxiety and fatigue.[73] Declines have also been seen in 27% of younger women undergoing neo-adjuvant therapy.[58] However, not all researchers have demonstrated impairment.[74-79] Many of these studies have been criticized for failing to consider practice effects; when such effects are considered deficits are usually more consistent.[80] Overall, the fact that a subgroup of cancer patients experience persistent post-treatment cognitive changes is near universally accepted.[5,81]

The results of virtually all prior studies have focused on younger women. However, there is strong evidence to support the concept that older women will experience cognitive decline after systemic treatment. Analysis of our data shows that older patients have worse cognitive performance after chemotherapy than older controls and younger patients, especially on tests of working memory and spatial ability. While the number of older women in this analysis was small (n=30), these results support the premise of the current study - that older women will have cognitive declines after chemotherapy and that these declines will be of greater magnitude than reported for younger women. Second, aging is associated with a progressive loss of cognitive function.[82] Such deficits are enhanced by vascular disease and other chronic conditions that are prevalent in older populations.[27-29,83-85] Third, our group and others have used structural MRI to show that chemotherapy is associated with reductions in gray and white matter in younger patients that mimic those seen with aging.[86,87] Finally, the one pilot study with older patients (n=50) did show

cognitive decrements after systemic treatment.[2] Since the rates of exposure to chemotherapy and hormonal treatment are increasing in the growing older patient population, risk for poor cognitive outcomes is likely to increase in the coming decades.

3.3 Chemotherapy and Cognition

A causal relationship between chemotherapy and cognitive decline is supported by several lines of evidence. First, the relationship is consistently observed.[61,62,64,65,73,88-97] Second, effects show a dose-response relationship. For instance, van Dam noted that patients on high-dose chemotherapy had a risk of cognitive impairment 8.2 times higher than controls and 3.5 times greater than patients on standard chemotherapy, after considering other factors.[89] Our group has also shown dose-like effects.[91] Third, a causal relationship between chemotherapy and cognition is biologically plausible.[98-101]

3.4 Potential Mechanisms

Animal studies have demonstrated that even small amounts of chemotherapy can cause cell death and decreased cell division in areas important for normal cognitive functioning; consequently, systemic agents do not have to cross the blood-brain barrier in high doses to impact brain function.[102] In addition, in animal models, drugs such as methotrexate decrease hippocampal and striatal concentrations of neurotransmitters involved in the maintenance and regulation of memory and attention.[98,103,104] Human imaging studies also support the idea that chemotherapy is directly neurotoxic. For instance, our group and others have shown that there is a reduction in volume of frontal brain structures and changes in the integrity of white matter tracks after chemotherapy.[86,105-107] One of our studies evaluating young breast cancer patients with functional MRI showed a pattern of reduced frontal cortex activation during a working memory task compared to patients not treated with chemotherapy and healthy controls.[108] Similar results have been observed using functional positron emission tomography (PET) and electro-physiological studies.[109] Taken as a whole, these data suggest that chemotherapy has direct adverse effects on cognition.

3.5 Hormonal Therapy and Cognition

Recent studies have found evidence for negative cognitive outcomes in breast cancer patients receiving hormonal therapies.[110,111] Castellon et al. found a dose-response like pattern of deficits among breast cancer survivors, where patients treated with chemotherapy and tamoxifen had lower cognitive performance than those treated with chemotherapy.[90] Cognitive effects of hormonal therapies are also biologically plausible since estrogen receptors are found in many parts of the central nervous system.[47,112,113] In non-cancer populations, hormone replacement therapy (HRT) seems to improve cognition in post-menopausal women[114] and appears in some studies to decrease the risk of AD by up to 29%,[115-1178] In Turner's syndrome, our team has shown that absent estrogen and androgen production leads to cognitive deficits that can be ameliorated by replacement therapy.[118-121] Other possible mechanisms by which hormonal treatment could affect cognition include decreases in cholinergic activity,[122,123] reduced induction of serotonin receptors,[124] direct toxic effects on dendrites and synaptic connectivity,[114,125] and changes in lipids.[126] Interestingly, polymorphisms of estrogen receptors influence APOE synthesis[127,128] and interact with APOE in risk for AD.[129] In addition, HRT only appears to be protective of cognitive decline among women without an APOE ε4 allele.[130] Thus, there are several plausible mechanisms of action of hormonal therapy on cognition.[131]

3.6 Aging

Aging is associated with a gradual loss of cognitive function, especially in domains that rely on frontal systems (e.g., processing speed and working memory).[82] The precise biological basis of cognitive aging is unknown,[28] but several processes have been implicated, including declines in IGF-1 and growth hormone, changes in the pre-frontal cortex and hippocampus, declines in dopamine, increases in cytokines and decreased ability to remodel synapses.[27,28,132-135]These processes may be mediated by physical activity,[27,136] lifelong learning and education and occupation level;[46] these factors contribute to "cognitive reserve".[75,27-29] As noted above, there is also evidence to suggest that systemic therapy effects may accelerate or mimic the aging process.[86,137] Several groups have also shown that age (at least up to age 60, the oldest age included) is associated with cognitive declines in breast cancer patients.[56,80,138,139] Frailty is another age-related process that appears to accelerate cognitive decline. In addition, cognitive aging appears to vary as a function of gene-environment interactions.[140] This will be the first large study of cognition in older cancer patients. Inclusion of APOE testing will allow us to examine gene-treatment exposure interactions.

3.7 Genes

Polymorphisms of repair/plasticity genes and genes that influence neurotransmitters can increase the risk for negative cognitive outcomes associated with aging and injury.[141,141-143] In this study we focus on APOE and COMT for several reasons. First, APOE and COMT are the most important genetic risk factor for Alzheimer's,[20,24-26] and its polymorphisms are associated with pre-clinical memory declines.[144,145] Second, there is strong evidence linking APOE genotype to cognitive outcomes in younger cancer patients.[20,24-26] For instance, we have demonstrated that younger survivors treated with chemotherapy who had at least one ε4 allele scored significantly lower in visual memory and spatial ability than survivors without an ε4 allele,[89] although it is not clear if this result can be extrapolated to older patients. Third, APOE 4 and COMT val+ occur in about 25% and 75% of the population, respectively, so have a large potential public health impact.[146] Moreover, moderation of effects by APOE status has been used in pharmacogenetic studies to successfully identify patients who do and do not respond to new therapies for AD;[147,148] our results could extend this paradigm to evaluating systemic therapy for breast cancer patients. Finally, there is an increasing background risk of AD and cognitive impairment with age, so there is every reason to believe that APOE and COMT polymorphisms will be important markers of older women who have a high risk for cognitive decline from breast cancer systemic therapy. Both APOE and COMT have been associated with cancer-related cognitive decline, have readily available tests, are frequent and are of interest to survivors. Results for other polymorphisms (e.g., DRD2, MDR) are interesting, but have not yet been sufficiently detailed. Therefore, we will obtain blood to store DNA to test emerging genes in future research under separate funding as they become clinically validated. [149-154] If the subject is unable to give a blood sample the day of their visit, saliva will be collected. Overall, the inclusion of APOE and COMT will yield important new information in a very relevant, but unstudied population at minimal marginal cost; this information will lay the foundation for new therapeutic and mechanistic research targeted to older patients.

3.8 Biomarkers

3.8.1 Inflammatory Biomarkers

Aging-related processes such as inflammation,[220-224] altered DNA repair,[225, 226] cell senescence,[227, 228] telomere shortening, and lipid metabolism may increase risk for cognitive decline.[226, 229, 230, 231] We focus on inflammation because it is associated with cognitive decline in older non-cancer populations [223, 232, 233] and younger cancer survivors.[234, 235] The markers most commonly

reported in cancer-related cognitive decline and other cancer symptoms are CRP, IL6, and sTNFRII.[236-250] Inflammation is also increased in multi-morbidity[251-255]and can be reduced by physical activity[256] and other lifestyle factors.

3.8.2 Alzheimer's Disease Biomarkers

Cognitive aging is a heterogeneous process, ranging from mild memory problems without dementia to frank dementia seen in diseases like AD. The framework used to guide testing hypotheses that cognitive aging seen in CRCD and AD, especially early AD, share risk factors and clinical-pathological features (i.e., pathology, cognitive profiles, and brain alterations), and that inflammation is central to these relationships.[16,21,48,49] With aging, cellular stress and damage accumulation result in apoptotic, necrotic, and senescent cells that release danger-associated molecular patterns (DAMPs). DAMPS activate secondary immune responses and the release of cytokines, amplifying the signaling cascade.[50] This cycle is thought to be a critical element in "inflammaging" (rising inflammation with increasing age), further driving age-related progression of neurodegeneration.[51] Well-characterized DAMPS with links to AD include soluble amyloid β (Aβ), S100 proteins, and HMBG1.[52] AD is further known to have bidirectional effects on inflammation.[53 54-59]

3.8.3 Receptor for Advanced Glycation End Product (RAGE)

A major mechanism associated with cognition and brain aging is chronic inflammation. Our team has shown that the Receptor for Advanced Glycation End-products (RAGE) is a major driver of inflammation. Recently, we have shown that blocking RAGE can prevent cognitive problems in mice pre-treated before chemotherapy. TLC samples will test the relationships between RAGE biomarkers and cognitive decline. The results will have high impact by informing future clinical trials of RAGE inhibitors to prevent older women from having cognitive problems after their cancer therapy.

3.9 Vascular Disease

Vascular disease increases with age and is associated with dementia and mild cognitive deficits.[155] Factors that affect vascular function also are associated with cognitive performance, including obesity, smoking, and low levels of high density lipoproteins (HDL), independent of stroke.[84,85] Interestingly, statin medications are protective of cognitive decline after considering lipid levels.[155] Since these studies generally used the Mini-mental State Exam (MMSE) as the measure of cognition, the results must be interpreted with caution. However, in the Cardiovascular Health Study, where cognition was measured using neuropsychological tests, the presence of cerebrovascular disease or diabetes and the APOE ε4 allele was associated with memory impairments.[156,157] Similar results were seen in the Netherlands.[158] Given the high prevalence of these illnesses in older breast cancer patients, patients with the ε4 allele might be especially vulnerable to cognitive decline after systemic therapy.

4.0   Eligibility Criteria

We have selected eligibility criteria to ensure that cases and controls are comparable in all aspects (except cancer status) and that participants are able to complete the neuropsychological tests as specified in this protocol. Since the neuropsychological assessments were designed and validated in English, and are not currently available in other languages, we have limited eligibility

to English speaking women. Eligibility will be determined based on medical records and/or self-report.

4.1   Subject Inclusion Criteria

For **cancer patients,** eligibility includes:
- being female
- Age 60+ at diagnosis of a new primary histological confirmed adenocarcinoma breast cancer
- AJCC stages 0-3 or planning on undergoing neoadjuvant therapy
- In the judgment of the consenting professional, able to communicate well enough in English through verbal and written communication to complete the study assessments and provide informed consent
- If currently taking psychoactive medications (including, but not limited to anticonvulsants, antidepressants, and anxiolytics), dose must have been stable at least two months prior to enrollment.
- Participant report of no previous or current chemotherapy or hormonal treatment use (anastrazole, exemestane, etc.)
    - This does not include hormonal replacement therapy, synthetic thyroid hormones, etc.

For **controls,** eligibility includes:
- being female
- Age 60+
- In the judgment of the consenting professional, able to communicate well enough in English through verbal and written communication to complete the study assessments and provide informed consent
- If currently taking psychoactive medications (including, but not limited to anticonvulsants, antidepressants, and anxiolytics), dose must have been stable at least two months prior to enrollment.

4.2   Subject Exclusion Criteria

We apply the same exclusion criteria for **patients** and **controls.**
- Participant report of a history of formal diagnosis of neurological problems (i.e. Alzheimer's disease, Parkinson's disease, Multiple Sclerosis, Dementia, Seizure Disorders, brain tumors, etc.)
- Participant report of surgery on the brain for any reason (cancerous or non-cancerous tumors, subdural hematomas, AV malformations, increased intracranial pressure, etc.)
- Participant report of a history of stroke (with the exception of TIA if ≥1 year ago)
- Participant report of HIV/AIDS
- Participant report of moderate to severe head trauma (loss of consciousness > 60 min or with evidence of structural brain changes on imaging)
- History of major psychiatric disorder (DSM-IV Axis 1) (i.e. major depressive disorder (untreated or poorly treated), bipolar disorders, schizophrenia, or substance abuse disorders (self-reported and/or stated in medical record).

- Participant report of a history of prior breast or other cancer with the exception of non-melanoma skin cancer.
  - An exception for *cases only*: women who completed treatment for a previous cancer at least 5 years ago and have not undergone any chemotherapy or hormonal therapy. This previous cancer cannot be breast cancer.

- Participant report of previous or current chemotherapy or hormonal therapy use
- Participant use of methotrexate (Amethopterin, Rhematrex, Trexall) or rituximab (Rituxin) for rheumatoid arthritis, psoriasis or Crohn's disease, or cyclophosphamide (Cytoxan, Neosar) for Lupus.
- Visual or hearing impairment that would preclude ability to complete interviews or neuropsychological testing, such as significant macular degeneration or being unable to correct hearing with hearing aides
- Non-English speaking
- To participate in the optional neuroimaging portion of the study:
  - Participant cannot be claustrophobic
  - Participant cannot have a pacemaker, aneurysm clip or other implants that are not MRI safe
  - Participant cannot have any type of implanted electrical device

5.0 STUDY DESIGN

The overarching objective of this study is to use the vulnerability model of cancer survivorship to define the impact of systemic treatment on cognition in a cohort of older breast cancer patients and controls. We will also examine whether cognition is associated with QOL and whether APOE and COMT polymorphisms and physical activity moderate cognitive decline.

To accomplish these goals, we will prospectively enroll 850 newly diagnosed older breast cancer patients from five tertiary care cancer centers, and an equal number of matched non-cancer friend controls. When friends cannot be recruited we will frequency match cases to local controls from similar source populations based on age, education, race and area (i.e., NY, DC, FL, CA, NJ, IN).

All women will undergo study visits at baseline (pre-systemic therapy) and every 12 months up to approximately 60-months post-baseline. The study timepoints include interviews, vitals when possible, BMI measurement, neurocognitive testing, actigraph monitoring , blood collection and optional neuroimaging (IU). The preference is to interview patients before radiation (if planned), but patients who receive intensity modulated radiation therapy (IMRT) or other RT before seeing an oncologist for adjuvant therapy will still be eligible. We will control for timing of radiation in analysis. We expect this situation to be uncommon since current rates of IMRT are very low and RT is generally given after any planned chemotherapy. The 12-month follow up corresponds to 3-6 months post-chemotherapy completion, provides a standardized anchor point for all subjects, and is consistent with the design of comparable prospective research in the field.[58] We acknowledge that that early effects could diminish over time. A total of up to 27ml of blood will be collected at each time point to examine genetic polymorphisms (Indiana University) and inflammatory biomarkers (UCLA). Up to 15ml of blood will be stored at Georgetown University's Tissue Culture Shared Resource from each study visit. If women refuse to give blood or saliva, they are still eligible to participate. If women are unable to provide a blood sample at their study visit, 2ml of saliva will be collected and blood will be attempted at the next visit. Blood samples will be collected at least 2 weeks after any vaccinations if possible.

We will review medical and pathology records of the cases once for tumor factors and cancer treatment. Patients and controls will provide self-reported information on general health and comorbidities. We will compare patients on any systemic therapy to controls as our primary comparison. We will also compare patients who receive systemic therapy to patients who receive no systemic therapy as another "control" group to capture any non-specific effects of a cancer diagnosis on cognition.[58,87] We will explore if there are differences in cognitive effects by type of therapy (chemotherapy and hormonal vs. hormonal alone). Results for imaging cases will be compared to their own prior pre-treatment baseline studies (if available) and matched controls at yoked time points.

Our primary cognitive outcome is change in score on tests in the Executive Functioning, Working Memory, and Psychomotor Speed Domain (EWP); in secondary analysis we also examine changes in scores on 4 additional domains: Language; Attention; Learning and Memory; Visuospatial. The primary imaging outcomes are changes in 1) gray matter atrophy, 2) white matter diffusivity, and 3) functional brain activation during working memory. Secondary outcomes include: 1) functional brain activation during episodic memory, 2) default mode activity during resting state, and 3) white matter hyper-intensities.

5.1 Recruitment Plan

5.1.1   Expected cancer Patient Sample

We expect 539 women with non-metastatic cancer annually. We estimate that 30-40% will not be eligible (see below), leaving an average of 350 women per year. In our past studies we have obtained physician consent to approach 80-90% of older women. Since this study involves interviews and cognitive testing, we estimate that physicians will provide consent to approach 75% (262 per year). In our work on similar protocols with younger women, 75-80% of women have consented.[20] We assume consent rates for older women will be lower. Therefore, we conservatively estimate that 60% will consent, yielding 158 potential women/year. Since we must identify and test women prior to initiation of any systemic therapy, we may lose some women (non-systemic losses due to staffing limits and administrative delays), so we conservatively estimated that we could enroll ~170 women each year from MSKCC, LCCC (and satellites), Moffitt, COH (discontinued study visits 11/2021), HUMC (discontinued study visits 1/2020) and IU. Since the required sample is 850, we have enough women for our goals, even under conservative assumptions. If there are fewer subjects than anticipated at our six sites, we will use other area hospitals as additional recruitment sites; these sites will follow the same procedures as outlined herein. A greater number of controls will be enrolled to ensure that we are able to match them to cases. A subset of the women recruited from Indiana University and satellites will have the option to participate in neuroimaging. We estimate that we can enroll ~75 cases and ~75 controls during the accrual period that will be matched by age, race and area.

5.1.2. Cancer Participant Recruitment-LCCC, MSKCC, Moffitt, COH, HUMC, IU and their satellites

At LCCC, we will recruit from the breast cancer clinics in the LCCC/MedStar network. The network includes the main academic hospital and several local community referral hospitals in the metro-DC area. The network sees a population with diverse economic status and race/ethnicity and 20-25% of older breast cancer patients are from minority groups. At MSKCC, patients will be identified through the Breast Cancer Medicine Service clinic schedule. At MSKCC, we will recruit from the main hospital and its affiliated community hospitals and practices in Manhattan, Long Island, Westchester and New Jersey. At LCCC, MSKCC, Moffitt, COH (discontinued study visits

11/2021), HUMC (discontinued study visits 1/2020) and IU patient recruitment will be facilitated by our co-investigators who care for older patients and/or are the directors of our breast clinics. At LCCC we will also work with existing shared resources (e.g., SRBSR) to use their established mechanisms for ascertaining newly diagnosed breast cancer patients that meet our eligibility criteria.

We will follow the same procedures at all study recruitment sites. We will identify women in the period between initial diagnosis and the start of any planned systemic therapy, generally 1-2 to 10-12 weeks after diagnosis. Physicians will be contacted to obtain blanket permission for research staff to screen patient schedules and charts for potentially eligible patients. (See Appendix D). Research staff will use doctor referrals and clinic schedules to approach patients in person, by phone, by mail, or by email. Research staff will make every effort to approach all possible participants to avoid any selection bias. If individual physicians prefer, they will first describe the study to patients and get their permission to be contacted by the study team.

To ensure compliance at all satellite sites, research staff from LCCC, MSKCC, Moffitt, COH (discontinued study visits 11/2021) , HUMC (discontinued study visits 1/2020) and IU will conduct all research at all sites in order to adhere to the approved IRB procedures for the study. Site investigators or recruitment personnel will identify eligible patients and research staff from LCCC, MSKCC, Moffitt, COH (discontinued study visits 11/2021), HUMC (discontinued study visits 1/2020) and IU will contact the patients and coordinate their participation in order to ensure that sites do not exceed enrollment and to eliminate the potential for numerous minor and major protocol deviations. The LCCC research coordinator will be responsible for managing the regulatory submissions for LCCC and their satellites (Montgomery General Hospital, Virginia Cancer Specialists, PC, Washington Hospital Center, Reston Breast Care Specialists) and will ensure that these sites receive updated regulatory communication and documents in a timely manner.

Women who are interested in the study will be contacted to review medical history for eligibility screening (Appendix E). Some participants may be unavailable to answer questions for the eligibility screen during the initial conversation with the research staff because of time constraints. If the patient has expressed interest in the study, and is unable to complete the eligibility screen in person, they will be contacted over the phone to complete the screen. We will use mail contact as a backup procedure if necessary.

If women are eligible, they will be given the study materials and consent to read (Appendices C, G and K), or verbally consented (if allowable by site IRBs). All procedures will be explained by the research staff and all questions will be answered. If eligibility is confirmed, patients will be asked to sign the written consent form or give verbal consent (if allowable by site IRBs). (See Appendix K) The patients will also be asked to sign a HIPAA waiver for permission to review medical records for cancer and cancer treatment related data. (See Appendix M) If the patient refuses the blood draw or is unable to provide a sample, she will be given a saliva kit for the purpose of collecting DNA. If she refuses either of these options for DNA collection, she is still eligible to participate. Patients are asked to wear an actigraph for one week to measure sleep. If the patient refuses to wear the actigraph, she is still eligible to participate. Subjects at Indiana University are also given the option of participating in neuroimaging. If a subject refuses the neuroimaging, she is still eligible to participate.

If the patient is ineligible for the research study, the research staff will destroy all information collected during the initial eligibility determination, except for any minimal information maintained for screening log purposes (e.g., patient initials, date and outcome of approach, age and race).

The recruitment process outlined presents no more than minimal risk to the privacy of the patients who are screened and minimal PHI will be maintained as part of a screening log. For these reasons, we seek a (partial) limited waiver of authorization for the purposes of (1) reviewing medical records to identify potential research subjects and obtain information relevant to the enrollment process; (2) conversing with patients regarding possible enrollment; (3) handling of PHI contained within those records and provided by the potential subjects; and (4) maintaining limited information in a screening log of patients approached (if applicable).

5.1.3. Research Proxy

Cognitive declines could limit ability to continue participation and/or decisional capacity and lead to informative missing data. This would under-estimate the true effects of treatment on cognition or lead to spurious conclusions if data are missing differentially by case-control group. To mitigate the impact of this issue, we will obtain contact information for a family member or friend and ask participants to designate a "research proxy" for this project. This is standard in Alzheimer's and other aging research. The proxy can make decisions related to research participation based on the best interests of the participant but participants do not relinquish rights to refuse participation in any or all research activities. A proxy consent form (Appendix LL) will be filled out primarily at baseline, but can be filled out at any time point in addition to the standard informed consent and HIPAA form. Subjects who refuse to assign a proxy can still participate in the study. Proxies are only contacted if research staff believe the participant lacks the decisional capacity to continue independently.

5.1.4 Control Recruitment at LCCC, MSKCC, Moffitt, COH, HUMC and IU

5.1.4a Friend Control Recruitment

To recruit friend controls, each enrolled cancer patient will be asked to list the names, addresses and telephone numbers of 5-7 female friends aged 60 years and older who they think might be interested in study participation. We will give each breast cancer patient a letter, stamped envelope, study brochure and a pre-paid response card and envelope that she can give or mail to her friends. (See Appendix H) Or, with their permission, we will contact their friends directly. If the case gives permission or the friend indicates by response card that she is willing to be contacted, the study team will call the friend to explain procedures. If more than one friend per case consents to contact, we will enroll the friend who is most closely matched to the case on age. Potential friend controls will be asked to confirm eligibility by answering routine medical questions (See Appendix F). If the control is eligible, she will be asked to provide consent (See Appendix L). If the control refuses the blood draw or is unable to provide a sample, she will be given a saliva kit for the purpose of collecting DNA. If she refuses either of these options for DNA collection, she is still eligible to participate. Controls are asked to wear an actigraph for one week to measure sleep. If the control refuses to wear the actigraph, she is still eligible to participate. The control is also given the option of participating in neuroimaging. If she refuses the neuroimaging, she is still eligible to participate.

5.1.3b Community Control Recruitment

When necessary, friend recruitment will be supplemented with local recruitment methods to generate frequency matched controls. We will use this approach if patients: a) chose to not identify friends, b) have friends who live out of local vicinity, c) do not have a consenting friend, or d) none of the friends is eligible. We will use area retirement communities and frequency match to cases in the area on age (within 5 years), education (< high school, HS to < college, college graduate) and race. We will monitor control accrual on a monthly basis, and if we are not finding friends or

well matched controls using the above strategies, we will supplement recruitment with outreach using flyers to senior centers and churches in the communities of residence of the cases. The research staff will approach the potential community control in the same manner as the cases and friend controls. Potential community controls will be asked to confirm eligibility by answering routine medical questions (See Appendix F). If the community control is eligible, she will be asked to provide consent (See Appendix L). If the control refuses the blood draw or is unable to provide a sample, she will be given a saliva kit for the purpose of collecting DNA. If she refuses either of these options for DNA collection, she is still eligible to participate. Controls are asked to wear an actigraph for one week to measure sleep. If the control refuses to wear the actigraph, she is still eligible to participate. The control is also given the option of participating in neuroimaging. If she refuses the neuroimaging, she is still eligible to participate.

If the friend or community control turns out to be ineligible for the research study, the research staff will destroy all information collected during the initial eligibility determination, except for any minimal information maintained for screening log purposes (e.g., control initials, date, age, race, source of recruitment and outcome of approach). The recruitment process outlined presents no more than minimal risk to the privacy of the controls who are screened and minimal PHI will be maintained as part of a screening log. For these reasons, we seek a (partial) limited waiver of authorization for the purposes of (1) conversing with controls regarding possible enrollment; (2) handling of PHI provided by the potential subjects; and (3) maintaining limited information in a screening log of patients approached (if applicable).

6.0 INFORMED CONSENT AND REGISTRATION AT ALL SITES

6.1 Procedures at LCCC, MSKCC, Moffitt, COH, HUMC and IU Sites

Research staff will obtain informed consent from eligible patients/controls. All participants will be informed as to their rights as volunteers in a research study. At Moffitt, COH and HUMC (discontinued study visits 1/2020), cases will be asked to sign three copies of the consent form, while at LCCC and IU, cases will be asked to sign two copies (See Appendix K). One copy will be given to the participant to keep and one copy will be stored in the participant's research file. At MSKCC, Moffitt, COH (discontinued study visits 11/2021) and HUMC (discontinued study visits 1/2020), the third copy will become part of the medical record (cases only). At LCCC, Moffitt, COH, HUMC (discontinued study visits 1/2020), and IU, non-cancer control group participants will sign two copies (Appendix L). One will be given to the participant and one will be kept in the research file. At MSKCC, in addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form. Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form. Consent procedures for MSKCC are further outlined in the MSK Addendum document at their site.

All protocols and consent forms will be reviewed and approved by the Institutional Review Board. All data gathered will be kept in a secure location and available only to members of the research study team. The key elements of the informed consent procedure which will be explained to participants are: 1) the research status of the study; 2) the potential risk and the provisions for it; 3) the lack of guarantee of benefit from participation; 4) the voluntary nature of the study; 5) the lack of consequence to medical care of the decision to consent or refuse to participate; 6) the freedom to withdraw from the study or to refuse to answer specific questions or to participate in any aspect of the study at any time; and 7) the confidentiality of subjects' responses to assessments.

Once the participant has consented, they will be registered for the study.

During the registration process, research staff will record the following information (Appendices N and O):

Registering Individual	[Last, First Name]
Notice of Privacy Status	[Yes, No, N/A]
Research Authorization	[Date]
IRB Protocol#	
Attending of Record (if no Oncologist, then Surgeon) (cases only):	[Last, First Name]
Primary Care Physician (optional) (controls only)	[Last, First Name]
Consenting Professional (if different than registering staff)	[Last, First Name]
Informed Consent Date	
Participant's Full Name	[Last, First Name]
Participant date of birth	[mm/dd/year]
Participant MRN (cases only)	
Participant case/control status	
Participant study ID number	

Participant address, phone numbers, email, alternative addresses, cell phone numbers and schedules
Participant alternative contact information
Registration will also include the completed signature page of the informed consent form (if written consent), the completed signature page of the Research Authorization and a completed Eligibility Checklist.

6.2 Retention

We will use several methods to retain registered cases and controls, including maintaining a file of contact information on friends and relatives who will know where to locate them, sending birthday and holiday greeting cards (with address corrections) and use of national directories to track women who have moved. We will use study branding, as well as the involvement of referring doctors to keep women engaged. In addition, we will send newsletters periodically on general health topics to keep women engaged. Annual luncheons will be held to thank subjects for their participation. Subjects will receive a letter in the mail informing them that their follow-up window is approaching so they can contact us to schedule or expect a call from our office. If we are unable to get in touch with them and their follow-up window is closing, we will send another letter in the mail informing the subject that we have been trying to contact them. If subjects are unable to complete their study visit during their follow-up window, we will still complete follow-up as close to the window as is possible. We will draw on the experience of our consumer advocate in maintaining contact with women. Our expertise in approaching older women and sensitivity to their needs and concerns will enhance our ability to retain women. On a case-by-case basis, if the patient is unable to find transportation to provide blood or neuroimaging, then they will be reimbursed for car service. Study visits can be done primarily by phone, lessening the burden. A home visit can also be done if needed. We have found that women are very willing to help other women like themselves and this altruism contributes to their continued participation in the study. Women generally enjoy the contact from the study team and look forward to follow-up and interactions. To support this, we will aim to maintain continuity as much as possible with study staff. We expect that the use of a research proxy and learning when subjects may be unavailable for extended periods of time will help follow-up retention.

6.3 Criteria for removal from study

Participants will be removed from the study if:
- The participant chooses to discontinue participation at any time.
- The study investigators believe it is in the participant's best interest.
- There is a participant self-report of new acute neurological insults (Stroke or Head Injury) between assessment points. However, if a participant experiences a TIA ≥12 months before a follow-up appointment, they may continue to participate in the study.
- There is a participant self-report of a diagnosis of a psychiatric disorder that has not (untreated or poorly treated)
- Cases will be removed if they develop a cancer recurrence after baseline or if they progress to stage 4.
- Cases and controls who develop a new cancer (except non-melanoma skin cancer) will be excluded
- WRAT-4 test results of <3rd grade reading (making the participant unable to complete testing) (see below).
- A score of <24 on the Mini-Mental State Examination or a score of >11 on the Blessed Orientation Memory Concentration Test to ensure ability to provide consent and complete the testing required (see below).

7.0   DATA COLLECTION

7.1 Data Collection for patients and controls

7.1a Enrollment Visit

Once the participant is registered, research staff will first administer the MMSE or BOMC and WRAT-4 to ensure sufficient literacy and cognitive functioning to complete the study.

Mini-Mental State Examination (MMSE)[159] (In-person battery)- is a commonly used instrument to evaluate general cognitive function. The MMSE evaluates orientation, attention, short- and intermediate-term recall, language, and command-following capability. The conventional cutpoint of ≤24 is used to indicate impairment. A MMSE score of <24 will be considered a screen failure.

Blessed Orientation Memory Concentration (BOMC). (Remote battery) This test is a cognitive screener to assess impairment. The score for 6 items are multiplied to yield a "weighted" score. The higher the total weighted score, the more likely the patient has cognitive disability. A score >11 is considered a screen failure.

Wide Range Achievement Test – 4th Ed (WRAT-4) Reading Test.[160,161]. This is a 42-word reading recognition/pronunciation test. It is commonly used as a measure of premorbid ability and/or literacy and has been used with ethnically diverse older individuals.[162] It has been shown to have a one-year test-retest reliability of .90.[163] A test result of <3rd grade reading on the WRAT-4 will be considered a screen failure.

If participants fail either of these two tests, they will be thanked for their time, given the $50 cash or gift card incentive for their time and will be removed from the study. If the participant passes both screening tests, then they will continue with the study.

The enrollment time point consists of vital signs (if possible), collecting blood samples, administering the neuropsychological tests, administering the timed "get up and go" test if the subject is completing the in-person battery, measurement or self-report of the patients' height and weight for BMI and completing the questionnaire. If the patient/control is unable to complete the questionnaire at the same time as the neuropsychological tests, the research staff will contact the participant to complete the questionnaire over the telephone as close to the testing date as is possible. If a subject cannot complete the survey over the phone, she may be given a copy of the survey to complete and mail back to study staff. Participants may complete the survey online via a personalized Redcap link. Participants will wear an actigraph for one week to measure sleep.

All enrolled patients and controls will receive $50 cash or gift card for their time associated with participation. The $50 cash or gift card will be given for each assessment (every 12 months up to approximately 60-months post-baseline). The procedures are detailed in the following sections. After each assessment, participants will also receive a thank you letter. After the 60 month follow-up visit, they will receive a certificate of completion.

Subjects who participate in optional neuroimaging will receive an additional gift card for $50 for their time and travel. The $50 gift card will be given for each assessment (every 12 months up to approximately 60-months post-baseline).

7.2 Biospecimen Collection

A total of up to 27ml of blood will be collected at each time point by trained staff. Subjects can have blood collected at their site's clinic or office, or can choose to have a trained phlebotomist come to their home to draw the sample. Vital signs will be taken and then blood will be collected for APOE and COMT DNA testing, inflammatory biomarkers, plasma AD-pathology markers ($A\beta_{1-42}$, tau, p-tau, and neurofilament light chain [NFL]), the receptor for advanced glycation end-products (RAGE) and danger-associated molecular patterns (DAMPs: $A\beta$, S100 proteins, and HMBG1) and for storage of DNA for future tests. 2-3 6mL lavender top vacutainer tubes containing ethylenediamine tetraaceticacid (EDTA) will be used for DNA extraction, biobanking and inflammatory biomarkers. One optional 4ml CPT tube can be collected for biobanking. Up to 2 2.5ml PAXgene tubes will be collected for future DNA and RNA research. Blood samples will be stored at site labs until batched shipment. If the subject is unable to provide a blood sample at their visit, 2ml of saliva will be collected using Oragene DNA Collection kits. Trained staff will provide the participant with a small cup to fill with approximately 2mL of saliva. Once the sample is taken, the lid of the cup is attached, releasing a DNA preserving fluid that is then mixed with the saliva. Saliva samples will be stored at room temperature until batched shipment. If subjects are unable to provide a full specimen of blood or saliva, they can still participate in the study. Samples will be labeled with bar codes provided by the genetics lab that will include the patient ID number, and the date the sample was obtained. The date and time corresponding to when the sample was processed will be recorded by the Genetics lab and available in a database. Specimens will be labeled with appropriate biohazard labels and comply with federal regulations for transport (See Appendices S and W). If a sample is found to be insufficient for analysis, an additional sample will be requested.

The site staff will maintain logs of specimens obtained, dates shipped, confirmation of receipt, and results. Blood or saliva collected for genetic testing will be stored at local sites and shipped in batches to the Indiana University Genetics Biobank. Samples will be mailed to: Indiana University Genetics Biobank, Attn: Colleen Mitchell (or appropriate designee), 980 West Walnut Street, R3-C102, Indianapolis, IN 46202.

The investigators conducting DNA genetic testing will be blind to patient/control, treatment status and cognitive test results. The lab has on-going quality assurance procedures.

7.2.1 Procedures for APOE Testing

At the Indiana University Genetics lab, QIAamp DNA Blood Maxi Kits are used for purification of total DNA whole human blood. After lysis, the lysate is loaded onto the QIAamp spin column. DNA binds to the QIAamp membrane while impurities are effectively washed away in two centrifugation steps. Finally, ready-to-use DNA is eluted. ApoE genotyping is performed using LightMix® Kit APOE C112R R158C (cat.No. 40-0445-16) from TIB and Roche Diagnostics LightCycler® 480 instrument. The hybridization probes are used to determine the genotype by performing a melting curve analysis after the amplification cycles are completed and the amplicon is formed. Control DNA is used to allow accurate comparison with unknown samples. We will define women as having an ε4 allele vs. not based on the APOE assay results.

At the Indiana University Genetics Lab, saliva samples will be transferred to a new microcentrifuge tube or 1.2 mL storage plate for manual processing after they are received. Buffers will be added and will bind to the DNA, then placed on an Agencourt SPRIPlate Super Magnet to separate out the DNA. The sample is rinsed with ethanol and is placed on the magnet again three times. The ethanol is then removed and a new buffer is added to the solution, then placed on the magnet until the solution is clear. The DNA is removed and stored at -80°C.

7.2.2 Procedures for COMT Testing

The DNA will also be utilized for *COMT* 158val/met testing using Taqman gene expression assays from Applied Biosystems (Foster City, CA) for rs4680.

7.2.3 Plasma AD (Alzheimer's Disease) Biomarkers
We will use plasma $A\beta_{1-42}$, tau, p-tau, and NFL. Plasma $A\beta_{1-42}$ and p-tau may be AD-specific. Single Molecule assay (Simoa) kits are commercially available for these analytes and will be sent out for testing using the Quanterix platform. All testing will be done in one batch to limit variability.

7.2.4 Procedures for RAGE
Circulating levels of sRAGE and S100A8/9 will be performed in a blinded manner in the Hudson Laboratory on samples using ELISAs. These ELISAs include the Human RAGE Quantikine ELISA (R&D Systems) and Calprotectin (S100A8/9) Human ELISA kit (Hycult). We have found that inter- and intraassay variability for these assays to be <10%. Quality control will be monitored by inclusion of an internal laboratory control. Assays will be performed in duplicate, with all samples from each subject tested within the same plate. sRAGE and S100A8/9 levels are highly stable despite repeated freeze/thaw cycles.

7.2.4 DNA storage for future testing

As noted above, participants will also be asked for permission to store DNA for future evaluation of genetic polymorphisms related to other genes that may be related to chemotherapy-induced cognitive changes as they become clinically validated. DNA will be frozen and stored at the Indiana University Genetics lab. If additional funding has not been obtained within 10 years, the stored DNA samples will be destroyed.

7.3 Blood Collection for Inflammatory Biomarkers

Of the up to 27ml of blood collected at each time point, approximately 2ml of blood will be used for inflammatory biomarker analysis. Given diurnal variation, [263, 264] we will collect a morning sample for the inflammatory markers the day of the neuropsychological testing at baseline and all follow-up appointments; [265] most survivors have morning appointments for other services. If subjects cannot make a morning appointment, the blood draw will be done in the afternoon and the time will be noted so follow-up blood collection can be done in the same window of time. If subjects cannot do the blood collection the day of the neuropsychological testing, blood will be collected as close to the appointment as possible. Since exercise impacts cytokines, [266, 267] we will ask participants not to exercise the day of the visit; we will log NSAID use in the past 48 hours and any infection, illness, injury, diagnosis or exposure to COVID, medical procedures or vaccination in the past month or since their neuropsychological assessment, if it was over a month prior. [268] Whole blood will be collected in up to 2 6 ml EDTA tubes, placed in a cooler on ice, and centrifuged within 60 minutes. Plasma will be divided into aliquots and stored at -80^C until being shipped in batches on dry ice to UCLA to avoid repeated freeze-thaw cycles. Staff and lab personnel will follow all routine safety precautions when handling specimens. Circulating levels of CRP (a generalized marker of systemic inflammation), IL6 (a pro-inflammatory cytokine), and sTNFRII (a surrogate marker of pro-inflammatory TNF activity) will be determined in a blinded manner in the UCLA Inflammatory Biology Core Laboratory on plasma samples using high sensitivity (CRP, IL6) and regular sensitivity (sTNFRII) ELISAs as previously described; [265] inter- and intra-assay variability for these assays was <10%. Due to differences in concentration ranges, these biomarkers cannot be multiplexed. Quality control will be monitored by inclusion of an internal laboratory control; assays will be performed in duplicate, with all samples from each subject tested within the same assay plate. Given the older age of our sample, we expect detectable levels on all markers. We will bank remaining specimens as a resource as additional markers are identified in the future. If women refuse blood collection, they are still eligible to participate in the study.

7.4 Blood collection for banking

Of the up to 27ml of blood to be collected at each time point, up to 15 mL of blood will be collected at each time point and sent to the Tissue Culture Shared Resource Lab at Georgetown University for storage. If a subject refuses blood collection, they are still eligible to participate in the study.

All samples will be sent to:
Tissue Culture Shared Resource
New Research Building, W314
Georgetown University
3970 Reservoir Rd. NW
Washington DC 20057-1468

7.5 In-Person Neuropsychological testing-Patients and Controls

Participants with an MMSE score >24 or a BOMC score >11 and a WRAT- 4 score >3rd grade reading will proceed to neuropsychological testing. Testing will be done at the hospitals (MSKCC and its affiliates in NYC, LCCC and its affiliates in DC, Moffitt and its affiliates in FL, COH (discontinued study visits 11/2021) and its affiliates in CA, HUMC (discontinued study visits 1/2020) and its affiliates in the NJ area and IU and its affiliates in IN). If women cannot come to the hospital, study staff can conduct testing at the participant's home under controlled conditions with no interruptions and quietness. Place of testing must be noted and considered in this analysis. Trained testers will follow a standard protocol to minimize observer biases.

The neuropsychological tests will be administered in a quiet room that has a desk, two chairs, and limited other objects/pictures in the room to minimize distraction to the participant. The participant will be seated across from the research staff. The research staff will then give a brief overview of the neuropsychological tests that they will be administering. The research staff will ensure that the patient understands the testing process and will answer any questions.

The research staff will begin to administer the neuropsychological tests in the order specified on the neuropsychological test battery. (See Appendix P) To avoid fatigue, women will complete half of the tests, take a 10-minute break, and then will complete the remainder of the tests. Our battery takes 55 minutes to complete; this battery is similar to one developed by Dr. Ahles that was successfully used with older women.[2]

7.5.1 Remote Neuropsychological Testing- Patients and Controls

To accommodate our cohort and to maintain retention, the study will transition to remote neuropsychological testing of cases and controls. Approximately 100 women were randomized to complete both the in-person test as well as the remote test to guide statistical co-calibration. Tests will be administered using the mode available to subjects. Women will be able to complete the test by phone, smartphone, tablet or computer. Prior to administering the battery over the phone, tablet, smartphone or computer, study staff will review the process with subjects and ensure that there are limited disruptions or technical issues (Appendix FFF). The remote measure is approximately 40 minutes and the in-person battery is approximately 55 minutes long. Women who agreed to participate in the co-calibration and completed both the in-person battery and the remote battery received an additional $25 as compensation for their time and effort on the remote battery. The co-calibration was completed in October, 2021. Moving forward, women may choose the mode of administration that is preferable to them to ensure their safety and comfort.
The neuropsychological tests in both the in-person battery and the remote battery that will be administered were selected based on one or more of the following criteria: 1) sensitivity to deficits associated with systemic therapy, 2) sensitivity to mild cognitive impairment, 3) available age- and education- and race-based normative data and established geriatric norms, 4) reliability and validity in older patients and good reliability across different education and literacy levels, 5) available alternate forms to diminish practice effects, 6) use in studies with diverse older individuals, including African Americans and ethnic minorities and 7) short and easy to administer.[164-169]

Based on these considerations, we use tests from the Neuropsychological Assessment Battery (NAB)[169] since it has good normative data. The NAB is a comprehensive battery of 33 neuropsychological tests, each with two equivalent forms, developed to assess a wide array of cognitive functions in adults ages 18-97. In the initial stages of test development, items for all NAB tests were rated by members of an advisory council of senior neuropsychologists (Drs. Cimino, Heaton, Larrabee, van Gorp, Welsh-Bohmer, and Williamson) with regard to potential ethnic/racial/cultural bias and applicability across different educational groups; all items viewed as being biased or inappropriate were deleted. The normative sample for the NAB consisted of approximately 1500 subjects; 47% were $\geq$ 65 years and care was taken in the sampling to include adequate representation with respect to race/ethnicity, education, and geographic regions of the US. Reliability and validity has been well established in diverse older populations. [170]

1. <u>Executive Functioning, Working Memory, and Psychomotor Speed (EWP).</u> This is our primary cognitive outcome. There are 7 tests in this domain. For analysis we will create a summary composite z-score from the primary scores on each test. The tests are briefly outlined below.

Trailmaking – Part A (TMT-A).[171](In-person battery) This commonly used test from the Halstead-Reitan Battery is designed to measure psychomotor speed and visual scanning. Participants are required to quickly connect numbers spread about a page. In older patients the intra-item reliability ranges from .50-.98 and test-retest reliabilities are .64-.94. Psychometric properties of Trailmaking has also been studied in geriatric normative samples with ethnic and racial diversity and found to be reliable in all groups.[165,166,168] Score is based on completion time.

Trailmaking - Part B (TMT-B).[171](In-person battery) This commonly used test from the Halstead-Reitan Neuropsychological Battery requires psychomotor speed, visual scanning and attention and ability to maintain and shift response sets. The subject is asked to connect a series of circles on a page sequentially, alternating between numbers and letters (alpha .50-.98). Test-retest reliabilities of .66-.88 have been reported in various groups including older subjects. The primary score is the completion time.

Oral Trailmaking – Part A. (Remote battery) This is a neuropsychological measure that provides an assessment of sequential set-shifting without the motor and visual demands of the written TMT. Part A requires a subject to count from 1-25 as quickly as they are able.

Oral Trailmaking – Part B. (Remote battery) This is a neuropsychological measure that provides an assessment of sequential set-shifting without the motor and visual demands of the written TMT. Part B requires a subject to alternate from numbers to letters from 1-A to 13-M.

Digit Symbol Subtest-Wechsler Adult Intelligence Test-III.[172](In-person battery)   This test measures visual-motor coordination, psychomotor speed, visual attention and incidental learning. Adequate performance on the test requires intact functioning across several domains, so it is very sensitive to impairment.[173] Test-retest reliability in individuals age 75-89 years has been shown to be .91. Age-corrected scaled scores are used for summary scoring.

Symbol Digit Modalities Test. (Remote battery) This test detects cognitive impairment by looking at visual attention and incidental learning. The test involves seeing the digit-symbol key and orally telling the examiner the correct number that is paired with a random symbol.

Controlled Oral Word Association Test (COWAT).[174] (In-person and remote battery**)** This test is a measure of verbal fluency, cognitive flexibility, and semantic knowledge. Alternate forms exist and have been studied in African Americans. Reliability ranges from .70-.90 in older individuals and test-retest reliability is .88. [166,168,174] Participants are given 3 one-minute trials to generate words as quickly as possible to each of 3 letter cues (F, A, and S). The test is scored based on the total number of words generated.

Mental Control Subtest-Weschler Memory Scale (Remote battery) This subtest of the WMSIII assesses speeded performance for reciting the alphabet, counting forward and backward, days of the week forward and backward, months of the year forward and backward, counting by 6s while stating days of the week in order.

Driving Scenes Test from the NAB.[169](In-person battery) This test of working memory, selective attention, and visual scanning is a Daily Living test with excellent ecological validity.[175] Participants are shown a color line drawing of a road scene (from the driver's perspective) each for a 30-second exposure and then shown another scene and asked to report new and missing items from the previous scene; this is repeated 6 times. Scores range from 0 (worst) to 70 (best). Reliability (G coefficient) is reported as 0.89 in older and in low education groups. The

demographically-corrected t-score based on norms for age, education, and gender will be used in scoring.

The Timed Instrumental Activities of Daily Living (TIADL).[176](In-person battery) The TIADL is a standardized timed assessment of performance of five instrumental activities of daily living: finding a telephone number in a phone directory, finding and counting out correct change, finding and reading out the first 3 ingredients on a food can, finding 2 specific food items on a shelf of food, and finding and reading the directions on a medicine container. Each task has a preset maximum time duration after which the task is terminated. Scoring is based on a combination of the completion time and an error code for each task. Times for the 5 tasks are converted to z scores using normative data and summed to yield a total score. The total score has been associated with self-reported performance of IADLs and neuropsychological assessments of processing speed.[176,177]

Figure Drawing from the NAB – Organization Subscale.[169,178](In-person battery) This subscale of the test is designed to measure fragmentation, planning, and overall organizational skill. The complex figure is presented and the participant is instructed to copy the figure on a separate piece of paper. The examiner switches the color pen the participant is using in order to record the order in which the figure was drawn. The forms will be alternated for each visit, with form 1 administered at baseline, form 2 at 12-month follow-up, and form 1 at 24-month follow-up. Planning and fragmentation of the lines are together scored to give an overall organization score. Figure copy organization scoring has an interrater reliability of .93.

2. <u>Language.</u> A summary score for this domain will be based on scores for the following 2 tests:

Boston Naming Test (BNT).[179] (In-person battery) The BNT is the most commonly used test of confrontation naming (i.e., lexical retrieval) and has been found to be sensitive to minor or early aphasic deficits. We use the 30-item short form test[180] that has extensive geriatric norms and internal reliability of .57-.75. We calculate an age, education, and gender- corrected standard score, based on the number correct.

Verbal Naming. (Remote Battery) The measure is a nonvisual measure of word finding with stimuli chosen based on rare frequency of usage in spoken English. Fifty-five objects or verbs are described and subjects must name the object or verb. Subjects are given a phonemic cue if they are unable to find the correct word.

Category Fluency Test. (In-person and remote battery) This test is a measure of verbal fluency and ability to access semantic knowledge. Test-retest reliability is 0.56 and normative data exist for older Whites and African Americans.[166,181] Participants are given one minute to name as many words as possible that belong to a particular semantic category (e.g., animals). The overall score is the number of words correctly generated. [182]

3. Attention

NAB Digits Forward.[169] (In-person and remote battery) This test is a version of the commonly used digit span paradigm, which evaluates auditory attentional capacity. The NAB test involves 7 items, each with two trials, in which the examinee is asked to repeat series of digits orally, with spans ranging from 3 to 9 digits. Reliability (G coefficient) is reported as 0.87 in older subjects. We will calculate a demographically-corrected t-score.

NAB Digits Backward.[169] (In-person and remote battery) This test is considered a measure of attention and to a lesser extent, working memory.[173] It involves 7 items, each with two trials, in which the examinee is asked to repeat series of digits orally in reverse order. Reliability is 0.88 in older subjects. The demographically-corrected t-score will be used in calculating the overall score.

Brief Test of Attention. (Remote battery) is a commonly used neuropsychological measure of auditory-divided **attention** that was developed to reduce the influence of confounding task demands such as motor speed and visual scanning.

4. Learning and Memory. This secondary cognitive outcome is comprised of a summary score on two tests:

Logical Memory I and II, Wechsler Memory Scale (WMS-IV).[172,183] (In-person and remote battery) This test is one of the most commonly used measures of verbal memory. It involves the examinee listening to a brief paragraph/story and then immediately freely recalling as much as remembered. Following a 30-minute delay, the examinee is asked to recall as much as possible from one story only (IA and IIA). There have been numerous psychometric studies of the WMS-IV with excellent reliability in most all age/education groups (alpha for older adults =.76).[173] We will use the Scaled Score for Logical Memory II in our summary score.

List Learning from the NAB.[169] (In-person and remote battery) This is a 12-word list learning task with 3 learning trials, followed by an interference list, and then a short delay free recall. The word list includes 3 embedded semantic categories with 4 words in each category. Following a 10-15 minute delay, there is a free recall of the initial list, followed by a 36-item forced-choice recognition task. The test is very similar in structure to the CVLT, though its shorter length is better suited for older subjects. Reliability is reported as 0.80 in older adults.[170] The two alternative forms of the NAB list have been shown to be highly equivalent. Therefore, the forms will be alternated for each visit with Form 1 being administered at baseline, Form 2 at 12-month follow-up, and Form 1 at 24-month follow-up. Scores resulting from this test include measures of sensitivity to interference, the use of semantic encoding as an organizational mnemonic strategy, delayed free recall, improvement from free recall to recognition, and discrimination. The result for this test will be the demographically-corrected t-score for the total number of words recalled over the 3 trials. Recent studies have evaluated the application of the NAB List Learning to differentiate participants with amnestic MCI (aMCI) from those with Alzheimer's disease (AD) (Gavett et al., 2009). The test has a sensitivity of .47 and a specificity of .91 in identifying aMCI and a sensitivity of .65 and a specificity of .97 in identifying AD.

5. Visual-spatial Functioning

Figure Drawing from the NAB – Copy Subscale[169,178] (In-person battery) This subscale of the test is designed to measure visuospatial and visuoconstruction skills. A complex figure is presented and the participant is instructed to copy the figure on a separate piece of paper. The examiner switches the color pen the participant is using in order to record the order in which the figure was drawn. The forms will be alternated for each visit. Form 1 will be administered at baseline, Form 2 at 12-month follow-up, and Form 1 at 24-month follow-up. The primary score used in this visuospatial domain is based on the ability to reproduce the figure correctly/accurately, distinct from the organizational aspects of the production. The reliability (G coefficient) of this variable has been shown to be .77.

7.6 Physical Measures
1. Timed Get Up and Go Test (In-person battery)

At the conclusion of the neurocognitive testing, the research staff will then administer the Timed "Get up and Go" test (See Appendix R). The *Timed Get Up and Go Test* measures basic functional mobility, motor strength, position sense and balance in people who are able to walk on their own using a combination chair test and timed walk. This test is also an excellent measure of frailty. (The staff will have set up the testing room prior to the participant's arrival using the necessary materials for this test as outlined in the protocol). The staff will explain the test and then demonstrate the test to the participant. The participant will be asked to sit in a straight-backed chair that has no arms, get up from the chair without using her arms or other aids, walk a designated distance of ten feet, turn around, and return to the chair and sit down without using her arms or other aids. After explaining and demonstrating the test, the participant will be asked if she feels safe doing this test. If not, this will be noted on the scoring sheet and this test will not be continued. If yes, then the RA will proceed with the test. Participants who use a cane or other mobility assist device are allowed to use this for the walking portion of the test (but not to get out of the chair). The RA will time the tests and record and score the data.

2. Actigraphy

To obtain an objective assessment of both daytime and nighttime sleeping, participants will wear the actigraph on the dominant wrist (unless that arm is paralyzed) for one week. The Actigraph Motionlogger (Ambulatory Monitoring, Inc. Ardsley, NY), is a wrist-mounted actigraph that records activity and illumination exposure using an accelerometer, a light transducer and a microprocessor. Commercially available software uses validated algorithms that take into account wrist movement immediately before and after an epoch of interest; wrist activity below an established threshold is interpreted as sleep and wrist activity above that threshold is interpreted as wakefulness as validated in older adults. Agreement between wrist actigraphy and EEG (the gold standard method for sleep assessment) scoring of sleep variables (e.g., total sleep time) is 89-95% in older adults. Subject will also fill out a modified Pittsburgh Sleep Diary (PghSD) during the week of wear.

3. Grip Strength Test

The participant should be in a standing position, arms at their side, not touching their body. Keep elbow bent slightly. If subjects are unable to stand comfortably, they will be seated in a chair with their feet touching the ground with their elbow bent to 90 degrees and the arm against their trunk with a neutral wrist. Participants squeeze the Jamar Plus Digital dynamometer as hard as they can for a count of three. The dynamometer provides a digital reading of force in pounds. A practice trial at less than full force and one test trial are completed with each hand. The test takes approximately three minutes to administer and is recommended for ages 3-85. Dominant vs. Non-Dominant Hand (i.e., handedness) is assessed at the outset.

4.   Four Meter Walk Gait Speed Test

The Four Meter Walk Gait Speed Test is adapted from the 4 meter walk test in the Short Physical Performance Battery. Participants are asked to walk a short distance (four meters) at their usual pace. Participants complete one practice and then two timed trials. Raw scores are recorded as the time in seconds required to walk four meters on each of the two trials, with the better trial used for scoring. The test takes approximately three minutes to administer (including instructions and practice).

5. Body Mass Index (BMI)

The research staff will measure or abstract height and weight from medical records to calculate their BMI. If a subject does not have height and weight included in their records, the subject can provide this information as self-reported.

6. Sit to Stand Chair Test (30 seconds)
Research staff will count the number of times a subject can fully stand up from a seated position without using their hands to push up in 30 seconds. After explaining and demonstrating the test, the participant will be asked if she feels safe doing this test. If not, this will be noted on the scoring sheet and this test will not be continued. If yes, then the RA will proceed with the test.

7.8 Patient Interviews-Questionnaire

Research staff will give a brief overview of the questionnaire and answer any questions the patient may have, then continue with the questionnaire. If the participant is too tired, the session will end and women will be given a copy of the questionnaire and the 30-45 minute interview will be scheduled over the telephone within one week of the cognitive testing or the subject can mail it back to research staff to decrease participant burden. Subjects will also be given the option of completing the survey online through REDcap. No identifying information will be collected. All interviews need to be completed within 1 week after neuro-cognitive testing. The women will be called at a date and time that is convenient for them. The interviewer will establish rapport and administer the structured interview. The same staff person who administered the neuropsychological tests will do the telephone interview if possible. Once the questionnaire is completed, the participant will receive 50 cash or gift card for their time.

7.8.1 Questionnaire Data Collection

The Measures that will be used are summarized on Table 1.

Individual Influences

Factors that will be used as controlling variables for patients and controls include: 1) socio-demographics, 2) health habits and history, 3) social and other support, 4) personality, 5) mood, 6) fatigue, and 7) physical ability/activity. (See Appendices U, V and W)

Socio-demographics. We will measure age, family history of dementia, marital status, education, occupation, race, ethnicity and insurance. Education will include years of school and vocational training. Occupation will capture job category (clerical, administrative, management, etc) and length of time working, since occupation is closely related to cognition and cognitive reserve. Race/ethnicity will be self-identified using standard categories (e.g., Hispanic vs. non-Hispanic; white, black, AAPI, etc). Insurance will include Medicaid and private insurance in addition to Medicare and HMO vs. non-HMO setting of care.

Health habits/history includes factors that may

Table 1. Summary of Measures, Source, & Time of Collection				
Variable	Source	Base-line*	Follow-ups	One-time during COVID-19
Predictors				
Patient/Control	Staff	√		
Systemic therapy	Chart	√	√	
Moderator				
APOE E4, COMT, inflammation, DAMPS, AD-plasma biomarkers	Venipuncture	√	√	
Controlling Variables				
Treatment propensity	Physician	√		
Sociodemographics	Patient	√		
Comorbidity	Patient	√	√	
Frailty, IADLs	Patient	√	√	
Medications used, HRT	Patient	√	√	
Age of menopause	Patient	√		
Health habits	Patient	√	√	√
Psychosocial, literacy	Patient/WRAT	√		
Mood, Fatigue	Patient	√	√	√
Tumor characteristics	Chart	√		
Surgery, recurrence	Chart	√		
Site (type of control)	Staff	√		
Physician factors	Physician	√		
Social Support	Patient	√		√
Time from Rx to F/U	Charts		√	
Impact of COVID-19	Patient			√
Outcomes				
Cognitive domains	Neuropsych tests	√	√	
Self reported cognition**	Patient	√	√	√
QOL- FACT B, MOS SF12	Patient	√	√	
* Baseline is at enrollment and before systemic therapy.				
** This will be used for exploratory analysis.				

affect cognition and/or QOL, including prior use of hormonal replacement therapy (total years used), age of menopause, self-reported cigarette and alcohol use (alcohol abuse will be defined as use of daily intake of >2 drinks per day).

Social support will be measured using the MOS social support scale (emotional, tangible, affectionate, positive social interaction, and additional support).[184] We have used this scale with excellent reliability (.85) in our research with older women.[185]

Mood includes depression and anxiety. We will use the short form of CES-D (20 items) to measure depressive symptoms.[188] The CES-D has been widely used in epidemiological studies of depression, has strong data supporting its validity and reliability, is a good screening tool and produces valid results in older populations.[189] Patients are asked to rate how frequently they have experienced symptoms on a 4-point scale ranging from "Rarely or none of the time" to "Most or all of the time".

We will use the 20-item State Anxiety scale (the level of <u>current anxiety</u>) from the Spielberger Inventory to measure anxiety. Extensive data on reliability and validity support the utility of this test.[190]

We will also use the Visual Analog Mood Scale (VAMS) at in-person study visits.[191] The VAMS consists of eight scales with 100mm vertical lines, each evaluating a different mood state. Each scale displays a specific cartoon-like mood face at the bottom, and a neutral cartoon-like face at the top. The word "neutral" is printed above the neutral face, and the name of the mood (i.e. "sad," "tense," etc.) is printed below the corresponding mood face. By printing the word along with the face, issues of impaired facial recognition are avoided. While the addition of a mood word also provides additional information for individuals who are able to interpret and retain the word, it is not necessary for completing the task. The patient places a horizontal mark across the line to indicate current mood state. This mark is converted to a 0-100 scale based on distance in mm from the top of the scale (i.e., Neutral pole). Therefore, a score of 100 indicates extreme endorsement of the specific mood. The faces have a minimum number of features in order to avoid excessive subtleties and detail. Several validation studies have examined the VAMS with samples varied by age, neurologic deficit.

<u>Fatigue</u> will be assessed using the Functional Assessment of Cancer Therapy-Fatigue (FACT-F), a 13-item self-report measure designed to assess the presence and intensity of fatigue, as well as its perceived interference with quality of life.[192]

<u>Physical activity/ability</u> can affect cognition. We will use the physical function sub-scale of the MOS SF-12 to assess general activity level since it is brief and has excellent reliability in general and older populations. The SF-12 contains one or two items that measure each of the eight concepts included in the original SF-36. We will be using the Physical Component Summary. The SF-12 is a reliable measure of overall health status, and has often been used in large population health surveys. [193,194] In addition, we will use the International Physical Activity Questionnaire (IPAQ) to assess level of activity. The IPAQ contains 4 questions looking at the level of vigorous and moderate physical activities, as well as time spent sitting.[218] An ad hoc list of other activities, such as trivia, crossword puzzles and reading will look at cognitive reserve.

We will also use the "timed get up and go" described above (combination of the chair test and the timed walk), as well as a grip strength test and sit to stand chair test at in-person visits as another measure of physical function and frailty.[195] We chose these measures since it is a sensitive indicator of physical activity and mortality in geriatric populations and involves minimal patient burden.[159]

<u>Functional Assessment of Cancer Therapy-Cognition (FACT-Cog)</u>[196]We have used this tool in our prior research with good reliability and ease of administration over the telephone with older women.[81] This 29-item tool includes self-reported difficulty in memory, concentration, and intellectual activities. Responses are rated from 0 "not at all" to 4 "very much". Scores correlate more with emotional well-being than objective measures of cognition, suggesting that self-report and standardized tests capture different aspects cognition. [196] We will use the summary (and sub-scale) scores in exploratory analyses of systemic treatment effects on self-reported cognition.

We will use the FACT-B to measure QOL outcomes (QOL is also included as a controlling variable in analyses of cognition outcomes). We will describe QOL at follow-up, controlling for baseline. The FACT-B is a 44-item disease-specific tool that includes general and breast cancer specific items that capture physical, emotional, functional and social domains; the breast specific concerns

will not be asked of controls. The scales have excellent reliability in our prior studies with older women (.76-.96), can detect change over time,[197] and have been correlated with changes in cognition.[111]

Sleep

To measure sleep, we are employing both objective and subjective measures. Subjects will wear a Motionlogger watch to monitor their sleep for one week. With the monitor, they will fill out a daily sleep log. Subjects will also complete the Pittsburgh Sleep Quality Inventory, Berlin Sleep Apnea Questionnaire and the Insomnia Severity Inventory.

7.8.2 Questionnaire Data Collection- Clinical control variables

Clinical factors are considered as controlling variables in our model and will largely be used to create treatment propensity scores. For patients we will measure pathological stage, treatment (mastectomy, breast conservation, node dissection or sentinel node biopsy and radiation), ER status, HER2 expression (if done) and tumor grade from records. For patients and controls we will measure self-reported baseline comorbidity, current medications and frailty.

Comorbidity will be defined along two dimensions. First, we will ascertain all chronic illnesses, including major vascular diseases (e.g., CHF, angina, MI, peripheral vascular disease). We will also ask women to list all medications, with special attention to drugs that could affect cognition, such as narcotics, anxiolytics and anti-depressants, and statins. We will also use the Instrumental Activities of Daily Living (IADLs) in the two months prior to diagnosis (or enrollment). This scale assesses the need for and degree of assistance required in bathing, dressing, shopping, and other activities. We will query women at the follow-up about new diagnoses and changes in IADLs.

Frailty will be assessed at enrollment using a modification of the Frailty Index developed by Fried and colleagues.[34] This index predicts disability, hospitalization and death.[198] It includes unintentional weight loss $\geq$10 pounds, items on exhaustion from the CES-D and the Functional Assessment of Cancer Treatment-Fatigue (FACT-F), and low physical activity/ability. We will also use the "timed get up and go" test described above [159] as a frailty measure. Results for frailty indicators will be summed by adapting the algorithm developed by Fried.

7.8.3 Questionnaire data collection- COVID-19 survey

Physical activity, sleep, social isolation, and a sedentary lifestyle are well-reported factors in overall quality of life and well-being. The COVID-19 pandemic has had significant psychosocial effects on a global scale. Populations with chronic illnesses such as cancer and people over the age of 60 are particularly at risk for worse infections and outcomes from the disease. With the unprecedented spread of this virus in so many areas of the world, an increase in anxiety, stress, social isolation, and sleep disturbance are inevitable. In many areas, the socially isolating effects of prolonged quarantine will likely be reported in all populations and these factors could particularly impact the elderly. Although the goals of the TLC study focus on the study of cancer-related cognitive decline, the enrolled participants and future subjects of this study will inevitably be impacted by the COVID-19 virus pandemic in significant ways and accounting for this major life event will be important in analyzing information from the study moving forward. Studying these factors in the setting of such an active, ongoing global health issue will be important in the understanding of this virus's impact on health in the future. Initiating an examination of psychosocial factors stemming from this pandemic is a time-sensitive opportunity to capture data from this cohort.

During the COVID-19 pandemic, we will conduct a one-time survey with all active TLC participants. As of May 2020, there are 565 active participants (participants who are still eligible to participate and who have not completed their 60-month follow-up).

We have email addresses for 64% of participants. These subjects will receive an email with language from the consent script introducing the survey and providing a link where they can complete the survey online through REDCap. We will email them up to three times. If they do not respond to the third email, we will try calling them up to three times. For participants without email addresses on file, we will call them up to six times.

Participants with email addresses and internet access can complete the survey online. Participants who express interest in completing the survey online will receive a unique link for REDCap. They will read the online consent addendum (Appendix BBB) and click "I consent" to access the survey and complete it.

Participants can also complete the survey by phone with an RA. The RA will read the phone consent script (Appendix CCC) and obtain verbal consent. If possible, the RA will email the survey to the participant so that she can have the questions and answer options in front of her. The RA will enter the answers into the participant's REDCap during the phone call. Appendix DDD has answers to potential FAQs. This will be 1) sent on the email to participants, 2) on the bottom of the REDCap consent page, and 3) sent to RAs so that they can use it if questions arise during the phone consent.

Participants will be compensated 25 for completing the survey. When RAs are safely able to return to work on site, they will mail the compensation to participants.

7.9 Actigraphy

Actigraph GT3X (stopped 1/11/2021)

We have added objective measurement using the ActiGraph GT3X (ActiGraph, Pensacola, FL) as a secondary measure to provide data on actual physical activity levels that affect cognition and biomarkers. It uses a piezoelectric accelerometer to monitor and store the degree and intensity of motion, sampling every second. Wrist and waist placements demonstrate comparable output. [269] Actigraphy has been used in several studies of cancer patients and older adults, [270-273] and shows good criterion [269, 342] and predictive validity for functional status and quality of life. [5] Data will be downloaded and transformed into METs using the Crouter [274] two-regression model, which has been shown to be more accurate than other algorithms in calculating METs across a range of activity levels. [275] We will require at least four valid days for inclusion of data in analysis. We will look at continuous data or established categorical levels; we will also examine cut-points based on sample distributions. [276] We will consider in analyses of physical activity the distribution of season at by survivor-control group. Since each participant is assessed at the same time each year, there should be minimal impact of season on intra-individual variations.

The ActiGraph GT3X will be given to subjects with graphic instructions on use. Study staff will review procedures in person or by phone. Participants will be instructed to wear the Actigraph on their waist for 7 days and to return the devices in person or by mail. Preferably the Actigraph will be worn the week prior to cognitive testing. If this timing is not possible due to treatment schedules, subjects should wear the Actigraph as close to their appointment as

possible, for as close to 7 days as possible. If the Actigraph is worn after the appointment, subjects will be given an envelope and prepaid postage to mail it back to study staff. If needed, study staff will send a reminder letter to subjects who have not returned Actigraphs. Older adults and cancer survivors show high compliance (88%) with actigraphy (e.g., worn 4-7 days of over a 7-day period).

Motionlogger

To obtain an objective assessment of both daytime and nighttime sleeping, participants will wear the actigraph on the dominant wrist (unless that arm is paralyzed) for one week. The Actigraph Motionlogger (Ambulatory Monitoring, Inc. Ardsley, NY), is a wrist-mounted actigraph that records activity and illumination exposure using an accelerometer, a light transducer and a microprocessor. Commercially available software uses validated algorithms that take into account wrist movement immediately before and after an epoch of interest; wrist activity below an established threshold is interpreted as sleep and wrist activity above that threshold is interpreted as wakefulness as validated in older adults. Agreement between wrist actigraphy and EEG (the gold standard method for sleep assessment) scoring of sleep variables (e.g., total sleep time) is 89-95% in older adults. Subject will also fill out a modified Pittsburgh Sleep Diary (PghSD) during the week of wear.

7.10 Neuroimaging

Controls enrolled at Indiana University School of Medicine are eligible to participate in optional neuroimaging at any time point in the study. Cases must be enrolled prior to the start of systemic treatment. Participants will be asked to arrive 30-45 minutes early to review and fill out safety screening forms and receive instructions for the scan. All participants will be familiarized with the experimental procedures including familiarization with tasks. The MRI experimental session will last approximately one hour with a set-up time of approximately 10-15 minutes to allow the subjects to move between tasks. Scanning begins with a short scan (~1:00 min) used to position subsequent acquisitions. The scans collected will include both structural connectivity using diffusion tensor imaging (DTI) with 55-directions (~8:00 min) and functional connectivity computed from resting state fMRI scan (~6:00 min). Additional scans include a high-resolution structural scan (~9:00 min) and a 3D FLAIR to detect white matter lesions (7:55 min). Two working memory fMRI scans will be collected using the N-back (6:09 each) and Episodic memory tasks (5:15 min). A short scan (~2:37 min) to identify distortions in the magnetic is also collected for use in the analysis of the fMRI data.

7.11 Physician data

We will ask patients' physicians (oncologists or if no oncologist, surgeon) to complete a one time Physician Assessment Form at the start of the study (when their first patient is enrolled) to capture demographics, practice patterns, tendencies to prescribe systemic treatment and attitudes towards patient participation in decisions. (See Appendices Z and AA) We have used this approach in our prior work,[42] and have shown that physician tendency to recommend chemotherapy is related to actual treatment. Since these data will only be used in analyses of treatment propensity for cases, these data will not be collected from providers of controls.

7.12 Clinical data and Exposure to Systemic Therapy

For cases only, we will collect data from medical records on tumor size and number of nodes, estrogen receptor and HER2 status and treatment received (surgery including reconstruction,

radiation and systemic therapy). (See Appendix BB) If women may get care from more than one provider, consent (and HIPAA waivers) will include permission to contact all physicians providing cancer care.

We will use the medical records to define exposure to systemic therapy (chemotherapy and hormonal therapy). Our primary definition will be any use vs. none. However, since some women may not complete treatment, we will also measure quantity of exposure to explore dose response effects (e.g., none, <75% of cycles, completed $\geq$75% or more cycles but <100%, completed 100%). We will base this categorization on dates and cycles expected based on standard regimens as defined by our clinicians and professional groups.[11] We will collect dose data, but it will be more difficult to explore medication doses and dose reductions because many agents are adjusted for individual metabolism (e.g., based on renal and liver function). Thus, we will only consider regimens as dose-dense vs. routine. We will also measure types of agents for exploratory analysis. Hormonal treatment will classified as any vs. none, as well as compliance during time recommended (e.g., takes all doses, misses 1-2 per week, or misses > 2 doses per week on a regular basis). We will record type of hormonal therapy (e.g., tamoxifen, AIs, etc.). We will also measure time from therapy initiation and completion to follow-up (at follow-up visits, patients on hormonal therapy will still be taking medication since it is recommended for $\geq$5 years of treatment).

After each follow-up visit, an annual medical record review will be performed. (See Appendix ZZ) We will record data from medical records on vital status (alive or deceased), recurrence status, Herceptin administration, and hormonal therapy administration.

7.13 Follow up visits: Every 12 months up to approximately 60 months post-baseline

We will contact participants (Appendices II, JJ, KK) for follow-up every 12 months up to approximately 60 months after baseline to collect blood, measure BMI and vital signs if possible, repeat neuropsychological testing (See Appendices Q and P), repeat optional neuroimaging and conduct a brief interview to assess self-reported cognition and QOL using the same measures used in the enrollment visit (See Appendices V and W). Subjects will wear an actigraph for one week at each follow-up to measure physical activity and sleep. After each follow-up visit, an annual medical record review will be performed. If a participant was enrolled under the previous grant and consented only to 24 months, she will be contacted and given the opportunity to continue in the study, no matter how long she has been off-study. Subjects will be complete their follow-up assessments as close to 12-, 24-, 36-, 48-, and 60 months after baseline as their schedule allows. When possible, the same interviewer who conducted the baseline interview will contact women for follow-up to maintain continuity.

The neuropsychological tests to be administered are as follows: (Please refer to section 7.2 for full test descriptions)

Baseline and 12-month Assessments (In-person visits):

- *Visual Analog Mood Scale (VAMS)*
- *NAB Digits Forward*
- *NAB Digits Backward*
- *NAB List Learning-Immediate Recall and Short Delay*
- *Digit Symbol Test*
- *NAB Driving Scenes*

- *NAB List Learning-Long Delay and Recognition*
- *NAB Figure Drawing*

TEN MINUTE BREAK

- *Controlled Oral Word Association Test (COWAT)*
- *Logical Memory I*
- *Trail Making*
- *The Timed Instrumental Activities of Daily Living (TIADL)*
- *Timed Get-Up-and-Go*
- *Logical Memory II*
- *Category Fluency Test*
- *Boston Naming Test (BNT)*

24-, 36-, 48-, and 60-month Assessments (In-person visits):
- *Visual Analog Mood Scale (VAMS)*
- *NAB List Learning-Immediate Recall and Short Delay*
- *NAB Digits Forward*
- *NAB Digits Backward*
- *Digit Symbol Test*
- *NAB Figure Drawing*
- *NAB List Learning-Long Delay and Recognition*

TEN MINUTE BREAK

- *Controlled Oral Word Association Test (COWAT)*
- *Logical Memory I*
- *Trail Making*
- *The Timed Instrumental Activities of Daily Living (TIADL)*
- *Timed Get-Up-and-Go*
- *Logical Memory II*
- *Category Fluency Test*
- *Boston Naming Test (BNT)*

Baseline, 12-, 24-, 36-, 48-, 60- month visits (Remote visits)
- *NAB List Learning – Immediate Recall and Short Delay*
- *NAB Digits Forward*
- *NAB Digits Backward*
- *Verbal Naming*
- *Mental Control Test*
- *NAB List Learning – Long Delay and Recognition*
- *Logical Memory I*
- *Oral Trail Making A*
- *Oral Trail Making B*
- *COWAT*
- *Category Fluency*
- *Brief Test of Attention*
- *Logical Memory II*
- *Symbol Digit Modalities Test*

The measures in the participant follow-up questionnaires are as follows: (Please refer to section 7.6 for full test descriptions)

- Socio-Demographics: change in socio-demographic information
- Insurance: change in insurance
- SF-12: A 12-item short-form health survey
- Health Habits/History, International Physical Activity Questionnaire (IPAQ): change in self-report of cigarette and alcohol use and physical activity
- Functional Assessment of Cancer Treatment-Breast (FACT-B)
- Functional Assessment of Cancer Treatment-Cognition (FACT-Cog)
- MOS Social Support Survey
- Depression Scale (CES-D)
- State-Trait Anxiety Inventory (STAI)
- OARS Instrumental Activities of Daily Living
- Functional Assessment of Cancer Treatment-Fatigue (FACT-F)
- Comorbidities and medications: any new illnesses and list of medications
- Pittsburgh Sleep Quality Index (PSQI)
- Berlin Sleep Apnea Questionnaire
- Insomnia Severity Inventory
- Adverse Childhood Experiences
- Everyday Discrimination
- Impact of Events Scale (cases only)
- Perceived Stress Scale
- Adult Life Stress measure
- Unintentional Weight Loss

8.0 PRIMARY OUTCOMES

Our principal cognitive outcome is change (12-, 24-, 36-, 48, up to 60- months vs. baseline) in the EWP Domain summary score; secondary domains include Language, Attention, Learning and Memory, and Visuospatial. This will allow us to focus our hypothesis testing and also see which domains are most sensitive to systemic therapy. For each domain we will sum the primary scores from the tests included within the group to calculate a domain-specific cognition score at each time point. We will do this by first using z-transformations for each test (using the mean and standard deviations of the control group). The z-scores will then be summed to create the domain summary score. We will examine changes over time, where decline is defined as failure to show the expected practice effect or to show improvement with repeat administration.

9.0 STATISTICAL CONSIDERATIONS

9.1 Power and Data Analysis

9.1a Power

We use the numbers of participants anticipated to have complete data for power analyses to provide conservative estimates for the minimal effect size to be detected. Because we do not expect 100% pair-matching through the use of friend controls, our power calculation assumes frequency matching. We assume that some women will be lost to or refuse follow up (10%) or will

die (10%) in the up to approximately 60 month study period, resulting in about 342 surviving patients (and controls) of the 850 enrolled per group that complete all assessments. We assume similar attrition rates across treatment and patient/control groups. Since our current study with older women indicates that 40-50% of women are accepting chemotherapy, but national rates are somewhat lower, we estimate that 30-40% of women enrolling will receive chemotherapy.[199] We also estimate that 80% of these women will also receive hormonal therapy (the proportion that will be ER positive).[17,200] The remaining 20% of the women receiving only chemotherapy will be ER negative. Among the 60-70% of women not receiving chemotherapy, we estimate that 80% will receive a hormonal agent based on ER status and that the remainder will receive no systemic treatment.

The first hypothesis tests whether acute survivor declines will persist, late effects will manifest, and there will be trajectory differences by survivor-control and survivor-treatment groups. In the first set of analyses, we will model longitudinal changes in cognitive function between the survivor and control groups using MLM. Each model will include fixed effects of time, group (survivor vs. control), a time by group interaction, and subject-level random effects. We will also test polynomial effects given the richness of the longitudinal follow-up with five measurement points. The latter analyses will allow us to evaluate whether the changes in either group level off or accelerate at any point in the follow-up period. These analyses evaluate the hypothesized poorer performance among the survivors vs. controls and the differences among the two survivor groups based on treatment exposure (chemotherapy +/- hormonal vs. hormonal; we can repeat these analyses excluding those receiving chemotherapy alone). We will use propensity methods described above to assess confounding by indication and conduct sensitivity analysis to evaluate the impact of unmeasured confounders.

Although the above analyses are informative as to the group-level changes over time, they do not consider the inter-individual differences in intra-individual change in cognitive function. Therefore, to complement the standard MLM analyses, we will use growth mixture modeling (GMM) to examine heterogeneity of change over time and identify trajectories of each participant's cognitive function (growth curve) over time. [257-262] The assumption of GMM is that women's individual growth curves can be classified into distinctive patterns such as the three trajectories ("latent classes") described in our conceptual model: normal aging, phase shift, and accelerated decline. Figure 2 provides an example of possible GMM results using hypothetical cognitive data. These may not be the exact patterns that we find. What makes GMM useful is that it uses statistical fit indices to determine the actual number and types of latent

Figure 2. Exemplar Cognitive Trajectories

classes. Once the latent classes are identified, we will evaluate the association between survivor-control and treatment exposure-control status and the identified trajectories by using chi-square tests. Moreover, we will compare the latent classes on key variables (e.g., multi-morbidities, genotype, physical activity level) that distinguish the groups using a multinomial logistic regression model with the latent class membership as the outcome. These analyses will allow us to identify risk factors for accelerated as well as possible non-linear patterns (e.g., initial decline, later improvement).

For the next hypothesis (aim #2), non-modifiable phenotypes and genotypes will decrease cognitive function, while modifiable lifestyle factors will protective, controlling for time and covariates, and effects will be moderated by treatment exposure.

We will use MLM to identify factors that affect cognition during the 4 years of follow-up by comparing factors of interest (e.g., APOE ε4+ vs ε4-) with respect to continuous standardized cognitive domain score across time (from baseline up to 60 months). The main predictors are multi-morbidity, gene polymorphisms, and physical activity; treatment group (chemotherapy vs. hormonal vs. control) is the moderator, where we expect a time by factor interaction, which, if statistically significant would suggest that the factor exerts a differential effect on changes in cognitive function depending upon treatment group. Based on our conceptual framework, if the three-way interaction is significant, we will use separate models for the survivors and controls to evaluate individual risk factors in terms of the main effects of non-modifiable (e.g., multi-morbidity [or cardiovascular illness or frailty], genotype) and modifiable (e.g., physical activity, cognitive stimulation) variables controlling for time and covariates (e.g., age, education, race, and site), and consider other factors like anxiety (State-Trait) and fatigue (FACT-fatigue) as confounders if they are associated with cognition and the predictor. The IPAQ will be the primary measure of physical activity since we will have these data from all assessments. We will examine distributions over time of physical activity measures (continuous and categorical on self-report and objective measurement) to review variability and sensitivity to change over time. We will also examine correlations between self-reported activity on the IPAQ and actigraphy and evaluate if there are any differences by groups based on season. We will aim for at least 4 valid days of actigraphy for inclusion in analysis. Next, we will look for multi-morbidity interactions with treatment based on our baseline results. If significant, these characteristics would identify factors that make persons susceptible to longitudinal declines.

For the model that includes survivors only, we will consider the effects of treatment exposure and use propensity score methods to correct for chemotherapy selection bias. This will be interesting because the chemotherapy group, which was the healthiest and best-educated group, experienced the steepest declines in the initial phase of the study. If this pattern persists, then propensity score adjusted results could show a greater impact of treatment exposure than analyses that do not consider this favorable (for cognitive function) effect of treatment selection. We can repeat analyses excluding the ER-negative cases that only received chemotherapy to directly compare the differences between chemotherapy + hormonal treatment to hormonal treatment alone. In secondary analyses, we will use the same methods to evaluate self-reported declines of 7+ points on the FACT-cog and conversion to MCI. We will also assess relationships between objective and self-reported cognitive changes. In analysis of genotype effects, we will consider the effects of *APOE* and *COMT* individually and jointly such that persons may have low genetic burden (*APOE* ε4- and *COMT* met), moderate burden (*APOE* ε4+ or *COMT* val+) or high burden (*APOE* ε4+ and *COMT* val+). Last, we will repeat analyses for QOL.

For the third hypothesis (aim #3), levels of inflammatory markers will co-vary with trajectories of cognition; and H3b: Inflammation will mediate the protective effect of physical activity and risk of multi-morbidity on cognitive decline. Based on current evidence, we will measure IL6, CRP, and sTNF-RII. Each will be used separately as a continuous measure. Although there are no established cut points for these markers in relationship to cognition, we will also explore as dichotomous variables levels such as CRP $\leq$ 3 mg/L vs. > 3 based on cardiac risk. [317,318]

Log transformations are expected to be necessary for analyses of inflammatory biomarker concentrations. As in other aims, our primary cognitive outcome is based on neuropsychological testing; we will also examine how inflammation relates to secondary outcomes, including self-

reported cognition and conversion to MCI. We will consider covariates such as sleep, fatigue, BMI, etc. in these analyses. Also, since cancer and its treatments affect inflammation, we will consider stage, surgery, radiation, and systemic therapy in survivor-only analyses. Similar to Aim 1, we will use MLMs to evaluate how each inflammation marker co-varies with trajectories of cognition. We will include subject-level random effects and run models treating the markers of inflammation as time-varying covariates to determine if changes in inflammation co-vary with changes in cognitive performance. For the second part of the aim, we will perform longitudinal mediation analyses to explore how inflammation mediates over time the relationship between changes in levels of physical activity (or multi-morbidity) and trajectories of cognition. In these models, we will apply a latent difference score approach to estimate the direct effects of physical activity (considering season if needed) on changes in cognition, and indirect effects acting through changes in inflammation. These models have the advantage of allowing changes between time intervals (e.g., from baseline to 12 months or 36 months to 48 months) to be different and for the roles of the mediators to change dynamically over time. Last, we will evaluate independent contributions of each marker in multiple mediator models. We will examine correlations between inflammatory markers to evaluate whether creating a composite score will be reasonable in secondary analyses.

9.1b Analysis Plan

Our primary outcome is the standardized score on the attention, psychomotor speed, and executive function domain; global decline and the other domains will also be examined. Test scores are standardized to baseline controls (since not all tests have external norms), and z-scores are combined into domain scores. Self-reported cognition, conversion to MCI, and QOL are added outcomes.

We selected multi-level models (MLM) to evaluate our study outcome based on our prior research [277] and because they: 1) capture the intra-individual correlation and clustering within sites; 2) allow testing of inter-individual differences in patterns of responses over time; 3) allow for inclusion of all available data, providing greater flexibility and statistical power than other methods (e.g., repeated-measures MANOVA); [278] 4) handle heteroscedascity and departures from assumptions; 5) can incorporate covariates and strategies to correct for treatment selection bias if needed (e.g., propensity score adjustments); and 6) can readily deal with unbalanced follow-up times, a design element that may occur in this study. [279] Prior to statistical modeling, we will examine distributions of variables and descriptive statistics, describe missing data patterns, and evaluate the association of missingness with enrollment characteristics. We will consider multiple imputation techniques for missing data. [280, 281] We will also evaluate the impact of potential covariates that relate to cognitive function and treatment exposure; evaluate the impact of additional covariates, such as anxiety, depression, and fatigue; and confirm that the distribution of genotypes continues to be comparable among survivor and control groups.

Since predictors of chemotherapy selection can affect longitudinal cognitive function independent of treatment, propensity score analyses will address treatment selection: 1) using the propensity score as a covariate, 2) using propensity score matching methods, and 3) using the inverse probability of treatment weighting method. [282-284] We will repeat analyses excluding DCIS cases. Lastly, we will evaluate adjustment for multiple testing (e.g., using false discovery rate procedures). [285, 286]

We start with 850 survivors and 850 matched controls. At each time period we assume that 5% of women will die each year and that 5% may become ineligible due to cancer recurrence/occurrence or stroke since this is a fairly healthy volunteer sample, for a range of 90-

95% survival in each period. We estimate a retention rate of 80% based on current experience. Thus, the estimated sample sizes per group vary from 342-360 alive (274-288 complete) at 12 months to 250-308 alive (200-246 complete) at 60 months. If rates vary from expectation, we will supplement enrollment to ensure robust power. Among survivors, based on current data, a minimum of 30% is estimated to receive chemotherapy. *APOE* ε4+ is expected in 20-25% of women and any *COMT* val+ allele is expected in approximately 75%, with 26% homozygous for val. [287] Power calculations are provided only for primary domain (attention, psychomotor speed, and executive function).

Aim #1. Conduct assessments every 12 months up to approximately 60-months *to identify trajectories of longitudinal cognitive function (normal, phase shift, or accelerated aging). H1: 12-month declines among survivors will persist; late effects will manifest; and there will be sustained trajectory differences in the treatment-exposure survivor groups (chemotherapy, hormonal) vs. the controls.*

In the first set of analyses, we will model longitudinal changes in cognitive function between the survivor and control groups using MLM. Each model will include fixed effects of time, group (survivor vs. control), a time by group interaction, and subject-level random effects. We will also test polynomial effects given the richness of the longitudinal follow-up with five measurement points. The latter analyses will allow us to evaluate whether the changes in either group level off or accelerate at any point in the follow-up period. These analyses evaluate the hypothesized poorer performance among the survivors vs. controls and the differences among the two survivor groups based on treatment exposure (chemotherapy +/- hormonal vs. hormonal; we can repeat these analyses excluding those receiving chemotherapy alone). We will use propensity methods described above to assess confounding by indication and conduct sensitivity analysis to evaluate the impact of unmeasured confounders.

Although the above analyses are informative as to the group-level changes over time, they do not consider the inter-individual differences in intra-individual change in cognitive function. Therefore, to complement the standard MLM analyses, we will use growth mixture modeling (GMM) to examine heterogeneity of change over time and identify trajectories of each participant's cognitive function (growth curve) over time. [257-262] The assumption of GMM is that women's individual growth curves can be classified into distinctive patterns such as the three trajectories ("latent classes") described in our conceptual model: normal aging, phase shift, and accelerated decline. Figure 2 provides an example of possible GMM results using hypothetical cognitive data. These may not be the exact patterns that we find. What makes GMM useful is that it uses statistical fit indices to determine the actual number and types of latent classes. Once the latent classes are identified, we will evaluate the association between survivor-control and treatment exposure-control status and the identified trajectories by using chi-square tests. Moreover, we will compare the latent classes on key variables (e.g., multi-morbidities, genotype, physical activity level) that distinguish the groups using a multinomial logistic regression model with the latent class membership as the outcome. These analyses will allow us to identify risk factors for accelerated as well as possible non-linear patterns (e.g., initial decline, later improvement).

Power for the MLM is based upon standard conventions.[288] With our projected sample, five assessments (baseline, every 12 months up to 60 months), and two groups (survivor vs. control), we can detect a 5% (Cohen's d = .05) group difference in slope of the change in cognition scores in the attention, psychomotor speed and executive function domain, and 20% differences at the level of the intercept for any given covariate (d = .2), with .80 power, alpha of .05. Further, the study is powered to detect small effect size differences at the 60 month point (d = .25), so is very well powered to detect even larger cognitive declines in survivors than those expected based on

aging in the controls. In comparing those exposed to chemotherapy vs. hormonal vs. controls (three groups), the power is .80 to detect a three-group effect size of f = .15. For the GMM portion of the analysis, there is no general consensus on adequate sample size. Adequate extraction of latent classes depends upon a number of characteristics such as the magnitude of between-class differences, the heterogeneity of change processes, relative group sizes and reliability of measurement. [262] Given the heterogeneity in change that we have observed in our earlier work and the reliability of our primary domain, we are confident that the sample size will allow for the adequate identification of latent classes with GMM.

Aim #2. Identify risk factors for decline in cognitive function in the period up to *60 months post-enrollment. H2: Some non-modifiable phenotypes (e.g., multi-morbidity) and genotypes (APOE and COMT) will decrease cognitive function, while modifiable factors (e.g., physical activity) will be protective of declines; and these main effects will be moderated by treatment exposure (chemotherapy>hormonal>control).*

We will use MLM to identify factors that affect cognition during the 4 years of follow-up by comparing factors of interest (e.g., APOE ε4+ vs ε4-) with respect to continuous standardized cognitive domain score across time (from baseline up to 60 months). The main predictors are multi-morbidity, gene polymorphisms, and physical activity; treatment group (chemotherapy vs. hormonal vs. control) is the moderator, where we expect a time by factor interaction, which, if statistically significant would suggest that the factor exerts a differential effect on changes in cognitive function depending upon treatment group. Based on our conceptual framework, if the three-way interaction is significant, we will use separate models for the survivors and controls to evaluate individual risk factors in terms of the main effects of non-modifiable (e.g., multi-morbidity [or cardiovascular illness or frailty], genotype) and modifiable (e.g., physical activity, cognitive stimulation) variables controlling for time and covariates (e.g., age, education, race, and site), and consider other factors like anxiety (State-Trait) and fatigue (FACT-fatigue) as confounders if they are associated with cognition and the predictor. The IPAQ will be the primary measure of physical activity since we will have these data from all assessments. We will examine distributions over time of physical activity measures (continuous and categorical on self-report and objective measurement) to review variability and sensitivity to change over time. We will also examine correlations between self-reported activity on the IPAQ and actigraphy and evaluate if there are any differences by groups based on season. We will aim for at least 4 valid days of actigraphy for inclusion in analysis. Next, we will look for multi-morbidity interactions with treatment based on our baseline results. If significant, these characteristics would identify factors that make persons susceptible to longitudinal declines.

For the model that includes survivors only, we will consider the effects of treatment exposure and use propensity score methods to correct for chemotherapy selection bias. This will be interesting because our data to date indicate that the chemotherapy group, which was the healthiest and best-educated group, experienced the steepest declines. If this pattern persists, then propensity score adjusted results could show a greater impact of treatment exposure than analyses that do not consider this favorable (for cognitive function) effect of treatment selection. We can repeat analyses excluding the ER-negative cases that only received chemotherapy to directly compare the differences between chemotherapy + hormonal treatment to hormonal treatment alone. In secondary analyses, we will use the same methods to evaluate self-reported declines of 7+ points on the FACT-cog and conversion to MCI. We will also assess relationships between objective and self-reported cognitive changes. In analysis of genotype effects, we will consider the effects of *APOE* and *COMT* individually and jointly such that persons may have low genetic burden (*APOE* ε4- and *COMT* met), moderate burden (*APOE* ε4+ <u>or</u> *COMT* val+) or high burden (*APOE* ε4+ and *COMT* val+). Last, we will repeat analyses for QOL.

Given the five assessments (baseline, every 12 months up to 60 months) and expected sample sizes for the levels of the modifiable and non-modifiable factors of interest (e.g., multi-morbidity, *APOE, COMT*, physical activity, and cognitive stimulation), we will have 80% power to detect small to moderate effect sizes for comparisons with respect to the primary cognitive domain at 60 months, at a significance level of 0.05. The mean differences will range from 0.25 SDs (e.g., for the comparison of high vs. low multi-morbidity levels) to 0.36 SDs (e.g., for the comparison of high vs. low physical activity). We will be able to detect smaller effect sizes with 80% power at the other time points where the expected sample sizes are larger. Given the large effect seen for the APOE ε4 genotype in our preliminary analyses, we will have >95% power (at alpha=.05) to detect changes in cognitive function by genotype. For the stratified analyses by treatment group (survivors vs. controls), we will have 80% power to detect small to moderate effect sizes of modifiable and non-modifiable factors on cognitive function at 60 months, ranging from 0.36 to 0.53 SDs, at a significance level of .05.

Aim #3. Assess inflammation as a potential mechanism for cognitive decline. H3a: Levels of circulating inflammatory markers (CRP, IL6, and sTNFRII) will co-vary with trajectories of cognition; and H3b: Inflammation will mediate the protective effect of physical activity and risk of multi-morbidity on cognitive decline.

Log transformations are expected to be necessary for analyses of inflammatory biomarker concentrations. As in other aims, our primary cognitive outcome is based on neuropsychological testing; we will also examine how inflammation relates to secondary outcomes, including self-reported cognition and conversion to MCI. We will consider covariates such as sleep, fatigue, BMI, etc. in these analyses. Also, since cancer and its treatments affect inflammation, we will consider stage, surgery, radiation, and systemic therapy in survivor-only analyses. Similar to Aim 1, we will use MLMs to evaluate how each inflammation marker co-varies with trajectories of cognition. We will include subject-level random effects and run models treating the markers of inflammation as time-varying covariates to determine if changes in inflammation co-vary with changes in cognitive performance. For the second part of the aim, we will perform longitudinal mediation analyses [289] to explore how inflammation mediates over time the relationship between changes in levels of physical activity (or multi-morbidity) and trajectories of cognition. In these models, we will apply a latent difference score approach to estimate the direct effects of physical activity (considering season if needed) on changes in cognition, and indirect effects acting through changes in inflammation. These models have the advantage of allowing changes between time intervals (e.g., from baseline to 12 months or 36 months to 48 months) to be different and for the roles of the mediators to change dynamically over time. Last, we will evaluate independent contributions of each marker in multiple mediator models. We will examine correlations between inflammatory markers to evaluate whether creating a composite score will be reasonable in secondary analyses. [290]

For analyses of the extent to which inflammation covaries with cognition, we have 80% power to detect correlations of at least +0.16 within a single exposure group (chemotherapy, hormonal, control). These values are smaller than the correlation reported by Ganz and colleagues[265] (r = -.34) between changes in proinflammatory cytokines (e.g., sTNF-RII) and changes in memory complaints. For the power for mediation analyses, we used methods of Vittinghof et. al.[291] implemented in R by Qiu. [292] In our sample, we have 80% power to detect a reduction of 13% in the total effect of changes in physical activity on changes in cognitive performance among all participants, and a reduction of 20% for the within exposure group analyses.

Aim #4: To use neuroimaging to assess structural and functional effects of cancer treatment.

MRI data analysis will use a combination of data analysis software packages including Statistical Parametric Mapping (SPM). Statistical analyses will be performed to examine group differences related to case vs. control status. Results for imaging cases will be compared to their own prior pre-treatment baseline studies (if available) and matched controls at yoked time points. Correction for Multiple Comparisons will use Gaussian random field theory, which takes into account not only the multiplicity of simultaneous tests but also the spatial smoothness of the data.[219] The parameter estimate maps from the first-stage (single-subject) analysis will also be used in an ROI analysis.

10.0   DATA MANAGEMENT

The research staff will be responsible under the direction of the PIs for data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordination of the activities of the protocol study team. Research staff will receive training in data collection and management; all staff will sign confidentiality agreements and will maintain human subjects certification.

Patients and controls will be assigned a unique study identification number (ID) that includes a code for the study site, physician (for the cancer patients), case/control status, and a randomized number.

Data will be managed through Georgetown University and entered by individual recruitment sites. Registration information, as well as consent information, neuropsychological test scores, APOE and COMT test results, inflammatory biomarkers, clinical variables, interview responses and physician survey data will be captured through a secure, central electronic data capture system (EDC) managed and maintained through Georgetown. The data system will have logical checks and error codes for out of range values. The program will not allow the operator to exit without saving the data.

All recruitment sites will be required to maintain hard copies of all study source documents. The PIs will maintain the hard copy forms with the link between ID number and patient name in a separate locked file.

Data and applications will be stored on secure servers managed by the Georgetown University Information (UIS) or a UIS-approved vendor. In all cases servers are secured and maintained using industry-standard best practices, including twenty-four hour a day security, failover protection, power backup, environmental controls, fire suppression, and nightly off-site back-ups. User access will be controlled via ID/password authentication, and users may only be granted access with the approval of authorized study management personnel with authority to grant permissions. Administrator privileges to the systems are tightly controlled and monitored. UIS and its vendors use security systems that are HIPAA-compliant.

If a subject chooses to have their blood drawn at home by a third party trained phlebotomist, research staff will schedule the appointment through the secure and HIPAA compliant client portal.

No reports will identify patients or physicians by name in reports or publications.

10.1 Training and Quality Assurance

The project coordinator will ensure that all staff are trained in study procedures. Staff will undergo online completion of a course on human subjects' research. Training for neurocognitive testing will be coordinated by Dr. Root. Training for interviews and chart reviews will be led by Georgetown. All staff will use a project field manual with detailed instructions on all study procedures to ensure that we have standard procedures. We will have the research staff from each site talk on monthly conference calls convened by the project coordinator to discuss issues in data collection.

In order to ensure that subject eligibility procedures are being followed, this study has a checklist for eligibility. Study personnel use this checklist to ensure all subjects approached for participation are eligible. While filling out follow-up eligibility checklists, study staff will ask the participant for up to three alternate contacts at each time point.

Project staff will audit these checklists on a regular basis to ensure participants meet eligibility criteria. In terms of questionnaire data collected, regular checks are performed of data collected to ensure that questionnaires completed by participants contain all study items. Weekly reports will be generated to monitor patient accruals and completeness of registration and interview data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action.

Random-sample data quality and protocol compliance audits will be conducted by the study team, at a minimum of two times per year, more frequently if indicated.

The training for patient recruitment, consenting, interviews, records review and cognitive testing will include a multi-day session at the start of the project and will include modules on: 1) the study, its design, research ethics and procedures for obtaining informed consent; 2) background material on breast cancer and medical terms; 3) cultural sensitivity; 4) interacting with older patients and controls; 5) data collection procedures and maintenance of study forms and data security; 6) interviewing techniques; and 7) cognitive testing procedures. For interview training, we include didactic sessions, practice obtaining consent and interviewing volunteers, being videotaped conducting an interview, and having that session reviewed by trainers. We will have volunteers role-play difficult situations. Staff will also receive training and practice on the REDcap database. The coordinator will ensure that data are complete and that staff receive feedback on any systematic errors in use of the system. The coordinator will listen in on telephone interviews (or in-person) periodically (with knowledge of the patients) to ensure fidelity to the protocol. Training for review of the medical records will include education about cancer treatment, practice completing the forms using de-identified medical records, re-reviewing each other's abstractions, and review of completeness and accuracy.

To assure that all neuropsychological evaluations are administered and scored in a reliable and consistent fashion across sites and examiners, extensive training procedures will be employed for study staff under the direction of Dr. Root. Within the training, most of the time will be dedicated to cognitive testing procedures. All examiners will be required to review and study training materials, including written administration and scoring guidelines and a training video of two complete "gold-standard" mock examinations. After studying these materials, examiners will practice administering and scoring the neuropsychological battery several times, with questions and answers regarding administration and scoring reviewed. Following training, each examiner

will submit a videotape of a practice protocol, which will be evaluated for examiner behavior/rapport, administration instructions and scoring accuracy. Examiners will receive comprehensive written and oral feedback on their practice case. If the examiner is not deemed ready to begin testing, additional training and a repeat video evaluation will be conducted and rated. Examiners will submit a videotape of test administration every six months for review by Dr. Root for the first year. In order to maintain consistency throughout the project, any questions regarding administration and scoring procedures will be posted and answered by Dr. Root via email. In addition, a sub-sample of subjects' test protocols will be scored a second time by another staff member at the same site. Inconsistencies will be discussed and if a consensus cannot be reached by the two scorers, the question will be posted for a final determination by Dr. Root.

10% of all test files will be reviewed on a regular basis for scoring, appropriate notations and record form completion, and data entry. Testers will receive feedback on any errors with the specific action required to correct the error. Each file audited will be checked for scoring errors, correct form use (which form used and appropriately labeled with date and ID#), appropriate notations (e.g., when queries were made, error correction), and to ensure the record forms were appropriately entered.

10.2 Data Sharing

All data will be available for use by outside investigators after review by the investigators. All work will be HIPAA compliant and no patient identifying information will be shared as per both IRB regulations and the Privacy Rule under HIPAA regulations. No protected health information, including personally identifiable information such as name, address, telephone, medical record number, or other identifying information will be shared outside of the research team.

We will invite other investigators not associated with the study to also analyze data that we have collected, as we see this study as an important resource for examining issues in care of older breast cancer patients. Any such requests from non-study investigators will be reviewed by the investigators, to ensure that it does not conflict with planned analyses, is otherwise respectful of the study participants, and complies with relevant IRB and HIPAA regulations.

We will make study data available to other investigators under data sharing agreements that ensure that the data will be used only for research purposes, that any individual participant's data will not be disseminated, that the data will not be used to identify an individual participant, that data will be protected under appropriate security measures including encryption and password protection, and that the data will be destroyed or returned to us upon completion of relevant analyses. If appropriate, we will also determine whether at least one study investigator should be involved scientifically in any projects that result from data sharing requests.

11.0   PROTECTION OF HUMAN SUBJECTS

Prior to enrollment the risks, benefits, and study objectives will be reviewed with each participant. There are no specific benefits to participants, and the risks are limited to those of phlebotomy and potential mild psychological distress as a result of completing the assessment battery.

Some minor physical pain may result from having the blood sample drawn. The overall physical risks associated with drawing blood for laboratory tests, such as momentary local pain and bruising are minimal, but will be explained to subjects. Should a participant require medical assistance, the oncologist on-call will be notified. Blood will be drawn by an experienced phlebotomist who is familiar with and practices standard precautions when drawing blood.

Additionally, it is possible that some patients may find some of the neuropsychological and psychological tests difficult to complete, and this may be associated with mild, transient psychological distress. Minimal risk of psychological distress may also be posed by study questions that ask participants to identify their current problems. However, since study items were chosen to reflect what are likely to be existing concerns, the present study is not expected to markedly increase participants' psychological distress above their routine concerns. Patients may refuse to answer questions that they find distressing.

Informed consent will be obtained and documented according to institutional policy. No patient identifiers will be used in any reports or publications that result from this study. Patients may terminate participation in the study at any time, although information that has already been acquired will not be removed from the overall analysis. Any hard copy records containing patient identifiers will be maintained in a secure location. Electronic records will be maintained on Georgetown, MSKCC, Moffitt, COH (discontinued study visits 11/2021), HUMC (discontinued study visits 1/2020) and IU servers, with password protected log-on and secure back-ups per procedures. Appropriate authority for review of medical records will be obtained by means of the Research Authorization.

We will identify breast cancer patients or controls who either: 1) screen positive for clinical depression on the CES-D (based on score of 16 or above), 2) have high scores on anxiety scales (>2 SD), 3) show moderate or severe cognitive declines at the follow-up, or 4) elicit any concerns by the study staff. We will refer these participants to the designated study clinicians at each site from our study team - Dr. Tim Ahles (at MSKCC), Dr. Scott Turner (neurologist at LCCC) and Dr. Kimberly Davis (psychologist at LCCC) and on-call clinicians at COH (discontinued study visits 11/2021), Moffitt, HUMC (discontinued study visits 1/2020) and IU. They will evaluate the participant and refer for clinical care if needed. We will also forward the relevant study information (with explicit written permission) to the participant's physicians (oncology team if applicable and primary care providers). The details of protection against risk are further detailed for each study procedure.

1. Overall burden-We have designed the data collection to minimize burden to participants. For example, we will attempt to collect blood at times when patients are otherwise scheduled to come to the hospital for other reasons, or to ease subject burden, they can choose to have their blood drawn at home by a third party trained phlebotomist. The battery can be given over landline, smartphone, tablet or computer to accommodate the subjects' access to modes of administration.

We also provide the option of staggering the telephone interviews and cognitive testing to minimize time that participants must spend at any one time. Women will receive 50 cash or gift card for their time and travel for each assessment. Overall, we think that the participant burden is reasonable.

Women who agree to participate in the co-calibration period and complete both the in-person battery and the remote battery will receive an additional 25 as compensation for their time and effort on the remote battery.

2. Genetic and inflammatory biomarker testing-The main risk of undergoing venipuncture to obtain blood for this study is mild discomfort and the possibility of bruising. They will have the subject sitting in a comfortable blood drawing chair, explain the procedure, and be as gentle as possible. They will apply gentle pressure to the site after the blood draw to stop bleeding and minimize bruising. These are the same procedures used in our sites' laboratories, so we expect to minimize

risk. Standard infection control/sterile procedures will be used in all blood and saliva testing and handling procedures for the protection of the subject and the research staff Another potential risk associated with having blood or saliva drawn for genetic testing is that it might create anxiety about the results. Participants will be told that the test is only used for research at this point in time and that we will not provide results.

3. Neuropsychological testing-The main risks associated with completing the test battery are fatigue and mild performance anxiety. To avoid fatigue, we have selected tests that take 30-55 minutes to complete, compared to standard 2-hour batteries; tests were selected for ease in older populations. To minimize any anxiety, the research staff will explain the study rationale, describe procedures, and put women at their ease. Women will be told that there are no wrong answers, only that we want to know how they are doing at the time of testing. We will also assure women that their information will not be shared with anyone (except as below for problems) and that their names will not be used. All materials will be labeled with study ID numbers.

Staff will undergo rigorous training so that they are familiar with concerns and needs of older women. Our consumer advocate will participate in this training. Our staff is experienced, will undergo rigorous training and will be working in existing testing centers that have experience in conducting these exams and in putting subjects at ease, so that these measures should be very effective.

If women show moderate or severe cognitive impairment or decline on follow-up testing, they will be referred for evaluation to the site study clinician (e.g., Dr. Ahles at MSKCC, Dr. Turner or Dr. Davis at Georgetown) and on-call clinicians at COH (discontinued study visits 11/2021), Moffitt, HUMC (discontinued study visits 1/2020) and IU. The study clinician will evaluate the participant and make appropriate referrals; women will be asked for permission to share results with their primary care provider and (for patients) oncology team if indicated.

4. Interviews-Most women enjoy these interviews, but some women may feel a bit anxious about talking about their cancer experience (for cases); friend controls could also be a bit anxious because of their friend's cancer. We will use trained interviewers; the same interviewer will talk to women for each of the interviews (baseline, every 12 months up to 60- month). This familiarity and continuity should decrease any discomfort. Women will also be told that they do not have to answer any questions that they are uncomfortable with and that they can take a break if they need to. We will also schedule interviews at times that are convenient for women so that they are comfortable and undisturbed and can talk in private. Women will be told that we only use study ID numbers on the surveys and that they will not be identified by name. In our past studies in this age group, women were able to easily complete similar interviews and found them and the staff very pleasant. In the rare instance that the interview uncovers problems (e.g., scores on the CES-D in the range of clinical depression based on score of 16 or above) women will be referred to our study clinicians for evaluation and any needed referrals. During routine weekly meetings, the interviewers will also discuss participants that they felt had any other difficulties needing attention by the team.

5. Neuroimaging-Some women may feel anxious about the requirements of neuroimaging, which includes lying still in the scanner for approximately 60 minutes. To attenuate any fears, subjects have the ability to visit the imaging lab prior to their participation to lay in a mock scanner that allows them to understand and feel comfortable with the process. Subjects will also be in constant visual and verbal contact with research staff and will have access to television and movies in the scanner to make them more comfortable.

Since the MRI technique is non-invasive, there are few potential risks associated with this technique. It uses powerful magnetic fields and weak electromagnetic radiation, which have not been associated with significant adverse biological effects in patients. The 3.0T MRI system meets FDA requirements for field strength, gradient switching and RF power disposition for all acquisitions used in the proposed research. Some possible risks include anxiety in the scanner and noise during the MRI experiments. Due to the small bore of the scanner, very claustrophobic subjects may not tolerate the confinement in the magnet and the head coil. Subjects will be in visual and verbal contact with the experimenter throughout the scan and can be removed quickly at their request. Some subjects have experienced dizziness or a metallic taste if they move their heads rapidly in the magnet. This, however, is only temporary and does not occur if the head is still. Acoustical noise is generated by the charging and discharging of the gradient coils, which create the magnetic fields used to generate an image. Generally, this is not a significant problem in clinical scanners, but we will take the added precautions of providing the subjects with earplugs that reduce acoustic noise >30dB. All possible measures will be taken to educate research personnel concerning the dangers of metallic projectiles in the magnet room and any individuals entering the magnet room will be thoroughly screening for ferromagnetic material.

6. Physician Assessment Form-Most physicians are very busy, so we have designed this one-time survey to be as short (15-20 minutes) and easy as possible. There are no risks to the physicians in completing this, except any minimal inconvenience. We allow them to fax the survey back, or to complete the survey over the phone if this is more convenient. We have gotten excellent responses in our prior work (>95% completion), so we expect that these procedures are adequate.

7. Actigraphy (Motionlogger): Most women are familiar with physical activity and sleep monitors with the popularity of Fitbits, etc. We expect women will enjoy this aspect of the study. Study staff will help women understand how the device should be worn and how it works and will be available to answer any questions they have throughout the week of use. The device is easy to use and is minimally burdensome. If women do not feel comfortable with this monitoring, they can opt out of wearing the device and are still eligible to participate.

11.1 Privacy

MSKCC: It is the responsibility of the Research Staff to ensure that protocol subjects receive the Center's Notice of Privacy Practices. If the subject has not received one, MSKCC personnel will provide a Notice of Privacy Practices and obtain acknowledgment before the subject participates in the study.

MSKCC's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board.

Georgetown University/ LCCC sites: Georgetown University may disclose health information for medical research that has been approved by one of the official research review boards, which has evaluated the research proposal and established standards to protect the privacy of the patient's health information. Georgetown may disclose the patient's health information to a researcher preparing to conduct a research project.

Moffitt: Moffitt may disclose protected health information collected for research purposes only as approved by the University of South Florida Institutional Review Board approved protocol

covering the research. Moffitt may disclose the patient's health information to a researcher preparing to conduct a research project.

COH (discontinued study visits 11/2021): COH may disclose protected health information collected for research purposes only as approved by the City of Hope Comprehensive Cancer Center Institutional Review Board approved protocol covering the research.

HUMC (discontinued study visits 1/2020): HUMC may disclose protected health information collected for research purposes only as approved by the HUMC Institutional Review Board approved protocol covering the research.

IU: IU may disclose protected health information collected for research purposes only as approved by the IU Institutional Review Board approved protocol covering the research.

11.2 Serious Adverse Event (SAE) Reporting

We do not expect any SAEs since this is not an intervention or treatment study. If women show moderate or severe cognitive impairment or decline on follow-up testing (based on testing) or depression (based on CES-D scores of 16 or above), they will be referred for evaluation to the site study clinician (e.g., Dr. Ahles at MSKCC, Dr. Turner or Dr. Davis at Georgetown) and on-call clinicians at COH (discontinued study visits 11/2021), Moffitt, HUMC (discontinued study visits 1/2020) and IU). The study clinician will evaluate the participant and make appropriate referrals; women will be asked for permission to share results with their primary care provider and (for patients) oncology team if indicated. We expect that our patients could be hospitalized related to their cancer. However, due to the nature of our questionnaire/interview study, we do not expect that these events will be related to our procedures, so will not consider these SAEs.

If there are any events that might be considered SAEs, they will be reported to the IRB as soon as possible but no later than 5 calendar days. The AE report will be delivered to the Institutional SAE Manager (307 East 63rd Street, 1st Floor at MSKCC, SW104 Med-Dent Building, 3900 Reservoir Road, NW, Washington, DC 20057 at Georgetown, 3702 Spectrum Blvd., Suite 155 UTA, Research Park at Moffitt, 1500 East Duarte Road, Modular 141 at COH, the eIRB of HUMC and the IRB of IU) containing the following information:

- Subject's name (generate the report with only underline initials if it will be sent outside of MSKCC, LCCC/Georgetown, Moffitt, COH, HUMC and IU)
- Medical record number
- Disease/histology (if applicable)
- Protocol number and title
- The date the adverse event occurred
- The adverse event
- Relationship of the adverse event to the study procedures
- If the AE was expected
- The severity of the AE
- Detailed text that includes the following information:
  - A explanation of how the AE was handled
  - A description of the subject's condition
  - Indication if the subject remains on the study
  - If an amendment will need to be made to the protocol and/or consent form, the PI's signature and the date it was signed are required on the completed report.

12.0   REFERENCE(S)

1. Nelson CJ, Nandy N, Roth AJ. Chemotherapy and cognitive deficits: mechanisms, findings, and potential interventions. *Palliat Support Care* 2007; 5(3):273-280.

2. Hurria A, Rosen C, Hudis C, Zuckerman E, Panageas KS, Lachs MS et al. Cognitive function of older patients receiving adjuvant chemotherapy for breast cancer: a pilot prospective longitudinal study. *J Am Geriatr Soc* 2006; 54(6):925-931.

3. Matsuda T, Takayama T, Tashiro M, Nakamura Y, Ohashi Y, Shimozuma K. Mild cognitive impairment after adjuvant chemotherapy in breast cancer patients-- evaluation of appropriate research design and methodology to measure symptoms. *Breast Cancer* 2005; 12(4):279-287.

4. Cimprich B, Ronis DL. Attention and symptom distress in women with and without breast cancer. *Nurs Res* 2001; 50(2):86-94.

5. Taillibert S, Voillery D, Bernard-Marty C. Chemobrain: is systemic chemotherapy neurotoxic? *Curr Opin Oncol* 2007; 19(6):623-627.

6. American Cancer Society. Breast Cancer Facts and Figures 2007-2008. Online Internet. Accessed February 1, 2008.

7. U.S.Census Bureau. Total Population by Age and Sex for the United States: 2000. Online Internet.   http://www.census.gov/population/cen2000/phc-t08/tab01.pdf. Accessed January 18, 2008.

8. U.S.Cancer Statistics Working Group. United States Cancer Statistics: 1999-2004 Incidence and Mortality Web-based Report. 2007. Atlanta: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute.

9. Stovall E. Introductions to the symposium for representatives of the American Society of Clinical Oncology and the Institute of Medicine. In: Hewitt M, Greenfield S, Stovall

E., editors. From cancer patient to cancer survivor: Lost in Transition. Washington, DC: National Acadamies Press, 2005: 7-55.

10. NIH Consensus Statement Online. Adjuvant therapy for breast cancer. http://consensus.nih.gov/, 1-23. 2000.

11. NCCN. Clinical practice guidelines in oncology. J Natl Comp Cancer Network http://www.nccn.org. 2008.

12. National Comprehensive Cancer Center Network. Practice guidelines: Management of psychosocial distress in cancer patients. NCCN presentation on patient distress. 1998.

13. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, Goldhirsch A, Untch M, Smith I et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. *N Engl J Med* 2005; 353(16):1659-1672.

14. Muss HB, Berry DA, Cirrincione C, Budman DR, Henderson IC, Citron ML et al. Toxicity of older and younger patients treated with adjuvant chemotherapy for node-positive breast cancer: the Cancer and Leukemia Group B Experience. *J Clin Oncol* 2007; 25(24):3699-3704.

15. Friedenberg RM. Dementia: one of the greatest fears of aging. *Radiology* 2003; 229(3):632-635.

16. West RL, Bagwell DK, Dark-Freudeman A. Self-Efficacy and Memory Aging: The Impact of a Memory Intervention Based on Self-Efficacy. *Neuropsychol Dev Cogn B Aging Neuropsychol Cogn* 2007;1-28.

17. Mandelblatt J, Schechter C, Yabroff KR, et al. Towards optimal screening strategies for older women: Costs, benefits and harms of breast cancer screening by age, biology and health status. J Gen Intern Med 20[6], 487-496. 2005.

18. Pathak DR, Osuch JR, He J. Breast carcinoma etiology: current knowledge and new insights into the effects of reproductive and hormonal risk factors in black and white populations. *Cancer* 2000; 88(5 Suppl):1230-1238.

19. Kornblith AB. Psychosocial adaptation of cancer survivors. New York N, editor. Oxford Univesity Press, 223-254. 1998.

20. Ahles TA, Saykin AJ, Noll WW, Furstenberg CT, Guerin S, Cole B et al. The relationship of APOE genotype to neuropsychological performance in long-term cancer

survivors treated with standard dose chemotherapy. *Psychooncology* 2003; 12(6):612-619.

21. Watters JM, Yau JC, O'Rourke K, Tomiak E, Gertler SZ. Functional status is well maintained in older women during adjuvant chemotherapy for breast cancer. *Ann Oncol* 2003; 14(12):1744-1750.

22. Satariano WA, Ragheb NE, Branch LG, Swanson GM. Difficulties in physical functioning reported by middle-aged and elderly women with breast cancer: a case-control comparison. *J Gerontol* 1990; 45(1):M3-11.

23. Martin M, Pienkowski T, Mackey J, Pawlicki M, Guastalla JP, Weaver C et al. Adjuvant docetaxel for node-positive breast cancer. *N Engl J Med* 2005; 352(22):2302-2313.

24. Hartman RE, Laurer H, Longhi L, Bales KR, Paul SM, McIntosh TK et al. Apolipoprotein E4 influences amyloid deposition but not cell loss after traumatic brain

injury in a mouse model of Alzheimer's disease. *J Neurosci* 2002; 22(23):10083-10087.

25. Laws SM, Clarnette RM, Taddei K, Martins G, Paton A, Hallmayer J et al. APOE-epsilon4 and APOE -491A polymorphisms in individuals with subjective memory loss. *Mol Psychiatry* 2002; 7(7):768-775.

26. Parasuraman R, Greenwood PM, Sunderland T. The apolipoprotein E gene, attention, and brain function. *Neuropsychology* 2002; 16(2):254-274.

27. Hogan M. Physical and cognitive activity and exercise for older adults: a review. *Int J Aging Hum Dev* 2005; 60(2):95-126.

28. Whalley LJ, Deary IJ, Appleton CL, Starr JM. Cognitive reserve and the neurobiology of cognitive aging. *Ageing Res Rev* 2004; 3(4):369-382.

29. Stern Y. The concept of cognitive reserve: a catalyst for research. *J Clin Exp Neuropsychol* 2003; 25(5):589-593.

30. Manly J, Schupe N, Tang M, Weiss C, Stern Y. Literacy and cognitive decline among ethinically diverse elders. In: Stern Y., editor. Cognitive Reserve. New York, NY: Taylor & Francis, 2006: 219-236.

31. Fotenos AF, Mintun MA, Snyder AZ, Morris JC, Buckner RL. Brain volume decline in aging: evidence for a relation between socioeconomic status, preclinical Alzheimer disease, and reserve. *Arch Neurol* 2008; 65(1):113-120.

32. Helzner EP, Scarmeas N, Cosentino S, Portet F, Stern Y. Leisure activity and cognitive decline in incident Alzheimer disease. *Arch Neurol* 2007; 64(12):1749-1754.

33. Strawbridge WJ, Shema SJ, Balfour JL, Higby HR, Kaplan GA. Antecedents of frailty over three decades in an older cohort. *J Gerontol B Psychol Sci Soc Sci* 1998; 53(1):S9-16.

34. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J et al. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci* 2001; 56(3):M146-M156.

35. Fried L, Solomon C, Shlipak M, Seliger S, Stehman-Breen C, Bleyer AJ et al. Inflammatory and prothrombotic markers and the progression of renal disease in elderly individuals. *J Am Soc Nephrol* 2004; 15(12):3184-3191.

36. Newman AB, Gottdiener JS, McBurnie MA, Hirsch CH, Kop WJ, Tracy R et al. Associations of subclinical cardiovascular disease with frailty. *J Gerontol A Biol Sci Med Sci* 2001; 56(3):M158-M166.

37. Mitnitski AB, Graham JE, Mogilner AJ, Rockwood K. Frailty, fitness and late-life mortality in relation to chronological and biological age. *BMC Geriatr* 2002; 2:1.

38. Carlson JE, Zocchi KA, Bettencourt DM, Gambrel ML, Freeman JL, Zhang D et al. Measuring frailty in the hospitalized elderly: concept of functional homeostasis. *Am J Phys Med Rehabil* 1998; 77(3):252-257.

39. Jacobsen PB, Donovan KA, Small BJ, Jim HS, Munster PN, Andrykowski MA. Fatigue after treatment for early stage breast cancer: a controlled comparison. *Cancer* 2007; 110(8):1851-1859.

40. Mehnert A, Scherwath A, Schirmer L, Schleimer B, Petersen C, Schulz-Kindermann F et al. The association between neuropsychological impairment, self-perceived cognitive deficits, fatigue and health related quality of life in breast cancer survivors following standard adjuvant versus high-dose chemotherapy. *Patient Educ Couns* 2007; 66(1):108-118.

41. O'Shaughnessy JA, Vukelja SJ, Holmes FA, Savin M, Jones M, Royall D et al. Feasibility of quantifying the effects of epoetin alfa therapy on cognitive function in

women with breast cancer undergoing adjuvant or neoadjuvant chemotherapy. *Clin Breast Cancer* 2005; 5(6):439-446.

42. Mandelblatt JS, Berg CD, Meropol NJ, Edge SB, Gold K, Hwang YT et al. Measuring and predicting surgeons' practice styles for breast cancer treatment in older women. *Med Care* 2001; 39(3):228-242.

43. Woo J, Goggins W, Sham A, Ho SC. Social determinants of frailty. *Gerontology* 2005; 51(6):402-408.

44. Ballantyne PJ. Social context and outcomes for the ageing breast cancer patient: considerations for clinical practitioners. *J Clin Nurs* 2004; 13(3a):11-21.

45. Woo J, Ho SC, Yu AL. Walking speed and stride length predicts 36 months dependency, mortality, and institutionalization in Chinese aged 70 and older. *J Am Geriatr Soc* 1999; 47(10):1257-1260.

46. Brunner EJ. Social and biological determinants of cognitive aging. *Neurobiol Aging* 2005; 26 Suppl 1:17-20.

47. Bender CM, Paraska KK, Sereika SM, Ryan CM, Berga SL. Cognitive function and reproductive hormones in adjuvant therapy for breast cancer: a critical review. *J Pain Symptom Manage* 2001; 21(5):407-424.

48. Jenkins V, Shilling V, Deutsch G, Bloomfield D, Morris R, Allan S et al. A 3-year prospective study of the effects of adjuvant treatments on cognition in women with early stage breast cancer. *Br J Cancer* 2006; 94(6):828-834.

49. Meyers CA, Byrne KS, Komaki R. Cognitive deficits in patients with small cell lung cancer before and after chemotherapy. *Lung Cancer* 1995; 12(3):231-235.

50. Silliman RA, Dukes KA, Sullivan LM, Kaplan SH. Breast cancer care in older women: Sources of information, social support and emotional health outcomes. *Cancer* 1998; 83:706-711.

51. Cassileth BR, Zupkis RV, Sutton-Smith K, et al. Information and participation preferences among cancer patients. *Ann Intern Med* 1980; 92:832-836.

52. Morris J, Ingham R. Choice of surgery for early breast cancer psychosocial considerations. *Soc Sci & Med* 1988; 27(11):1257-1262.

53. Kornblith AB, Herndon JE, Weiss RB, Zhang C, Zuckerman EL, Rosenberg S et al. Long-term adjustment of survivors of early-stage breast carcinoma, 20 years after adjuvant chemotherapy. *Cancer* 2003; 98(4):679-689.

54. Boyd CM, Darer J, Boult C, Fried LP, Boult L, Wu AW. Clinical practice guidelines and quality of care for older patients with multiple comorbid diseases: implications for pay for performance. *JAMA* 2005; 294(6):716-724.

55. Blaum CS, Ofstedal MB, Liang J. Low cognitive performance, comorbid disease, and task-specific disability: findings from a nationally representative survey. *J Gerontol A Biol Sci Med Sci* 2002; 57(8):M523-M531.

56. Schagen SB, van Dam FS, Muller MJ, Boogerd W, Lindeboom J, Bruning PF. Cognitive deficits after postoperative adjuvant chemotherapy for breast carcinoma. *Cancer* 1999; 85(3):640-650.

57. Cull A, Hay C, Love SB, Mackie M, Smets E, Stewart M. What do cancer patients mean when they complain of concentration and memory problems? *Br J Cancer* 1996; 74(10):1674-1679.

58. Hermelink K, Untch M, Lux MP, Kreienberg R, Beck T, Bauerfeind I et al. Cognitive function during neoadjuvant chemotherapy for breast cancer: results of a prospective, multicenter, longitudinal study. *Cancer* 2007; 109(9):1905-1913.

59. Mandelblatt J, Hadley J, Kerner J, et al. Patterns of breast carcinoma treatment in older women: Patient preferences and clinical and physician influences. *Cancer* 2000; 89(3):561-573.

60. Carlson MC, Fried LP, Xue QL, Bandeen-Roche K, Zeger SL, Brandt J. Association between executive attention and physical functional performance in community-dwelling older women. *J Gerontol B Psychol Sci Soc Sci* 1999; 54(5):S262-S270.

61. Wieneke M, Dienst E. Neuropsychological assessment of cognitive functioning following chemotherapy for breast cancer. *Psycho-Oncology* 1995; 4:61-66.

62. Anderson-Hanley C. Possible cognitive effects of systemic treatment for cancer: A meta-analysis. J Inter Neuro Soc 8, 254. 2002.

63. Brezden CB, Phillips KA, Abdolell M, Bunston T, Tannock IF. Cognitive function in breast cancer patients receiving adjuvant chemotherapy. *J Clin Oncol* 2000; 18(14):2695-2701.

64. Tchen N, Juffs HG, Downie FP, Yi QL, Hu H, Chemerynsky I et al. Cognitive function, fatigue, and menopausal symptoms in women receiving adjuvant chemotherapy for breast cancer. *J Clin Oncol* 2003; 21(22):4175-4183.

65. Wefel JS, Lenzi R, Theriault RL, Davis RN, Meyers CA. The cognitive sequelae of standard-dose adjuvant chemotherapy in women with breast carcinoma: results of a prospective, randomized, longitudinal trial. *Cancer* 2004; 100(11):2292-2299.

66. Ferrell BR, Dow KH, Grant M. Measurement of the quality of life in cancer survivors. *Qual Life Res* 1995; 4(6):523-531.

67. Ahles TA. Neuropsychological impact of systemic chemotherapy. National Cancer Advisory Board, NCI, February 21. 2005.

68. Silberfarb PM. Chemotherapy and cognitive defects in cancer patients. *Annu Rev Med* 1983; 34:35-46.

69. Kingma A, van Dommelen RI, Mooyaart EL, Wilmink JT, Deelman BG, Kamps WA. Slight cognitive impairment and magnetic resonance imaging abnormalities but normal

school levels in children treated for acute lymphoblastic leukemia with chemotherapy only. *J Pediatr* 2001; 139(3):413-420.

70. Espy KA, Moore IM, Kaufmann PM, Kramer JH, Matthay K, Hutter JJ. Chemotherapeutic CNS prophylaxis and neuropsychologic change in children with acute lymphoblastic leukemia: a prospective study. *J Pediatr Psychol* 2001; 26(1):1-9.

71. Walch S, Ahles T, Saykin A. Cognitive sequelae of treatment in children. 945. 1998: New York, NY-940.

72. Downie FP, Mar Fan HG, Houede-Tchen N, Yi Q, Tannock IF. Cognitive function, fatigue, and menopausal symptoms in breast cancer patients receiving adjuvant

chemotherapy: evaluation with patient interview after formal assessment. *Psychooncology* 2006; 15(10):921-930.

73. President's Cancer Panel. Cancer care issues in the United States: Quality of care, quality of life. National Cancer Program, National Cancer Institute, Washington, DC. 1999.

74. Ferguson RJ, Eastern Main Medical Center, McDonald BC, Saykin A., Ahles TA. Brain structure and function differences in monozygotic twins: possible effects of breast cancer chemotherapy. Journal of Clinical Oncology, editor. 2007.

75. Heflin LH, Meyerowitz BE, Hall P, Lichtenstein P, Johansson B, Pedersen NL et al. Cancer as a risk factor for long-term cognitive deficits and dementia. *J Natl Cancer Inst* 2005; 97(11):854-856.

76. Ahles TA, Saykin AJ, Furstenberg CT, Cole B, Mott LA, Titus-Ernstoff L et al. Quality of life of long-term survivors of breast cancer and lymphoma treated with standard-dose chemotherapy or local therapy. *J Clin Oncol* 2005; 23(19):4399-4405.

77. Ganz PA, Desmond KA, Leedham B, Rowland JH, Meyerowitz BE, Belin TR. Quality of life in long-term, disease-free survivors of breast cancer: a follow-up study. *J Natl Cancer Inst* 2002; 94(1):39-49.

78. Harder H, Cornelissen JJ, Van Gool AR, Duivenvoorden HJ, Eijkenboom WM, van den Bent MJ. Cognitive functioning and quality of life in long-term adult survivors of bone marrow transplantation. *Cancer* 2002; 95(1):183-192.

79. Logsdon RG, Gibbons LE, McCurry SM, Teri L. Assessing quality of life in older adults with cognitive impairment. *Psychosom Med* 2002; 64(3):510-519.

80. Schagen SB, van Dam FS. Does cognitive impairment after chemotherapy for breast cancer improve over time or does practice make perfect? *J Clin Oncol* 2006; 24(32):5170-5171.

81. Hurria A, Lachs M. Is cognitive dysfunction a complication of adjuvant chemotherapy in the older patient with breast cancer? *Breast Cancer Res Treat* 2007.

82. Keller JN. Age-related neuropathology, cognitive decline, and Alzheimer's disease. *Ageing Res Rev* 2006; 5(1):1-13.

83. Fischer P, Zehetmayer S, Bauer K, Huber K, Jungwirth S, Tragl KH. Relation between vascular risk factors and cognition at age 75. *Acta Neurol Scand* 2006; 114(2):84-90.

84. Kilander L, Nyman H, Boberg M, Lithell H. Cognitive function, vascular risk factors and education. A cross-sectional study based on a cohort of 70-year-old men. *J Intern Med* 1997; 242(4):313-321.

85. van Exel E, de Craen AJ, Gussekloo J, Houx P, Bootsma-van der Wiel A, Macfarlane PW et al. Association between high-density lipoprotein and cognitive impairment in the oldest old. *Ann Neurol* 2002; 51(6):716-721.

86. Helgeson VS, Snyder P, Seltman H. Psychological and physical adjustment to breast cancer over 4 years: identifying distinct trajectories of change. *Health Psychol* 2004; 23(1):3-15.

87. Ahles TA, Saykin AJ. Candidate mechanisms for chemotherapy-induced cognitive changes. *Nat Rev Cancer* 2007; 7(3):192-201.

88. Jansen CE, Miaskowski CA, Dodd MJ, Dowling GA. A meta-analysis of the sensitivity of various neuropsychological tests used to detect chemotherapy-induced cognitive impairment in patients with breast cancer. *Oncol Nurs Forum* 2007; 34(5):997-1005.

89. van Dam FS, Schagen SB, Muller MJ, Boogerd W, vd WE, Droogleever Fortuyn ME et al. Impairment of cognitive function in women receiving adjuvant treatment for high-risk breast cancer: high-dose versus standard-dose chemotherapy. *J Natl Cancer Inst* 1998; 90(3):210-218.

90. Castellon SA, Ganz PA, Bower JE, Petersen L, Abraham L, Greendale GA. Neurocognitive performance in breast cancer survivors exposed to adjuvant chemotherapy and tamoxifen. *J Clin Exp Neuropsychol* 2004; 26(7):955-969.

91. Ahles TA, Saykin AJ, Furstenberg CT, Cole B, Mott LA, Skalla K et al. Neuropsychologic impact of standard-dose systemic chemotherapy in long-term survivors of breast cancer and lymphoma. *J Clin Oncol* 2002; 20(2):485-493.

92. Olin JJ. Cognitive function after systemic therapy for breast cancer. *Oncology (Williston Park)* 2001; 15(5):613-618.

93. Falleti MG, Sanfilippo A, Maruff P, Weih L, Phillips KA. The nature and severity of cognitive impairment associated with adjuvant chemotherapy in women with breast cancer: a meta-analysis of the current literature. *Brain Cogn* 2005; 59(1):60-70.

94. Stewart A, Bielajew C, Collins B, Parkinson M, Tomiak E. A meta-analysis of the neuropsychological effects of adjuvant chemotherapy treatment in women treated for breast cancer. *Clin Neuropsychol* 2006; 20(1):76-89.

95. Bender CM. Chemotherapy may have small to moderate negative effects on cognitive functioning. *Cancer Treat Rev* 2006; 32(4):316-319.

96. Donovan KA, Small BJ, Andrykowski MA, Schmitt FA, Munster P, Jacobsen PB. Cognitive functioning after adjuvant chemotherapy and/or radiotherapy for early-stage breast carcinoma. *Cancer* 2005; 104(11):2499-2507.

97. Scherwath A, Mehnert A, Schleimer B, Schirmer L, Fehlauer F, Kreienberg R et al. Neuropsychological function in high-risk breast cancer survivors after stem-cell

supported high-dose therapy versus standard-dose chemotherapy: evaluation of long-term treatment effects. *Ann Oncol* 2006; 17(3):415-423.

98. Troy L, McFarland K, Littman-Power S, Kelly BJ, Walpole ET, Wyld D et al. Cisplatin-based therapy: a neurological and neuropsychological review. *Psychooncology* 2000; 9(1):29-39.

99. Blasiak J, Arabski M, Krupa R, Wozniak K, Rykala J, Kolacinska A et al. Basal, oxidative and alkylative DNA damage, DNA repair efficacy and mutagen sensitivity in breast cancer. *Mutat Res* 2004; 554(1-2):139-148.

100. Migliore L, Fontana I, Trippi F, Colognato R, Coppede F, Tognoni G et al. Oxidative DNA damage in peripheral leukocytes of mild cognitive impairment and AD patients. *Neurobiol Aging* 2005; 26(5):567-573.

101. Rolig RL, McKinnon PJ. Linking DNA damage and neurodegeneration. *Trends Neurosci* 2000; 23(9):417-424.

102. Dietrich J, Han R, Yang Y, Mayer-Proschel M, Noble M. CNS progenitor cells and oligodendrocytes are targets of chemotherapeutic agents in vitro and in vivo. *J Biol* 2006; 5(7):22.

103. Quinn CT, Kamen BA. A biochemical perspective of methotrexate neurotoxicity with insight on nonfolate rescue modalities. *J Investig Med* 1996; 44(9):522-530.

104. Madhyastha S, Somayaji SN, Rao MS, Nalini K, Bairy KL. Hippocampal brain amines in methotrexate-induced learning and memory deficit. *Can J Physiol Pharmacol* 2002; 80(11):1076-1084.

105. Saykin AJ, Ahles TA, McDonald BC. Mechanisms of chemotherapy-induced cognitive disorders: neuropsychological, pathophysiological, and neuroimaging perspectives. *Semin Clin Neuropsychiatry* 2003; 8(4):201-216.

106. Stemmer SM, Stears JC, Burton BS, Jones RB, Simon JH. White matter changes in patients with breast cancer treated with high-dose chemotherapy and autologous bone marrow support. *AJNR Am J Neuroradiol* 1994; 15(7):1267-1273.

107. Inagaki M, Yoshikawa E, Matsuoka Y, Sugawara Y, Nakano T, Akechi T et al. Smaller regional volumes of brain gray and white matter demonstrated in breast cancer survivors exposed to adjuvant chemotherapy. *Cancer* 2007; 109(1):146-156.

108. Saykin A. Altered brain activation following systemic chemotherapy for breast cancer: Interim analysis from a prospective study. 34th Annual Meeting of International Neuropsychological Society, Boston, MA. 2006.

109. Tannock IF, Ahles TA, Ganz PA, van Dam FS. Cognitive impairment associated with chemotherapy for cancer: report of a workshop. *J Clin Oncol* 2004; 22(11):2233-2239.

110. Paganini-Hill A, Clark LJ. Preliminary assessment of cognitive function in breast cancer patients treated with tamoxifen. *Breast Cancer Res Treat* 2000; 64(2):165-176.

111. Schilling V, Jenkins V, Morris R. The effects of adjuvant chemotherapy on cognition in women with breast cancer: Preliminary results of an observational study. *The Breast* 2005; 14:142-150.

112. Ciocca DR, Roig LM. Estrogen receptors in human nontarget tissues: biological and clinical implications. *Endocr Rev* 1995; 16(1):35-62.

113. Shilling V, Jenkins V, Fallowfield L, Howell A. The effects of oestrogens and anti-oestrogens on cognition. *Breast* 2001; 10(6):484-491.

114. Sherwin BB. Estrogen and cognitive aging in women. *Neuroscience* 2006; 138(3):1021-1026.

115. Kawas C, Resnick S, Morrison A, Brookmeyer R, Corrada M, Zonderman A et al. A prospective study of estrogen replacement therapy and the risk of developing Alzheimer's disease: the Baltimore Longitudinal Study of Aging. *Neurology* 1997; 48(6):1517-1521.

116. Yaffe K, Sawaya G, Lieberburg I, Grady D. Estrogen therapy in postmenopausal women: effects on cognitive function and dementia. *JAMA* 1998; 279(9):688-695.

117. Paganini-Hill A, Henderson VW. Estrogen replacement therapy and risk of Alzheimer disease. *Arch Intern Med* 1996; 156(19):2213-2217.

118. Ross JL, Roeltgen D, Stefanatos GA, Feuillan P, Kushner H, Bondy C et al. Androgen-responsive aspects of cognition in girls with Turner syndrome. *J Clin Endocrinol Metab* 2003; 88(1):292-296.

119. Ross JL, Roeltgen D, Feuillan P, Kushner H, Cutler GB, Jr. Effects of estrogen on nonverbal processing speed and motor function in girls with Turner's syndrome. *J Clin Endocrinol Metab* 1998; 83(9):3198-3204.

120. Ross JL, Roeltgen D, Kushner H, Wei F, Zinn AR. The Turner syndrome-associated neurocognitive phenotype maps to distal Xp. *Am J Hum Genet* 2000; 67(3):672-681.

121. Ross JL, Stefanatos GA, Kushner H, Zinn A, Bondy C, Roeltgen D. Persistent cognitive deficits in adult women with Turner syndrome. *Neurology* 2002; 58(2):218-225.

122. O'Malley CA, Hautamaki RD, Kelley M, Meyer EM. Effects of ovariectomy and estradiol benzoate on high affinity choline uptake, ACh synthesis, and release from rat cerebral cortical synaptosomes. *Brain Res* 1987; 403(2):389-392.

123. Singh M, Meyer EM, Millard WJ, Simpkins JW. Ovarian steroid deprivation results in a reversible learning impairment and compromised cholinergic function in female Sprague-Dawley rats. *Brain Res* 1994; 644(2):305-312.

124. Sumner BE, Grant KE, Rosie R, Hegele-Hartung C, Fritzemeier KH, Fink G. Effects of tamoxifen on serotonin transporter and 5-hydroxytryptamine(2A) receptor binding sites

and mRNA levels in the brain of ovariectomized rats with or without acute estradiol replacement. *Brain Res Mol Brain Res* 1999; 73(1-2):119-128.

125. McEwen BS, Woolley CS. Estradiol and progesterone regulate neuronal structure and synaptic connectivity in adult as well as developing brain. *Exp Gerontol* 1994; 29(3-4):431-436.

126. Phillips KA, Bernhard J. Adjuvant breast cancer treatment and cognitive function: current knowledge and research directions. *J Natl Cancer Inst* 2003; 95(3):190-197.

127. Srivastava RA, Bhasin N, Srivastava N. Apolipoprotein E gene expression in various tissues of mouse and regulation by estrogen. *Biochem Mol Biol Int* 1996; 38(1):91-101.

128. Lee J. Understanding cognitive reserve through genetic epidemiology. In: Stern Y., editor. Cognitive Reserve. New York, NY: Taylor & Francis, 2006: 5-34.

129. Monastero R, Cefalu AB, Camarda C, Noto D, Camarda LK, Caldarella R et al. Association of estrogen receptor alpha gene with Alzheimer's disease: a case-control study. *J Alzheimers Dis* 2006; 9(3):273-278.

130. Yaffe K, Haan M, Byers A, Tangen C, Kuller L. Estrogen use, APOE, and cognitive decline: evidence of gene-environment interaction. *Neurology* 2000; 54(10):1949-1954.

131. Jenkins V, Atkins L, Fallowfield L. Does endocrine therapy for the treatment and prevention of breast cancer affect memory and cognition? *Eur J Cancer* 2007; 43(9):1342-1347.

132. Sonntag WE, Ramsey M, Carter CS. Growth hormone and insulin-like growth factor-1 (IGF-1) and their influence on cognitive aging. *Ageing Res Rev* 2005; 4(2):195-212.

133. Bodles AM, Barger SW. Cytokines and the aging brain - what we don't know might help us. *Trends Neurosci* 2004; 27(10):621-626.

134. Hedden T, Gabrieli JD. Healthy and pathological processes in adult development: new evidence from neuroimaging of the aging brain. *Curr Opin Neurol* 2005; 18(6):740-747.

135. Head D, Snyder AZ, Girton LE, Morris JC, Buckner RL. Frontal-hippocampal double dissociation between normal aging and Alzheimer's disease. *Cereb Cortex* 2005; 15(6):732-739.

136. Lautenschlager NT, Almeida OP. Physical activity and cognition in old age. *Curr Opin Psychiatry* 2006; 19(2):190-193.

137. Maccormick RE. Possible acceleration of aging by adjuvant chemotherapy: a cause of early onset frailty? *Med Hypotheses* 2006; 67(2):212-215.

138. Cimprich B, So H, Ronis DL, Trask C. Pre-treatment factors related to cognitive functioning in women newly diagnosed with breast cancer. *Psychooncology* 2005; 14(1):70-78.

139. Reid-Arndt SA. The potential for neuropsychology to inform functional outcomes research with breast cancer survivors. *NeuroRehabilitation* 2006; 21(1):51-64.

140. Deater-Deckard K, Mayr U. Cognitive change in aging: identifying gene-environment correlation and nonshared environment mechanisms. *J Gerontol B Psychol Sci Soc Sci* 2005; 60 Spec No 1:24-31.

141. McAllister TW, Ahles TA, Saykin AJ, Ferguson RJ, McDonald BC, Lewis LD et al. Cognitive effects of cytotoxic cancer chemotherapy: predisposing risk factors and potential treatments. *Curr Psychiatry Rep* 2004; 6(5):364-371.

142. Small BJ, Rosnick CB, Fratiglioni L, Backman L. Apolipoprotein E and cognitive performance: a meta-analysis. *Psychol Aging* 2004; 19(4):592-600.

143. Bathum L, Christiansen L, Jeune B, Vaupel J, McGue M, Christensen K. Apolipoprotein e genotypes: relationship to cognitive functioning, cognitive decline, and survival in nonagenarians. *J Am Geriatr Soc* 2006; 54(4):654-658.

144. Caselli RJ, Reiman EM, Osborne D, Hentz JG, Baxter LC, Hernandez JL et al. Longitudinal changes in cognition and behavior in asymptomatic carriers of the APOE e4 allele. *Neurology* 2004; 62(11):1990-1995.

145. Negash S, Petersen LE, Geda YE, Knopman DS, Boeve BF, Smith GE et al. Effects of ApoE genotype and mild cognitive impairment on implicit learning. *Neurobiol Aging* 2007; 28(6):885-893.

146. Haan MN, Shemanski L, Jagust WJ, Manolio TA, Kuller L. The role of APOE epsilon4 in modulating effects of other risk factors for cognitive decline in elderly persons. *JAMA* 1999; 282(1):40-46.

147. Roses AD, Saunders AM, Huang Y, Strum J, Weisgraber KH, Mahley RW. Complex disease-associated pharmacogenetics: drug efficacy, drug safety, and confirmation of a pathogenetic hypothesis (Alzheimer's disease). *Pharmacogenomics J* 2007; 7(1):10-28.

148. Risner ME, Saunders AM, Altman JF, Ormandy GC, Craft S, Foley IM et al. Efficacy of rosiglitazone in a genetically defined population with mild-to-moderate Alzheimer's disease. *Pharmacogenomics J* 2006; 6(4):246-254.

149. Malhotra AK, Kestler LJ, Mazzanti C, Bates JA, Goldberg T, Goldman D. A functional polymorphism in the COMT gene and performance on a test of prefrontal cognition. *Am J Psychiatry* 2002; 159(4):652-654.

150. Goldberg TE, Weinberger DR. Genes and the parsing of cognitive processes. *Trends Cogn Sci* 2004; 8(7):325-335.

151. Bartres-Faz D, Junque C, Serra-Grabulosa JM, Lopez-Alomar A, Moya A, Bargallo N et al. Dopamine DRD2 Taq I polymorphism associates with caudate nucleus volume

and cognitive performance in memory impaired subjects. *Neuroreport* 2002; 13(9):1121-1125.

152. Tsai SJ, Yu YW, Lin CH, Chen TJ, Chen SP, Hong CJ. Dopamine D2 receptor and N-methyl-D-aspartate receptor 2B subunit genetic variants and intelligence. *Neuropsychobiology* 2002; 45(3):128-130.

153. Marzolini C, Paus E, Buclin T, Kim RB. Polymorphisms in human MDR1 (P-glycoprotein): recent advances and clinical relevance. *Clin Pharmacol Ther* 2004; 75(1):13-33.

154. Siddiqui A, Kerb R, Weale ME, Brinkmann U, Smith A, Goldstein DB et al. Association of multidrug resistance in epilepsy with a polymorphism in the drug-transporter gene ABCB1. *N Engl J Med* 2003; 348(15):1442-1448.

155. Yaffe K, Barrett-Connor E, Lin F, Grady D. Serum lipoprotein levels, statin use, and cognitive function in older women. *Arch Neurol* 2002; 59(3):378-384.

156. Lopez OL, Jagust WJ, Dulberg C, Becker JT, DeKosky ST, Fitzpatrick A et al. Risk factors for mild cognitive impairment in the Cardiovascular Health Study Cognition Study: part 2. *Arch Neurol* 2003; 60(10):1394-1399.

157. Irie F, Fitzpatrick AL, Lopez OL, Kuller LH, Peila R, Newman AB et al. Enhanced risk for Alzheimer disease in persons with type 2 diabetes and APOE epsilon4: the Cardiovascular Health Study Cognition Study. *Arch Neurol* 2008; 65(1):89-93.

158. Kalmijn S, Feskens EJ, Launer LJ, Kromhout D. Cerebrovascular disease, the apolipoprotein e4 allele, and cognitive decline in a community-based study of elderly men. *Stroke* 1996; 27(12):2230-2235.

159. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975; 12(3):189-198.

160. Wilkinson GS. WRAT-3: The Wide Range Achievement Test administration manual. Wilmington, DE. 1993.

161. Wilkinson G, Robertson G. Wide Range Achievement Test 4 (WRAT4). Lutz, FL: Psychological Assessment Resources, 2006.

162. Manly JJ, Schupf N, Tang MX, Stern Y. Cognitive decline and literacy among ethnically diverse elders. *J Geriatr Psychiatry Neurol* 2005; 18(4):213-217.

163. Ashendorf L, Jefferson AL, O'Connor MK, Chaisson C, Green RC, Stern RA. Trail Making Test errors in normal aging, mild cognitive impairment, and dementia. *Arch Clin Neuropsychol* 2008; 23(2):129-137.

164. Elderkin-Thompson V, Boone KB, Kumar A, Mintz J. Validity of the Boston qualitative scoring system for the Rey-Osterrieth complex figure among depressed elderly patients. *J Clin Exp Neuropsychol* 2004; 26(5):598-607.

165. Heaton RK, Miller S, Taylor M, Grant I. Revised comprehensive norms for an expanded halstead-reitgan battery: Demographically adjusted neuropsychological norms for african american and caucasian adults. Psychological Assessment Resources, Inc . 2004. Lutz, FL.

166. Lucas JA, Ivnik RJ, Smith GE, Ferman TJ, Willis FB, Petersen RC et al. Mayo's Older African Americans Normative Studies: norms for Boston Naming Test, Controlled Oral Word Association, Category Fluency, Animal Naming, Token Test, Wrat-3 Reading, Trail Making Test, Stroop Test, and Judgment of Line Orientation. *Clin Neuropsychol* 2005; 19(2):243-269.

167. Lucas JA, Ivnik RJ, Smith GE, Ferman TJ, Willis FB, Petersen RC et al. Mayo's Older African Americans Normative Studies: WMS-R norms for African American elders. *Clin Neuropsychol* 2005; 19(2):189-213.

168. Steinberg BA, Bieliauskas LA, Smith GE, Ivnik RJ. Mayo's Older Americans Normative Studies: Age- and IQ-Adjusted Norms for the Trail-Making Test, the Stroop Test, and MAE Controlled Oral Word Association Test. *Clin Neuropsychol* 2005; 19(3-4):329-377.

169. Stern RA, White T. Neuropsychological Assessment Battery (NAB). Psychological Assessment Resources (PAR), Lutz, Fl.-http://www3.parinc.com/products/product.aspx?Productid=NAB. 2003.

170. White T, Stern R. NAB Psychometric and Technical Manual. Psychological Assessment Resources (PAR), Lutz, Fl. 2003.

171. Reitan R, Wolfson D. The Halstead-Rietan neuropsychological test battery. 1985. Tucson, AZ, Neuropsycohological Press.

172. Wechsler D.. Wechsler Adult Intelligence Scale - Third Edition. New York NY, editor. Psychological Corporation. 1997.

173. Lezak M, Howieson D, Loring D. Neuropsychological Assessment Fourth Edition. 2004. New York, NY, Oxford University Press.

174. Benton A. Differential behavioral effects in frontal lobe disease. Neuropsychologia 6[53], 60. 2006.

175. Brown LB, Stern RA, Cahn-Weiner DA, Rogers B, Messer MA, Lannon MC et al. Driving scenes test of the Neuropsychological Assessment Battery (NAB) and on-road

driving performance in aging and very mild dementia. *Arch Clin Neuropsychol* 2005; 20(2):209-215.

176. Owsley C, Sloane M, McGwin G, Jr., Ball K. Timed instrumental activities of daily living tasks: relationship to cognitive function and everyday performance assessments in older adults. *Gerontology* 2002; 48(4):254-265.

177. Goverover Y, Genova HM, Hillary FG, DeLuca J. The relationship between neuropsychological measures and the Timed Instrumental Activities of Daily Living task in multiple sclerosis. *Mult Scler* 2007; 13(5):636-644.

178. Stern RA, White T. NAB Psychometric and Technical Manual. Lutz, FL: Psychological Assessment Resources, 2003.

179. Kaplan E, Goodglass H., Weintraub S. The Boston naming test. 1983. Philadelphia, PA, Lea Febiger.

180. Jefferson A, Wong S, Gracer TS, et al. Geriatric norms for an abbreviated version of the Boston Naming Test. *Applied Neuropsychology* 2006.

181. Lucas JA, Ivnik RJ, Smith GE, Bohac DL, Tangalos EG, Graff-Radford NR et al. Mayo's older Americans normative studies: category fluency norms. *J Clin Exp Neuropsychol* 1998; 20(2):194-200.

182. Benton AL. Neuropsychological assessment. *Annu Rev Psychol* 1994; 45:1-23.

183. Wechsler D. Wechsler Memory Scale. 4th (WMS-4) ed. San Antonio, TX: Pearson Education, 2008.

184. Sherbourne CD, Stewart AL. The MOS Social Support Survey. *Soc Sci & Med* 1991; 32(6):705-714.

185. Mandelblatt JS, Lawrence WF, Cullen J, Stanton AL, Krupnick JL, Kwan L et al. Patterns of care in early-stage breast cancer survivors in the first year after cessation of active treatment. *J Clin Oncol* 2006; 24(1):77-84.

186. Carver CS, Pozo C, Harris SD, Noriega V, Scheier MF, Robinson DS et al. How coping mediates the effect of optimism on distress: A study of women with early stage breast cancer. *J Pers Soc Psychol* 1993; 65(2):375-390.

187. Liang W, Burnett CB, Rowland JH, Meropol NJ, Eggert L, Hwang YT et al. Communication between physicians and older women with localized breast cancer: implications for treatment and patient satisfaction. *J Clin Oncol* 2002; 20(4):1008-1016.

188. Radloff LS. The CES-D scale: A self-report depression scale for research in the general population. *Appl Pscyhol Measurement* 1977; 1:385-401.

189. Plutchik R. Measuring emotions and their derivatives. In: Plutchik R, Kellerman H., editors. The measurement of emotions. San Diego, CA: US: Academic Press, 1989: 1-35.

190. Spielberger CD. Manual for the State-Trait Anxiety Inventory (STAI: Form Y). Consulting Psychologists Press, Palo Alto. 1983.

191. Stern RA. Visual Analog Mood Scales: Professional Manual. Odessa, FL: Psychological Assessment Resources, 1997.

192. Cella D. Factors influencing quality of life in cancer patients: anemia and fatigue. *Semin Oncol* 1998:25(suppl7):43-6.

193. Mandelblatt J.S., Lawrence W.F., Womack S.M., Jacobson D., Yi B., Hwang Y.T. et al. Benefits and costs of using HPV testing to screen for cervical cancer. *JAMA* 2002; 287(18):2372-2381.

194. Ware J, Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: Construction of scales and preliminary tests of reliability and validity. *Med Care* 1996; 34(3):220-233.

195. Guralnik JM, Winograd CH. Physical performance measures in the assessment of older persons. *Aging (Milano)* 1994; 6(5):303-305.

196. Jacobs SR, Jacobsen PB, Booth-Jones M, Wagner LI, Anasetti C. Evaluation of the functional assessment of cancer therapy cognitive scale with hematopoietic stem cell transplant patients. *J Pain Symptom Manage* 2007; 33(1):13-23.

197. Brady MJ, Cella DF, Mo F, Bonomi AE, Tulsky DS, Lloyd SR et al. Reliability and validity of the Functional Assessment of Cancer Therapy-Breast quality-of-life instrument. *J Clin Oncol* 1997; 15(3):974-986.

198. Rockwood K, Song X, MacKnight C, Bergman H, Hogan DB, McDowell I et al. A global clinical measure of fitness and frailty in elderly people. *CMAJ* 2005; 173(5):489-495.

199. Elkin EB, Hurria A, Mitra N, Schrag D, Panageas KS. Adjuvant chemotherapy and survival in older women with hormone receptor-negative breast cancer: assessing

outcome in a population-based, observational cohort. *J Clin Oncol* 2006; 24(18):2757-2764.

200. Gapstur SM, Dupuis J, Gann P, Collila S, Winchester DP. Hormone receptor status of breast tumors in black, Hispanic, and non-Hispanic white women. An analysis of 13,239 cases. *Cancer* 1996; 77(8):1465-1471.

201. Cohen J. Statistical power analysis for the behavioral sciences. 2nd ed. Hillsdale, NJ: Lawrence Erlbaum Associates, 1998.

202. Anderson-Hanley C, Sherman ML, Riggs R, Agocha VB, Compas BE. Neuropsychological effects of treatments for adults with cancer: a meta-analysis and review of the literature. *J Int Neuropsychol Soc* 2003; 9(7):967-982.

203. Figueiredo MI, Cullen J, Hwang YT, Rowland JH, Mandelblatt JS. Breast cancer treatment in older women: does getting what you want improve your long-term body image and mental health? *J Clin Oncol* 2004; 22(19):4002-4009.

204. Vardy J, Rourke S, Tannock IF. Evaluation of cognitive function associated with chemotherapy: a review of published studies and recommendations for future research. *J Clin Oncol* 2007; 25(17):2455-2463.

205. Jacobson NS, Truax P. Clinical significance: a statistical approach to defining meaningful change in psychotherapy research. *J consult clin Psychol* 1991; 59(1):12-19.

206. Heaton RK, Temkin N, Dikmen S, Avitable N, Taylor MJ, Marcotte TD et al. Detecting change: A comparison of three neuropsychological methods, using normal and clinical samples. *Arch Clin Neuropsychol* 2001; 16(1):75-91.

207. Rosenbaum DA, Kenny SB, Derr MA. Hierarchical control of rapid movement sequences. *J Exp Psychol Hum Percept Perform* 1983; 9(1):86-102.

208. D'Agostino RB, Wolf PA, Belanger AJ, Kannel WB. Stroke risk profile: adjustment for antihypertensive medication. The Framingham Study. *Stroke* 1994; 25(1):40-43.

209. Rubin EH, Kinscherf DA, Figiel GS, Zorumski CF. The nature and time course of cognitive side effects during electroconvulsive therapy in the elderly. *J Geriatr Psychiatry Neurol* 1993; 6(2):78-83.

210. Judkins DR, Morganstein D, Zador P, Piesse A, Barrett B, Mukhopadhyay P. Variable selection and raking in propensity scoring. *Stat Med* 2007; 26(5):1022-1033.

211. Tewari A, Johnson CC, Divine G, Crawford ED, Gamito EJ, Demers R et al. Long-term survival probability in men with clinically localized prostate cancer: a case-control,

propensity modeling study stratified by race, age, treatment and comorbidities. *J Urol* 2004; 171(4):1513-1519.

212. Hadley J, Polsky D, Mandelblatt J, Mitchell J, Weeks J, Wang Q et al. An exploratory instrumental variable analysis of the outcomes of localized breast cancer treatments in a medicare population. *Health Econ* 2003; 12(3):171-186.

213. Fairclough D. Design and analysis of Quality of Life Studes in Clinical Trials - Interdisciplinary Statistics. Boca Raton, FL: Chapman & Hall/CRC, 2002.

214. Fairclough DL, Peterson HF, Chang V. Why are missing quality of life data a problem in clinical trials of cancer therapy? *Stat Med* 1998; 17(5-7):667-677.

215. Pauler DK, McCoy S, Moinpour C. Pattern mixture models for longitudinal quality of life studies in advanced stage disease. *Stat Med* 2003; 22(5):795-809.

216. Touloumi G, Pocock SJ, Babiker AG, Darbyshire JH. Estimation and comparison of rates of change in longitudinal studies with informative drop-outs. *Stat Med* 1999; 18(10):1215-1233.

217. Moinpour CM, Sawyers TJ, McKnight B, Lovato LC, Upchurch C, Leichman CG et al. Challenges posed by non-random missing quality of life data in an advanced-stage colorectal cancer clinical trial. *Psychooncology* 2000; 9(4):340-354.

218. Craig CL, Marshall AL, Sjostrom M, Bauman AE, Booth ML, Ainsworth BE, et al. International physical activity questionnaire: 12-country reliability and validity. *Med Sci Sports Exerc* 2003; 35(8):1381-95.

219. Nichols, T and S Hayasaka. Controlling the familywise error rate in functional neuroimaging: a comparative review. Stat Methods Med Res 2003; 12(5): 419-46.

220. Nithianantharajah J, Hannan AJ. Mechanisms mediating brain and cognitive reserve: experience-dependent neuroprotection and functional compensation in animal models of neurodegenerative diseases. Prog Neuropsychopharmacol Biol Psychiatry 2011;35:331-339.

221. Wilson CJ, Finch CE, Cohen HJ. Cytokines and cognition--the case for a head-to-toe inflammatory paradigm. J Am Geriatr Soc 2002;50:2041-2056.

222. Rosano C, Marsland AL, Gianaros PJ. Maintaining brain health by monitoring inflammatory processes: a mechanism to promote successful aging. Aging Dis 2012;3:16-33.

223. Marsland AL, Gianaros PJ, Abramowitch SM, Manuck SB, Hariri AR. Interleukin-6 covaries inversely with hippocampal grey matter volume in middle-aged adults. Biol Psychiatry 2008;64:484-490.

224. Pawelec G, Goldeck D, Derhovanessian E. Inflammation, ageing and chronic disease. Curr Opin Immunol 2014;29:23-28.

225. Vermeij WP, Hoeijmakers JH, Pothof J. Aging: not all DNA damage is equal. Curr Opin Genet Dev 2014;26:124-130.

226. Conroy SK, McDonald BC, Smith DJ et al. Alterations in brain structure and function in breast cancer survivors: effect of post-chemotherapy interval and relation to oxidative DNA damage. Breast Cancer Res Treat 2013;137:493-502.

227. Sanoff HK, Deal AM, Krishnamurthy J et al. Effect of Cytotoxic Chemotherapy on Markers of Molecular Age in Patients With Breast Cancer. J Natl Cancer Inst 2014;106.

228. Campisi J. Aging, Cellular Senescence, and Cancer. Annu Rev Physiol 2012.

229. Kirkland JL. Translating advances from the basic biology of aging into clinical application. Exp Gerontol 2013;48:1-5.

230. Mapstone M, Cheema AK, Fiandaca MS et al. Plasma phospholipids identify antecedent memory impairment in older adults. Nat Med 2014;20:415-418.

231. Lim KC, Lim ST, Federoff HJ. Neurotrophin secretory pathways and synaptic plasticity. Neurobiol Aging 2003;24:1135-1145.

232. Marsland AL, Petersen KL, Sathanoori R et al. Interleukin-6 covaries inversely with cognitive performance among middle-aged community volunteers. Psychosom Med 2006;68:895-903.

233. Schram MT, Euser SM, de Craen AJ et al. Systemic markers of inflammation and cognitive decline in old age. J Am Geriatr Soc 2007;55:708-716.mc

234. McAfoose J, Baune BT. Evidence for a cytokine model of cognitive function. Neurosci Biobehav Rev 2009;33:355-366.

235. Kesler S, Hadi Hosseini SM, Heckler C et al. Cognitive training for improving executive function in chemotherapy-treated breast cancer survivors. Clin Breast Cancer 2013;13:299-306.

236. Alexander S, Minton O, Andrews P, Stone P. A comparison of the characteristics of disease-free breast cancer survivors with or without cancer-related fatigue syndrome. Eur J Cancer 2009;45:384-392.

237. Bower JE, Ganz PA, Aziz N, Olmstead R, Irwin MR, Cole SW. Inflammatory responses to psychological stress in fatigued breast cancer survivors: relationship to glucocorticoids. Brain Behav Immun 2007;21:251-258.

238. Bower JE, Ganz PA, Tao ML et al. Inflammatory biomarkers and fatigue during radiation therapy for breast and prostate cancer. Clin Cancer Res 2009;15:5534-5540.

239. Bower JE. Cancer-related fatigue: links with inflammation in cancer patients and survivors. Brain Behav Immun 2007;21:863-871.

240. Collado-Hidalgo A, Bower JE, Ganz PA, Irwin MR, Cole SW. Cytokine gene polymorphisms and fatigue in breast cancer survivors: early findings. Brain Behav Immun 2008;22:1197-1200.

241. Orre IJ, Murison R, Dahl AA, Ueland T, Aukrust P, Fossa SD. Levels of circulating interleukin-1 receptor antagonist and C-reactive protein in long-term survivors of testicular cancer with chronic cancer-related fatigue. Brain Behav Immun 2009;23:868-874.

242. Wang XS, Shi Q, Williams LA et al. Inflammatory cytokines are associated with the development of symptom burden in patients with NSCLC undergoing concurrent chemoradiation therapy. Brain Behav Immun 2010;24:968-974.

243. Wang XS, Williams LA, Krishnan S et al. Serum sTNF-R1, IL-6, and the development of fatigue in patients with gastrointestinal cancer undergoing chemoradiation therapy. Brain Behav Immun 2012;26:699-705.

244. Bower JE, Ganz PA, Aziz N, Fahey JL. Fatigue and proinflammatory cytokine activity in breast cancer survivors. Psychosom Med 2002;64:604-611.

245. Bower JE, Ganz PA, Irwin MR, Kwan L, Breen EC, Cole SW. Inflammation and behavioral symptoms after breast cancer treatment: do fatigue, depression, and sleep disturbance share a common underlying mechanism? J Clin Oncol 2011;29:3517-3522.

246. Collado-Hidalgo A, Bower JE, Ganz PA, Cole SW, Irwin MR. Inflammatory biomarkers for persistent fatigue in breast cancer survivors. Clin Cancer Res 2006;12:2759-2766.
247. Alexander JJ, Jacob A, Cunningham P, Hensley L, Quigg RJ. TNF is a key mediator of septic encephalopathy acting through its receptor, TNF receptor-1. Neurochem Int 2008;52:447-456.

248. Wang Y, Niu XL, Qu Y et al. Autocrine production of interleukin-6 confers cisplatin and paclitaxel resistance in ovarian cancer cells. Cancer Lett 2010;295:110-123.

249. Wang Y, Xu RC, Zhang XL et al. Interleukin-8 secretion by ovarian cancer cells increases anchorage-independent growth, proliferation, angiogenic potential, adhesion and invasion. Cytokine 2012;59:145-155.

250. Ganz PA, Castellon SA, Silverman DHS, Kwan L, Bower JE, Irwin MR et al. Does circulating tumor necrosis factor (TNF) play a role in post-chemotherapy cerebral

dysfunction in breast cancer survivors (BCS)? Abstract presented at Annual Meeting of the American Society of Clinical Oncology, Chicago, June 3, 2011.

251. Payette H, Roubenoff R, Jacques PF et al. Insulin-like growth factor-1 and interleukin 6 predict sarcopenia in very old community-living men and women: the Framingham Heart Study. J Am Geriatr Soc 2003;51:1237-1243.

252. Taekema DG, Westendorp RG, Frolich M, Gussekloo J. High innate production capacity of tumor necrosis factor-alpha and decline of handgrip strength in old age. Mech Ageing Dev 2007;128:517-521.

253. Yaffe K, Lindquist K, Penninx BW et al. Inflammatory markers and cognition in well-functioning African-American and white elders. Neurology 2003;61:76-80.

254. Walston J, McBurnie MA, Newman A et al. Frailty and activation of the inflammation and coagulation systems with and without clinical comorbidities: results from the Cardiovascular Health Study. Arch Intern Med 2002;162:2333-2341.

255. Cesari M, Penninx BW, Pahor M et al. Inflammatory markers and physical performance in older persons: the InCHIANTI study. J Gerontol A Biol Sci Med Sci 2004;59:242-248.

256. Hamer M, Sabia S, Batty GD et al. Physical activity and inflammatory markers over 10 years: follow-up in men and women from the Whitehall II cohort study. Circulation 2012;126:928-933.

257. Muthen B. Statistical and substantive checking in growth mixture modeling: comment on Bauer and Curran (2003). Psychol Methods 2003;8:369-377.

258. Collins LM, Lanza ST. Latent class and latent transition analysis. Hoboken, NJ: John Wiley & Sons., 2010.

259. Elliott MR, Gallo JJ, Ten Have TR, Bogner HR, Katz IR. Using a Bayesian latent growth curve model to identify trajectories of positive affect and negative events following myocardial infarction. Biostatistics 2005;6:119-143.

260. Muthen B, Brown CH, Masyn K et al. General growth mixture modeling for randomized preventive interventions. Biostatistics 2002;3:459-475.

261. Muthen B, Shedden K. Finite mixture modeling with mixture outcomes using the EM algorithm. Biometrics 1999;55:463-469.

262. Ram N, Grimm KJ. Growth Mixture Modeling: A Method for Identifying Differences in Longitudinal Change Among Unobserved Groups. Int J Behav Dev 2009;33:565-576.

263. Petrovsky N, McNair P, Harrison LC. Diurnal rhythms of pro-inflammatory cytokines: regulation by plasma cortisol and therapeutic implications. Cytokine 1998;10:307-312.

264. de Jager W., Bourcier K, Rijkers GT, Prakken BJ, Seyfert-Margolis V. Prerequisites for cytokine measurements in clinical trials with multiplex immunoassays. BMC Immunol 2009;10:52.

265. Ganz PA, Bower JE, Kwan L et al. Does tumor necrosis factor-alpha (TNF-alpha) play a role in post-chemotherapy cerebral dysfunction? Brain Behav Immun 2013;(Suppl:S99-108).

266. Suzuki K, Nakaji S, Yamada M, Totsuka M, Sato K, Sugawara K. Systemic inflammatory response to exhaustive exercise. Cytokine kinetics. Exerc Immunol Rev 2002;8:6-48.

267. Woods JA, Vieira VJ, Keylock KT. Exercise, inflammation, and innate immunity. Neurol Clin 2006;24:585-599.

268. Irwin M, Olmstead R, Breen E et al. Tai chi, cellular inflammation, and transcriptome dynamics in breast cancer survivors with insomnia: a randomized controlled trial. J Natl Cancer Inst Monogr 2014;50:295-301.

269. Hildebrand M, VAN Hees VT, Hansen BH, Ekelund U. Age group comparability of raw accelerometer output from wrist- and hip-worn monitors. Med Sci Sports Exerc 2014;46:1816-1824.

270. Prinsen H, Bleijenberg G, Heijmen L et al. The role of physical activity and physical fitness in postcancer fatigue: a randomized controlled trial. Support Care Cancer 2013;21:2279-2288.

271. Phillips SM, McAuley E. Social cognitive influences on physical activity participation in long-term breast cancer survivors. Psychooncology 2013;22:783-791.

272. Buchman AS, Wilson RS, Yu L, James BD, Boyle PA, Bennett DA. Total daily activity declines more rapidly with increasing age in older adults. Arch Gerontol Geriatr 2014;58:74-79.

273. Miller NE, Strath SJ, Swartz AM, Cashin SE. Estimating absolute and relative physical activity intensity across age via accelerometry in adults. J Aging Phys Act 2010;18:158-170.

274. Crouter SE, Bassett DR, Jr. A new 2-regression model for the Actical accelerometer. Br J Sports Med 2008;42:217-224.

275. Lyden K, Kozey SL, Staudenmeyer JW, Freedson PS. A comprehensive evaluation of commonly used accelerometer energy expenditure and MET prediction equations. Eur J Appl Physiol 2011;111:187-201.

276. Rogers LQ, Fogleman A, Trammell R et al. Inflammation and psychosocial factors mediate exercise effects on sleep quality in breast cancer survivors: pilot randomized controlled trial. Psychooncology 2014.

277. Wefel JS, Vardy J, Ahles T, Schagen SB. International Cognition and Cancer Task Force recommendations to harmonise studies of cognitive function in patients with cancer. Lancet Oncol 2011;12:703-708.

278. Bagiella E, Sloan RP, Heitjan DF. Mixed-effects models in psychophysiology. Psychophysiology 2000;37:13-20.

279. Singer JD, Willett JB. Applied longitudinal data analysis: modeling change and event occurrence. Oxford University Press, 2003.

280. Enders CK. Applied missing data analysis. New York, NY: The Guilford Press, 2010.

281. Graham JW. Missing data analysis: making it work in the real world. Annu Rev Psychol 2009;60:549-576.

282. D'Agostino RB, Jr., D'Agostino RB, Sr. Estimating treatment effects using observational data. JAMA 2007;297:314-316.

283. Lunceford JK, Davidian M. Stratification and weighting via the propensity score in estimation of causal treatment effects: a comparative study. Stat Med 2004;23:2937-2960.

284. Robins JM, Hernan MA, Brumback B. Marginal structural models and causal inference in epidemiology. Epidemiology 2000;11:550-560.

285. Benjamini Y, Hochberg Y. On the adaptive control of the false discovery rate in multiple testing with independent statistics. J Educ Behavior Stat 2000;25:60-83.

286. Hochberg Y, Benjamini Y. More powerful procedures for multiple significance testing. Stat Med 1990;9:811-818.

287. The international HapMap project. Genome browser release #28 (phases 1, 2 & 3 - merged genotypes & frequencies). Retrieved 5/30/2014, from http://hapmap.ncbi.nlm.nih.gov/index.html.en. 2014.

288. Diggle PJ, Heagerty P, Liang KY, ger SL. Analysis of longitudinal data. New York, NY: Oxford University Press, 2002.

289. Selig JP, Preacher KJ. Mediation models for longitudinal data in development research. Research in human development 2009;6:144-64.

290. Bandeen-Roche K, Walston JD, Huang Y, Semba RD, Ferrucci L. Measuring systemic inflammatory regulation in older adults: evidence and utility. Rejuvenation Res 2009;12:403-410.

291. Vittinghoff E, Sen S, McCulloch CE. Sample size calculations for evaluating mediation. Stat Med 2009;28:541-557.

292. Qiu W. Power/sample size calculation for medication analysis. 0.1.0 ed2012

13.0 APPENDICES

Please see attached documents.