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Cross sectional association between cytomegalovirus seropositivity, inflammation and cognitive impairment in elderly cancer survivors

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Abstract

Purpose—The higher prevalence of cognitive impairment/ dementia among cancer survivors is likely multifactorial. Since both exposures to cytomegalovirus (CMV) and inflammation are common among elderly cancer survivors, we evaluated their contribution towards dementia.

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Authors' contributions SV, BT and HHN designed the study. SV completed the statistical analysis and wrote the manuscript. BT developed the hypothesis, oversaw statistical analysis and manuscript preparation. HHN also provided critical feedback to the analysis strategy and comments to the manuscript. AEP, JF and EC reviewed the manuscript and suggested specific analysis for this project.

Declarations

Conflict of interest There is no competing financial or non-financial interests in relation to this manuscript. The authors declare no conflict of interest.

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Data availability Data used in this manuscript are accessed from Health and Retirement Study website (https://hrs.isr.umich.edu/data-products?_ga=2.8747955.705712069.1606796306-411200660.1601442014). Cognition and basic demographic data used in this study is publicly available to registered members of Health and Retirement Study. The venous blood biomarker data is under sensitive health data and can be accessed by submitting sensitive health data order form (https://hrsdata.isr.umich.edu/data-products/sensitive-health/order-form).

Ethical approval All study participants in HRS were consented for study participation and the study was approved by the Institutional Review Board at the University of Michigan, Ann Arbor.

Consent for publication There is no individually identifiable data in this manuscript. All HRS participants consented to study participation and to use their data and samples for additional analysis.

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Methods—Data from 1387 cancer survivors and 7004 participants without cancer in the 2016 wave of the Health and Retirement Study (HRS) was used in this study. Two inflammatory biomarkers, C-reactive protein (CRP) and neutrophil–lymphocyte ratio (NLR), were used to create an inflammation score. We used survey logistic regression adjusted for survey design parameters.

Results—CMV seropositivity was not associated with cognitive impairment among cancer survivors ($p = 0.2$). In addition, inflammation was associated with elevated odds of cognitive impairment (*OR* = 2.2, 95% CI [1.2, 4.2]). Cancer survivors who were both CMV seropositive and had increased inflammation had the highest odds of cognitive impairment compared to those who were CMV seronegative and had low inflammation (*OR* = 3.8, 95% CI [1.5, 9.4]). The stratified analysis among cancer survivors showed this association was seen only among cancer survivors in whom the cancer was diagnosed within three years of measurement of inflammation score and CMV serostatus (*OR* = 18.5; 95% CI [6.1, 56.1]).

Conclusion—The CMV seropositivity and high inflammation was associated with higher cognitive impairment among cancer survivors. The stronger associations seen among cancer survivors diagnosed within the last three years suggest that strategies to reduce CMV activation and inflammation during or immediately after cancer treatment may be important in reducing the prevalence of cognitive impairment/ dementia among cancer survivors.

Keywords

CMV seropositivity; Cancer survivor; Dementia; Inflammation; Older adults

Background

The higher prevalence of cognitive impairment/ dementia among cancer survivors as compared to similarly aged adults without cancer is multifactorial [1, 2]. Though most research has focused on chemotherapy, there is substantial evidence to suggest that cognitive impairment occurs in cancer survivors who have not been exposed to any systemic therapies and that the cancer itself or pre-existing conditions can increase the risk of dementia among cancer survivors [3]. There are several studies in the general population that show an association between low grade inflammation and cognitive impairment [4–11]. A recent study has shown that long-term cancer survivors have increased levels of inflammatory biomarkers [12]. In addition, a study on breast cancer survivors who received chemotherapy 20 years ago showed a cross-sectional association between higher levels of inflammatory markers and higher prevalence of cognitive impairment [13]. Despite literature supporting a higher inflammatory state among cancer survivors and an association between higher inflammation and cognition, the underlying cause of the increased inflammation remains unclear. An important contributor to ongoing inflammation in the general population is cytomegalovirus (CMV) infection, which is a ubiquitous β-herpes virus that infects about 60–100% of most human populations [14]. A vast majority of CMV infections are not completely cleared and can remain latent or get reactivated in individuals. Thus, chronic CMV infection that causes low level inflammation is thought to be an important pathway that contributes to immunological exhaustion and other chronic age related diseases including cognitive impairment/ dementia [15]. Despite an extensive literature on the association between CMV infection and cognitive decline in the general population, [16–21]

the role of CMV infection in determining cognitive function among cancer survivors has not been previously evaluated. Though several large studies in the general population, including a recent report from the Health and Retirement Study, do not support an association between CMV exposure as assessed by CMV IgG serology and subsequent cognitive decline after adjustment for educational status [20]. CMV IgG serology reflects only past exposure to CMV and cannot distinguish between reactivation of latent CMV infection that results in low grade inflammation and latent CMV infection that does not result in inflammation [22, 23]. In addition, there may be a bi-directional association between inflammation and CMV infection where CMV infection induces low grade inflammation [24]. Mediators of inflammation, such as interferon gamma and tumor necrosis factor alpha, promote differentiation of monocytes into CMV permissible macrophages, which are the primary cells for CMV infection [25]. These associations could also be different in cancer survivors that have different levels of inflammation. Previous studies among cancer survivors showed that a combination of CRP and NLR is a better prognostic factor than CRP and NLR individually in the model [26, 27]. Hence, we evaluated the cross-sectional association between CMV infection (estimated using CMV IgG) and inflammation (estimated using high sensitivity C-reactive protein (hsCRP) and neutrophil–lymphocyte ration (NLR)) measured during the 2016 wave and cognitive function in cancer survivors measured at the same time point in the Health and Retirement Study (HRS), a nationally representative study of older adults in the United States.

Methods

Study population

The Health and Retirement Study (HRS) is a large nationally representative biannual comprehensive household panel survey of older adults in the United States of America over 50 years old since 1992. We utilized data from the 2016 HRS survey wave linked to cognitive function and biomarker data measured from venous blood collected from 9,934 participants in 7,227 households during 2016–2017. In the 2016 wave 56% were interviewed in person and 44% on the telephone. After excluding participants with missing covariates and ineligible age (n = 1050), 8883 participants (1454 cancer survivors and 7429 participants without cancer) were included in the final analysis. The final weighted sample is representative of adults in the United States with age 56 years and older. Cancer survivors were identified if the participants responded “yes” to whether they were ever diagnosed by a physician with cancer other than minor skin cancers or underwent any cancer treatment. Among cancer survivors, the year of recent cancer diagnosis ranges from 1970 – 2017.

Measures of cognition/ dementia

HRS cognitive performance tests, which were previously validated were administered through the telephone and in person using trained interviewers who followed standardized protocols [28]. Cognitive performance tests included measures of episodic memory (using immediate and delayed 10-noun free recall test) and measures of mental processing and working memory (using counting backward from 20, serial subtraction of factor 7) [28]. These scores were combined to create a composite score ranging from 0 to 27 that was used to estimate cognitive function. Individual item level missing responses were imputed to

minimize bias due to non-response. The three mental status questions (date naming, object naming and naming the president and vice president of United States) to determine the total cognitive functioning were not included as they were not asked of participants less than 65 years old [29]. We used the Langa-Weir classification based on the 27 point cognitive function score to group participants into three categories: participants with dementia (0–6); Cognitively Impaired but No Dementia (CIND) (7–11); and Normal (0–6) [29]. Since we had a limited number of participants with dementia in the study population, participants in the Dementia and CIND categories combined were defined as the Cognitively Impaired group. We also used other dementia classification algorithms such as Hurd, Expert and Lasso classifiers [30, 31] to evaluate the sensitivity of observed association to specific dementia classification algorithms.

Measurement of CMV infection

CMV seroprevalence was measured using IgG antibodies to cytomegalovirus (CMV) in serum using the Roche e411 immunoassay analyzer (Roche Diagnostics Corporation, Indianapolis, IN). Results were reported as seronegative(< 1.0 COI) or seropositive (≥ 1.0 COI) [32].

Measurement of inflammatory biomarkers

High sensitivity C-reactive Protein (hsCRP) was measured in serum using a latex-particle enhanced immunoturbidimetric assay kit (Roche Diagnostics, Indianapolis, IN 46,250) and read on the Roche COBAS 6000 Chemistry analyzer (Roche Diagnostics). Neutrophil to lymphocyte ratio (NLR) was calculated using % neutrophils and % lymphocytes which were obtained from complete blood counts measured using a Sysmex hemocytometer.

Since the correlation between CRP and NLR was very modest ($r = 0.22$; $p = < 0.0001$) indicating both CRP and NLR reflect different aspects of the overall systemic inflammatory milieu, we created an inflammation score by categorizing participants based on their circulating hsCRP and NLR levels. Each biomarker was dichotomized; hsCRP > 5 mg/L and NLR > 4 were used to classify inflammation at each biomarker as 0 vs 1. Additional sensitivity analysis using different cut points (75th percentile, 90th percentile etc.) did not alter the results of the study (data not shown). The two biomarkers were then combined to get a composite categorical inflammation score: “0” if both biomarkers were 0, “1” if just one biomarker was high, and “2” if both biomarkers were high. Participants with inflammation score of 0 or 1 were categorized as having a low inflammation score while participants with an inflammation score of 2 were categorized as having a high inflammation score. Detailed description of pro-inflammatory biomarkers such as IL-6, IL-1RA, TGF-beta and sTNFR1 used in additional analyses are described in the supplementary material.

Statistical analysis

The primary outcome variable was cognitive impairment and the primary predictor variables were exposure to CMV infection (seropositive/seronegative) and the inflammation score. We subsequently combined the CMV seropositivity status and the inflammation score to create a measure of ‘CMV seropositivity and inflammation’ with the ‘CMV Seronegative and Low

inflammation' as the reference category in the analysis and compared the odds of having cognitive impairment across different CMV and inflammation categories.

To evaluate the difference in characteristics between cancer survivors and participants without cancer, we used a survey regression model for parametric continuous variables and the survey χ^2 test for categorical variables. We used survey generalized logit models to evaluate the cross-sectional association between CMV seropositivity, systemic inflammation score and cognitive impairment among cancer survivors and participants without cancer separately; a priori adjustment factors included age, sex, race/ethnicity, years of education, comorbidity index (the cumulative number of self-reported chronic conditions such as hypertension, diabetes, lung disease, cardiac disorders, stroke, arthritis, and psychiatric problems) and survey design parameters (strata and cluster to account for sampling error and participant sampling weights for the 2016 HRS Venous Blood Study to account for sample design). We also performed a subset analyses to evaluate the impact of time of cancer diagnosis on the association between inflammation status and CMV serostatus on cognitive function by categorizing the cancer survivors into two groups; those who were diagnosed within three years of measurement of inflammatory biomarkers and CMV serostatus and those who were diagnosed prior to three years from measurement of inflammatory biomarkers and CMV serostatus after adjustment for all the covariates mentioned above.

For sensitivity analyses, we evaluated the association between cognitive impairment and quantitative CMV IgG levels. We also evaluated the association between cognitive impairment, inflammation and CMV serostatus among study participants who were 65 years or older and had full cognition measures including TICS score available in 2016 survey. Finally, we also evaluated the association between CMV serostatus, inflammation status and dementia using dementia predictions from three other dementia classifier algorithms developed in HRS [30, 31] such as Hurd algorithm, Expert algorithm and Lasso algorithm. All statistical analysis performed using SAS v9.4 of the SAS system for Windows.

Results

Table 1 shows descriptive statistics of study participants among cancer survivors and participants without cancer. Among the 8883 participants included in this analysis, 54% (n = 4798) were women and 78% (n = 6921) were non-Hispanic whites. Among the study participants, 16.4% (n = 1454) were cancer survivors and 17% (n = 1514) had cognitive impairment. Among cancer survivors, we had 313 (21.5%) participants who were diagnosed with cancer within three years of measurement of inflammatory biomarkers and CMV serostatus and a 78.5% of cancer survivors (n = 1141) were diagnosed with cancer more than three years prior to measurement of inflammatory biomarkers and CMV serostatus. CMV seropositivity was similar among cancer survivors (63.5% (n = 923)) and those without cancer (63.4% (n = 4707), p = 0.97)). A high inflammation score was more prevalent in cancer survivors as compared to those without cancer (3.9% (n = 56) vs. 2.8% (n = 205); p = 0.06). There were no significant differences in the prevalence of high inflammation score and CMV seropositivity among cancer survivors who were diagnosed within the last three years as compared to those diagnosed prior to three years of measurement of inflammatory biomarkers (5.1% vs. 3.5%; p = 0.2) and CMV serostatus (63.6% vs. 63.4%; p = 0.9). There

were 33 participants with a cancer diagnosis (2.3%) and 114 participants (1.5%) without cancer in the 'CMV Seropositive and High inflammation' group whereas 508 (35.9%) of cancer survivors and 2631 (35.4%) of participants without cancer were in the 'CMV Seronegative and Low inflammation' group ($p = 0.35$).

Among cancer survivors, there was no difference in cognitive impairment among CMV seropositive and CMV seronegative categories [$OR = 1.4$ (95% CI 0.9, 2.2)] (Table 2). Additional analyses evaluating the association between tertiles of CMV IgG antibody levels and cognitive impairment also showed no association between the tertiles of CMV IgG antibodies and cognitive impairment (Supplementary Table S1). Cancer survivors with a high inflammation score had higher odds of having cognitive impairment compared to those who had a low inflammation score [$OR = 2.2$, (95% CI 1.2, 4.2)] (Table 2). Cancer survivors who were CMV seropositive and had a high inflammation score had higher odds of having cognitive impairment compared to those who were CMV seronegative and had a low inflammation score [$OR = 3.7$, (95% CI 1.6, 9)] (Table 2). Additional analysis that included pro-inflammatory biomarkers such as IL-6, IL-1RA, TGF-beta and sTNFR1 did not substantially change the observed results (Supplementary Table S2). Among participants without cancer, we observed similar but attenuated associations between CMV seropositivity, high inflammation and cognitive impairment compared to what was observed in cancer survivors (Table 2). There was no statistically significant interaction between cancer survivor status and the combined CMV seropositivity/inflammation score in determining cognitive function ($p = 0.50$). Additional analysis using cognitive function as a continuous outcome did not change the observed associations (Supplementary Table S3). Stratified analysis among cancer survivors showed that the statistically significant associations between CMV seropositivity, high inflammation and cognitive impairment seen among cancer survivors was mainly driven by the participants who were diagnosed with cancer within three years of measurement of inflammatory biomarkers and CMV serostatus [$OR = 18.5$, (95% CI 6.1, 56.1)] (Table 3). There was a significant interaction between duration of cancer diagnosis and measurement of inflammatory biomarkers/CMV serostatus in determining cognitive function ($p = 0.02$). Additional analysis that included additional pro-inflammatory biomarkers such as IL-6, IL-1RA, TGF-beta and sTNFR1 did not change the observed findings in the stratified analysis (Supplementary Table S4).

Among 8883 participants, 58.7% ($n = 5215$) had full cognition score (HRS-TICS score) available in 2016 survey. We observed that there were no statistically significant associations between CMV seropositivity, high inflammation and cognitive impairment in the subsample of study population that had full cognition score available, though the directionality of association was similar to what we observed in the overall study population (Supplementary Table S5). Among 8883 participants, 54.2% ($n = 4817$) had dementia predictions available in 2016 survey from all 4 dementia classification approaches. Supplementary table 6 shows the results of comparison of associations between CMV seropositivity, high inflammation and cognitive impairment from 4 dementia classifiers developed in HRS. We found statistically significant associations between CMV seropositivity, high inflammation and cognitive impairment seen among cancer survivors when we used dementia predictions from Hurd, Expert or Lasso algorithms. We found associations in the same direction but not significant when we used Langa-Weir approach. We also observed positive associations

among participants without cancer but the association was significant only when we used Expert algorithm.

Discussion

This is the first study to show a cross sectional association between CMV seropositivity and inflammation and cognitive impairment among cancer survivors. Though CMV seropositivity alone was not significantly associated with higher prevalence of cognitive impairment among cancer survivors, CMV seropositive cancer survivors who had inflammation were at increased risk of having lower cognitive function. A similar pattern was observed among those without cancer indicating the importance of identifying older individuals with CMV seropositivity and higher inflammation and evaluate their risk of developing dementia.

A higher proportion of cancer survivors showed cognitive impairment (19.1%) as compared to age matched controls without cancer (16.6%). This is consistent with previous studies that showed increased prevalence of cognitive impairment in cancer survivors [1, 2]. The causes of increased prevalence of cognitive impairment among cancer survivors include cancer-related factors (cancer stage, cancer type), cancer treatment related factors (types and duration of chemotherapy), and host factors (genetics, age, race etc.) playing important roles in determining susceptibility to cognitive impairment [1]. Cancer survivors have higher levels of pro-inflammatory biomarkers as compared to participants without cancer [33, 34]. Furthermore, those who received systemic cytotoxic treatments such as chemotherapy or radiation therapy have higher levels of pro-inflammatory biomarkers as compared to cancer survivors who only received surgical interventions as part of their cancer treatment [35]. This study confirmed that cancer survivors had higher levels of pro-inflammatory biomarkers as compared to those without cancer. Though not statistically significant, the prevalence of high inflammatory score was higher among cancer survivors who were diagnosed with cancer within the last three years as compared to those diagnosed with cancer for longer than three years. Cancer survivors with higher levels of pro-inflammatory biomarkers had higher risk of cognitive impairment and this association was more pronounced among cancer survivors diagnosed within the last three years. In addition, this study also showed that cancer survivors who were both CMV seropositive and had higher levels of pro-inflammatory biomarkers had a substantially higher odds of being cognitively impaired suggesting that CMV seropositivity and ongoing inflammation may be important in the development of cognitive impairment among cancer survivors. However, the contribution of CMV infection and the increased pro-inflammatory state towards cognitive impairment seen in cancer survivors has not been previously evaluated. Though this study does not provide direct evidence that ongoing CMV replication, as evidenced by detection of CMV DNA in monocytes, previous studies have shown that chemotherapy activates latent CMV infection that results in higher CMV viral load after chemotherapy and also results in increased levels of pro-inflammatory biomarkers such as IL-6 and tumor necrosis factor alpha after chemotherapy [36]. In addition, a study on long term survivors of childhood leukemia showed that pro-inflammatory markers such as IL-6 and CRP were increased in long term childhood cancer survivors 19 years after cancer diagnosis as compared to controls [37]. In addition, T-cell responses specific to CMV were also increased in

survivors compared to controls while CMV IgG levels in survivors were comparable to levels measured in the elderly (> 50 years) and correlated with IL-6 and CRP [37]. Thus, the CMV reactivation observed in cancer survivors leads to an activated immune system that results in an exhausted immune system and ongoing chronic inflammation. In addition, higher levels of inflammation may itself facilitate differentiation of monocytes in CMV permissive macrophages, the primary reservoirs for latent CMV infection [25].

Previous epidemiological studies conducted in the general population have largely shown increased levels of inflammatory biomarkers measured in midlife were associated with lower cognitive function in later life. Several pro-inflammatory biomarkers such as CRP, IL-6, IL-1 beta and tumor necrosis factor have all been associated with increased risk of lower cognitive function in later life [4–11]. However, other large studies have subsequently shown a lack of association between increased levels of chronic inflammation and risk of dementia [38, 39]. In addition, four longitudinal studies that measured pro-inflammatory biomarkers at multiple time points showed discrepant associations with cognitive function with some studies showing no association with cognitive function [40, 41] while others have shown either a positive [42] or a negative [43] association with cognitive function in later life. Thus, it is unclear as to whether the inflammatory process play a causative role in cognitive function decline over time. Our study showed a positive association between inflammation and cognitive impartment among those without cancer. A majority of epidemiological studies conducted in the general population do not show any association between CMV seropositivity and cognitive function [17–19, 21]. One study showed an association between higher CMV specific IgG levels and lower cognitive function in a Hispanic population that was predominantly CMV seropositive (96% seropositivity rate) [16]. A recently published study from HRS showed that both CMV seropositivity and higher IgG were associated with lower cognitive function, though the relationship was not statistically significant after adjustment for important confounders such as educational status [20]. A major limitation of these large studies in the general population on CMV infection and cognitive function is that CMV IgG serology reflects only past exposure to CMV and cannot distinguish between chronic ongoing low replicating CMV virus that causes low grade inflammation and past or latent or resolved infections that does not cause inflammation. The present cross sectional study addresses this limitation of previous studies by simultaneously evaluating both CMV IgG exposure and inflammatory biomarkers. Among participants without cancer, we found that those who were CMV seropositive and had elevated inflammatory markers had a higher significantly increased risk of cognitive impairment though the magnitude of effect was attenuated as compared to cancer survivors. The higher CMV reactivation and higher levels of inflammation seen in cancer survivors may be possible reasons for the strong associations seen in cancer survivors. These findings support the idea that reactivation of latent CMV infection that causes inflammation may result in reduced cognitive function among older individuals and this association was stronger in cancer survivors. The stronger associations seen among cancer survivors who were recently diagnosed with a cancer (within three years) suggests that the pro-inflammatory milieu created due to systemic cancer treatment and the possible CMV reactivation in cancer patients undergoing chemotherapy/radiation therapy may be an important mechanism through which systemic cancer treatment adversely affects cognitive function. Even among the recent cancer survivors, only a small fraction

of survivors has high inflammation, CMV seropositivity or both. This suggests that the pro-inflammatory status observed with systemic cancer treatment is seen only in a small subset of cancer patients. Thus, identifying the inflammatory status and CMV reactivation in cancer patients who have recently undergone systemic treatment may be helpful in identifying a subgroup of cancer survivors who are at high risk for developing future cognitive dysfunction. The sensitivity analysis we performed on participants over 65 years old with complete measurement of cognitive function also showed similar results though that the magnitude of effect was attenuated. The lower sample size in the subset analysis likely contributes to the non-significant associations observed as compared to the full cohort analyses. A small study among 15 women from the Women's Health and Aging Study (WHAS) II with 12 years of follow up also showed that CMV IgG serology titers did not change over twelve years but only women with detectable CMV DNA that indicates ongoing CMV replication had higher IL-6 levels, a pro-inflammatory biomarker both at baseline and at the 12 year follow up [44]. Another study on 161 elderly individuals also showed a significant association between pro-inflammatory biomarkers and lower cognitive function among CMV seropositive individuals [45]. We have compared our study findings from HRS 2016 full cohort analyses using Langa-Weir classification approaches to other dementia classifier algorithms developed in HRS which have higher sensitivity and specificity in dementia classification compared to Langa-Weir approach [30]. Both the Hurd and Lasso algorithms showed a significant positive association between between CMV seropositivity, high inflammation and dementia among cancer survivors while the Expert algorithm showed significant positive associations between CMV seropositivity, inflammation and dementia among both cancer survivors and participants without cancer. We used dementia classifications from Langa-Weir approach as our primary study outcome as that is the only dementia classification available for participants less than 65 years old and hence we could use the Langa-Weir classification for the entire HRS cohort that have biomarker data.

Limitations of this study include lack of detailed information on cancer treatment received by individuals. Thus, this study cannot evaluate the effect of individual treatment regimens or the effect of time interval between cancer diagnosis and measurement of cognitive function on cognitive impairment. This study is also not well-powered to address specific types of cancer. This study did not directly measure CMV viral load to estimate active CMV infection. Instead we used a combination of CMV seropositivity and levels of inflammatory biomarkers to infer potential CMV reactivation. Direct measurement of CMV viral load along with inflammatory biomarkers in future studies of cancer survivors that include detailed information on cancer types and cancer treatments will be helpful in confirming the results of the current study. The reported association between CMV seropositivity and cancer specific mortality in the general population [46] may also introduce a potential survivor bias in the study findings. However, this is likely to result in the cancer survivors having lower CMV titers and the observed associations may be biased towards the null value. Strengths of this study include the large sample size and the population representativeness of the Health and Retirement Study. Hence, results from this study are generalizable to the population of adults older than 55 years in the United States. Future studies that evaluate the longitudinal association between CMV, inflammation and

cognitive function may provide additional evidence for the causal role of CMV infection and inflammation in determining cognition function among older cancer survivors. If these findings are confirmed, strategies to reduce CMV activation and inflammation may be important to reduce the prevalence of cognitive impairment among older adults and particularly among cancer survivors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Characteristics of cancer survivors and participants without cancer at the 2016 wave of the health and retirement study

Variables	Cancer survivors *n* = 1454 (16.4%)	Participants without cancer *n* = 7429 (83.6%)	*p*-value
	Mean ± SEM/ N (%)	**Mean ± SEM/ N (%)**	
Age (years)	72 ± 0.5	67.9 ± 0.2	< 0.0001
Sex (%Female)	780 (53.6%)	4017 (54.1%)	0.83
Race			
Hispanics	80 (5.5%)	733 (9.9%)	< 0.0001
Non hispanic whites	1213 (83.4%)	5709 (76.8%)	
Non hispanic blacks	131 (9.0%)	733 (9.9%)	
Other	30 (2.1%)	254 (3.4%)	
Years of education	13.7 ± 0.1	13.6 ± 0.1	0.6
Comorbidity	2.4 ± 0.1	2.0 ± 0.02	< 0.0001
CMV seropositivity (% Reactive)	923 (63.4%)	4707 (63.4%)	0.97
C-Reactive protein (High Sensitivity) mg/L *	6 ± 0.7	4.4 ± 0.1	< 0.0001
Neutrophil-to-Lymphocyte ratio *	2.6 ± 0.1	2.2 ± 0.02	< 0.0001
Inflammation score (% High)	56 (3.9%)	205 (2.8%)	0.02
Cognitive scores	15.3 ± 0.2	15.7 ± 0.1	0.02
Cognitive status			0.14
Normal	1176 (80.9%)	6193 (83.4%)	
CIND	223 (15.3%)	1012 (13.6%)	
Dementia	55 (3.8%)	224 (3.0%)	
Cognitive impairment (%Yes)	278 (19.1%)	1236 (16.6%)	0.08

* These variables were logarithmically transformed to approximate a normal distribution in the regression model

SEM Standard Error of Mean, *CIND* Cognitive Impairment Not Dementia, *CMV* Cytomegalovirus

The models were adjusted for survey design parameters (strata and cluster for sampling error and participant sample weights for the 2016 HRS Venous Blood Study)

Table 2

Cross-sectional association between CMV seropositivity, inflammation score and cognitive impairment among cancer survivors and participants without cancer

Predictors	Cancer survivors *n* = 1454 (16.4%) OR (95% CI)	Participants without cancer *n* = 7429 (83.6%) OR (95% CI)
CMV seropositivity		
CMV seropositive	1.4 (0.9,2.2)	1.1 (0.9,1.3)
CMV seronegative	Ref	Ref
Inflammation score		
High	2.2 (1.2,4.2)	1.8 (1.1,3.0)
Low	Ref	Ref
CMV seropositivity and inflammation		
CMV seropositive and high inflammation score	3.8 (1.5,9.4)	2.4 (1.2,4.8)
CMV seropositive and low inflammation score	1.4 (0.8,2.3)	1.1 (0.9,1.3)
CMV seronegative and high inflammation score	1.9 (0.7,5.5)	1.3 (0.6,2.5)
CMV seronegative and low inflammation score	Ref	Ref

The models were adjusted for age, sex, race/ethnicity, years of education, comorbidity index and survey design parameters (strata and cluster for sampling error and participant sample weights for the 2016 HRS Venous Blood Study)

CMV Cytomegalovirus

Table 3

Cross-sectional association between CMV seropositivity, inflammation score and cognitive impairment among cancer survivors diagnosed within three years of biomarker measurement and those diagnosed with cancer ≥ 3 years prior to biomarker measurement

Predictors	Cancer diagnosed within three years of measurement of inflammation score/CMV status *n* = 313 (21.5%) OR (95% CI)	Cancer diagnosed ≥ three years of measurement of inflammation score/CMV status *n* = 1141 (78.5%) OR (95% CI)
CMV seropositivity		
CMV seropositive	2.3 (1.1,5.2)	1.2 (0.7,1.9)
CMV seronegative	Ref	Ref
Inflammation score		
High	6.4 (2.5,16.6)	1.3 (0.6,2.6)
Low	Ref	Ref
CMV seropositivity and inflammation		
CMV seropositive and high inflammation score	18.5 (6.1,56.1)	1.78 (0.6,5.4)
CMV seropositive and low inflammation score	2.6 (1.0,6.9)	1.2 (0.7,2.0)
CMV seronegative and high inflammation score	6.9 (1.3,38.1)	1.1 (0.2,5.1)
CMV seronegative and low inflammation score	Ref	Ref

The models were adjusted for age, sex, race/ethnicity, years of education, comorbidity index and survey design parameters (strata and cluster for sampling error and participant sample weights for the 2016 HRS Venous Blood Study)

CMV Cytomegalovirus