Central arterial stiffness is associated with cognitive decline and cardiovascular disease manifestation in cancer survivors in the Framingham Heart Study

by

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Abstract

Introduction – Cancer survivors experience disproportionate prevalence of cognitive deficits and higher risk of CVD, due to a combination of shared biological mechanisms and anticancer treatment cardiotoxicity. Central artery stiffening, which increases following cancer diagnosis, inhibits pulsatile flow damping and potentiates microvascular damage, particularly within the cerebral circulation. Associations between central arterial stiffness and the risks of incident mild cognitive impairment (MCI), CVD diagnosis, and all-cause mortality have been previously established in the general population. However, there is a paucity of evidence on the association between arterial stiffness and cognitive decline among cancer survivors.

Hypothesis – We hypothesized that declines in cognitive function would be associated with a higher central arterial stiffness and that cognitive function and central arterial stiffness would predict risk of CVD diagnosis and all-cause mortality in a large cohort of diverse cancer survivors.

Methods – We evaluated dementia-free cancer survivors in the Framingham Original and Offspring Cohorts (n=277, 80±12.3 years old, 56.7%women, 9.3±8.8 years from first diagnosis) with baseline carotid-femoral pulse wave velocity (cfPWV) measurements. During baseline and subsequent examinations (mean follow-up 7.7±3.9 years), the Mini-Mental State Examination (MMSE; global cognitive function) and neuropsychological exams (NP; executive function, learning and memory) were evaluated. Multivariable linear and logistic regression models determined the relationship between cfPWV and cognitive decline and MCI. Multivariate Cox Regression related cfPWV and cognitive function to the risk of CVD diagnosis and all-cause mortality. Multivariate models were adjusted for age, sex, depressive symptoms, and traditional CVD risk factors.

Results – Higher cfPWV at baseline was significantly associated with a greater rate of decline in global cognitive function (ΔMMSE) (p=0.003). Higher cfPWV was also significantly associated with clinically defined MCI, whether denoted by an impaired MMSE (OR(95%CI): 9.2(2.5-33.5), p=0.001) or NP score (4.3 (1.4-13.0), p=0.009) in univariate logistic models. In the final model, there was a 3.4-fold increase in risk of CVD in cancer survivors with high cfPWV (HR (95%CI): 3.45 (1.04-11.66), p=0.04). Changes in cognitive function were not associated with CVD outcomes.

Conclusion – Our findings suggest an association between central arterial stiffness, future cognitive decline, and an increased risk of CVD in a diverse cohort of cancer survivors. Our findings support the potential adverse consequences of a stiffening arterial vasculature following cancer diagnosis; specifically, those related to cognitive function and long-term CVD outcomes.

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Acknowledgements

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Dedication

This work is dedicated to the late Tucker Lee, a dear friend of mine and many others, whose battle with cancer ended on June 9th, 2021. Tucker's story has been close to my heart while working on this project and provided enigmatic perspective and motivation.

Chapter 1 - Introduction

Over the past 30 years, advancements in cancer detection, treatment, and supportive care have reduced the cancer death rate by 31% (56), with approximately 17 million cancer survivors alive in the United States as of 2019 (37). Importantly, by 2040 this number is projected to grow to 26 million and consist predominantly of survivors who are 65 or older (9). Thus, with the number of aged cancer survivors progressing at an unprecedented rate (55), a majority of cancer patients are expected to live long enough to develop secondary pathologies. Recent studies across a spectrum of cancer types have demonstrated that many patients who survive their cancer diagnosis are at a higher risk of both cognitive decline across multiple domains (e.g., executive function, learning and memory, attention, and processing speed) (34, 41) as well as cardiovascular disease (CVD) manifestation (6, 31) compared to the general population. Therefore, for this population, maintaining quality of life years into survivorship is dependent on our understanding of risk factors within the pathological continuum of secondary outcomes.

Adverse age-related stiffening of the large central arteries, like that which occurs during cancer treatment and into survivorship (10, 12, 19, 47, 57), promotes pressure pulsatility entering distal vasculature. In youth, primary pulsatile flow damping occurs in the highly compliant aorta whose distensibility and elastic recoil redistribute energy throughout the cardiac cycle. Conversely, conduit arteries (e.g. carotid) branching off the aorta are much less compliant, which presents an impedance mismatch that reflects the pulse wave and protects downstream microvasculature from pulsatile energy. The pulse wave reflection returns to the heart during diastole, beneficially raising pressure in the proximal aorta that drives perfusion in coronary circulation when its resistance is at its lowest (38, 44). With aging, elastin fragmentation occurs

in elastic arteries and aortic distensibility moves from highest to lowest in the body causing pulsatile damping in the aorta to be inhibited. Thus, the velocity at which pulse waves travel down the aorta can increase 2–3-fold (59). This increased pulse wave velocity means reflections now return to the heart during systole, compromising coronary perfusion and augmenting systolic blood pressure instead of diastolic (38, 44). Critically, flow reaching the peripheral conduit arteries now has greater pressure and velocity pulsatility. This, in conjunction with the now less profound impedance mismatch, and hence, less pulse wave reflection, results in penetration of pulsatile flow into the downstream vasculature (29). This pulse wave propagation in distal vasculature potentiates microvascular distress, structural and functional abnormalities, and end-organ damage (38).

Importantly, organs such as the brain and kidney that require both high flow and low resistance vasculature are more susceptible to end-organ damage as they are not well equipped to dampen flow pulsatility (2, 61). With respect to cerebral circulation, these pulsations travel through cerebral microvasculature and can be detected on the venous side even prior to loss of large central artery compliance (65). In the middle cerebral artery, which is a continuation of the internal carotid artery and one of three major arteries perfusing the cerebrum, pulsatility index has been demonstrated to be significantly influenced by discordant aortic versus carotid artery stiffening, increase with age (29), and be higher in those with Alzheimer's disease and vascular dementia (23, 52). Mechanistically, a chronic increase in pulse pressure can functionally and structurally compromise cerebrovascular endothelium, whose crucial roles involve matching perfusion to neural activity (i.e., functional hyperemia or neurovascular coupling), and modulation of vascular tone in response to mechanical shear stress (13, 14, 24). Cerebral

microvascular endothelial damage involves disruption of tight junctions, increased blood brain barrier (BBB) permeability, and dysregulation of cerebral blood flow — all of which may lead to microhemorrhages, white matter hyperintensities, and silent lunar infarcts, and are associated with senescence, inflammation, oxidative stress, cerebral hypoperfusion, and cognitive decline (14, 61).

Despite numerous studies demonstrating an association between measures of arterial stiffness and cognitive decline in the general population (40, 48, 63, 71), there remains a paucity of evidence which demonstrates the relationship between increases in central arterial stiffness and cognitive decline during cancer survivorship. Therefore, the primary aim of our study was to determine the relationship between carotid-femoral pulse wave velocity, cognitive decline, and risk of incident mild cognitive impairment (MCI) determined by Trail Making Test (TMT), Paired Associate Learning (PAS), and changes in Mini-Mental State Examination (MMSE) scores during cancer survivorship. Because cancer and CVD have common risk factors and a shared biology (1, 25, 46), our secondary aim was to characterize the contributions of central arterial stiffness and MCI (5) to the risk of all-cause mortality and CVD diagnosis in this sample.

Chapter 2 - Methods

Subjects and Study Design

The Framingham Heart Study (FHS) is an ongoing, prospective, community-based cohort study in Framingham, MA originally aimed at identifying the risk factors that contribute to CVD. Through 73 years of recurring examination cycles, the FHS has aided in the investigation and identification of CVD risk factors as well as risk factors for dementia and relationships between human genotypes and phenotypes. During each examination cycle, participants attend a clinical evaluation, which includes a physical examination, laboratory testing, and medical history, with additional assessments occurring at some, but not all cycles. Data collection commenced with recruitment of the Original cohort in 1948. Subsequently, offspring of the Original cohort and their spouses were recruited and a second cohort of participants, the Offspring cohort, was added in 1971. To date, the FHS has conducted 32 and 9 examination cycles within the Original and Offspring cohorts, respectively.

Examination cycle 26 of the Original cohort and examination cycle 7 of the Offspring cohort began in 1999 and 1998, respectively. This examination cycle will be referred to as baseline henceforth. At baseline, arterial tonometry and assessments of cognitive function were performed. Assessments of cognitive function were repeated in subsequent examination cycles in each cohort. Participant outcomes, including cause of death and major medical diagnoses, are validated, reviewed, and recorded by Framingham investigators throughout the study. These records are current to January 2019 in the Original cohort and October 2019 in the Offspring cohort. From these records, we identified CVD diagnoses and all-cause mortality occurring in

our sample between February 1999 and October 2019. This period lasting 20 years and 8 months will be referred to as follow-up.

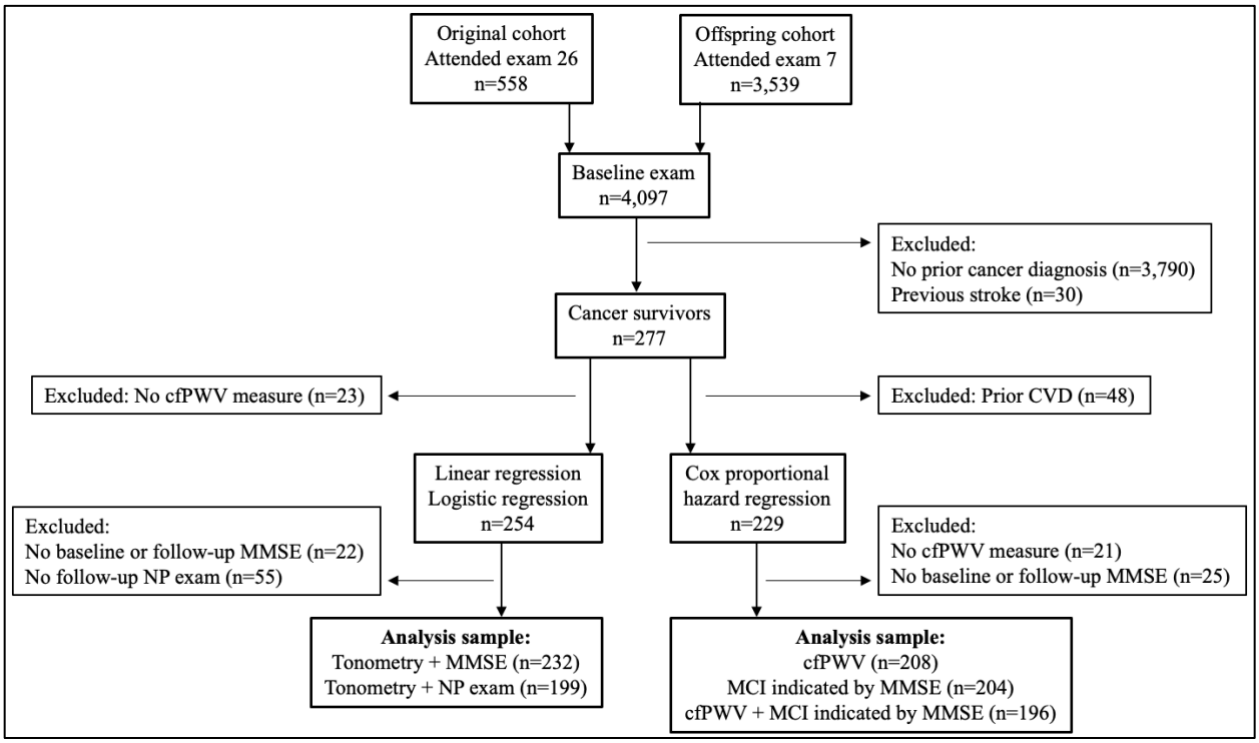

Figure 2.1. Inclusion of study participants.

Five-hundred and fifty-eight participants attended examination cycle 26 of the Original cohort and 3,539 attended examination cycle 7 of the Offspring cohort resulting in a total of 4,097 participants attending the baseline examination cycle (**Figure 2.1**). Of these, 307 were diagnosed with cancer prior to baseline. This included all primary cancers indicated by self-report at clinical evaluation, which was confirmed by blind review of pathology and clinical records by an FHS physician and a trained staff member or research fellow. We did not make exclusions based on cancer type or site, except in the case of metastatic cancers. Participants were excluded if they had a stroke prior to baseline testing (n=30), resulting in inclusion of 277 participants (80 ± 12.3 years old, 56.7% women, 9.3 ± 8.8 years from first diagnosis) for further analysis. In the current study, omissions were made from this sample based on the availability of

individual measures included in each analysis. Details of the samples included in each analysis are described below and in **Tables 3.1 and 3.2**.

Assessment of Central Arterial Stiffness

Carotid-femoral pulse wave velocity (cfPWV) was used as an assessment of arterial stiffness. As a measure of arterial stiffness, cfPWV is considered the 'gold-standard' (28) and is recommended by the American Heart Association (62). The arterial tonometry procedures have been previously described (39), but in brief, were performed on femoral and carotid arteries with simultaneous ECG following 5 minutes of rest in the supine position. Carotid-femoral transit distance was estimated by the difference between body surface measurements from the suprasternal notch to the femoral and carotid recording sites and corrected for parallel pulse wave transmission around the aortic arch and three branch arteries originating therein. Tonometry waveforms were aligned according to the ECG R wave. Carotid-femoral pulse wave transit time is the time delay of the foot of the pressure wave at carotid and femoral arteries, calculated as [the time between ECG R-wave and pulse wave arrival at the femoral measurement site] minus [this time interval for the carotid site]. cfPWV was calculated as the quotient of carotid-femoral transit distance divided by pulse wave transit time. Analysis reproducibility of cfPWV in the FHS has been assessed through blind reanalysis by a second observer of 50 randomly sampled participants (correlation coefficient, r=0.972) (39).

Assessment of Cognitive Decline and Incident MCI

Mini-Mental State Examination (MMSE)

The MMSE is regarded as a measure of global cognitive function (18). In this study, baseline and follow-up MMSE scores for each participant were selected. On an absolute scale, scores on the MMSE range from 0-30 (higher scores indicating better cognitive function), with scores adjusted relative to the participant's maximum possible score according to answered questions, per standard procedures. To evaluate cognitive decline, the difference between follow-up and baseline MMSE scores was divided by the time between tests generating a change per year score (ΔMMSEy). Further, identification of MCI was made according to ΔMMSEy -0.5 or greater, as previously defined (50).

Neuropsychological Exams

Full details of the FHS neuropsychological (NP) exams have previously been described (7). In the current study, Paired Associate Learning (PAS) and the Trail Making Test (TMT) were selected from the battery of NP exams to assess incident MCI during follow-up. PAS, a measure of learning and memory, contains both an immediate (PASI) and delayed (PASD) component. PASI and PASD were scored from 0-21 and 0-10, respectively, with the scales representing a composite score of the easy and hard component associated with each test, and higher composite scores reflecting better memory. The TMT, a measure of executive function, contains part A (TMT A) and part B (TMT B). TMT scores reflect the time taken to complete the task, with lower scores reflecting better cognitive function. TMT B minus TMT A (TMT B-A) was used as a third measure of executive function. Described in the Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association 2013), 1-2 standard deviations in

performance relative to the group mean in one or more cognitive domain can be classified as mild impairment. In our analysis, identification of MCI was made according to scoring ≥ 1.5 SD worse than the mean of the present cohort on any of these tests.

Outcome Measures

The primary outcome measures of this study are all-cause mortality and CVD diagnosis. All-cause mortality was confirmed by death certificate. CVD development was constituted by: myocardial infarction; angina pectoris; intermittent claudication; congestive heart failure; cerebrovascular accident including stroke, transient ischemic attack, atherothrombotic brain lesion; or related death in the absence of previous occurrence by any of these diseases. Included in these cases are those with a definitive CVD development diagnosis evidenced by medical record, clinical evaluation, or autopsy record and validated by Framingham Endpoint Review Committee or physician review. Follow-up time for each person was calculated as the number of days between their arterial tonometry measurement and outcome or most recent update to the FHS outcome file.

Covariates

Covariates were assessed at the clinical evaluation during baseline examination. Regression models in each analysis were built in a step-wise manner, beginning with a univariate model (model 1), while latter models contain the predictors of the predecessor with additions. These covariates included age, sex, depressive symptoms (Center for Epidemiologic Studies Depression Scale > 16), and time between tonometry and last available exam (model 2); high-density lipoprotein-cholesterol (HDL), total cholesterol, brachial systolic blood pressure (SBP),

brachial diastolic blood pressure (DBP), hypertension medication, statin medication, smoking status, and prior CVD diagnosis (model 3).

Statistical Analysis

Continuous data are presented as mean ± SD. Categorical data are presented as counts and percentages. All analyses were performed using IBM SPSS Statistics for Windows (Ver. 27; IBM, Armonk, NY). Linear regression analysis was used to evaluate the relationship between cfPWV and cognitive decline (ΔMMSEy). ΔMMSEy was log transformed to improve homoscedasticity and kurtosis. Linear analysis of change in NP battery scores was not feasible due to unavailable data corresponding to either baseline or follow-up examination in a majority of participants.

Logistic regression analyses were done in order to assess likelihoods of incident MCI during follow-up in relation to aortic stiffness. MCI defined by either impaired MMSE or NP scores, was modeled using cfPWV as a categorical predictor as the assumption of linearity was violated. cfPWV was binned into quartiles and analyzed in reference to the lowest quartile ($cfPWV_1$).

Cox proportional hazard regression was used to evaluate the risk of CVD diagnosis during follow-up using (1) aortic stiffness, (2) cognitive function, and (3) aortic stiffness and cognitive function in combination as predictors. In addition, the risk of all-cause mortality during follow-up was evaluated in the same manner. Those who had been diagnosed with CVD at baseline (n=48) were excluded from these analyses and obesity (BMI ≥ 30) was included as an

additional covariate to those previously described. Kaplan–Meier plots were used to show the difference in time to event by cfPWV quartile and statistically compared with the log-rank test. All significance tests were two-sided using $p<0.05$ as the level of statistical significance.

Chapter 3 - Results

Baseline Characteristics

Baseline demographics and subject characteristics are outlined in **Table 3.1**. A total of 277 adults (120 men, 157 women) with a history of a cancer diagnosis were included in the analysis. In the cancer patients with the highest arterial stiffness ($cfPWV_4$), ΔMMSEy scores were significantly greater compared to those of patients within the lowest quartile ($cfPWV_1$) (**Figure 3.1**). Similarly, across cfPWV quartiles, a higher prevalence of MCI occurred in the highest cfPWV group compared to $cfPWV_1$ (**Table 3.1**).

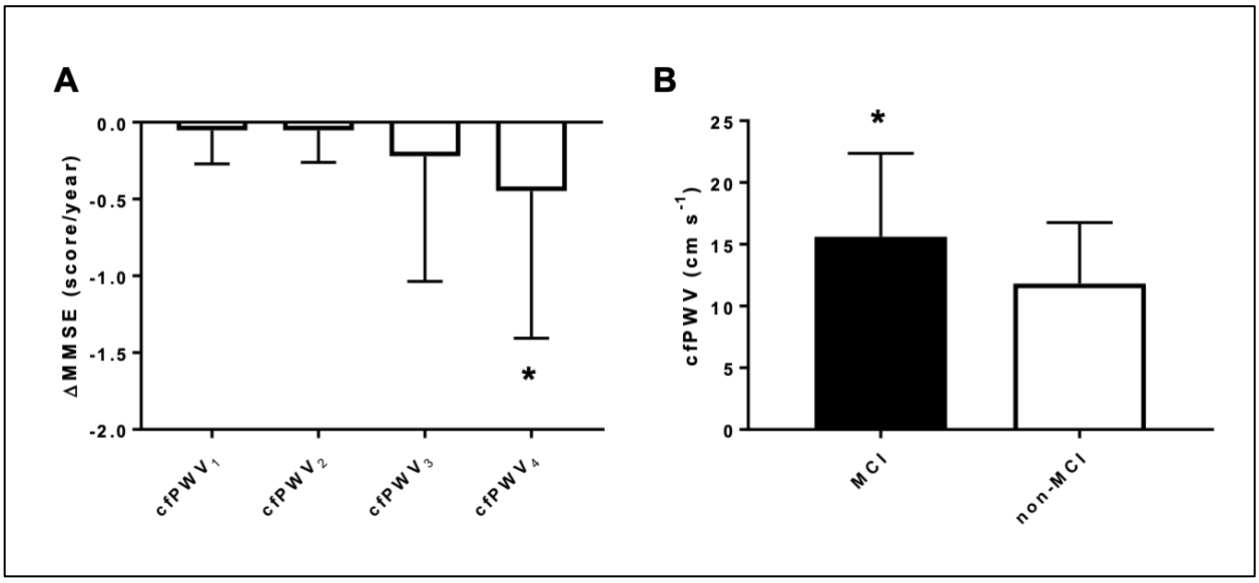

Figure 3.1. A: Patients with the highest central arterial stiffness ($cfPWV_4$) had significantly greater rates of cognitive decline compared to reference ($cfPWV_1$). **B**: Average baseline cfPWV was significantly higher in patients whose rates of cognitive decline were indicative of MCI. $p < 0.05$.

Table 3.1. Demographic and clinical characteristics by cfPWV

	All	$cfPWV_1$	$cfPWV_2$	$cfPWV_3$	$cfPWV_4$
N	277	64	78	49	63
Age, y	71 ± 12	60 ± 10	67 ± 10*	79 ± 8*	82 ± 7*
Women, n (%)	157 (56.7%)	40 (62.5%)	42 (53.9%)	26 (53.1%)	36 (57.1%)
BMI, kg/m^2	27.0 ± 4.3	26.3 ± 4.0	26.9 ± 3.7	27.6 ± 4.3	26.6 ± 4.1
cfPWV, m/s	12.4 ± 5.2	7.5 ± 0.82	10.0 ± 0.81*	13.0 ± 0.81*	19.9 ± 4.4*
ΔMMSEy	-0.17 ± 0.617	-0.052 ± 0.218	-0.053 ± 0.212	-0.22 ± 0.815	-0.45 ± 0.958*
[a]MCI defined by MMSE, n (%)	32 (13.8%)	3 (4.8%)	3 (4.1%)	9 (21.4%)*	17 (31.4%)*
[b]MCI defined by NP, n (%)	27 (13.6%)	5 (9.3%)	4 (6.8%)	3 (8.1%)	15 (30.6%)*
Systolic BP, mmHg	127 .1 ± 18.9	116.1 ± 13.4	123.6 ± 14.6*	133.8 ± 17.6*	138.2 ± 21.8*
Diastolic BP, mmHg	68.7 ± 10.7	66.3 ± 9.8	70.0 ± 11.0	68.6 ± 11.7	70.8 ± 10.1
Antihypertensive therapy, n	127 (45.8%0	13 (20.3%)	32 (41.0%)*	32 (65.3%)*	40 (63.5%)*
Statin therapy, n (%)	76 (27.4%)	8 (12.5%)	25 (32.0%)*	13 (26.5%)*	24 (38.1%)*
Current smoker, n (%)	14 (5.1%)	5 (7.8%)	4 (5.1%)	1 (2.0%)	2 (3.2%)
Cholesterol, mmol/L	196.7 ± 35.4	194.6 ± 32.2	198.4 ± 34.8	194.1 ± 33.5	195.3 ± 37.1
HDL cholesterol, mmol/L	55.5 ± 17.7	59.3 ± 16.3	56.9 ± 17.8	54.3 ± 19.6	52.8 ± 15.8
Cancer Type					
Breast, n (%)	48 (17.3%)	15 (23.4%)	12 (15.4%)	10 (20.4%)	7 (11.1%)
Colon, n (%)	15 (5.4%)	3 (4.7%)	3 (3.8%)	4 (8.1%)	4 (6.3%)
Time since 1st cancer diagnosis, yr	9.3 ± 8.8	7.9 ± 8.1	8.2 ± 8.6	11.2 ± 10.0*	10.0 ± 8.0
Multiple cancers, n (%)	151 (54.5%)	31 (48.4%)	49 (62.8%)	27 (55.1%)	31 (49.2%)

Values are mean ± SD except as noted.

*Significantly different vs. $cfPWV_1$ ($P<0.05$). [a]Percentages calculated with respect to participants included in MMSE analysis: Total, n=232; $cfPWV_1$, n=63; $cfPWV_2$, n=73; $cfPWV_3$, n=42; $cfPWV_4$, n=54. [b]Percentages calculated with respect to participants included in NP analysis: Total, n=199; $cfPWV_1$, n=54; $cfPWV_2$, n=59; $cfPWV_3$, n=37; $cfPWV_4$, n=49.

Associations of Central Arterial Stiffness and Cognitive Decline

Baseline demographics and subject characteristics based on cognitive function are outlined in **Table 3.2**. Over a median follow-up of 11.4 years, we observed 232 cases with an average ΔMMSEy of -0.17 ± 0.617, with 32 cases (13.8%) of MCI. In unadjusted linear regression analysis, a higher cfPWV was significantly associated with an increased rate of yearly decline in global cognitive function (r=0.35, p<0.001) (**Figure 3.2**). In multivariable-adjusted models, aortic stiffness remained significantly associated with ΔMMSEy (model 2: [β±SE] -0.004±0.55, r=0.39, p=0.002; model 3: -0.004±0.001, r=0.44, p=0.003). Univariate logistic regression revealed that compared to the reference $cfPWV_1$, the odds of MCI were 5.5-fold and 9.2-fold higher for those patients with elevated aortic stiffness in $cfPWV_3$ and $cfPWV_4$ groups,

respectively (**Table 3.3**). However, on multivariate analysis this relationship was no longer significant and older age, higher SBP, lower DBP, and lower total cholesterol significantly increased the likelihood of incident MCI during survivorship.

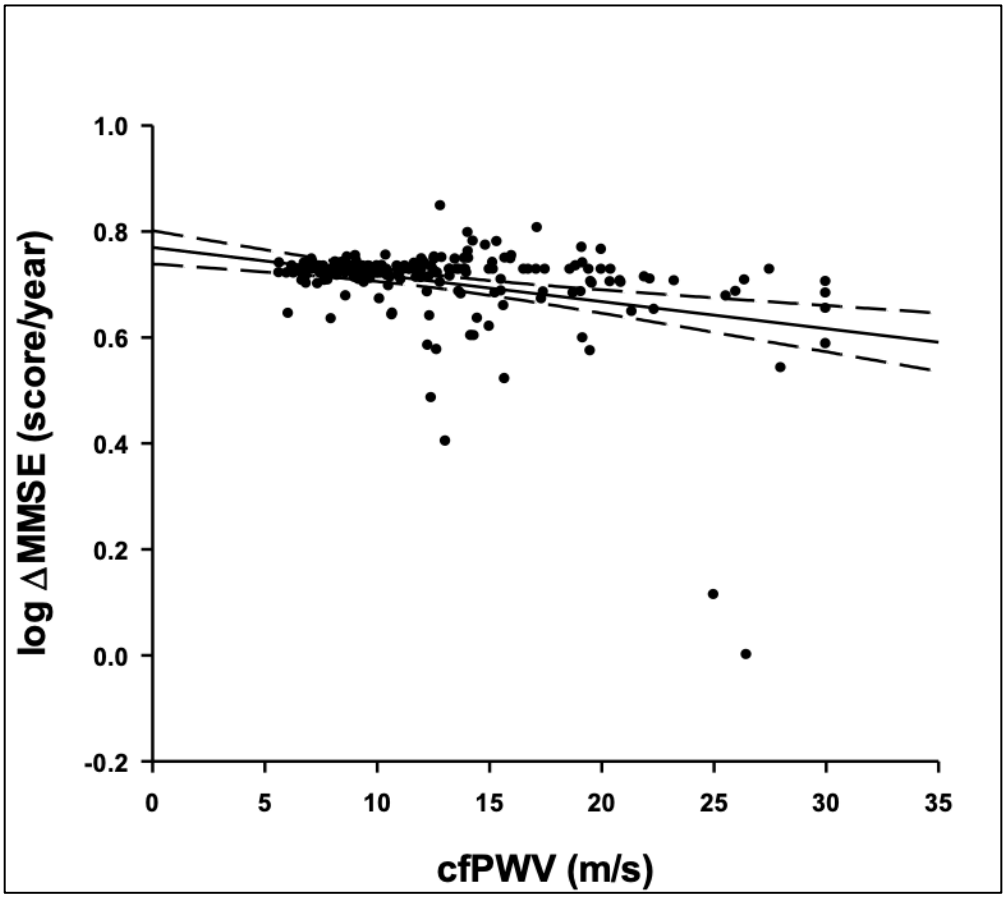

Figure 3.2. Significant relationship between higher cfPWV and increased rate of cognitive decline shown by univariate linear regression.

Adequate NP battery data was not available for 55 participants, leaving n=199 patients for analysis. The unadjusted logistic regression analysis revealed that compared to the reference ($cfPWV_1$), the risk of MCI indicated by NP examination scores were 4.3-fold higher for highest $cfPWV_4$ group (P=0.009). On multivariate analysis, cfPWV the relationship was inverted with higher cfPWV quartiles protective (**Table 3.3**).

Table 3.2. Demographic and clinical characteristics by MCI

	MMSE normal	MMSE impaired	P Value	NP normal	NP impaired	P Value
N	200	32	<0.001	172	27	<0.001
Age, y	67.4 ± 11.4	84 ± 5.4	<0.001	68.7 ± 11.5	81.5 ± 7.43	<0.001
Women, n	114 (57.0%)	18 (56.3%)	0.94	102 (59.3%)	14 (51.8%)	0.465
BMI, kg/m^2	27.1 ± 3.9	25.1 ± 4.1	0.018	21.1 ± 4.0	25.9 ± 4.3	0.167
cfPWV, m/s	11.4 ± 4.5	17.1 ± 6.8	<0.001	11.8 ± 4.9	15.6 ± 6.7	0.009
Systolic BP, mmHg	125.3 ± 17.5	136.1 ± 22.3	0.012	125.3 ± 17.4	133.7 ± 20.6	0.053
Diastolic BP, mmHg	69.5 ± 10.3	65.0 ± 10.9	0.033	168.9 ± 10.2	67.1 ± 10.5	0.401
Antihypertensive therapy, n	84 (42.0%)	21 (65.6%)	0.013	78 (45.3%)	13 (48.1%)	0.786
Statin therapy, n	53 (26.5%)	11 (34.4%)	0.355	48 (27.9%)	8 (29.6%)	0.853
Current smoker, n	10 (5.0%)	2 (6.2%)	0.779	7 (4.1%)	1 (3.7%)	0.928
Cholesterol, mmol/L	198.4 ± 34.1	183.8 ± 34.7	0.032	199.0 ± 34.9	193.5 ± 35.6	0.457
HDL cholesterol, mmol/L	56.1 ± 17.2	55.8 ± 17.9	0.922	56.4 ± 17.6	55.3 ± 16.6	0.740
Cancer Type						
Breast, n	37 (18. 5%)	6 (18.8%)	0.973	32 (18.6%)	6 (22.2%)	0.657
Colon, n	10 (5.0%)	3 (9.4%)	0.318	12 (7.0%)	1 (3.7 %)	0.522
Time since 1st cancer diagnosis, yr	8.5 ± 7.8	13.1 ± 12.6	0.049	8.2 ± 8.2	13.3 ± 11.3	0.033
Multiple cancers, n	117 (58.5%)	14 (43.8%)	0.118	100 (58.1%)	15 (55.6%)	0.800

Table 3.3. Association of cfPWV with Mild Cognitive Impairment on Unadjusted and Multivariable-Adjusted Analysis

		Unadjusted			Multivariable Adjusted*		
Outcome	Event rate, n/N (%)	OR	95% CI	p Value	OR	95% CI	p Value
MMSE							
$cfPWV_1$	3/73 (4.1%)	-	-	-	-	-	-
$cfPWV_2$	3/63 (4.8%)	0.857	0.167–4.406	0.854	0.344	0.031–3.799	0.384
$cfPWV_3$	9/42 (21.4%)	5.455	1.381–21.551	**0.016**	0.272	0.026–2.848	0.277
$cfPWV_4$	17/54 (31.5%)	9.189	2.520–33.514	**0.001**	0.432	0.040–4.678	0.490
NP							
$cfPWV_1$	4/59 (6.8%)	-	-	-	-	-	-
$cfPWV_2$	3/37 (8.1%)	0.713	0.181–2.805	0.628	0.224	0.038–1.326	0.099
$cfPWV_3$	5/54 (17.4%)	0.865	0.194–3.863	0.849	0.034	0.004–0.321	**0.003**
$cfPWV_4$	15/49 (30.6%)	4.324	1.435–13.023	**0.009**	0.117	0.015–0.909	**0.040**

*Multivariable model adjusted for age, sex, depressive symptoms, and HDL cholesterol, total cholesterol, systolic blood pressure, diastolic blood pressure, hypertension medication, statin medication, smoking status, and prior CVD diagnosis.

MMSE, Mini-Mental State Examination; NP, Neuropsychological examination; cfPWV, carotid-femoral pulse wave velocity.

Associations of Central Arterial Stiffness, Cognitive Impairment, and CVD Diagnosis

Arterial Stiffness

In all models arterial stiffness was significantly associated with the risk of CVD diagnosis during follow-up. Univariate Cox regression analysis revealed significant associations between each cfPWV quartile and risk of CVD diagnosis during follow-up and suggested that, compared to the reference $cfPWV_1$, patients with higher cfPWV had 4.5-fold, 9.0-fold, and 10.3-fold greater risk, with risks corresponding to $cfPWV_2$ ($p=0.002$), $cfPWV_3$ ($p<0.001$), and $cfPWV_4$ ($p<0.001$), respectively (**Figure 3.3)**. After controlling for age, sex, and depression symptoms, model 2 revealed significant associations between the upper three cfPWV quartiles and suggested that patients in $cfPWV_2$, $cfPWV_3$, and $cfPWV_4$ had 3–4-fold greater risk of CVD diagnosis compared to $cfPWV_1$. Similar to model 2, full multivariate analysis revealed significant associations between the upper three cfPWV quartiles and suggested 3.3–3.5-fold greater CVD diagnosis risk for patients with higher cfPWV. Compared to the reference $cfPWV_1$, model 2 suggested patients in $cfPWV_3$ had a 3.8-fold greater risk of CVD diagnosis ($p=0.017$), while risk increased 3.6-fold in $cfPWV_4$ ($p=0.032$). Similarly, the fully adjusted model 3 indicated that risk increased 3.5-fold for patients in $cfPWV_2$ ($p=0.017$) and $cfPWV_4$ ($p=0.044$) alike, while risk increased 3.3-fold in $cfPWV_3$ ($p=0.038$).

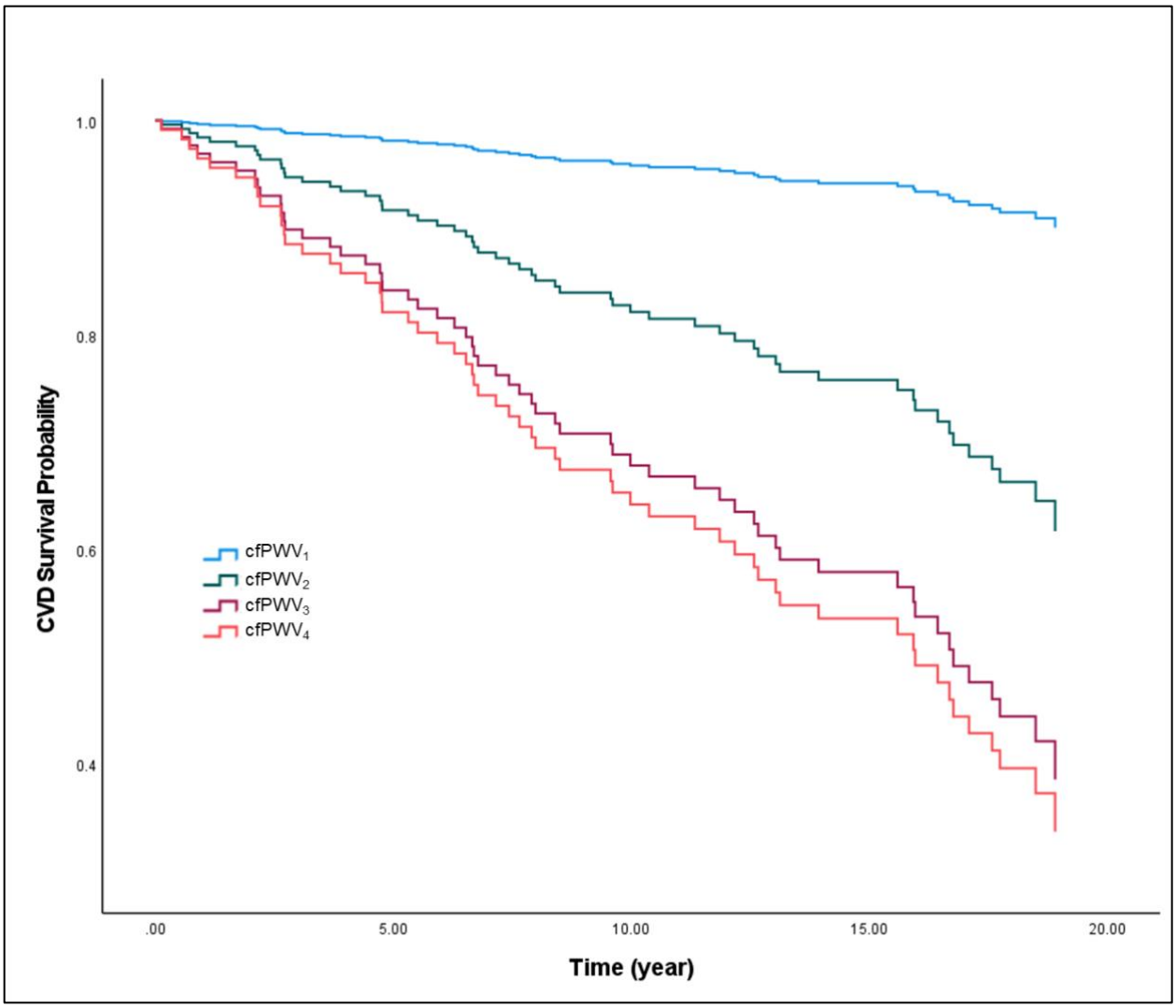

Figure 3.3. Kaplan-Meier curve analysis of CVD diagnosis across cfPWV quartile.

Cognitive Impairment

Univariate Cox regression analysis revealed a significant association between MCI and the risk of CVD diagnosis during follow-up, suggesting cognitively impaired patients had a 2.8-fold greater risk of CVD diagnosis compared to unimpaired patients. However, on multivariate analysis this relationship was no longer significant.

Combined

In all models using arterial stiffness and cognitive impairment in tandem as predictors, arterial stiffness was significantly associated with the risk of CVD diagnosis during follow-up, with MCI not significant. Model 1 revealed significant associations between each cfPWV quartile and risk of CVD diagnosis during follow-up and suggested that, compared to the reference $cfPWV_1$, patients with higher cfPWV had 4.3, 8.5-, and 9.3-fold greater risk, with risks corresponding to $cfPWV_2$, $cfPWV_3$, and $cfPWV_4$, respectively. Similar to the cfPWV multivariate Cox regression analysis, models 2 and 3 revealed significant associations between the upper 3 cfPWV quartiles and CVD diagnosis risk. Both models suggested patients with elevated aortic stiffness had a greater risk of CVD diagnosis and that the greatest risk was to those in $cfPWV_4$, whose risk increased 3.7-fold from reference $cfPWV_1$.

Associations of Central Arterial Stiffness, Cognitive Impairment, and All-Cause Mortality

Arterial Stiffness

Aortic stiffness was not significantly associated with the risk of all-cause mortality in univariate or multivariate analysis. The only model as a whole to reach statistical significance was the full multivariate model, which suggested patients who were male, had higher SBP, had higher total cholesterol, and who smoked had an increased risk of all-cause mortality.

Cognitive Impairment

Cognitive impairment was not significantly associated with the risk of all-cause mortality in univariate or multivariate analysis. The only model as a whole to achieve statistical

significance was the full multivariate model, which suggested patients who were male, had higher SBP, had higher total cholesterol, and who smoked had an increased risk of all-cause mortality.

Combined

In all models using arterial stiffness and cognitive impairment in tandem as predictors, aortic stiffness and cognitive impairment were not significantly associated with the risk of all-cause mortality. The only model as a whole to gain significance was the full multivariate model, which suggested patients with higher SBP, higher total cholesterol, who do not take hypertension medication, and who smoked had an increased risk of all-cause mortality.

Chapter 4 - Discussion

We present longitudinal analyses of cancer survivors in the Framingham Heart Study unburdened by dementia or stroke which demonstrate that central arterial stiffness, indexed as cfPWV, is a predictor of cognitive decline, incident MCI, and CVD in cancer survivorship. Importantly, after controlling for age, sex, depressive symptoms, and CVD risk factors, the adverse relationships between cfPWV, cognitive decline, and incident CVD persisted. In the general population, associations have been previously demonstrated between arterial stiffness and cognitive decline (30, 40, 45, 48, 63, 66, 69). As the amount of cancer survivors continues to grow, our understanding of the interactions that predispose this community to adverse outcomes is vital to the improvement of survivor's long-term care and quality of life. Our results warrant further investigation into the predictive capability of a non-invasive cfPWV assessment of central arterial stiffness, with the goal of early identification of patients who are at risk of adverse secondary outcomes in clinical practice.

While often viewed as two distinct disease entities, cancer and CVD may coincide due to anticancer treatment cardiotoxicities (6, 36) or shared risk factors and biological mechanisms. Risk factors shared within cancer and CVD etiologies include obesity, diabetes mellitus, tobacco or smoking, diet, dyslipidemia, and hypertension (1, 25, 32, 36, 51). Common pathogenic biological mechanisms include a genetic predisposition and systemic signaling involved in chronic inflammation and oxidative stress (1, 43). Adding strength to the correlation between cancer and CVD is that the onset of one of these diseases potentiates risk of the other. Indeed, many forms of CVD are oncogenic including heart failure, hypertension, atrial fibrillation,

atherosclerosis, myocardial ischemia or infarction, and stroke (1, 46, 58) and cancer survivors are at greater risk of CVD-related mortality than the general public (60).

Evidence linking cancer with increased incidence of CVD has been suggested previously in large epidemiological studies. An observational study comparing the US general population to over 3 million cancer patients across 28 cancer sites, demonstrated that cancer survivors are at a higher risk of CVD related morality than the general population regardless of cancer site and time since diagnosis and their risk is greatest in the first year after diagnosis (60). An analysis of 1.8 million cancer patients demonstrated that heart disease is the leading cause of noncancer mortality, with cancer patients at a significantly greater risk of heart disease compared to the general population (70). In addition, this increased risk of heart disease in cancer patients is independent of the cancer site, time since diagnosis, and age at diagnosis (58, 70). Between cancer survivors, the long-term risk of heart disease related mortality, while still elevated compared to the general population, is more prevalent according to index-cancer site. Risk continually increases following the first year after diagnosis in melanoma, breast, and prostate cancers (60) and is greater than that of primary cancer ≥ 10 years post diagnosis in melanoma, prostate, colorectal, bladder, kidney, endometrial, oral cavity, and pharynx cancers (58). Our study demonstrates that increased cfPWV is predictive of risk of incident CVD during survivorship — consistent with a recent retrospective analysis from our group which was the first to establish increased arterial stiffness, assessed via pulse pressure, to be predictive of increased CVD mortality in cancer survivors (47).

In addition to the shared risk factors and biological mechanisms between these two diseases, the use of anticancer therapies may be a significant contributor to the relationship between cancer and cardiovascular outcomes. While advancements in anticancer treatment regimens have aided in improvement of cancer prognosis, detrimental side effects from these drugs potentially promote secondary pathology in survivorship. Work from our group and others have demonstrated that vascular toxicities and vascular dysfunction occur following various anti-cancer treatments (19, 47). Of note, arterial stiffness is a critical vascular toxicity associated with cancer treatments in both the short and long-term (27, 57). Anthracyclines, e.g., Doxorubicin, represent one of the most widely used classes of chemotherapy drugs (8). In a prospective study following survivors receiving anthracycline treatment for a variety of cancer types, a 2-fold increase in aortic PWV was documented subsequent to four months of treatment compared to pre-treatment measurements, suggesting that aortic stiffness is significantly increased with anthracycline therapies (12). Similar findings have resulted from Sunitinib, a tyrosine kinase inhibitor, which increased cfPWV and changed other vascular measures related to hemodynamic pulsatility following the initial treatment cycle (10). In addition, following treatment with alkylating agents, chronic increases in arterial stiffness have been demonstrated (54). FOLOX and XELOX, combination therapies using alkylating agent oxaliplatin and antimetabolite 5-fluorouracil (5FU) or it's oral prodrug capecitabine, have also been shown to significantly increase multiple indices of arterial stiffness (64).

In addition to the above vasculo-toxicity, cognitive deficits during cancer survivorship, colloquially referred to as 'chemofog' or 'chemo-brain', are commonly experienced during survivorship. In a 2014 review by Janelsins et al., it is noted that cognitive impairment effects

between 17–75% of patients during chemotherapy, and up to 35% of patients years after treatment is complete (22). The variability in reported cognitive impairment among patients during anticancer treatment often results from the heterogeneity of tests and definitions used to define cognitive impairment in this population (49), differences in anticancer therapies and patient populations (20), and the multifactorial etiology of these deficits. Interactions between trauma associated with receiving a diagnosis, the biology of the neoplasm, and an array of treatment-specific, direct or indirect effects of anticancer treatments on cerebral parenchyma or vasculature combine to drive cognitive changes throughout the cancer treatment continuum (34, 42, 49). While research into the precise mechanisms of treatment-mediated neurotoxicity continues, concomitant work has been aimed at identifying patients who are most susceptible to cognitive decline. To date, commonly identified risk factors for acute cognitive decline include age, cognitive reserve, genetic predisposition, and comorbid factors (3, 4, 16, 17, 21, 68). Importantly, cognitive changes which are secondary to treatment-mediated toxicity have been previously suggested, and include altered cerebrovascular hemodynamics (3). We present evidence supporting central arterial stiffness, a known factor contributing to altered cerebrovascular hemodynamics, as a risk factor for cognitive change with cancer survivorship.

Chemotherapy has long-term effects on cognitive function. After an average of 21 years subsequent to diagnosis, breast cancer survivors who received adjuvant chemotherapy performed significantly worse than a cancer-free reference group on tests across multiple cognitive domains including immediate and delayed verbal memory, processing speed, executive function, and psychomotor speed (26). Chemotherapy-receiving patients may be subject to early onset frailty due to acceleration of natural aging processes such as accumulation of DNA damage,

accumulation of oxidative stress, shortened telomeres or reduced telomerase activity, and neuroendocrine or immunologic dysfunction (11, 21, 35). Demonstrated herein, cfPWV assessed an average of 9.1 years after first cancer diagnosis is associated with cognitive decline an average of 8.7 years subsequent to cfPWV measurement. In the general population, cfPWV has been previously demonstrated to be associated with future cognitive decline and impairment. To our knowledge, this is the first study to suggest that cfPWV can significantly predict future cognitive decline during cancer survivorship. Further research is needed to understand: 1) what role central arterial stiffness plays within the multitude of pathways that contribute to acute and long-term cognitive decline and 2) the prevalence of this role in the case that stiffness is present prior to treatment or is a result of chemotherapy-induced vascular toxicity.

Our finding that cancer patients with higher cfPWV experienced greater rates of cognitive decline may, putatively, be explained by pathophysiologic mechanisms, which drive both cancer-mediated and vascular-mediated cognitive change. Both etiologies include inflammation, oxidative stress, astrocyte and microglial activation, oligodendrocyte reduction, reduced cerebral blood vessel density and blood flow, altered control of cerebral blood flow, and white and grey matter damage (14, 15, 20, 34, 42, 49, 53, 59, 61). In addition, greater central arterial stiffness, whether due to age or chemotherapy vasculo-toxicity, could beget direct chemotherapy-induced neuronal damage. As noted above, cancer treatment mechanisms of cognitive change vary between anticancer therapies. With regard to chemotherapy drugs this is partially due to the selective permeability of the BBB — the cerebral microvascular interface between vasculature and parenchyma (i.e., functional brain tissue) (20). Contained here are capillaries tasked with maintaining a homeostatic neural environment and protecting parenchyma

from foreign entities (34, 42, 67). Depending upon molecular size or lipophilicity, only specific chemotherapeutic agents (e.g. 5FU, methotrexate) are able to cross the BBB, though accumulations by larger chemotherapy drugs have also been found in brain parenchyma (34, 42, 67). Further, direct chemotherapy-mediated neurotoxicity, a proposed etiological component (42), may be propagated through chemotherapy-induced pathways which damage the BBB. Expression of either inflammatory cytokines or matrix metalloproteinases due to chemotherapy-induced peripheral inflammation or oxidative stress has been shown to disrupt tight junctions, increase BBB permeability, and cause neuronal dysfunction (33, 67). Concordantly, in the general population, cerebral microvascular pressure pulsatility subsequent to increased central artery stiffness is seen in parallel with increased cerebral inflammatory cytokine expression, oxidative stress, matrix metalloproteinase expression, aberrant BBB permeability, and cognitive dysfunction (14, 15, 61). When both cancer-mediated and vascular-mediated cognitive change etiologies are present, the possibility of overlapping pathways being exacerbated and driving increased cognitive decline is noteworthy. Whether disparate cognitive outcomes in chemotherapy-receiving patients with higher central artery stiffness may be influenced by exacerbated inflammatory or oxidative stress pathways or differences in BBB permeability is undetermined. Nevertheless, patients with higher central arterial stiffness have an additional known precursor to cerebral microvascular dysfunction and cognitive impairment and, as shown in the present study, are associated with greater rates of cognitive decline years into survivorship.

Experimental considerations

The present study has strengths and limitations. Strengths include the longitudinal design, use of standardized and validated cognitive assessments and empirical MCI cut-off scores, use of

the ‘gold-standard’ measure of central arterial stiffness, and heterogenous cancer site representation. Limitations include the potential influence of other, unaccounted for, variables. Although many potential cofounding variables were controlled for, it is possible that other cognitive influences or cardiovascular disease risk factors such as anxiety, cognitive reserve, genetic predisposition, diabetes mellitus, fasted blood glucose, diet, or exercise, may have affected present findings. Further, the participants were predominantly white, potentially limiting generalizability to a diverse group of cancer survivors. Additionally, due to medication data unavailability we were unable determine the influences that specific treatments may have had on cfPWV measures or cognitive assessments.

Conclusions

In closing, we demonstrate that cfPWV is associated with future cognitive decline and predictive of incident CVD during cancer survivorship independent of age, sex, depression, and CVD risk factors. With less patients now dying of their primary cancer, more patients living longer into cancer survivorship, and the proportion of survivors who are older continually increasing, early identification of survivors who are most susceptible to detrimental secondary outcomes is vital. These findings give important insight to our understanding of secondary outcome risk during survivorship.

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