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Cognitive Effects of Cancer and its Treatments at the Intersection of Aging: What do we Know; What do we Need to Know?

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Abstract

There is a fairly consistent, albeit non-universal body of research documenting cognitive declines after cancer and its treatments. While few of these studies have included those 65 and older, it is logical to expect that older patients are at risk of cognitive decline. In this paper, we use breast cancer as an exemplar disease for inquiry into the intersection of aging and cognitive effects of cancer and its therapies. There are a striking number of common underlying potential biological risks and pathways for the development of cancer, cancer-related cognitive declines, and aging processes, including the development of a frail phenotype. Candidate shared pathways include changes in hormonal milieu, inflammation, oxidative stress, DNA damage and compromised DNA repair, genetic susceptibility, decreased brain blood flow or disruption of the blood-brain barrier, direct neurotoxicity, decreased telomere length, and cell senescence. There are also similar structure and functional changes seen in brain imaging studies of cancer patients and those seen with “normal” aging and Alzheimer’s disease. Disentangling the role of these overlapping processes is difficult since they require aged animal models and large samples of older human subjects. From what we do know, frailty and its low cognitive reserve seem to be a clinically useful marker of risk for cognitive decline after cancer and its treatments. This and other results from this review suggest the value of geriatric assessments to identify older patients at the highest risk of cognitive decline. Further research is needed to understand the interactions between aging, genetic predisposition, lifestyle factors and frailty phenotypes to best identify the sub-groups of older patients at greatest risk for decline and to develop behavioral and pharmacological interventions targeting this group. We recommend that basic science and population trials be developed specifically for older hosts with intermediate endpoints of relevance to this group, including cognitive function and trajectories of frailty. Clinicians and their older patients can advance the field by active encouragement of and participation in research designed to improve the care and outcomes of the growing population of older cancer patients.

Introduction

Cancer is largely a disease of older age. [1] With the graying of America, one in five individuals will be 65 years or older (“older”) by the year 2030. [2] As these individuals develop cancer, they are at risk of experiencing adverse cognitive effects of this disease and its local and systemic therapies. Cancer-related cognitive declines were first described three decades ago, [3] and a fairly consistent, albeit not universal, picture of these deficits has evolved to the present. [4–6] There are a striking number of common underlying biological risks and pathways for the development of cancer and cancer-related cognitive declines and aging processes. These commonalities may have implications for the clinical care of the growing number of older cancer patients. [5,7–13]

Breast cancer is an ideal disease for inquiry into the intersection of aging and cognitive effects of cancer and its therapies because it is the second most common cancer in women, [14] with more than 50% of new cases occurring among women 65 and older, [1,15] and its treatment has historically included a high rate of use of systemic chemotherapy and/or

hormonal therapy. There is also the largest body of empiric evidence about the cognitive aspects of breast cancer and its treatments, compared to other cancers.

Most controlled investigations and meta-analyses of the studies of the effects of breast cancer therapy on cognitive function report decrements in one or more domains, including verbal working memory, visual memory and visual-spatial domains, executive function (including working memory), and/or processing speed compared to pre-treatment, cancer and/or population controls. [5,6,16–21] These cognitive declines have been observed to persist for variable periods of time from one [16,22] to as many as 10–20 years post-treatment. [23–25] Unfortunately, the mean age in the most recent meta-analysis of the cognitive effects of breast cancer therapy was 53 years [6] and only a few studies have been designed to examine outcomes for older patients.[4,26–29]

High rates of objective and subjective cognitive impairment have been reported in most studies of older breast cancer patients. [28–30] However, variable rates of cognitive decline have been noted in other studies that include older cancer patients. [4,27,31–34] All of these reports have had small samples of older patients (range of n=13–50), [4,27,30] some have focused on patients treated in mid-life and evaluated at age 65 or older [28] and only one was able to examine age interactions. [7] In that study, Ahles and colleagues found that women ages 60 to 70 with low baseline cognitive reserve that underwent chemotherapy had lower performance on tests of processing speed compared with those not receiving chemotherapy and controls (Figure 1). [5,7] Thus, it is possible that only a sub-group of older patients (or patients at any age) experience cognitive effects after systemic cancer therapy. [6,7,35] However, there is only limited empiric evidence about the risk factors that define vulnerable groups, and even less for older cancer patients.

In this paper, we present a framework for considering the relationships among the key constructs involved in evaluating the cognitive effects of cancer and its treatments at the intersection of aging, review some potential shared biological mechanisms and how they fit within current theories of aging, discuss methodological challenges in conducting research on this topic in the older population, and summarize the clinical implications of these results for the care of the growing older population diagnosed with and surviving with cancer.

Aging, Frailty, and Cognitive Decline

Aging is the net effect of the temporal accumulation of damage to cellular processes and systems, loss of compensatory mechanisms, and increased vulnerability to disease and death. Closely aligned to this definition is the clinical concept of frailty, which can be considered a phenotype of aging. This phenotype is characterized by a diminished biologic reserve and resistance to stressors caused by collective declines across physiologic systems, leading to vulnerability to insult and adverse outcomes. [36]

Fried and her colleagues initially described the frail phenotype as having three out of five of the following criteria: weight loss, exhaustion, low physical activity, slow walking gait, and poor grip strength. [36] Although this original phenotype did not include cognitive function, it is now widely recognized as one of the key factors involved in the impaired physiologic pathways leading to frailty. [37–40] The converse is also true: individuals with frailty are more vulnerable to the development of cognitive disorders (e.g., Alzheimer's disease) and to cognitive decline after stressors such as cancer therapy (Figure 2). [7,24,41] Further, frailty and cognitive deficits each are independently associated with high risks of dependence and mortality. For instance, selected measures of cognitive function, such as the Trail Making Test, have been noted to predict physical frailty as measured on the Short Physical Performance Battery, as well as mortality in older individuals in the general population. [42] Identifying the biological underpinnings of these associations and disentangling their

temporal and etiological relationships is an important research priority and an area of nascent discovery.

From what we do know, it seems that there are several potential common pathways. Observations that biomarkers of inflammation such as high C-reactive protein (CRP) and high interleukin-6 (IL-6) are seen in the frail phenotype, [43] senescence, [9,44,45] and cognitive declines in Alzheimer's disease [46] and after cancer therapy [22,47] suggest one potential common biological pathway. There is also overlap in the genotypes (e.g., *APOE* polymorphisms) associated with cancer related cognitive declines, Alzheimer's and their associated frailty phenotypes. [24,48–50] Further support of the concept of common underlying biological processes is based on the recent body of evidence demonstrating similar brain structural alterations in aging, cancer-related cognitive declines, and Alzheimer's disease, including decreases in overall brain volume, gray matter, white matter connectivity and hippocampal volume. [5,13,25,51–54] Finally, the observation that cancer patients have lower cognitive function than expected based on age and education even before any treatment [5,55] suggests, as depicted on Figure 3, that there are common underlying risks for cancer and cognitive decline, and that both are in part age-related phenomena. In the next section we highlight some of the research on the potential common pathways related to the pathogenesis of cognitive decline, frailty and aging.

Common Biological Pathways

Most consider that cancer and aging are linked, although the molecular mechanisms responsible for the increasing risk of cancer with increasing age and frailty are not completely understood. Aging is clearly related to neurodegenerative diseases such as Alzheimer's disease. It is also biologically plausible that cancer and neurodegenerative conditions are linked, since they have some common pathways related to the cell cycle (e.g., p53 proteins and the Pin1 protein), albeit in opposing directions, with cancer related to proliferation and Alzheimer's related to cell death. [56–58]

In this broad context, the precise biological mechanisms and pathways underpinning cognitive decline after cancer and/or its treatments remain uncertain. The common "candidate" pathways include changes in hormonal milieu, inflammation, oxidative stress, DNA damage and compromised DNA repair, genetic susceptibility, decreased brain blood flow or disruption of the blood-brain barrier, direct neurotoxicity or damage to specific brain regions, decreased telomere length, and cell senescence (Figure 3). [5,8,51,59–62]

Hormones

Hormonal levels decrease over the lifespan and have been implicated in cognitive function in non-cancer populations [63] and hormonal replacement therapy has been noted to decrease the risk of Alzheimer's disease by up to 29%. [64–69] Breast cancer hormonal therapies act by blocking or lowering hormonal levels in individuals with estrogen receptor positive tumors. Possible mechanisms by which hormonal treatment could affect cognition include decreases in cholinergic activity [66,70], reduced induction of serotonin receptors,[71] direct toxic effects on dendrites and synaptic connectivity,[72,73] and changes in lipids.[74] Since estrogen also has anti-oxidant effects [75,76] and maintains telomere length [77], breast cancer hormonal therapies that block estrogen may also exert their negative effects on cognition via accelerating aging.

The role of hormonal change is supported by the body of research demonstrating decrements in cognitive function among women receiving systemic hormonal therapy, either alone or with chemotherapy. [78–83] However, effects are not universal and may not be observed with all hormonal therapies. For instance, a recent clinical trial reported by Schilder and her colleagues noted cognitive declines in verbal memory and executive function among women

treated with tamoxifen but not exemestane. [79] This result is biologically plausible since estrogen can be neuroprotective and estrogen receptors, the target of tamoxifen and other drugs in its class, are found in large numbers in the frontal lobe and hippocampus; [84–87] these same areas have been noted to have abnormalities on imaging studies. [53,88] In contrast, exemestane, one type of aromatase inhibitor, blocks conversion of androgens into estrogens, and its metabolites have mild androgenic properties. Since androgens can enhance cognition, this may be one explanation for the relative lack of impairment due to this particular hormonal regimen. However, results for the effect of other hormonal therapies on cognition have been inconsistent. [7980,81] One intriguing result of the Schilder trial comparing hormonal therapies was a preliminary result that tamoxifen had larger effect sizes and affected a greater number of cognitive domains in women 65 and older compared to women less than 65 years of age. [79] It will be important to replicate this finding and to examine the role of different types of estrogen receptors in brain tissue, especially if hormonal therapies will be recommended for longer periods of administration..

Inflammation

Inflammatory responses involved in aging, cancer and/or generated by cancer-directed agents have been suggested as one pathway for cognitive declines via triggering of neurotoxic cytokines. [89] A study by Ganz and colleagues examined several pro-inflammatory cytokines in breast cancer patients. They found that soluble tumor necrosis factor-alpha receptor II (sTNF-RII) was significantly higher in those who received chemotherapy compared to those who did not, but that levels declined over time. Of note, the higher sTNF-RII levels were associated with self-reported memory complaints and decreased brain metabolism in frontal regions on positron emission tomography (PET) scans, and subjective cognitive function improved as sTNF-RII levels declined over the one year of follow-up. [22] Other inflammatory cytokines were not associated with neurocognition and the relationships were not significant after controlling for fatigue levels, suggesting that fatigue and cognitive declines might both share a common inflammatory etiology. Unfortunately, assessments occurred after initial therapy, so that the separate effects of having cancer could not be assessed; the study also lacked a control group and was focused on the effects of menopause and hormonal therapy in younger women, so may not be generalizable to pathways related to aging. Also, since aging is associated with the accumulation of multi-morbidities that affect or are the result of inflammatory pathways (e.g., diabetes, heart disease), [90] it will require careful sampling and sub-group analysis to segregate the impact of inflammation related to cancer in studying cognitive outcomes and to control for fatigue components of frailty phenotypes. This will be an important area for future research.

DNA Damage and Repair

Oxidative DNA damage, as measured in lymphocytes, has been noted in breast cancer patients both before any systemic therapy and after chemotherapy. [13,91,92] Conroy and her colleagues recently conducted an innovative study with breast cancer survivors and matched non-cancer controls. The sample ranged in age from 41 to 79 years old; the cancer patients were three to 10 years post-treatment. They found that oxidative DNA damage was higher in patients than controls and that DNA damage was correlated with self-reported cognitive problems, lower cognitive function and less frontal gray matter density and brain activation on functional MRI (fMRI). [13] While only small numbers of patients were assessed (n=48), the result is interesting because oxidative DNA damage and diminished DNA repair mechanisms are also markers of senescence, [44] and are seen in age-related diseases including Parkinson's disease, mild cognitive impairment, and Alzheimer's disease. [93,94] Hormonal therapies may also be associated with increased DNA damage. [95] The exact mechanisms and pathways whereby DNA damage leads to cognitive decline is unclear, but

it is postulated to be related to either production of defective proteins that lead to neuronal apoptosis [96] or problems in transcription that cause the loss of required gene protein products. [97] It should also be noted that DNA damage can trigger cytokine release, which in turn increases oxidative stress and further DNA damage. [98,99] How these processes are affected by age-related DNA damage or chronic inflammation related to other non-cancer comorbidities is unclear and will need to be disentangled to fully understand mechanisms of cognitive decline in older cancer patients.

Genetic Factors

There is considerable variability across individuals in presence and extent of cognitive changes associated with cancer and cancer treatment. The observation that a subgroup of patients appears differentially affected strongly suggests that genetic influences may modulate the influence of exposure to cancer pathophysiology or treatment. [12,51,100] Polymorphisms of the *APOE* and *COMT* genes have been studied for associations with cognitive changes after cancer treatment [21,24] but numerous other candidate genes may play a role. [51,100] Many of these genes have a role in age-related cognitive decline.

APOE is located on chromosome 19 and was first identified as a risk for Alzheimer's disease in the early 1990's, [101] and it remains the leading known genetic risk for this disease. It codes for apolipoprotein E (ApoE), a complex lipoprotein known to play a role in lipid transport and regulation of inflammatory immune activity, among other biological functions. In the central nervous system, ApoE is also involved in amyloid beta metabolism, a key substrate of Alzheimer's, as well as neural repair processes after brain injury and brain plasticity. *APOE* has three alleles (ε2, ε3 and ε4 variants) which are, in turn, determined by two single nucleotide polymorphisms (*SNP*s) - rs7412 and rs429358. *APOE* ε4 is the adverse risk allele that confers risk of Alzheimer's [102] and is associated with poor recovery after stroke and trauma. [103,104]

Ahles and colleagues noted that breast cancer survivors who received chemotherapy and were *APOE* ε4-positive had greater cognitive decline in the visual-spatial and visual memory domains compared to ε4-negative survivors receiving this treatment (average age 56).[24] However, the relationship between *APOE* and cognitive outcomes has not been consistent in the few other studies to examine this question among breast cancer patients, [54] although they were often not designed to have power to detect genetic influences. *APOE* has also been noted to be a risk factor for the development of breast cancer [105] or a moderator of fat and obesity risks of breast cancer. [106] If *APOE* polymorphisms are linked to risk of disease, especially more aggressive types of disease or larger tumors (seen in obese women), and women with these tumors are differentially more likely to receive chemotherapy, then *APOE*-post treatment relationships may be confounded.

Adding to the complexity are the observations that polymorphisms of estrogen receptors also influence ApoE synthesis [107,108] and interact with ApoE in risk for Alzheimer's, [109] so there may be treatment-gene interactions in producing cognitive decline. This idea is supported by one study of non-cancer patients where hormone replacement therapy was only protective of cognitive decline among women without an ApoE ε4 allele. [110] It will be important to test these hypotheses directly in future studies of cognitive outcomes in older breast cancer patients receiving different types of hormonal therapy, especially as recommendations for this modality are extended from five to ten years of treatment. [111,112]

The other gene studied specifically in cancer patients with regard to cognitive outcomes is *COMT*, located on chromosome 22q11. *COMT* codes for catechol-O-methyltransferase, an enzyme that metabolizes catecholamine neurotransmitters including dopamine, epinephrine, and norepinephrine; the Val158Met *SNP* (rs4680) in *COMT* (substitution of methionine with

valine) increases dopamine break down and decreases synaptic neurotransmitter levels. *COMT* plays an important role in dopamine regulation in the frontal lobes and has been shown to be associated with executive function in normal controls. In a study of cancer and cognition by Small and colleagues, breast cancer patients treated with chemotherapy who were *COMT*-valine carriers performed worse on measures of attention compared to *COMT*-methionine homozygotes, although the average age of these women was 51. [21] Of note, Lindenberger has found an age interaction with the *COMT* gene. [113]

Brain-derived neurotrophic factor (*BDNF*) is another gene involved in neuron growth and repair and is found primarily in the prefrontal cortex and hippocampus. [114,115] A functional polymorphism of *BDNF* has been associated with lower memory and executive function in non-cancer populations. [116–118] Lindenberger and colleagues observed interactions between *BDNF*, *COMT*, and age. [113] This result underscores the complex interplay between aging, declining reserve and genetic factors. Overall, the role of *BDNF* and other neural and glial growth factors appears promising for investigation in cancer patients.

Some other single nucleotide polymorphisms (*SNP*s) have also been implicated in cognitive decline among cancer patients. In a preliminary report, Ganz reported that the TNF-alpha-308 promoter *SNP* was associated with the level of self-reported memory problems after cancer treatment, [119,120] consistent with the posited role of an inflammatory mechanism in the etiology of this syndrome.

Variations in genes that affect blood-brain barrier transporter could also be involved in mediating the direct neuro-toxicity of some chemotherapeutic agents, since in animal models, only small doses are needed to produce neuronal cell death. [51,61,121] For example, the multidrug resistance 1 (*MDR1*) gene encodes the protein P-glycoprotein (P-gp); P-gp influences the level of a chemotherapeutic agent in the brain. [51,122] Polymorphisms of the *MDR1* gene (e.g., C3435T in exon 26) [123] could influence P-gp function such that a sufficient amount of drug reaches neuronal cells to directly cause toxicity.

An emerging area of genetic investigation is related to microRNAs (miRNA). miRNAs are very small non-coding RNAs that are becoming increasingly recognized as playing a major role in regulating gene expression and cell metabolism in cancer and neurodegenerative disease. [48] Holohan recently examined the relationship between the functional roles of miRNAs in cancer and Alzheimer's disease as two age associated disorders. [48] Numerous other candidate genes and pathways are thought to potentially may play a role in cognitive changes associated with cancer and cancer treatment and have been reviewed previously. [51,100]

Alterations in Blood-Brain Barrier and other Vascular Factors

Many systemic chemotherapies including anthracyclines do not appear to cross the blood-brain barrier. Exceptions may include those included in the cyclophosphamide, methotrexate and fluorouracil (CMF) regimen.[89,124] Since older patients may remain more likely to get CMF regimens due to the higher cardiac and other toxicity profiles seen with anthracycline regimens, older breast cancer patients may be at higher risk for direct neurotoxicity, underscoring the need to carefully consider specific agents when studying outcomes among older patients.

Other factors that affect vascular function[125] have been implicated in aging and cognitive performance, such as smoking and low levels of high density lipoproteins (HDL).[100,126,127] Interestingly, nicotine and statin medications seem to be protective of cognitive decline, so that these relationships are not straightforward.[125,128] Similar to observations in cancer patients, there also appear to be interactions between cerebrovascular disease or diabetes and

the ApoE ε4 allele in producing memory impairments.[17,18,129] These observations could help to identify subgroups of older cancer patients at risk for cognitive declines related to vascular factors.

Structural and Functional Brain Changes on Neuroimaging

To the extent that cancer treatments may accelerate or mimic the effects of aging, some overlap in brain structures affected by cancer treatments and aging is expected. Imaging studies have demonstrated that total gray matter volume reliably decreases with advancing age, with regional changes exhibited mainly in the frontal cortex and in regions around the central sulcus, including the hippocampus. [130] Lower hippocampal volume is related to memory functioning and has been observed in breast cancer patients after treatment. [131] White matter also diminishes with increasing age. [130,132] Reduction in volume of frontal brain structures and changes in the integrity of white matter tracts have been reported after chemotherapy, as have alterations in brain activation on functional neuroimaging. [12,13,25,133–139] Of note, there appear to be pre-treatment cancer effects as well, with altered frontal cortex activation during fMRI tasks in breast cancer patients relative to healthy controls. [140,141] Similar abnormalities related to breast cancer treatment have been observed using functional positron emission tomography (PET) and electro-physiological methods. [142] There are also differences in resting state between breast cancer patients and controls. [143] However, all of these imaging studies have been among breast cancer patients under age 65. Imaging studies in older patients will be critical to confirming the brain structural links between cancer and aging.

Telomeres

Over the life course, telomeres shorten with each cell replication, ultimately leading to cell senescence (see below) and apoptosis, so that leukocyte telomere length has been used an a marker of cellular age with shorter length indicating a greater degree of senescence. As such, telomere health has been linked to aging, Alzheimer's disease severity, cancer risk, and mortality rates.[144] For instance, patients with Alzheimer's have been observed to have shorter telomeres than controls, and shorter length has also been associated with greater disease severity.[144] Cancer chemotherapy also has effects on telomere length, and this could be another common pathway between aging and cancer related cognitive decline via effects on replicating cells. [62,145–147]

Senescence

Senescence refers to the state of cells that are metabolically active but can no longer replicate. Many of the same factors that we have been discussing as common potential causal pathways to aging and to cognitive decline after cancer and cancer therapy have been implicated as stressors that can lead to cell senescence. [8,148] Senescent cells evoke inflammatory responses and accumulate at sites of pathology, including Alzheimer's plaques. [8,148] Senescent cells can also be considered a biomarker of the frailty phenotype [9] that places cancer patients at risk for cognitive declines. The targets for cancer treatments could potentially negatively affect biologic markers of aging such as senescence, since there is a reciprocal relationship between tumor suppression and senescence in healthy cells. For instance, increases in tumor suppressor mechanisms through p53/p21 and p16INK4a/pRB and other pathways are under investigation as leverage points for treat cancer but are associated with increased cell senescence, and could therefore accelerate aging and increase risk for cognitive toxicity. [8,148] Thus, it will be important to consider senescence and the translation of the basic science of aging into clinical studies of the impact of cancer and new systemic cancer therapies on cognitive outcomes in older patients.

Taken together, this body of mechanistic research suggests that biologic processes underlying cancer, the impact of cancer treatments, aging, and cognitive decline are linked, and that cancer treatments may actually accelerate the aging process. [62] As with most conditions, not all breast cancer patients develop cognitive effects related to their cancer or its treatments, underscoring the need to identify the sub-group with the highest risk of cognitive decline. Overall, age-related phenotypes such as frailty and diminished cognitive and overall reserve and biomarkers reflecting senescence and aging processes are logical candidates for identifying patients at high risk of cognitive decline. [5]

Models of Aging

The constellation of intersecting factors related to cancer-related cognitive decline, frailty, and aging raises several provocative questions: If cancer therapy impacts cognitive function, does the trajectory of dysfunction parallel that of normal aging (phase shift hypothesis), or is the trajectory of dysfunction accelerated in comparison to normal aging (accelerated aging hypothesis)? [5] Is the lowest common denominator a depletion of reserve leading to a frail phenotype (reliability theory of aging)?

As depicted on Figure 4, the phase shift theory postulates that cancer patients experience decrements in cognitive function compared to their non-cancer counterparts, and those decrements remain constant over time. Alternatively, if cancer and its treatment are actually accelerating aging processes, we would expect the slope of decline in cognitive function would be steeper for patients relative to their non-cancer cohorts. The relativity theory of aging [149] further posits that declines in cognitive function are a function of overall system redundancy and repair (i.e., net reserve), so that patients who are frail would be expected to show the steepest decline and those with less frailty (and greater reserve) would decline at a slower rate. These differences would not be appreciated by only examining the average trajectory (see also Figure 2). Beyond cancer and cancer therapies, access to healthcare and management of chronic disease and lifestyle factors such as exercise or smoking would affect reserve and system failures. In the reliability theory, frailty would be considered as the failures of multiple systems.

An important strength of the reliability theory for studying cognitive effects of cancer and its treatments in older patients is that it does not depend on a given treatment affecting a specific biologic pathway. [5] As noted by Ahles and colleagues, different patterns of failure across various biologic systems may confer more or less risk of specific treatments for each patient: one patient may be vulnerable to DNA damaging effects of a particular chemotherapy regimen, whereas another patient may be susceptible to the impact on the hormonal milieu of endocrine treatments. Implicit in this conceptualization is the idea that the trajectories of cognitive decline are dependent on pre-morbid cognitive and other system reserve. One practical implication for future research is the need for pre-treatment assessments and evaluation of self-reported function prior to cancer diagnosis. Viewed through the lens of aging theories, researchers may also want to specifically investigate discrete trajectories, rather than group averages when assessing temporal trends in cognitive function. [150]

Measurement Issues

There are many methodological considerations in studying the complex interactions between cancer, cancer therapy and cognitive function. In this section we highlight several concerns specific to evaluations of the role of aging and needs of older patients. For excellent reviews of international consensus panels on methods for studying cancer and cognition the reader is referred to summaries of the International Cognition and Cancer Task Force. [35,142,151]

First, this is a field that will require transdisciplinary collaboration between basic scientists and clinical researchers, including gerontologists and geriatricians. One obvious methodological basic science issue is the need to use older animals or systems that mimic aging systems, since the aging tissue microenvironment can have important effects on age-related chronic disease phenotypes and cognitive processes. [9] Kirkland has suggested use of chronologically-aged mouse chronic disease models, progeroid bred with chronic disease mouse models, or chronic disease mouse models treated with "age accelerating" interventions such as high fat diets. [9]

Likewise, in human studies, the greatest challenge to understanding the complex interplay of cancer and its therapy against the backdrop of aging processes is the lack of inclusion of the older age group in many research studies and clinical trials. As noted in the preceding sections, it will be important to include sufficient numbers of older patients to capture variability in reserve and frailty, effects of different classes of therapeutic agents, and the impact of other chronic diseases and biological processes.

To fully understand the trajectory of cognitive declines, it is also essential to assess baseline function and follow patients longitudinally. A well-matched non-cancer control group is also essential to valid inference, but can be difficult in older populations given the high rates of cognitive disorders and other chronic diseases and medications that affect cognition. Thus, well specified inclusion criteria and matching based on multi-morbidities should be considered. Care must be taken to use instruments that are validated in the target population. Moreover, issues of "cognitive reserve" [7,152] must be taken into account through appropriate control for estimated premorbid ability, educational attainment, and other proxy measures of this construct. Although many investigators strive for abbreviated cognitive assessments with older patients, in part because of the need to avoid potential fatigue effects from longer test batteries, it is critical that the brevity is balanced by an adequate evaluation of the cognitive domains hypothesized to be impacted by treatment (Table 1).

Recruiting older participants also requires sensitivity to needs of this group, including the need for larger fonts, hearing and ambulatory assistance, pacing of testing sessions, and having protocols to address research-detected cognitive decline.

To the extent feasible, studies should include frailty measures and other markers of age-related processes and biospecimens for correlative science analyses to elucidate biologically plausible mechanisms specific to older hosts (e.g., markers of cell senescence).

Analyses of data from older patients could consider use of trajectory analysis [153] in addition to use of group means and changes in group means. Informative missing data on covariates and cognitive outcomes as well as the impact of practice effects will be especially important to consider when following older age groups longitudinally. As in other observational research, the analysts will need to consider the role of confounding due to the common factors affecting systemic treatment selection and those placing older women at risk for cognitive declines.

Across a variety of cancers and types of treatment, the magnitude of cognitive effect tends to vary by choice of control group; this has not been empirically evaluated in older patients, but should be even more important than in studies of younger patients. For instance, in several meta-analyses, the largest effects (medium to large effects based on SD-effect sizes) were noted when cancer patients were compared to population normative values; moderate changes were seen when patients were compared to healthy non-cancer controls matched on age and education. [17,18,20,154,155] In studies of younger breast cancer patients, effects appear to be the smallest when patients are compared to their own baseline, pre-treatment function, [154] although practice effects may account for some of the lack of effect if

alternative forms of tests are not employed. As suggested by Ahles, Wefel and others, these average effects may mask meaningful declines among sub-groups. As they note, when declines in performance are combined with improved performance as a result of practice for the majority of patients, the effect of chemotherapy on cognitive declines may be underestimated. [34,156]

Practice Implications

From the preceding review it is apparent that there is a fairly strong body of evidence linking aging processes to cancer-related cognitive declines. But it is also clear that there are many unanswered questions. While the research community grapples with how to provide rigorous empiric evidence for older cancer patients, clinicians are faced every day with caring for the growing number of older cancer patients presenting to their practices. What then are the implications of what we think we know about cancer-related cognitive decline for the care of older breast (and other) cancer patients?

The obvious implication for oncology training is that it includes education on geriatric assessment and that geriatric assessments should be part of routine care since they can provide information on frailty phenotypes and reserve. [157] The results of geriatric assessment could be used as a tool for identifying sub-groups of older patients who are likely to be at highest risk for cognitive decline after systemic therapy. This information could be used together with clinical data and results of tumor multi-gene profiles in discussions with patients about the balance of benefits and harms of systemic therapy. Geriatric assessment data could change treatment recommendations, especially when indications for systemic therapy are equivocal, since cognitive changes are among the symptoms most feared by older adults. [158–161]

Geriatric assessment could also be used to identify the population of “pre-frail” older cancer patients that might need close monitoring and intervention during and after cancer systemic therapy. In addition, our review suggests that interventions that prevent frailty and maintain function could be useful in preventing or ameliorating cognitive decline among cancer patients.

There is a relative paucity of human studies designed to evaluate interventions to treat cancer-related cognitive changes compared to the large body of literature describing the phenomenon, although there are data from animal models that are informing new approaches. Unfortunately, most studies in humans and animals have generally not included or not been focused on older patients (or animals). [162] There are, however, studies in Alzheimer’s disease with older patients that may have relevance to the cancer setting, including behavioral and pharmacological interventions. Existing interventions have reviewed elsewhere, [163] and are briefly summarized briefly.

One prominent behavioral approach is cognitive training. In younger cancer patients, cognitive therapy, including rehearsing compensatory strategies was noted to improve cognitive function, [164] but this effect was not noted in other studies. [165] Similar interventions have also been successful in older Alzheimer’s patients. [166] A review of factors associated with prevention of age-related cognitive decline reported evidence that physical exercise and possibly diet could be efficacious behavioral interventions.[166] Exercise has been protective of decline after chemotherapy in rodents. [167] Increasing antioxidants via dietary change has been shown to be protective of cognitive decline in animal models. [60] Interestingly, in preliminary trials with non-smoking, non-cancer patients with mild cognitive impairment, transdermal nicotine was safe and improved cognitive function, possibly via stimulation of nicotinic acetylcholine receptors. [168] These data suggest the value of conducting trials to provide evidence to support incorporation of some

of these approaches in to clinical care to preserve cognitive function in older cancer survivors.

There are several promising pharmacological interventions that have been tested largely in animal models.[163] Fluoxetine have been shown in animal models to prevent behavioral and hippocampal deficits associated with older chemotherapy regimens, such as 5-Flourouracil. [169,170] These approaches have not yet been replicated in older animals, translated to clinical settings with humans, or tested for safety or interactions with chemotherapy efficacy. It will be important to include sufficient numbers of older patients when these studies are conducted. In human research, two studies have demonstrated the efficacy of modafinil, a psycho-stimulant, in improving memory and attention and reducing fatigue in cancer patients. [171,172] Herbal compounds such as Gingko biloba are under evaluation in ongoing cancer trials[163] and Alzheimer's treatment drugs have been examined in patients undergoing brain irradiation.

Given the parallels between aging, frailty and cognitive decline in cancer patients, it is also logical that interventions that prevent frailty could be useful as targets for older cancer survivors. These "anti-aging" models have been examined largely in animal models and include caloric restriction, rapamycin, protein aggregation inhibitors, and removal of senescent cells. [9]

As the validity of personalized medicine becomes more established, understanding the genetic profiles of older patients at the greatest risk for cognitive decline could also be useful in clinical decision-making about systemic therapy and risk of cognitive decline. These data could also contribute to the next generation of pharmacogenetic studies that investigate which medications best prevent cognitive effects in vulnerable women and which systemic therapies are most and least likely to lead to cognitive toxicity in older women. [173,174]

Conclusions

There is a strong albeit non-universal body of literature supporting the phenomenon of cognitive decline after breast cancer and its systemic therapies. This side effect is likely to be only experienced by a sub-group of patients, and while risk factors have been identified, biological mechanisms and pathways have not been fully elucidated. From what we do know, it appears that there are common underlying processes at the intersection of cancer, aging and the frail phenotype. Geriatric assessment could be a useful tool to aid in treatment decision making and identify the sub-groups most vulnerable to adverse cognitive outcomes.

Given the demographic imperative of a rapidly growing older population, increasing cancer incidence with advancing age and the increasingly chronic nature of breast cancer, research in older cancer patients and survivors will be critical to providing the evidence for practice guidelines.

Thus, we recommend that designing and conducting basic science and population trials specifically for older cancer patients should receive high priority. These studies should include intermediate endpoints of relevance to this group, including cognitive function and trajectories of frailty. [175–177] Clinicians and their older patients can advance the field by active encouragement of and participation in research designed to improve the care and outcomes of older cancer patients.

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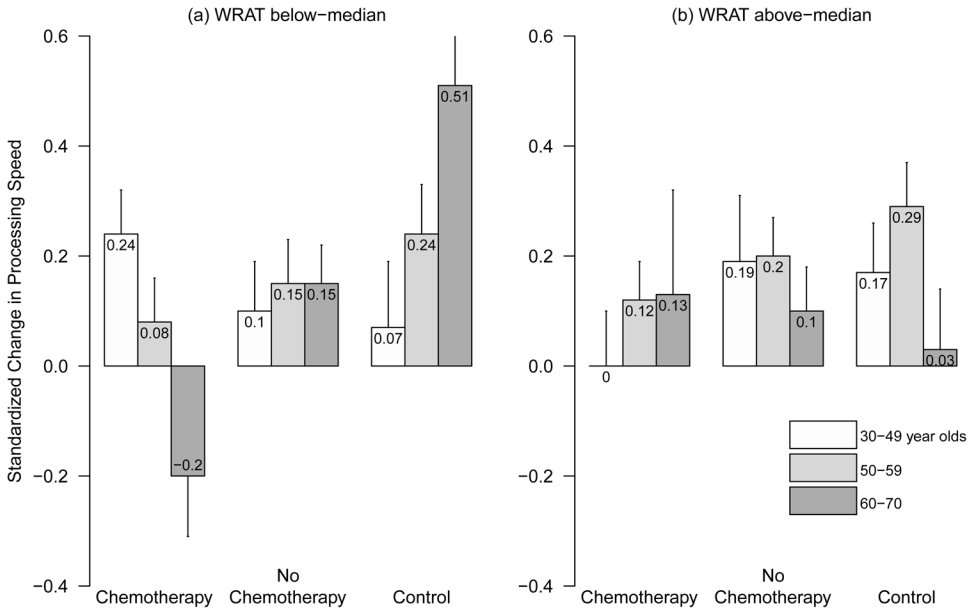

Figure 1.

Change in Processing Speed by Treatment, Age group, and Cognitive Reserve Among Breast Cancer Patients

Pre- to post-treatment change in processing speed by treatment, age groups, and level of cognitive reserve (assessed by the Wide Range Achievement Test (WRAT)-Reading). Reprinted with permission from Ahles et al 2012, *Journal of Clinical Oncology* [5]

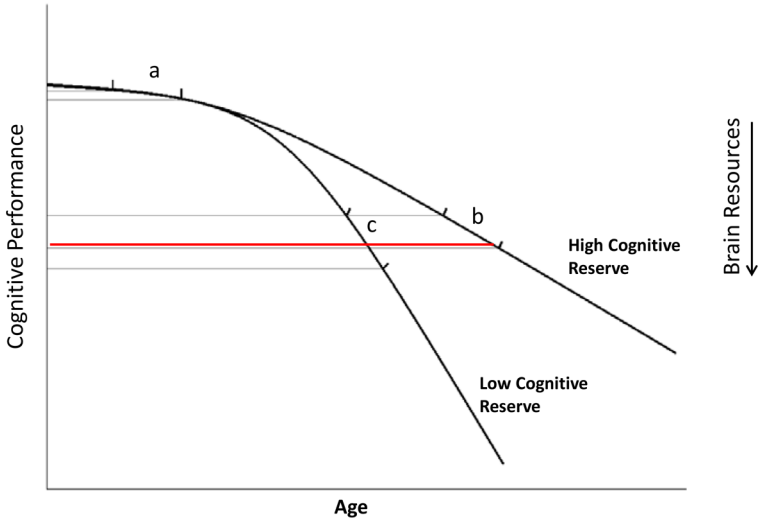

Figure 2.

Impact of Change in Brain Resources and Frailty Levels on Cognitive Performance by Age

The same change in brain resources can have a minimal effect on cognitive performance in a young adult (a), a moderate effect in an older adult with high cognitive reserve (b) and a greater effect on an older adult with low cognitive reserve (c). Likewise, the same change in frailty level will have differential effects on the individual as a function of overall system reserve.

Adapted and reprinted with permission from Ahles et al, *Psychooncology* 2012 [24]

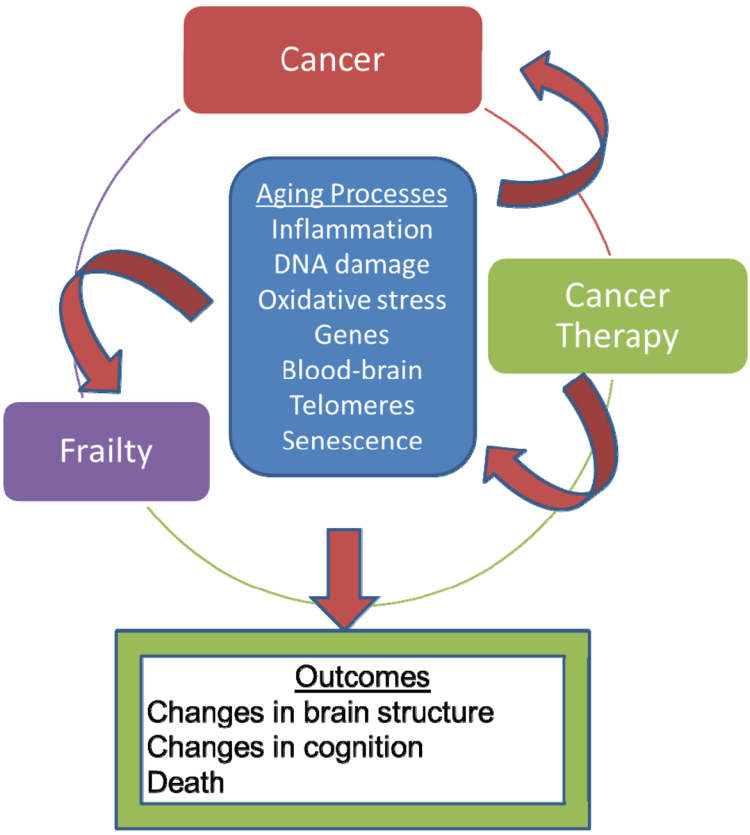

Figure 3.
Postulated Common Underlying Aging Processes Associated with Frailty, Cancer and Cancer Systemic Therapy and their Impact on Cognitive Outcomes

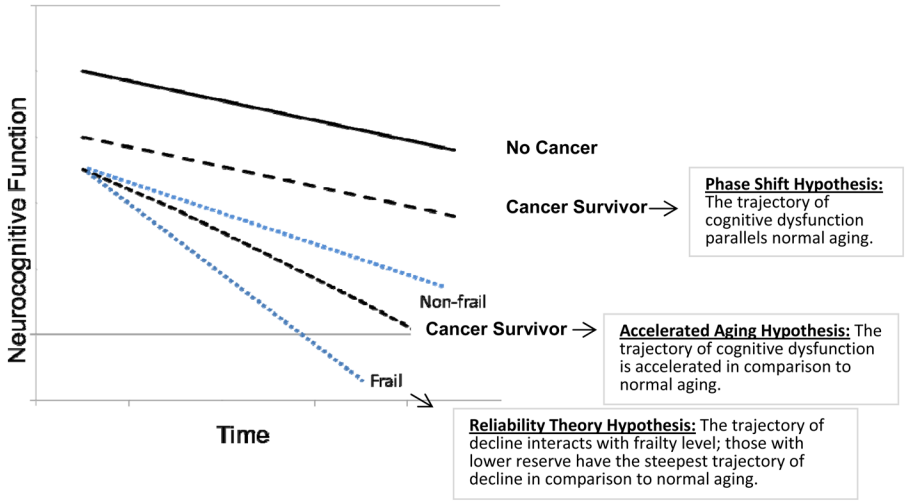

Figure 4.

Trajectories of Cognitive Decline Based on Theories of Aging and Frailty Phenotype Adapted from Ahles et al, 2012 *Journal of Clinical Oncology* [5]

Table 1

Domains of Cognitive Function Frequently Affect by Cancer and Cancer Systemic Therapy and their Implications for Daily Activities in Older Cancer Patients

Domain	Common Tests	Examples of Impact on Functioning
Executive Functioning, Working Memory, Psychomotor Speed	Trailmaking Parts A & B, Digit Symbol, Controlled Oral Word Association Test (COWAT), NAB Driving Scenes, Timed Instrumental Activities of Daily Living (TIADL), NAB Figure Drawing	Ability to organize activities, arrive on time, make plans and decisions, correct errors and conceptualize.
Attention	NAB Digits Forward, NAB Digits Backward	Ability to pay attention to new information and process the information quickly.
Language	Boston Naming Test, Category Fluency	Ability to fluently bring words to mind.
Learning and Memory	Logical Memory I and II Wechsler Memory Scale (WMS-4), NAB List Learning	Ability to learn or recall new information.
Visual spatial	NAB Figure Drawing Copy Subscale	Ability to integrate visual information with motor activities.