Published in final edited form as:

Sleep Med. 2015 July ; 16(7): 845–849. doi:10.1016/j.sleep.2015.02.531.

Self-Reported Memory Problems in Adult-onset Cancer Survivors: Effects of Cardiovascular Disease and Insomnia

Pascal Jean-Pierre, PhD, MPH^{1,2}, Michael A. Grandner, PhD^{3,4}, Sheila N. Garland, PhD^{4,5}, Elizabeth Henry, MD⁶, Girardin Jean-Louis, PhD⁷, and Thomas G. Burish, PhD¹

¹University of Notre Dame, Department of Psychology, Neurocognitive Translational Research Lab, Harper Cancer Research Institute

²Indiana University Melvin and Bren Simon Cancer Center

³University of Pennsylvania, Center for Sleep and Circadian Neurobiology

⁴University of Pennsylvania, Department of Psychiatry, Behavioral Sleep Medicine Program

⁵University of Pennsylvania, Department of Family Medicine and Community Health

⁶Loyola University Medical Center, Department of Hematology/Oncology, Cardinal Bernardin Cancer Center

⁷New York University, Department of Population Health, Center for Healthful Behavior Change

Abstract

Background—Cancer and its treatments can deleteriously affect memory. Cardiac function and insomnia can exacerbate memory problems.

Objective—To examine the relationships among cardiovascular disease, insomnia, and self-reported memory problems (SRMP) in adult-onset cancer survivors.

Methods—We included data from participants (41–64 year-old) of the 2007–2008 National Health and Nutrition Examination Survey, a nationally representative probability sample of the civilian, non-institutionalized population of the US. We excluded participants with brain cancer/stroke history since these conditions are expected to cause cognitive problems. Using binary logistic regression, we determined the prevalence of SRMP relative to cardiac problems and insomnia by weighting our results proportionally. We adjusted for predictors of memory problems: age, sex, race, education and general health.

© 2015 Published by Elsevier B.V.

Send correspondence requests to: Dr. Pascal Jean-Pierre, PhD, MPH, University of Notre Dame, Neurocognitive Translational Research Lab, Cancer Control & Survivorship Program, 109 Haggard Hall, Notre Dame, IN 46566, PJeanPierre@ND.edu, Tel: (574) 631-2589.

Conflict of Interest: Drs. Pascal Jean-Pierre, Michael A. Grandner, Sheila N. Garland, Elizabeth Henry, Girardin Jean-Louis, and Thomas G. Burish declare no conflict of interest.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Results—The sample included 2,289 adults (49% females), 9% with a cancer history. The results pertain only to cancer survivors. Those with insomnia were 16 times as likely to have SRMP. Only insomnia symptoms (OR, 15.74; 95%CI, 1.73 to 143.30; $p<0.01$) significantly predicted SRMP, uniquely explaining 12% of the variance. Insomnia accounted for 18.8% of the association between cardiac issues and SRMP, demonstrating mediation (Sobel $p<0.05$). The large CI is a consequence of analyzing a subgroup of a subpopulation. Among participants without a cancer history, cardiovascular disease and insomnia were not associated with SRMP ($p>0.05$).

Limitations—We could not determine severity and time-related changes in SRMP.

Conclusion—Likelihood of SRMP was higher in cancer survivors with a history of cardiovascular disease and insomnia symptoms. Future studies are needed to delineate the cardiac-insomnia-memory interrelationships.

Keywords

Chemobrain; Cancer and Memory Problems; Sleep problems; Cardiovascular Disease

INTRODUCTION

Cancer is one of the leading causes of morbidity and mortality worldwide, with substantial and growing financial and quality of life burden for patients, their families and society.^{1–2} In 2008, the prevalence of cancer in the United States was estimated at approximately 12 million individuals.³ Annual estimates of new cancers in the United States have also grown from 1.45 million in 2008 to 1.64 million in 2012.^{4–9} Advancements in early cancer screening and detection, availability of more potent cancer therapeutics, and increased survival rates means that people are living longer with cancer. As such, patients are also experiencing more debilitating diseases and treatment-induced toxicities such as neurocognitive dysfunction, cardiomyopathy, fatigue, sleep impairments, and pain. These adverse effects of cancer and its treatments can negatively impact patients and survivors on multiple physical, behavioral, emotional and psychosocial dimensions of well-being and overall quality of life.^{10–11}

Cancer and treatment-related neurocognitive dysfunction (CRND), commonly referred to as “chemobrain” or “chemo fog”, is an incapacitating adverse condition experienced by up to 75% of patients with non-central nervous system malignancies (e.g., breast, head and neck, cervical, prostate and colorectal cancers) during and many years after completion of cancer treatment [11–16]. CRND is a multifaceted adverse condition and involves impairments in various aspects of attention, memory, cognitive information processing speed, and executive function.^{10,17–19} The etiology of CRND is commonly attributed to various factors that both either independently or synergistically influence brain structures and cognitive outcomes. The hypothesized factors implicated in CRND include biological, genetic and psychological predispositions, as well as unknown aspects of malignant neoplasms (e.g., breast, prostate, cervical and colorectal cancers) and their various treatment modalities (e.g., radiation therapy, chemotherapy, and hormonal therapy) that can deleteriously impact the brain biochemical milieu.^{20–27} Memory concerns are some of the most common, enduring and frustrating aspects of CRND for patients and survivors. Other cancer and treatment-related

negative side effects (e.g., cardiac issues such as cardiomyopathy, and sleep impairment) may be implicated in CRND. This conjecture is based on known associations between brain processing outcomes and cardiac conditions and sleep.^{28–31} Nevertheless, studies that examine the relationships among cardiac conditions (e.g., congestive heart failure, coronary heart disease, angina pectoris and heart attack), insomnia symptoms (e.g., difficulty falling asleep and staying asleep), and cognitive dysfunction (e.g., attention and memory problems) in individuals with non-central nervous system cancers are still lacking. The present study addressed this paucity of data by examining the associations among history of cardiovascular disease, insomnia symptoms, and self-reported memory problems in adult-onset cancer survivors.

METHODS

Sample Description

We examined data from 2,289 participants (49% females), between 41 and 64 years of age, who completed the National Health and Nutrition Examination Survey (NHANES), a nationally representative, stratified, multistage probability sample of the civilian, non-institutionalized population of the United States from 2007 to 2008. NHANES data collection methods included an interviewer-administered questionnaire using computer-assisted interviewing technology and physical examinations that were performed in mobile examination centers. NHANES used standardized data collection methods in order to minimize site-specific errors, and oversampled for Blacks, Hispanics, and persons age 60 years and older. This approach helped facilitate the computation of more reliable and representative statistics to increase precision of the estimates. In the present analyses, we specifically excluded participants with a history of brain tumors and/or stroke since brain insults from these conditions are expected to result in cognitive impairments due to direct damage to brain tissue.

Memory Problems, Cardiovascular Disease, Depression, Sleep Disorder and Insomnia Symptoms

Assessment of self-reported memory problems (SRMP) was based on participants' self-reported "yes" or "no" responses to the following question from the Physical Functioning section of the NHANES Questionnaire: "Are you limited in any way because of difficulty remembering or because you experience periods of confusion?" We assessed cardiac issues from the Medical History section of the NHANES Questionnaire self-reported response to the question: "Has a doctor or other health professional ever told you that you have..." with positive endorsements of, congestive heart failure, coronary heart disease, angina, or heart attack. Depression was determined using a Depression Screener Questionnaire (DPQ) from the Patient Health Questionnaire used in the NHANES survey. Items of the DPQ were each scored from "0" (not at all) to "3" (nearly everyday), and assessed anhedonia, depressed mood, lack of energy, appetite changes, feelings of failure, difficulty concentrating, psychomotor symptoms, suicide ideation, and general sleep disturbance. Scores were summed (excluding the sleep disturbance item). Diagnoses of sleep disorders including insomnia, sleep apnea, restless legs syndrome, or "other" were assessed. Sleep disorder symptoms were determined by asking participants "how often you snore?" and "how often

do you snort/stop breathing?” Five or more nights per week were coded “yes” for snoring, and 1 night per week or more were code as “yes” for snorting. Sleep medication use was assessed and coded “yes” for use at least once per month. Presence of insomnia was based on the survey items, “In the past month, how often did you have trouble falling asleep” and “In the past month, how often did you wake up during the night and had trouble getting back to sleep?” If subjects responded “Almost always, 16 or more times a month” on either question, they were determined to have had insomnia, based on the diagnostic criteria of insomnia that suggest a cutoff point of 3 nights per week of difficulty falling asleep or difficulty maintaining sleep.³² Participants who declined to answer or provided a “Don’t know” answer were counted as missing data.

Determination of Cancer Status and Brain Cancer History

We assessed cancer status based on participants self-reported response to the question: “Have you ever been told by a doctor or other health professional that you had cancer or a malignancy of any kind?” from the Medical Conditions section of the NHANES Questionnaire. We assessed history of brain cancer based on participants’ responses to the question: “What kind of cancer?” Those who declined to answer or gave a “Don’t know” answer were counted as missing data.

Statistical Analyses

We estimated the prevalence of self-reported memory problems, cardiac disorders and insomnia symptoms in the United States by weighting our results proportionally. We included the following clinical and socio-demographic covariates: general health condition (i.e., excellent, very good, good, fair, or poor), depression (i.e., feeling down, depressed or hopeless), sleep disorder symptoms (i.e., incidence and frequency of snoring and snorting), age, race-ethnicity, sex, and education. Associations were determined on the basis of statistically significant p -values calculated with χ^2 tests for association. We used binary logistic regression to assess independent associations between cancer history and memory problems, cardiac problems, and insomnia symptoms. We also used mediation analysis to examine the relationship between effect of insomnia symptoms on the relationship between cardiac issues and SRMP. We controlled for age, race/ethnicity, sex, and education, sleep disorder symptoms, general health condition, and depression. Sleep medication was dichotomized as once per month only.

NHANES uses a complex sampling design that involves stratification, clustering, and oversampling of subgroups to increase the reliability and accuracy of estimates. However, this clustering design and its incorporated differential probabilities of selection generally results in an unequal probability of selection. Thus, to control for unequal probability of selection and produce unbiased estimates of the non-institutionalized population of the United States, we included stratum, primary sampling units, and appropriate sampling weights in our statistical analyses incorporated. All statistical analyses were conducted using STATA Data Analysis and Statistical Software Version 12 (StataCorp LP, College Station, Texas, USA). Alpha was set at 0.05, and all tests were two-tailed.

RESULTS

The sample consisted of 2,369 individuals (approximately 49% females), age 41 to 64 years, from diverse educational and racial/ethnic backgrounds: 72% Non-Hispanic White, 11% Black/African-American, 10% Hispanic/Latino, and 7% Asian/Other (Table 1). Of the total sample, 9% reported having had cancer. Albeit not statistically significant, memory problems were self-reported by a greater percentage of participants with a history of cancer (7.85%) than by those without a history of cancer (6.03%). Of the total sample, $N = 186$ reported a history of cancer and fell within the age range for the present study. Of these 186 participants, $N = 10$ were excluded due to a history of stroke or other brain complications, and an additional $N = 12$ were excluded for missing depression data. The final analytic sample comprised of the remaining $N = 164$ cancer survivors. Additionally, only $N = 13$ subjects reported a diagnosis of sleep apnea and $N = 9$ reported a diagnosis of insomnia, so these variables were excluded. There were <5 subjects with either sleep disorder who also had memory problems, precluding the inclusion of these variables. The following analyses and results pertain only to the subsample of 164 cancer survivors.

Results of binary logistic regression analyses are reported in Table 2. The variable general health was omitted from all subsequent binary logistic regression analyses because of collinearity. In a model adjusting for age, sex, race/ethnicity, education level, depression, and overall health, cancer survivors with a history of cardiovascular disease were approximately 11 times more likely to also experience memory problems (OR = 11.07, 95%CI: 2.03 to 60.22, $p < 0.002$). In the logistic regression model on cardiac issues and memory, depression revealed OR = 4.94, 95%CI = 1.08 to 1.57, sleep medication use (dichotomized as once per month or less) revealed an OR = 1.62, 95%CI = 1.09 to 2.41, and sleep disorder symptom (i.e., snoring) revealed an OR = 5.46, 95%CI: 1.29 to 23.12, $p < 0.021$. Overall, this cardiac model explained 38% of the variance in memory problems. When insomnia was added to the logistic regression model, the effect of cardiovascular disease was reduced (OR = 6.89, 95%CI: 1.13 to 41.97, $p = 0.04$). However, the relationship with insomnia was maintained. Specifically, cancer survivors with insomnia were approximately 13 times more likely to report experiencing memory problems (OR = 13.18, 95%CI: 1.31 to 132.93, $p < 0.03$). In the heart disease and insomnia logistic regression model, sleep disorder symptom (i.e., snoring (OR = 6.61, 95%CI: 1.39 to 31.57) also contributed to memory problems. The model with both heart disease and insomnia explained approximately 48% of the variance in memory problems. We subsequently completed a logistic regression model (including age, sex, race-ethnicity, education, depression, sleep medication, and sleep disorder symptoms) to determine the effect of insomnia only on self-reported memory difficulties in cancer survivors, which revealed OR = 15.74, 95%CI: 1.73 to 143.30, $p < 0.014$). In this insomnia only model, Sleep disordered symptoms significantly predict memory problems (OR = 9.7702, 95%CI: 1.68 to 56.86, $p < 0.011$). Among participants without a history of cancer, SRMP was not statistically significantly related to cardiac problems or insomnia in any of the logistic regression models ($p > 0.05$). Nonetheless, among non-cancer survivors, depression (OR = 1.2021, 95%CI: 1.14 to 1.27, $p = 0.001$) and sleep medication seem to influence self-reported experience of memory problems (OR=1.43, 95%CI: 1.19 to 1.72 seem to influence self-reported experience of

memory problems in the cardiovascular disease only model. In the insomnia only model, depression (OR = 1.20, 95%CI: 1.1.23 to 1.26, $p = 0.000$) and sleep disorders symptoms (OR = 1.41, 95%CI = 1.7077 1.7083, $p = 0.000$) influenced self-reported memory problems. In the heart disease and insomnia combined logistic regression model both depression (OR = 1.19, 95%CI: 1.13 to 1.26, $p < 0.000$) and sleep medication (OR = 1.40, 95%CI: 1.1597 to 1.1651, $p = 0.000$) influenced self-reported memory problems.

The large confidence intervals in the present study are due to the relatively small cell sizes in the analyses. Although the NHANES dataset is relatively large, the subset that includes cancer survivors is relatively small and subsample included in the present analyses is smaller still. Thus, precision of the estimates is relatively low. However, the robustness of the direction seems high, suggesting the probability that the direction of relation from this analysis is accurate, even though the magnitude is difficult to discern.

Given the change in effects of cardiac issues in the presence of insomnia symptoms, mediation analyses were conducted to determine whether the relationship between cardiac issues and memory problems in cancer was attributable to insomnia. In analyses adjusted for the contributions of all covariates, insomnia accounted for 18.8% of the association between heart problems and SRMP, and demonstrated a significant partial mediation (Sobel $p < 0.05$).

DISCUSSION

Cancer and treatment-related problems in memory and other aspects of cognitive functioning are serious and debilitating adverse effects experienced by a large number of patients and survivors. We examined the associations among self-reported memory problems, history of cardiac issues, and insomnia symptoms in a multicultural sample of adults previously diagnosed with cancer. Our analyses showed that heart diseases or disorders and insomnia symptoms independently predicted memory problems in cancer patients. We conducted a mediation analysis to systematically characterize and explain the underlying mechanistic pathways of the observed associations among cardiac conditions, insomnia symptoms, and SRMP in cancer survivors. Results of the mediation analysis revealed that insomnia symptoms fully mediated the relationship between cardiac disorders and self-reported memory problem. In contrast, our analyses revealed that among participants without a cancer history, neither cardiac problems nor insomnia symptoms were significantly associated with SRMP. Overall, the findings of the present study indicate a potentially important role of cardiovascular conditions and insomnia symptoms in memory functioning among cancer survivors. Specifically, heart disorders and insomnia symptoms may both independently and synergistically influenced memory performance in adult-onset cancer survivors.

Future prospective studies are needed to more systematically characterize and explain the cardiac-insomnia symptoms-memory relationships. These future studies could inform the development of more reliable assessment methods and interventions to mitigate cancer and treatment-related memory problems. Additionally, the statistically significant meditational relationship between cardiac problems and insomnia symptoms underscores the need to

investigate cancer and treatment-related adverse effects in a symptom-clustering model in lieu of a single symptom analysis model. A multivariate analytic approach to characterize symptoms could facilitate a more meaningful understanding of intricate aspects of the cancer survivorship experience, and could support the development and testing of tailored interventions to improve psychosocial functioning and quality of life for cancer patients and survivors.

Our analyses also showed a statistically significant contribution of depressive symptoms (i.e., feeling down, depressed or hopeless) to the prediction of self-reported experience of memory problems in both the cancer survivor subgroup and the larger non-cancer survivor sample. The association between memory and depression has been long established.³³ Future studies are needed to clearly explicate the relationship between depression and memory. These future studies can help cogently describe the processes or mechanistic pathways through which depression may negatively impact memory. A recent study reported a greater vulnerability to depressive symptom-related memory problems among African Americans compared to non-Hispanic White adults.³⁴ Future studies could also help identifying specific individual characteristics that are associated with depression and different aspects of memory.

While revealing important independent and meditational effects of cardiac problems and insomnia symptoms on SRMP in adult-onset cancer survivors, the findings of the present study should be interpreted cautiously because of inherent limitations in this cross-sectional dataset that could not be manipulated. First, we were unable to assess variations in severity of self-reported memory problems across time, differential cancer stages, and specific cancer treatment regimen that could influence the development and characteristics of self-reported difficulties in memory and neurocognitive performance in individuals diagnosed with a cancer history. Second, memory problems were determined by participants' self-report only. The available data did not include objective and psychometrically validated neuropsychological measures. Although previous studies have reported discrepancies between patient self-reported cognitive difficulties and scores on psychometrically validated objective neuropsychological tests, neuroimaging studies have also demonstrated that subjective experience of cancer and treatment-related problems in cognitive performance are associated with increased brain activations, indicating the presence of cognitive deficits at the pre-clinical levels that our currently available psychometrically validated objective measures of brain functioning cannot yet accurately capture.^{16,18} Additionally, global health may be an important factor unaccounted for. Lastly, the NHANES dataset did not include pertinent data to determine any plausible effects of time from cancer diagnosis, cancer type, and survival effects on memory performance. Previous epidemiologic studies have indicated that cancer stage and type could be confounded with time since diagnosis, whereas individuals with later stage and more fatal malignancies (e.g., lung and pancreatic cancers) may not have been included in data collection for this cross-sectional study.

Despite these limitations, the findings from the present study reveal important relationships among cardiac conditions, insomnia symptoms, and memory performance outcomes in adult-onset cancer survivors. Strategies to mitigate cancer and treatment-induced brain insults and cognitive impairments for cancer patients and survivors should integrate

pertinent information regarding cardiac history, sleep patterns, and other related biologic and behavioral variables.

Acknowledgments

Dr. Pascal Jean-Pierre acknowledges the support of the Walther Cancer Foundation. This publication was made possible in part by the National Institutes of Health, National Center for Advancing Translational Sciences, Clinical and Translational Sciences Award Grant Number KL2 TR000163 to Dr. Pascal Jean-Pierre, PhD, MPH (A. Shekhar, PI). Dr. Michael Grandner wishes to acknowledge funding from the National Heart, Lung, and Blood Institute (K23HL110216), The National Institute of Environmental Health Sciences (R21ES022931), and the Penn Clinical and Translational Research Center and Institute of Translational Medicine and Therapeutics, funded by the Clinical and Translational Sciences Award (UL1RR024134). Dr. Sheila Garland is a post-doctoral fellow funded by a Canadian Institutes for Health Research (CIHR) Bisby Fellowship. Dr. Girardin's contribution was supported by NIH grants R01MD007716 and U54NS081765.

References

1. Kochanek KD, Xu JQ, Murphy SL, et al. Deaths: Preliminary data for 2009. National Vital Statistics Reports. 2011; 59(4):1–51.
2. World Health Organization. The Global Burden of Disease: 2004 Update. Geneva: World Health Organization; 2008.
3. Parry C, Kent EE, Mariotto AB, Alfano CM, Rowland JH. Cancer survivors: A booming population. Cancer Epidemiol Biomarkers Prev. 2011; 20:1996–2005. [PubMed: 21980007]
4. American Cancer Society (ACS). Cancer Facts & Figures 2012. Atlanta: ACS; 2012.
5. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Murray T, Thun MJ. Cancer Statistics, 2008. CA Cancer J Clin. 2008 Mar-Apr;58(2):71–96. [PubMed: 18287387]
6. Jemal A, Center MM, Ward E, Thun MJ. Cancer Occurrence. Methods Mol Biol. 2009; 471:3–29. [PubMed: 19109772]
7. Jemal A, Center MM, DeSantis C, Ward EM. Global patterns of cancer incidence and mortality rates and trends. Cancer Epi Biomarkers Prev. 2010 Aug; 19(8):1893–907.
8. Siegel R, Ward E, Brawley O, Jemal A. Cancer statistics, 2011. CA: A Cancer Journal for Clinicians. 2011; 61:212–236. [PubMed: 21685461]
9. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. CA: A Cancer Journal for Clinicians. 2012; 62:10–29. [PubMed: 22237781]
10. Ahles TA, Saykin A, Furstenberg CT, Cole B, Mott LA, Skalla K, et al. Neuropsychologic impact of standard-dose systemic chemotherapy in long-term survivors of breast cancer and lymphoma. J Clin Oncol. 2002; 20:485–493. [PubMed: 11786578]
11. Boykoff N, Moieni M, Subramanian SK. Confronting chemobrain: an in-depth look at survivors' reports of impact on work, social networks, and health care response. J Cancer Surviv. 2009 Dec; 3(4):223–32. Epub 2009 Sep 16. 10.1007/s11764-009-0098-x [PubMed: 19760150]
12. Wefel JS, Lenzi R, Theriault R, Buzdar AU, Cruickshank S, Meyers CA. 'Chemobrain' in breast carcinoma? – A prologue. Cancer. 2004; 101(3):466–75. [PubMed: 15274059]
13. Correa DD, Ahles TA. Neurocognitive changes in cancer survivors. Cancer J. 2008; 14(6):396–400. [PubMed: 19060604]
14. Tannock IF, Ahles TA, Ganz PA, van Dam FS. Cognitive impairment associated with chemotherapy for cancer: Report of a workshop. Journal of Clinical Oncology. 2004; 22:2233–2239. [PubMed: 15169812]
15. Koppelmans V, Breteler M, Boogerd W, Seynaeve C, Gundy C, Schagen S. Neuropsychological performance in survivors of breast cancer more than 20 years after adjuvant chemotherapy. J Clin Oncol. 2012; 30:1080–1086. [PubMed: 22370315]
16. Jean-Pierre P, Winters PC, Ahles T, Antoni M, Armstrong FD, Penedo F, Lipshultz SE, Miller TL, Fiscella K. Prevalence of Memory Problems in Adult Cancer Survivors: A National Cross-Sectional Study. Journal of Oncology Practice. 2012; 8(1):32–34.

17. Brezden CB, Phillips KA, Abdoell M, Bunston T, Tannock IF. Cognitive function in breast cancer patients receiving adjuvant chemotherapy. *J Clin Oncol.* 2000; 18:2695–701. [PubMed: 10894868]
18. Saykin AJ, Ahles TA, McDonald BC. Mechanisms of chemotherapy induced cognitive disorders: Neuropsychological, pathophysiological, and neuroimaging perspectives. *Seminars in Clinical Neuropsychiatry.* 2003; 8:201–216. [PubMed: 14613048]
19. Scheibel RS, Valentine AD, O'Brien S, Meyers CA. Cognitive dysfunction and depression during treatment with interferon-alpha and chemotherapy. *J Neuropsych Clin Neurosci.* 2004; 16:185–191.
20. Bradbury J. Chemobrain: imaging shows changes in metabolism. *Lancet Oncol.* 2006 Nov.7(11): 890. [PubMed: 17099979]
21. Ahles TA, Saykin AJ. Candidate mechanisms for chemotherapy-induced cognitive changes. *Nat Rev Cancer.* 2007; 7(3):192–201. [PubMed: 17318212]
22. Verstaappen CCP, Heimans JJ, Hoekman K, Postma TJ. Neurotoxic complications of chemotherapy in patients with cancer: Clinical signs and optimal management. *Drugs.* 2003; 63:1549–1563. [PubMed: 12887262]
23. Dietrich J, Han R, Yang Y, Mayer-Proschel M, Noble M. CNS progenitor cells and oligodendrocytes are targets of chemotherapeutic agents in vitro and in vivo. *J Biol.* 2006; 5:22. [PubMed: 17125495]
24. Rolig RL, McKinnon PJ. Linking DNA damage and neurodegeneration. *Trends Neurosci.* 2000; 23:417–424. [PubMed: 10941191]
25. Kannarkat G, Lasher EE, Schiff D. Neurologic complications of chemotherapy agents. *Curr Opin Neurol.* 2007; 20(6):719–725. [PubMed: 17992096]
26. Ahles TA, Saykin AJ, McDonald BC, Li Y, Furstenberg CT, Hanscom BS, Mulrooney TJ, Schwartz GN, Kaufman PA. Longitudinal assessment of cognitive changes associated with adjuvant treatment for breast cancer: impact of age and cognitive reserve. *J Clin Oncol.* 2010; 28(29):4434–40. [PubMed: 20837957]
27. Joly F, Rigal O, Noal S, Giffard B. Cognitive dysfunction and cancer: which consequences in terms of disease management? *Psychooncology.* 2011; 20(12):1251–1258. [PubMed: 21254307]
28. Hajduk AM, Kiefe CI, Person SD, Gore JG, Saczynski JS. Cognitive change in heart failure: a systematic review. *Circ Cardiovasc Qual Outcomes.* 2013 Jul 1; 6(4):451–60. [PubMed: 23838109]
29. Hjelm C, Strömberg A, Arestedt K, Broström A. Association between sleep-disordered breathing, sleep-wake pattern, and cognitive impairment among patients with chronic heart failure. *Eur J Heart Fail.* 2013 May; 15(5):496–504. [PubMed: 23392278]
30. Mander BA, Rao V, Lu B, Saletin JM, Ancoli-Israel S, Jagust WJ, Walker MP. Impaired Prefrontal Sleep Spindle Regulation of Hippocampal-Dependent Learning in Older Adults. *Cereb Cortex.* 2013 Jul 30. Epub ahead of print.
31. Jiang F, VanDyke RD, Zhang J, Li F, Gozal D, Shen X. Effect of chronic sleep restriction on sleepiness and working memory in adolescents and young adults. *J Clin Exp Neuropsychol.* 2011 Oct; 33(8):892–900. Epub 2011 Jun 27. 10.1080/13803395.2011.570252 [PubMed: 21950514]
32. Edinger JD, Bonnet MH, Bootzin RR, Doghramji K, Dorsey CM, Espie CA, Jamieson AO, McCall WV, Morin CM, Stepanski EJ. Derivation of Research Diagnostic Criteria for Insomnia: Report of an American Academy of Sleep Medicine Work Group. *SLEEP.* 2004; 27(8):1567–1592. [PubMed: 15683149]
33. Burt DB, Zembar MJ, Niederehe G. Depression and memory impairment: A meta-analysis of the association, its pattern, and specificity. *Psychological Bulletin.* 1995; 117(2):285–305. [PubMed: 7724692]
34. Zahodne LB, Nowinski CJ, Gershon RC, Manly JJ. Depressive Symptoms Are More Strongly Related to Executive Functioning and Episodic Memory Among African American compared with Non-Hispanic White Older Adults. *Arch Clin Neuropsychol.* 2014 Oct 3. Epub ahead of print.

Highlights

- Sleep and cardiac problems may be implicated in cancer-related memory problems.
- We examined the links among cancer, cardiac problems, insomnia and memory problems.
- Insomnia uniquely explained 19% of the variance in cancer-related memory problems.
- Cancer patients with insomnia were 18 times more likely to have memory problems.
- Insomnia explained 38.5% of the association between cardiac and memory problems.

Table 1

Clinical and Socio-demographic Characteristics.

Variable	Category	Overall Sample	No Cancer	Cancer	p (t-test or X ²)
Memory Problems	Yes	6.27%	6.03%	8.81%	0.2305
Cardiac Complications	Yes	4.69%	4.42%	7.43%	0.0896
Insomnia	Yes	1.38%	1.34%	1.80%	0.4803
Age	Mean $\pm$ SD	51.46 $\pm$ 6.57	51.18 $\pm$ 6.55	54.41 $\pm$ 6.00	<0.0001
Sex	Female	48.78%	49.19%	44.47%	0.3359
Race/Ethnicity	White	71.71%	70.45%	84.78%	0.0036
	Hispanic	11.27%	11.78%	6.04%	
	Black	6.06%	6.36%	2.84%	
	Other	4.35%	4.57%	2.06%	
Education	Less Than High School	18.50%	19.00%	13.31%	0.4346
	High School Graduate	25.06%	25.07%	24.95%	
	Some College	27.95%	27.82%	29.28%	
	College Graduate	28.49%	28.11%	32.46%	
Depression Symptoms	Feeling down Depressed Hopeless	25.48%	25.33%	27.07%	0.679
Sleep Disorder Symptoms	Frequent Snoring	38.06%	38.30%	35.59	0.5608
	Snoring/Gasping during sleep	22.02%	22.30%	19.02%	0.3962
	Excellent	14.03%	14.53%	8.80%	0.0995
Health	Very Good	31.12%	31.72%	24.88%	
	Good	34.54%	33.89%	41.37%	
	Poor	15.49%	15.21%	18.42%	
	Very Poor	14.03%	14.53%	8.80%	

Odds ratios and 95% confidence intervals assessing the relationship of memory problems to cardiovascular disease and insomnia among cancer survivors aged 41–64, using binary logistic regression.

Table 2

	Model 1 Pseudo R ² = 0.379			Model 2 Pseudo R ² = 0.48		
	OR	95% CI	p-value	OR	95% CI	p-value
Cardiovascular Disease	11.07	2.03, 60.22	0.005	6.89	1.13, 41.97	0.04
Insomnia (> 15/30 Nights)				13.18	1.31, 132.93	<0.03

All models include age, sex, race/ethnicity, education level, depression, sleep disorder symptoms (i.e., snoring and snorting), and overall health.