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Cognitive Performance in Survivors of Breast Cancer and Markers of Biological Aging

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BACKGROUND: Biological aging pathways accelerated by cancer treatments may be a mechanism for cognitive impairment in cancer survivors. The goal of the current study was to examine whether indicators of biological aging, namely elevated levels of DNA damage, reduced telomerase enzymatic activity, and shorter peripheral blood mononuclear cell (PBMC) telomere length (TL) would be related to cognitive function in a cohort of survivors of breast cancer. **METHODS:** The authors evaluated a cross-sectional sample of 94 women aged 36 to 69 years who were treated for early-stage breast cancer 3 to 6 years previously. Leukocyte DNA damage, PBMC telomerase enzymatic activity, PBMC TL, and the inflammatory marker soluble tumor necrosis factor receptor II (sTNF-RII) were determined from blood samples. Cognitive function was assessed using a neuropsychological test battery and self-report. Linear regression models examined the relationship between biological aging predictors and cognitive outcomes. **RESULTS:** Both higher DNA damage and lower telomerase were found to be statistically significantly related to lower executive function scores adjusting for age, body mass index, race, years from treatment, and intelligence score (standardized coefficients [B], -0.23 and 0.30; all *P* values <.05). In addition, lower telomerase activity was associated with worse attention and motor speed scores (B values, 0.30 and 0.24; *P* <.05). sTNF-RII and TL were found to be unrelated to any of the neurocognitive domains. **CONCLUSIONS:** The results of the current study suggest a significant association between measures of biological aging and objective measures of cognitive performance in survivors of breast cancer. Future prospective studies are needed to confirm a causal role of biological aging as a driver of declines in cognitive function after cancer treatment. ***Cancer* 2018;000:000-000**. © *2018 American Cancer Society.*

KEYWORDS: biological aging, breast cancer, cognition, DNA damage, executive function, survivors, telomerase.

INTRODUCTION

Breast cancer is the most common cancer in women, with >260,000 new cases expected in the United States in 2018.[1] There are estimated to be >3 million survivors of breast cancer in the United States due to substantial advances in the detection and treatment of the disease.[1,2] However, treatments also increase the risk of long-term and late toxicities, including persistent fatigue, pain, and cognitive dysfunction. Further research is needed to better understand the factors that contribute to these adverse secondary health outcomes.[3–6]

In the current study, we focused on cognitive dysfunction in survivors of breast cancer and its association with processes that are part of biological aging, paralleling the aging related phenotype observed in some cancer survivors.[7,8] Cancer treatments, particularly radiotherapy and some chemotherapeutic agents, work by damaging the DNA of cancer cells, thus preventing cell replication and causing cell death. However, these same treatments can induce damage to the DNA of normal cells,[9,10] causing acute elevations in inflammation[5,11–13]; increasing expression of a marker of cellular senescence, $p16^{INK4A}$; and having detectable effects on telomerase activity and DNA damage years later,[15] all factors that contribute to accelerated biological aging.[14,16–24] However, to the best of our knowledge, few studies to date have examined whether biological aging plays a role in cognitive dysfunction in patients with cancer and cancer survivors.

Conroy et al reported that among survivors of breast cancer who were 3 to 10 years from treatment, elevated DNA damage was associated with reduced gray matter density, particularly in regions demonstrating compromise, suggesting that this marker could relate to cognitive function in cancer survivors many years after the completion of

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treatment.[9] More research has focused on the association between various markers of inflammation and cognitive dysfunction in cancer survivors.[13,25–28] The extant literature supports a role of biological aging and inflammation in cancer-related cognitive difficulties, but substantial gaps remain. Despite some initial investigations of the relationship in aging populations,[29–32] to our knowledge no study has yet examined whether cellular markers of biological aging correlate with objective and subjective cognitive function in cancer survivors. The goal of the current study was to test the hypothesis that cellular markers of biological aging and inflammation are related to worse subjective cognitive impairment and objective neuropsychological function in survivors of breast cancer.

MATERIALS AND METHODS

Participants

Participants for the current study were recruited from the University of California at Los Angeles Mind-Body Study (MBS), a longitudinal, prospective cohort study of women with early-stage breast cancer who enrolled after the end of primary treatment and prior to initiating adjuvant endocrine therapy if indicated.[33–35] Full details of the design, eligibility/exclusion criteria, recruitment, and procedures used in the MBS are described elsewhere,[33–37] and are summarized here. The MBS was designed to assess cognitive changes due to endocrine therapy for breast cancer. Study eligibility for the MBS required that women were aged 18 to 65 years, had received a diagnosis of stage 0 to stage IIIA breast cancer (TNM staging system), and were fluent in English. Women were excluded from participation if they had any immune-related conditions such as autoimmune disease, evidence of uncontrolled depression, or a neurological condition.

MBS participants underwent comprehensive neurocognitive assessments as well as blood specimen collection at the time of study enrollment and 6 months and 12 months later. Immediately after the 12-month MBS study visit, participants were invited to join a long-term follow-up study that included annual questionnaires that assessed cognitive symptoms and other behavioral symptoms on an annual basis. After several years of follow-up, these participants were invited for an in-person assessment that occurred between 3 to 6 years after the time of the initial study enrollment, the timepoint of the current analyses. Of the 190 women in the original MBS cohort, 170 agreed to participate in the follow-up study and 94 of these women ultimately attended an in-person visit that replicated the initial neuropsychological assessments and blood specimen collection for inflammatory markers, as well as the assessment of telomerase, DNA damage, and telomere length (TL). English was not the first language of 1 participant, and her neuropsychological data were excluded from the analyses, resulting in a sample of 93 participants for models of neuropsychological domains only; otherwise, the study sample comprised 94 participants. All procedures were approved by the University of California at Los Angeles institutional review board, and all participants provided informed consent.

Subjective Cognitive Function

Subjective cognitive function was measured with the Functional Assessment of Cancer Therapy–Cognitive Function (FACT-Cog; version 3),[38] a valid and reliable self-report instrument of cancer-related cognitive difficulties. The FACT-Cog subscale measuring perceived cognitive impairment (range, 0-72) was selected as the main outcome because it is recommended by the scale's developers, with psychometric properties and scoring guidelines available from the FACT Web site (https://www.facit.org/).

Neuropsychological Testing

A comprehensive neuropsychological battery was administered to all participants. Raw test scores were population normalized and transformed into z scores and averaged to produce the following 6 key domain scores: learning, memory, attention, visuospatial, executive function, and motor speed. Additional details regarding specific tests used in the assessments of each domain can be found in Table 1.[39–48]Analyses examining cognitive function were adjusted for age and premorbid estimates of intelligence quotient as determined by Wechsler Test of Adult Reading (WTAR) scores.[49]

Telomerase

To determine telomerase activity, the telomere repeated amplification protocol was performed as previously described.[15] Values were expressed as the total telomerase product generated per 10,000 cells.

DNA Damage

DNA damage was determined using the comet assay as reported by Singh et al[50] with minor modifications,[51] and has been described previously.[15] The comet assay is a single-cell gel electrophoresis assay that assesses the extent of DNA damage in nucleated white blood cells by applying a computerized scoring algorithm. The extent of DNA damage is estimated from approximately 100 comets per sample analyzed by CASP software (CaspLab, Wroclaw,

TABLE 1. Neuropsychological Tests Administered to Patients in the Mind-Body Study

Domain	Test/Measure
Learning	CVLT-II list A total trials 1-5[39] WMS-IV LM I[40] BVMT-R total trials 1-3[41]
Memory	CVLT-II list A long delay free recall[39] WMS-IV LM II[40] BVMT-R delayed recall[41] ROCFT 3-min delayed recall[42]
Attention	WAIS-IV digit span, coding, letter-number sequencing, and symbol search[43] TMT A[44] PASAT[45]
Visuospatial	ROCFT copy[42] WAIS-IV block design[43]
Executive functioning	TMT B Verbal fluency[46,47]
Motor speed	Grooved pegboard[48]

Abbreviations: CVLT-II, California Verbal Learning Test-II; BVMT-R, Brief Visuospatial Memory Test, Revised; PASAT, Paced Auditory Serial Attention Test; ROCFT, Rey-Osterrieth Complex Figure Test; TMT, Trail Making Test; WAIS-IV, Wechsler Adult Intelligence Scale–4th edition; WMS-IV LM, Wechsler Memory Scale, 4th edition, Logical Memory.

Poland)[52] and values are expressed as a mean score from 0 to 4 (maximum damage/large tail).[53]

Telomere Length

TL was determined using real-time quantitative polymerase chain reaction methodology as described in previously published TL protocols,[54–56] and in the previous study.[15] Genomic DNA was extracted from peripheral blood mononuclear cells (PBMCs). The telomere interassay and intra-assay coefficients of variation all were <5%. Using the standard curve method, values were determined for telomere DNA repeat sequences (T) and the <HGB single-copy gene (S); TL values are expressed as the T/S ratio.

Circulating Inflammatory Marker: Soluble TNF Receptor II

Previously, we reported soluble tumor necrosis factor receptor II (*s*TNF-RII) as being elevated after treatment, associated with cognitive symptoms, and higher in those with low telomerase activity and high DNA damage.[13,15,34] Thus we sought to determine the association between *s*TNF-RII and cognitive function in this follow-up study several years later. To do this, blood samples were collected at the time of the study visit by venipuncture into EDTA tubes, chilled, and centrifuged for the collection of plasma. Aliquots of plasma then were stored at -80 C until batch testing could be performed on all samples. *s*TNF-RII was assessed using enzyme-linked immunoadsorbent assays (R&D Systems, Minneapolis, Minnesota) as per the manufacturer's protocol; lower limits of detection were 234 pg/mL. All samples were run in duplicate with an average intra-assay and interassay precision of <5%.

Statistical Analyses

Analyses were conducted using SPSS statistical software (version 23; IBM Corporation, Armonk, New York). Descriptive statistics were calculated using the entire cohort of 94 participants. Distribution analyses demonstrated that DNA damage had modest skew and high kurtosis, such that the majority of individuals had low average damage scores. We created an upper quartile cutoff (≥0.85) to indicate high damage and compared this with the lowest 3 quartiles (<0.85), indicating low damage. Decile ranking of the telomerase data was performed to address nonnormal distribution of the data and these transformed values were used in statistical analyses whereas figures display raw telomerase values.

Linear regression models with adjustments for age, body mass index (BMI), race, and years from last treatment were performed to test the hypothesis that elevated levels of markers of biological aging, namely higher DNA damage, reduced telomerase enzymatic activity, shorter PBMC TL, and higher *s*TNF-RII, would be related to worse subjective cognitive impairment and objective neuropsychological function. Models testing predictors of neuropsychological test scores were adjusted further for WTAR. Linear regression models examined the relationship between predictors of DNA damage (highest quartile/lower 3 quartiles), telomerase enzymatic activity (in deciles), TL (shown as the T/S ratio), and *s*TNF-RII and self-reported cognitive functioning and neuropsychological testing domains (betas [β] reflect unstandardized coefficients and the standard error [SE], and "B" indicates standardized coefficients). To minimize the likelihood of false-positive observations, we corrected for multiple comparisons with the false discovery rate (FDR) procedure,[57] setting the FDR rate at 0.05 and calculating the threshold for tests within each cognitive domain. We report uncorrected *P* values, and the FDR-corrected q value threshold.

RESULTS

Demographics and clinical characteristics of the study participants are reported in Table 2. Participants ranged in age from 36 years to 69 years (mean age, 56.5 years), with an average time since treatment of 4.4 years. In

TABLE 2. Demographic Characteristics of Study Participants

Characteristic	Total N=94
Mean age (SD) [range], y	56.5 (8.1) [36.4-69.5]
Race	75 (80%)
White, non-Hispanic	8 (9%)
Hispanic	4 (4%)
Black	3 (3%)
Asian	4 (4%)
Other	
Mean BMI (SD) [range], kg/m^2	25.7 (5.1) [18-42.5]
Education	47 (50%)
After college	29 (31%)
College	18 (19%)
No college degree	
Mean y from treatment (SD) [range]	4.4 (0.6) [3-6.1]
Cancer treatment received	
Chemotherapy alone	11 (11.7%)
RT alone	28 (29.8%)
Both chemotherapy and RT	40 (42.6%)
Surgery alone	15 (16%)
Received endocrine therapy	72%
Postmenopausal status	80.9%

Abbreviations: BMI, body mass index; RT, radiotherapy; SD, standard deviation.

initial models, as was reported previously,[15] we examined the association between demographic and clinical characteristics and cellular aging measures. Age was found to be positively associated with DNA damage and inversely associated with telomerase activity, but was not found to be significantly associated with TL. Higher BMI was found to be related to shorter TL, a finding that is consistent with previous reports,[58] but unrelated to DNA damage and telomerase activity.

Self-Reported Cognitive Function

Neither DNA damage, telomerase activity, nor TL were found to be related to FACT-Cog perceived cognitive impairment scores after adjusting for age, BMI, years from last treatment, and race (all *P* values >.21). Likewise, sTNF-RII was not found to be a significant predictor of self-reported cognitive impairments (data not shown).

Neuropsychological Domains

For the most part, participants' neuropsychological domain scores were normally distributed, with mean scores consistently above 0, indicating generally intact status in the majority of the sample: learning: $\bar{x}$=0.46 (±0.85); memory: $\bar{x}$=0.43 (±0.74); attention: $\bar{x}$=0.54 (±0.56); visuospatial: $\bar{x}$=0.11 (±0.76); executive function: $\bar{x}$=0.43 (±1.12); and motor speed: $\bar{x}$=0.64 (±1.03). Likewise, very few participants' domain scores were <-2 the z score (ie, in the impaired range), and were ≤4 in any domain. High DNA damage was found to be associated with having a 0.23 lower standardized executive function score (*P*=.027; q=0.025) compared with low DNA damage, with a similar trend observed in the relationship between high DNA damage and lower memory scores (*P*=.06; q=0.013) in adjusted models (Table 3) (Fig. 1). Models testing the association between telomerase activity and cognitive domains demonstrated that with each decile decline in telomerase activity, there also was a 0.3 lower standardized attention (*P*=.006; q=0.013) and executive function (*P*=.002; q=0.013) score, and a 0.24 lower standardized motor speed (*P*=.037; q=0.013) score (Table 3) (Fig. 2). TL and sTNF-RII were found to be unrelated to cognitive domains in adjusted regression models (Table 3).

DISCUSSION

Cognitive difficulties after cancer treatment are a serious clinical concern and threat to quality of life in cancer survivorship. In the present cross-sectional analyses of a well-characterized cohort of survivors of breast cancer studied several years after the completion of treatment, we observed that markers of aging biology including high DNA damage and reduced telomerase activity were associated with worse neuropsychological performance after covariate adjustments. In particular, higher DNA damage was related to lower executive function scores, and low telomerase activity was related to lower executive function, attention, and motor speed scores. After adjusting for multiple comparisons, the association between DNA damage and executive function and between telomerase and motor speed were no longer considered significant at q=0.025.

The findings of the current study provide evidence of an association between aging biology and the cognitive domains commonly affected in both cancer-related cognitive impairment[59,60] and normal aging.[61] The observed relationships were not dramatic; in both the executive function and motor domains, the difference between those in the lowest and highest deciles was reported to be within 1 standard deviation. These modest differences in neuropsychological function are consistent with the subtle declines of both age-related and cancer-related cognitive changes. Furthermore, even those participants in the lowest decile were performing within the average range, an unremarkable performance clinically. However, subtle changes noted in cognitive function are consistent with what is known regarding cancer-related cognitive difficulties,[59] and nonetheless can result in noticeable changes in daily functioning and quality of life.

With regard to the role of inflammation, our previous work found that sTNF-RII was elevated early after

TABLE 3. Multivariate Analyses Examining Aging Biology Parameters as Predictors of Neuropsychological Test Scores, Adjusting for Age, BMI, Race, Years From Treatment, and Intelligence Score (WTAR)

	DNA Damage (High Versus Low) N=93			Telomerase, Deciles N=84			Telomere Length, T/S Ratio N=85			sTNF-RII, pg/mL N=91		
Neuropsychological test domain	β (SE)	B	*P*	β (SE)	B	*P*	β (SE)	B	*P*	β (SE)	Beta	*P*
Learning	−0.348 (0.22)	−0.18	.12	−0.001 (0.03)	−0.003	.98	0.092 (0.34)	0.029	.79	0.00 (0.00)	−0.08	.50
Memory	−0.371 (0.20)	−0.22	.06	0.019 (0.03)	0.076	.50	0.075 (0.31)	0.027	.81	0.00 (0.00)	−0.05	.70
Attention	−0.231 (0.15)	−0.18	.12	**0.058 (0.02)**[a]	**0.301**	**.006**	−0.155 (0.23)	−0.075	.50	0.00 (0.00)	−0.09	.45
Visuospatial	−0.289 (0.21)	−0.16	.16	0.044 (0.03)	0.162	.15	0.198 (0.32)	0.069	.54	0.00 (0.00)	−0.03	.78
Executive function	**−0.599 (0.27)**	**−0.23**	**.027**[b]	**0.118 (0.04)**	**0.300**	**.002**	0.042 (0.42)	−0.010	.92	0.00 (0.00)	−0.12	.28
Motor speed	−0.154 (0.28)	−0.07	.58	**0.083 (0.04)**	**0.239**	**.037**[b]	−0.515 (0.43)	−0.134	.24	0.00 (0.00)	−0.11	.38

Abbreviations: β, beta, unstandardized coefficient; B, standardized coefficient; BMI, body mass index; SE, standard error; sTNF-RII, soluble tumor necrosis factor receptor II; T/S ratio, ratio of telomere repeats to a single-copy gene; WTAR, Wechsler Test of Adult Reading.

[a]Bold type indicates statistical significance.

[b]Denotes criterion for significance was not met after correction for multiple testing using the false discovery rate (q = 0.025).

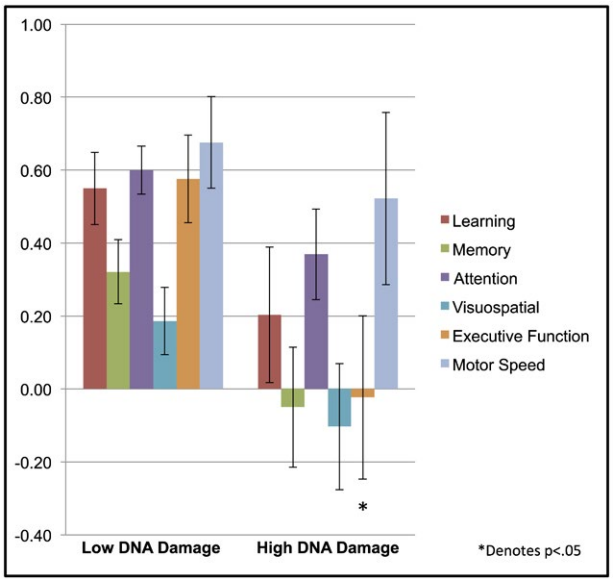

Figure 1. Mean population-normalized neuropsychological test score by domain in cancer survivors categorized by low DNA damage and high DNA damage.

chemotherapy, and was associated with cognitive difficulties.[13,33,34] In the current follow-up of 3 to 6 years after treatment, sTNF-RII was found to be unrelated to subjective or objective cognition cross-sectionally; however, we previously reported that both DNA damage and telomerase activity were associated with inflammation.[15] Exposure to elevated inflammation immediately after treatment with chemotherapy and/or radiotherapy could be an early indicator of risk of biological aging, with lasting DNA damage and changes in telomerase activity indicating sustained aging effects. In this regard, several other potential markers of aging might be considered for future research. For example, extensive cell replication cycles or cell stress pathways can induce cellular senescence.[62,63] Future work might consider whether cellular senescence in the periphery and in the brain are associated with cognitive function after treatment. Further research is needed to disentangle the temporal relationship between treatment, inflammation, DNA damage, cell senescence, and cognitive function. Because to the best of our knowledge the current study is among the first to begin investigating these mechanisms, substantial additional work is needed to address these hypotheses.

It is interesting to note that no associations were found between cellular aging markers and subjective cognitive functioning in the current study, similar to the findings of Conroy et al.[9] Subjective cognitive functioning in cancer survivorship is complex and does not consistently tightly correspond to neuropsychological performance,[64] but also may be associated with other factors such as mood and stress.[65] Therefore, despite our observed relationships between aging markers and neuropsychological performance, the multifactorial nature of subjective cognitive functioning may be less strongly linked to specific biological processes. Given the cross-sectional nature of the current study, it will be important to continue examining these relationships in longitudinal study designs.

Contrary to our hypothesis, PBMC TL was found to be unrelated to cognitive function domain scores. A lack of

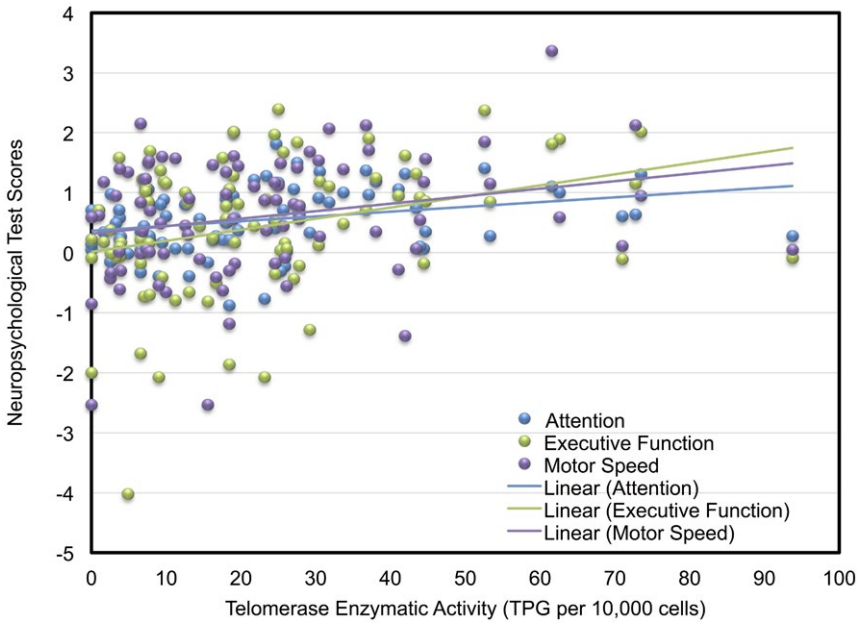

Figure 2. Scatterplot of population-normalized attention, executive function, and motor speed scores as a function of telomerase enzymatic activity in survivors of breast cancer. Lower scores indicate worse cognitive performance. TPG indicates telomerase product generated.

an association suggests that this measure of biological age is not necessarily capturing the specific pathways of aging that occur after cancer treatment. Consistent with this finding, we did not observe an effect of cancer treatment on TL in our previous report,[15] similar to other studies.[14] Thus, cancer treatments may not accelerate aging by contributing to blood cell TL shortening per se, but rather via induction of DNA damage and cell senescence.[14] Indeed, TL shortening is driven by cell replication, a process that often is halted during cancer treatments.[66] Conversely, cellular senescence is reached through either cell replication cycles (that shorten telomeres) or cell stress pathways (eg, extensive damage to DNA). It also is possible that a one-time sampling approach fails to capture temporal dynamics. Further research should consider within-individual changes in TL from before to after treatment as an indicator of cellular aging and assess the extent to which this is predictive of cognitive function.

Regardless of the pathway to senescence, senescent cells no longer divide and express very low levels of telomerase activity. Thus, our measure of telomerase activity may reflect the extent of senescence within PBMCs, regardless of whether it is replicative or stress-induced senescence.[21] Telomerase also can repair DNA damage, and helps to resist stress-induced growth arrest,[20–23] suggesting that the enzyme is important for defense against cell aging independent of its role in protecting telomeric ends.

The current analyses were performed in a cross-sectional sample of women after the completion of treatment of breast cancer, and therefore causal pathways cannot be confirmed. We recognize that an alternative interpretation also could be made, namely that cognitive function may impact telomerase activity and contribute to DNA damage by modifying behavior. Future research should consider the additional assessment of these markers earlier after the course of treatment including before, during, and after cancer treatment, which may yield important information regarding early indicators of vulnerability to developing cognitive difficulties that can signal the need for intervention or prevention. Additional study limitations include a relatively well-educated sample with generally intact cognitive function, limited diversity in terms of racial/ethnic groups, and a relatively young cohort of women, resulting in a possible sampling bias. The lack of representation of higher risk groups, including older women and those with a wider range of cognitive impairment, may contribute to smaller detected effects. Future studies in more diverse samples with regard to age, race and ethnicity, and socioeconomic backgrounds are needed. Another limitation is the small sample size,

which limited our ability to measure smaller effects, raising the possibility of a type II error. Studies with larger sample sizes are needed to determine whether effects that were subthreshold are detectable with more power. Along this line, the reported medium effects for the associations between DNA damage and executive function and telomerase and motor speed scores did not survive the FDR correction for multiple tests.

In light of the findings of the current study, future work is warranted to further investigate the mechanistic role of aging as a key factor contributing to elevated inflammation and poorer cognitive function, a symptom commonly experienced by patients with cancer years after completing treatment. Future research might consider examining aging pathways in current interventions that target cognitive function, diet, and physical activity. Such behaviors are known to modify inflammatory signaling,[67–72] telomerase activity,[73] and cellular aging pathways,[74] but to the best of our knowledge have not yet been tested within the context of cancer and aging. Other possible avenues of research may be manipulating mechanisms of cellular senescence with pharmaceutical agents and using mouse models[75–77] to characterize plausible targets for intervention.

The results of the current study add support for an accelerated aging model of cancer-related cognitive impairment, and harmonize with other studies in noncancer populations pursuing the link between these markers and cognition.[29,30] Together, these findings point to an aging-like effect of cancer treatments on cellular biology and further connect this to cognitive function. An important future research objective will be examining comprehensive and well-powered models that include repeated assessments of neuropsychological function, cellular aging markers, inflammation, and neuroinflammatory factors.

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CONFLICT OF INTEREST DISCLOSURES

Judith E. Carroll has served on the Peer Review Committee of the American Cancer Society. Patricia A. Ganz is a Scientific Advisory Board member of the Breast Cancer Research Foundation.

AUTHOR CONTRIBUTIONS

Judith E. Carroll: Conceptualization, data curation, formal analysis, methodology, visualization, and writing–original draft. **Kathleen Van Dyk**: Data curation, visualization, and writing–review and editing. **Julienne E. Bower**: Conceptualization, formal analysis, investigation, methodology, project administration, supervision, and writing–review and editing. **Zorica Scuric**: Data curation, investigation, methodology, and writing–review and editing. **Laura Petersen**: Data curation, formal analysis, investigation, methodology, and writing–review and editing. **Robert Schiestl**: Conceptualization, data curation, methodology, and supervision. **Michael R. Irwin**: Conceptualization, investigation, methodology, project administration, resources, supervision, and writing–review and editing. **Patricia A. Ganz**: Conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, software, supervision, validation, and writing–review and editing.

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