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Cognition and Cognitive Impairment in Older Adults with Cancer

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Abstract

Aging is a risk factor for cognitive impairment as well as cancer. However, the interplay between these three entities – aging, cognition and cancer – is not well understood. Mounting evidence indicates that both cancer and cancer therapies, such as chemotherapy, can negatively affect cognition and that older adults with pre-existing cognitive impairment may be more susceptible to cognitive decline with therapy than younger patients. For an older adult, decline in cognition may significantly compromise their ability to remain independent in the community. Pre-existing cognitive impairment, at the time of a cancer diagnosis, may also carry an increased risk of treatment-related adverse events in older adults receiving chemotherapy. Growing research suggests behavioral interventions may be helpful in improving chemotherapy-related cognitive changes; however, these interventions have been mainly evaluated in younger patients in whom pre-existing cognitive impairment is less prevalent. Here we review the studies on: cognitive changes associated with cancer and cancer therapies with an emphasis on studies conducted in older adults, relevant screening tools to evaluate cognition in the geriatric oncology setting, and possible intervention strategies for managing cognitive impairment.

Keywords

Geriatric oncology; cognitive impairment; chemotherapy; aging

Introduction

With the aging of the baby-boomer population, the number of older individuals is expected to double to 83.7 million by the year 2050.¹ Cancer incidence is greater in the elderly; thus this increase in the geriatric population will translate into an increase in cancer diagnoses. Between 2010 and 2030, cancer incidence will increase an estimated 67% for patients 65 and over.²

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Compliance with Ethics Guidelines

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Cognitive impairment is also common in older adults. The prevalence of dementia is 13.9% in patients aged 71 and older.³ Additionally, an estimated 22.2% of Americans have cognitive impairment without overt dementia.⁴ Because mild cognitive impairment (MCI) or dementia is already fairly prevalent in older patients at the time of cancer diagnosis, this represents a challenge in studying the role that cancer diagnosis and cancer treatment may play in the exacerbation of cancer-related cognitive impairment in older adults. SEER Medicare studies suggest that the estimated prevalence of dementia in cancer patients age 65 and over ranges from 3.8% to 7%,^{5–7} although this is likely lower than the true prevalence due to lack of capture of these diagnoses within Medicare claims. It is unknown how a prior diagnosis of dementia or MCI specifically impacts treatment decision making for cancer and what percentage of these patients with pre-existing cognitive impairments are offered various types of cancer therapies, such as surgery or chemotherapy.

The majority of studies evaluating cognition in cancer patients include patients of all ages; a few studies, however, have focused on older adults with cancer specifically. In this article, we will discuss cognitive changes associated with cancer and cancer treatments, with emphasis on the older adult population. We will review various screening tools to evaluate cognition in this population, discuss pre-existing cognitive impairment as a risk factor for treatment-related adverse events, and evaluate evidence of non-pharmacologic interventions for cognitive changes related to cancer and cancer therapy.

Cognitive changes associated with a cancer diagnosis

Due to early research reports suggesting that chemotherapy may impact cognition in cancer patients, systematic investigation of this phenomenon started to rapidly grow in the early 2000s.⁸ While we typically think of cancer-related cognitive impairments as being associated most strongly with chemotherapy, emerging research has suggested that cancer alone may impact cognitive function. The role of cancer itself is particularly important to consider because older patients may already have pre-existing cognitive impairments prior to a diagnosis of cancer and therapy initiation. Studies have demonstrated that 20–30% of patients with breast cancer have impaired cognition prior to receipt of adjuvant chemotherapy or endocrine therapy.^{9,10} Although the majority of these studies were performed in younger patients^{11,12}, Lange and colleagues examined a group of older adults to determine the impact of cancer on cognition prior to the receipt of systemic therapy.¹³ In this study, baseline cognitive function was assessed in 123 women over the age of 65 with newly diagnosed, early stage breast cancer. The investigators evaluated episodic memory, working memory, executive functions and information processing speed using neuropsychological tests and determined that 41% of patients had cognitive dysfunction prior to initiation of treatment (defined by z-score ≥ 1.5 standard deviations (SD) on two cognitive assessment tests or ≥ 2.0 SD on a single test). This rate was significantly higher than estimated population norms for older adults without a cancer diagnosis and was also higher than younger breast cancer patients. Of note, investigators excluded participants with major cognitive disorders or those with psychiatric comorbidities that may limit their capacity to participate; thus it is likely that individuals with dementia or more clinically significant cognitive impairment were excluded from this study. Mandelblatt and colleagues also evaluated older women with newly diagnosed breast cancer prior to receipt of systemic

chemotherapy and contrary to the Lange study, they detected no difference in cognition compared to age-matched controls without cancer. The prevalence of cognitive impairment observed in the Mandelblatt study was 14% in breast cancer patients and 15% in controls (cognitive impairment defined by z-score ≥ 1.5 SD below control mean on two cognitive assessment tests or ≥ 2.0 SD on a single test). Individuals with a diagnosis of neurodegenerative disorders or Mini-Mental Status Exam score of < 24 were excluded; thus patients with more advanced cognitive impairment were also not evaluated on this study. Mandelblatt and colleagues did observe that the subgroup of patients with more advanced stage cancer (stage II/III) had lower executive function than individuals with earlier stage disease. Additionally, presence of 2 or more comorbidities was strongly associated with cognitive impairment among patients with cancer, but not among controls.¹⁴ These findings were unique from the Lange study, where no correlation between comorbidity or cancer stage and cognitive impairment was observed. The results of Mandelblatt and colleagues suggest that cognitive impairment related to a cancer diagnosis may affect a subset of patients such as those with greater disease burden or higher comorbidity status. Although these studies demonstrate discordant results, this may be related to variation in the population sampled and study design. Both studies included older women receiving adjuvant chemotherapy for breast cancer, however, subjects in the Lange study had lower educational levels as compared to those on the Mandelblatt study (mean years of education 11 years versus 15 years), suggesting the possibility that individuals with lower educational levels may be more susceptible to developing cognitive impairment following a cancer diagnosis. In addition, the Mandelblatt study compared older patients receiving chemotherapy with a control group of older patients in contrast to the Lange study, which did not include a control group.

Cognitive changes associated with cancer treatment

Chemotherapy

Chemotherapy-related cognitive impairment (CRCI) has been reported in multiple cross-sectional and longitudinal studies, with the majority of studies performed in younger patients with breast cancer.^{8,11,12} In longitudinal studies, the reported frequency of post-treatment cognitive changes varies significantly based upon the population evaluated, the specific measurement tool utilized, definitions of impairment or change in cognition, and other study design features. The majority of longitudinal studies of CRCI in cancer patients demonstrate treatment-related cognitive changes, but some studies have failed to demonstrate any effect.¹² In the studies that report changes in cognition related to chemotherapy, impaired cognition is observed in 20–30% of patients after cancer diagnosis before treatment, up to 50–80% of patients during treatment, and up to 25–35% at later follow-up.^{8,11}

Although the majority of studies on CRCI have been performed in younger cancer patients, some studies have focused specifically on the geriatric population. Hurria and colleagues surveyed older patients with breast cancer (N=45) regarding their perception of how adjuvant chemotherapy affected their cognitive function. Investigators evaluated the self-reported cognitive status of breast cancer patients aged 65 and over prior to starting adjuvant chemotherapy and 6 months following the completion of treatment. Participants were asked about their ability to learn new information and working memory status. Approximately half

of patients reported a decline in memory between baseline and 6 months post-treatment. Subjects who reported their memory as “worse than average” prior to initiating chemotherapy were more likely to perceive a decline in cognitive function following treatment.¹⁵ However, contrary to this, Freedman and colleagues evaluated the self-reported cognitive function of 197 older women with breast cancer enrolled on the quality of life substudy of the Cancer and Leukemia Group B (CALGB) 49907, a large study evaluating outcomes related to adjuvant chemotherapy in older patients with breast cancer. In this sample, receipt of chemotherapy was not associated with longitudinal changes in self-reported cognition.¹⁶ The patient samples in these two studies evaluated varied slightly. Patients enrolled on the Freedman study generally had minimal concerns about their cognition at baseline and individuals with more significant cognitive impairment (defined by a Blessed-Orientation-Memory-Concentration score of > 11) were excluded. More patients included on the Hurria study had pre-existing concerns about their cognition, suggesting a more vulnerable population. The two studies also used different measures of memory self-rating (Squire Memory Self-Rating Questionnaire [Hurria] versus Memory, Cognitive and Concentration subscales of the Neurobehavioral Functioning and Activities of Daily Living scale [Freedman]).

In another study, Hurria and colleagues prospectively evaluated the cognitive function of women age 65 and over receiving adjuvant chemotherapy for breast cancer using an objective cognitive evaluation. Patients were evaluated with a neuropsychological assessment battery as well as a geriatric assessment at baseline and 6 months after chemotherapy to determine the change in cognitive function and its effect on functional outcome measures. Twenty-eight patients were included in the study; 11% demonstrated cognitive impairment at baseline (defined by scoring 2 standard deviations below normative data on two or more of the neuropsychological tests). At 6-month follow-up, 39% of patients had a decline in cognitive function from baseline; 50% had no change, and 11% had improvement in cognitive testing. There were no significant changes in functional measures (Activities of Daily Living, Instrumental Activities of Daily Living or performance status) between the two time points.¹⁷ Another study using objective neuropsychological evaluation by Ahles and colleagues included a subset of older patients (age > 60) within a larger sample (n=123). Investigators evaluated the cognitive function of 60 breast cancer patients receiving adjuvant chemotherapy and compared them to 72 breast cancer controls not receiving chemotherapy and 45 healthy controls without breast cancer at multiple time points. They observed that older patients with lower baseline cognitive reserve (assessed by reading ability) who received chemotherapy had lower processing speed post-treatment, as compared to younger patients as well as both age-matched control groups, suggesting that older adults with lower innate cognitive function may be the most vulnerable to cognitive changes following chemotherapy.¹⁸

Other than breast cancer, cognitive changes related to cancer therapy have been shown in other smaller studies of select populations. For example, Jones and colleagues evaluated the prevalence of cognitive deficits after induction chemotherapy in patients with multiple myeloma and assessed change in cognitive function post-autologous hematopoietic stem cell transplant in this population. Investigators observed that the rate of impaired cognitive functioning was high following induction chemotherapy, with 47.2% of patients

demonstrating cognitive impairment. Following transplant, nearly half of patients demonstrated clinically significant declines in at least one cognitive assessment measure (47.2 % demonstrating decline in 1 measure at one month post-transplant, 48% at three months post-transplant). Although this study included patients of all ages (n=53, average age 58 years), older patients represented one of several subgroups that demonstrated greater vulnerability to decline with therapy.¹⁹ Adjuvant chemotherapy for colon cancer has also been shown to impair cognition in some studies. Investigators evaluated 81 patients with localized colon cancer receiving adjuvant chemotherapy (average age 66) and determined that 56% of patients had a decline in cognition at the end of therapy, with verbal memory the main domain affected. Older age along with lower level of education was significantly associated with cognitive decline following receipt of therapy.²⁰

To date, no prospective studies have focused specifically on older cancer patients with pre-existing MCI or dementia who go on to receive chemotherapy. Given that individuals with pre-existing cognitive impairment appear to be at great risk for cognitive decline with therapy and are potentially at increased risk for treatment-related adverse events, it is important to focus research efforts on this population. Observational studies are needed to detail the impact of chemotherapy on cognition in this particularly vulnerable subgroup. Intervention studies are necessary to develop supportive care measures to minimize treatment impact on cognition and optimize patient's independence during and after therapy.

Endocrine Therapy

The impact of endocrine therapies, such as androgen deprivation therapy (ADT) and aromatase inhibitor (AI) therapy, on cognition has been explored. ADT is suspected to impair cognition based upon the observation in older men without cancer that lower testosterone levels are a factor in age-related cognitive decline.^{21,22} Overall, studies regarding the impact of ADT on cognition have yielded mixed results. A recent systematic review and metaanalysis including prostate cancer patients of all ages concluded that patients receiving ADT performed significantly worse on visuomotor cognitive tasks than non-cancer control groups.²³

Regarding endocrine therapy for breast cancer, both tamoxifen and AI therapy have been evaluated. Hurria and colleagues measured the impact of aromatase inhibition on cognitive function specifically in older adults with breast cancer. Patients aged 60 years and age-matched controls (n= 70) were evaluated with neuropsychological testing at baseline and six month follow-up. No significant decline in cognitive function was seen in patients receiving AI therapy at six-month follow-up. A subgroup of patients (n= 20) also underwent PET scan of the brain and investigators observed specific changes of in metabolic activity between the two time points in patients receiving AI therapy, although the clinical significance of this finding is unknown.²⁴ Schilder and colleagues evaluated the effects of tamoxifen versus AI therapy on cognitive function, and compared both groups to healthy controls. Investigators observed that tamoxifen users overall performed statistically significantly worse than healthy controls on verbal memory and executive functioning. This study included postmenopausal patients (average age 68.3, range 51–84) and exploratory analysis suggested that patients age > 65 receiving tamoxifen performed worse on processing speed at follow up as compared to

those patients receiving AI therapy.²⁵ Combined, these studies suggest that AI therapy may have a more favorable cognitive side effect profile than tamoxifen in older patients with breast cancer.

Impact of cancer on risk for cognitive impairment later in life

The majority of studies evaluating the impact of cancer and cancer treatment on cognition have focused on short-term effects (ie. less than one year post treatment). Some data suggests, however, that a diagnosis of cancer places an individual at increased risk for cognitive impairment later in life. Yamada and colleagues evaluated the cognitive status of older breast cancer survivors (n= 30) several years after the completion of breast cancer treatment (average duration since diagnosis 16.8 years, range 13.8–22.5 years). Subjects were evaluated with a cognitive assessment battery and compared to non-cancer controls matched for age, education and IQ. Investigators identified significant differences in attention, working memory, psychomotor speed and aspects of executive functioning, with cancer survivors performing worse than controls.²⁶ Another study evaluated the prevalence of cognitive dysfunction and dementia in patients age ≥ 65 with a history of cancer using a co-twin control design (n=702 pairs), and compared the prevalence of cognitive impairment in cancer survivors with their cancer-free twins. Investigators determined that cancer survivors were more likely than their co-twins to have cognitive dysfunction.²⁷ A study by Driver and colleagues, showed the opposite effect however– that cancer survivors had lower rates of Alzheimer's disease later in life (n= 1278).²⁸ Therefore, the true impact of cancer on long-term cognitive status is yet to be determined.

Evaluating cognition in older adults with cancer

The first step in managing cognitive impairment in the older patient with cancer is identification of pre-existing cognitive changes prior to cancer therapy. In cancer care, cognitive assessment is not routinely incorporated into the evaluation and management of older adults. Studies are needed to develop feasible methods to incorporate cognitive screening into cancer care to allow identification of this potentially higher risk group of patients. Several cognitive assessment tools can be used in the evaluation of older adults with cancer. Short cognitive screening tools are likely the most feasible options to incorporate into busy oncology clinical practice. Several short cognitive screening tools have been developed for use in the non-cancer setting, and a few of these measures have been evaluated in cancer patients specifically. Examples include the Montreal Cognitive Assessment (MoCA),²⁹ the Mini Mental Status Exam (MMSE),³⁰ the Mini-Cog,³¹ and the Blessed Orientation-Memory-Concentration (BOMC) test.³²

The MoCA is a brief screening tool that evaluates multiple cognitive domains including short-term memory, visuospatial abilities, executive function, and attention and takes approximately 10 minutes to administer.²⁹ The MoCA has been compared to the MMSE in non-cancer patients and demonstrated better sensitivity in detecting MCI (90%) and good specificity at 87%.²⁹ The MoCA also detected mild dementia with high sensitivity and specificity (100% and 87% respectively). The MoCA has been evaluated in oncology patients with brain metastases and has been shown to be feasible to administer and more

sensitive than the MMSE in this population.³³ However, the MoCA has not been validated in geriatric oncology patients specifically.

The MMSE is a brief screening tool for cognitive deficits and includes evaluation of orientation, registration, attention and calculation, recall, language and copying.³⁰ The MMSE has been used to evaluate cognition in older adults with cancer in prior studies, although it was not evaluated against full neuropsychologic testing in this population.³⁴

The Mini-Cog is a short cognitive screening tool that combines a delayed recall item and a clock-drawing test. The Mini-Cog takes approximately 3 minutes to administer and was developed and validated in community-dwelling older adults without cancer.³¹ When compared to the MMSE in this population, the Mini-Cog demonstrated similar sensitivity and specificity for identifying dementia.³¹ The Mini-Cog has been compared to the MMSE in older adults with cancer and found to have a sensitivity of 80.7% and specificity of 83.8%.³⁵

The BOMC test is a short cognitive screen comprised of six questions and has been shown to discriminate among mild, moderate, and severe cognitive deficits.³⁶ It has been studied as a component of an oncology-specific geriatric assessment and shown to be feasible.³⁷

Outside of the clinical trial setting, full neuropsychological evaluation is not feasible to incorporate into routine oncology practice. However, if brief evaluation with a short screening tool suggests possible cognitive impairment, referral for more comprehensive cognitive assessment may be warranted.

Broad clinical implications for studying cognitive function in older adults with cancer

Cognitive status can influence decision making and treatment planning along the continuum of care for the older adult with cancer. Initially cognition may influence a decision regarding cancer screening –an individual with significant cognitive impairment likely has a limited life expectancy due to their comorbid cognitive condition. Thus, this patient may not live long enough to derive the benefit of a cancer screening intervention. Following a cancer diagnosis, impaired cognition may affect a patient's ability to participate in some aspects of the decision-making and treatment planning process for cancer. With the increasing complexity of cancer care, patients with cognitive impairment may have difficulty processing and recalling the information required to engage in this complex decision making process and provide appropriate informed consent for treatments that are high risk. Many institutions now require consent for cancer therapy, including chemotherapy, and determining the capacity of a patient to provide this consent is critical in patients with cognitive impairment. Identification of a health care proxy to assist with this process can be vitally important in these situations, and may also be important for helping to consent for research studies evaluating this vulnerable population as well.

Pre-existing cognitive impairment may also be a risk factor for chemotherapy toxicity. The Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) Score was

developed from a prospective, multicentric study of patients age 70 initiating chemotherapy. Authors evaluated all patients with GA, including cognitive assessment with the MMSE, prior to treatment and determined that an impaired MMSE score (defined by score < 30) was correlated with grade 3/4 nonhematologic toxicity. Another chemotherapy toxicity prediction model failed to show impaired cognition as a risk factor; however, a different measure, the Blessed Orientation Memory and Concentration (BOMC), was used as the cognitive assessment in this study.³⁸

Managing cognitive impairment during and after cancer therapy

No studies to date have evaluated therapeutic or supportive care interventions in older adults with pre-existing cognitive impairment receiving chemotherapy. Given the complexity of cancer care and high risk of adverse events with chemotherapy in individuals with pre-existing cognitive impairment, developing interventions to improve care and outcomes for these patients is an important area of research. Following identification of older cancer patients with cognitive impairment, several supportive care interventions could be considered to help support these individuals through cancer therapy, although these are not evidence-based in this population.

Older adults may be living alone in the community, and enhancing social support may be an important safety intervention during cancer therapy. Depending on the severity of cognitive limitations, 24-hour supervision may be indicated to monitor for adverse events, particularly if the patient is unable to communicate side effects or reliably seek help in case of an emergency due to cognitive impairment. If an older adult with cognitive impairment is living independently and subsequently receives chemotherapy, they may develop difficulties with Instrumental Activities of Daily Living (IADL), such as finance management or medication administration, and this may compromise their ability to remain living independently in the community. Given the complexity of cancer treatments, patients with cognitive impairment receiving cancer treatment often need closer supervision by their treating oncologist with increased frequency of office visits and enhanced, written instructions with reminders and check-ins by the oncology team. Cancer therapy regimens frequently require additional medications, such as anti-emetics, which can add complexity to an older adult's medication regimen. Enhanced supervision and support for medication administration, such as home nursing and pillbox support, may be useful. Often supportive care medications used for chemotherapy include corticosteroids, anticholinergics (ie. Benadryl) and H₂-receptor antagonists, which are established "high-risk" medications for older adults, particularly with cognitive impairment.³⁹ Counseling patients and families about the potential impacts of cancer therapy and supportive care medications on cognition and monitoring for delirium and impact on IADL and function is also important. Such interventions are not evidence-based in the cancer population, however, and their impact on outcomes is unknown. Developing evidence-based, patient-tailored supportive care interventions to improve outcomes in this vulnerable population during cancer treatment is needed.

To date, the majority of studies evaluating interventions to prevent or improve symptoms of CRCI have focused on younger cancer patients. In general the younger patients enrolled in these studies likely did not have cognitive impairment prior to cancer therapy. Therefore, we

have limited data to guide supportive care cognitive interventions for older adults with pre-existing cognitive impairment receiving cancer therapy. Information regarding cognitive interventions can be extrapolated from these studies of younger cancer survivors. In general, behavioral therapies such as cognitive rehabilitation or exercise, have demonstrated the most success in improving CRCI symptoms.^{40–46} An observational study by Sprod, et al evaluated the impact of exercise on cancer treatment symptoms in older cancer patients specifically and found that older patients who exercised during treatment reported less memory loss than control, although this was not a randomized intervention study.⁴⁷ Studies are needed to determine the feasibility and benefit of incorporating these types of interventions into the care of older patients with cancer and cognitive limitations.

Conclusion

The incidence of cancer as well as cognitive impairment increases with age. Given the aging demographics of our population, cognitive impairment in older cancer patients will become an increasingly relevant issue. Cancer therapies, such as chemotherapy, have been shown to negatively impact cognition for some patients and it is likely that older individuals with pre-existing cognitive impairment are the most vulnerable. Pre-existing cognitive impairment can also increase the risks associated with chemotherapy. Screening for cognitive impairments prior to treatment is encouraged and several short screening tools exist. Additional studies are needed to understand supportive care interventions that will optimize treatment, cognitive, and overall quality of life outcomes for older adults with cancer and cognitive impairment.

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REFERENCES

Papers of particular interest, published recently, have been highlighted as:

- Of importance
  - Of major importance
1. 65+ in the United States: 2010. US Department of commerce, economics and statistics administration. US census Bureau; 2014.
  2. Smith BD, Smith GL, Hurria A, Hortobagyi GN, Buchholz TA. Future of cancer incidence in the United States: burdens upon an aging, changing nation. *J Clin Oncol.* 2009; 27:2758–2765. [PubMed: 19403886]
  3. Plassman BL, Langa KM, Fisher GG, et al. Prevalence of dementia in the United States: the aging, demographics, and memory study. *Neuroepidemiology.* 2007; 29:125–132. [PubMed: 17975326]
  4. Plassman BL, Langa KM, Fisher GG, et al. Prevalence of cognitive impairment without dementia in the United States. *Annals of internal medicine.* 2008; 148:427–434. [PubMed: 18347351]
  5. Gupta SK, Lamont EB. Patterns of presentation, diagnosis, and treatment in older patients with colon cancer and comorbid dementia. *J Am Geriatr Soc.* 2004; 52:1681–1687. [PubMed: 15450045]
  6. Gorin SS, Heck JE, Albert S, Hershman D. Treatment for breast cancer in patients with Alzheimer's disease. *J Am Geriatr Soc.* 2005; 53:1897–1904. [PubMed: 16274370]

7. Raji MA, Kuo YF, Freeman JL, Goodwin JS. Effect of a dementia diagnosis on survival of older patients after a diagnosis of breast, colon, or prostate cancer: implications for cancer care. *Archives of internal medicine*. 2008; 168:2033–2040. [PubMed: 18852406]
8. Janelsins MC, Kesler SR, Ahles TA, Morrow GR. Prevalence, mechanisms, and management of cancer-related cognitive impairment. *Int Rev Psychiatry*. 2014; 26:102–113. [PubMed: 24716504]
9. Ahles TA, Saykin AJ, McDonald BC, et al. Cognitive function in breast cancer patients prior to adjuvant treatment. *Breast cancer research and treatment*. 2008; 110:143–152. [PubMed: 17674194]
10. Wefel JS, Lenzi R, Theriault R, Buzdar AU, Cruickshank S, Meyers CA. 'Chemobrain' in breast carcinoma?: a prologue. *Cancer*. 2004; 101:466–475. [PubMed: 15274059]
11. Janelsins MC, Kohli S, Mohile SG, Usuki K, Ahles TA, Morrow GR. An update on cancer- and chemotherapy-related cognitive dysfunction: current status. *Seminars in oncology*. 2011; 38:431–438. [PubMed: 21600374]
12. Ahles TA, Root JC, Ryan EL. Cancer- and cancer treatment-associated cognitive change: an update on the state of the science. *J Clin Oncol*. 2012; 30:3675–3686. [PubMed: 23008308]
13. Lange M, Giffard B, Noal S, et al. Baseline cognitive functions among elderly patients with localised breast cancer. *Eur J Cancer*. 2014; 50:2181–2189. [PubMed: 24958735] **Impact of cancer diagnosis of cognitive function in older adults
14. Mandelblatt JS, Stern RA, Luta G, et al. Cognitive impairment in older patients with breast cancer before systemic therapy: is there an interaction between cancer and comorbidity? *J Clin Oncol*. 2014; 32:1909–1918. [PubMed: 24841981] **Impact of cancer diagnosis and comorbidity on cognitive function in older adults
15. Hurria A, Goldfarb S, Rosen C, et al. Effect of adjuvant breast cancer chemotherapy on cognitive function from the older patient's perspective. *Breast cancer research and treatment*. 2006; 98:343–348. [PubMed: 16541322]
16. Freedman RA, Pitcher B, Keating NL, et al. Cognitive function in older women with breast cancer treated with standard chemotherapy and capecitabine on Cancer and Leukemia Group B 49907. *Breast cancer research and treatment*. 2013; 139:607–616. [PubMed: 23681403]
17. Hurria A, Rosen C, Hudis C, et al. Cognitive function of older patients receiving adjuvant chemotherapy for breast cancer: a pilot prospective longitudinal study. *J Am Geriatr Soc*. 2006; 54:925–931. [PubMed: 16776787]
18. Ahles TA, Saykin AJ, McDonald BC, et al. Longitudinal assessment of cognitive changes associated with adjuvant treatment for breast cancer: impact of age and cognitive reserve. *J Clin Oncol*. 2010; 28:4434–4440. [PubMed: 20837957] **Impact of age and cognitive reserve on cognition in cancer patients receiving chemotherapy.
19. Jones D, Vichaya EG, Wang XS, Sailors MH, Cleeland CS, Wefel JS. Acute cognitive impairment in patients with multiple myeloma undergoing autologous hematopoietic stem cell transplant. *Cancer*. 2013; 119:4188–4195. [PubMed: 24105672]
20. Cruzado JA, Lopez-Santiago S, Martinez-Marin V, Jose-Moreno G, Custodio AB, Feliu J. Longitudinal study of cognitive dysfunctions induced by adjuvant chemotherapy in colon cancer patients. *Support Care Cancer*. 2014; 22:1815–1823. [PubMed: 24535240]
21. Holland J, Bandelow S, Hogervorst E. Testosterone levels and cognition in elderly men: a review. *Maturitas*. 2011; 69:322–337. [PubMed: 21696899]
22. Moffat SD, Zonderman AB, Metter EJ, Blackman MR, Harman SM, Resnick SM. Longitudinal assessment of serum free testosterone concentration predicts memory performance and cognitive status in elderly men. *J Clin Endocrinol Metab*. 2002; 87:5001–5007. [PubMed: 12414864]
23. McGinty HL, Phillips KM, Jim HS, et al. Cognitive functioning in men receiving androgen deprivation therapy for prostate cancer: a systematic review and meta-analysis. *Support Care Cancer*. 2014; 22:2271–2280. [PubMed: 24859915]
24. Hurria A, Patel SK, Mortimer J, et al. The effect of aromatase inhibition on the cognitive function of older patients with breast cancer. *Clin Breast Cancer*. 2014; 14:132–140. [PubMed: 24291380]
25. Schilder CM, Seynaeve C, Beex LV, et al. Effects of tamoxifen and exemestane on cognitive functioning of postmenopausal patients with breast cancer: results from the neuropsychological side study of the tamoxifen and exemestane adjuvant multinational trial. *J Clin Oncol*. 2010; 28:1294–1300. [PubMed: 20142601]

26. Yamada TH, Denburg NL, Beglinger LJ, Schultz SK. Neuropsychological outcomes of older breast cancer survivors: cognitive features ten or more years after chemotherapy. *J Neuropsychiatry Clin Neurosci.* 2010; 22:48–54. [PubMed: 20160209]
27. Heflin LH, Meyerowitz BE, Hall P, et al. Cancer as a risk factor for long-term cognitive deficits and dementia. *Journal of the National Cancer Institute.* 2005; 97:854–856. [PubMed: 15928306]
28. Driver JA, Beiser A, Au R, et al. Inverse association between cancer and Alzheimer's disease: results from the Framingham Heart Study. *Bmj.* 2012; 344:e1442. [PubMed: 22411920]
29. Nasreddine ZS, Phillips NA, Bedirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc.* 2005; 53:695–699. [PubMed: 15817019]
30. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res.* 1975; 12:189–198. [PubMed: 1202204]
31. Borson S, Scanlan JM, Chen P, Ganguli M. The Mini-Cog as a screen for dementia: validation in a population-based sample. *J Am Geriatr Soc.* 2003; 51:1451–1454. [PubMed: 14511167]
32. Kawas C, Karagiozis H, Resau L, Corrada M, Brookmeyer R. Reliability of the Blessed Telephone Information-Memory-Concentration Test. *Journal of geriatric psychiatry and neurology.* 1995; 8:238–242. [PubMed: 8561839]
33. Olson RA, Chhanabhai T, McKenzie M. Feasibility study of the Montreal Cognitive Assessment (MoCA) in patients with brain metastases. *Support Care Cancer.* 2008; 16:1273–1278. [PubMed: 18335256]
34. Iconomou G, Mega V, Koutras A, Iconomou AV, Kalofonos HP. Prospective assessment of emotional distress, cognitive function, and quality of life in patients with cancer treated with chemotherapy. *Cancer.* 2004; 101:404–411. [PubMed: 15241840]
35. Milian M, Leiherr AM, Straten G, Muller S, Leyhe T, Eschweiler GW. The Mini-Cog versus the Mini-Mental State Examination and the Clock Drawing Test in daily clinical practice: screening value in a German Memory Clinic. *International psychogeriatrics / IPA.* 2012; 24:766–774. [PubMed: 22172089]
36. Katzman R, Brown T, Fuld P, Peck A, Schechter R, Schimmel H. Validation of a short Orientation-Memory-Concentration Test of cognitive impairment. *Am J Psychiatry.* 1983; 140:734–739. [PubMed: 6846631]
37. Hurria A, Gupta S, Zauderer M, et al. Developing a cancer-specific geriatric assessment: a feasibility study. *Cancer.* 2005; 104:1998–2005. [PubMed: 16206252]
38. Hurria A, Togawa K, Mohile SG, et al. Predicting chemotherapy toxicity in older adults with cancer: a prospective multicenter study. *J Clin Oncol.* 2011; 29:3457–3465. [PubMed: 21810685]
39. By the American Geriatrics Society Beers Criteria Update Expert P. American Geriatrics Society 2015 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. *J Am Geriatr Soc.* 2015; 63:2227–2246. [PubMed: 26446832]
40. Cherrier MM, Anderson K, David D, et al. A randomized trial of cognitive rehabilitation in cancer survivors. *Life Sci.* 2013; 93:617–622. [PubMed: 24012579]
41. Ercoli LM, Petersen L, Hunter AM, et al. Cognitive rehabilitation group intervention for breast cancer survivors: results of a randomized clinical trial. *Psycho-oncology.* 2015
42. Oh B, Butow PN, Mullan BA, et al. Effect of medical Qigong on cognitive function, quality of life, and a biomarker of inflammation in cancer patients: a randomized controlled trial. *Support Care Cancer.* 2012; 20:1235–1242. [PubMed: 21688163]
43. Reid-Arndt SA, Matsuda S, Cox CR. Tai Chi effects on neuropsychological, emotional, and physical functioning following cancer treatment: a pilot study. *Complement Ther Clin Pract.* 2012; 18:26–30. [PubMed: 22196570]
44. Kesler S, Hadi Hosseini SM, Heckler C, et al. Cognitive training for improving executive function in chemotherapy-treated breast cancer survivors. *Clin Breast Cancer.* 2013; 13:299–306. [PubMed: 23647804]
45. Ferguson RJ, McDonald BC, Rocque MA, et al. Development of CBT for chemotherapy-related cognitive change: results of a waitlist control trial. *Psycho-oncology.* 2012; 21:176–186. [PubMed: 22271538]

46. Janelins MC, Peppone LJ, Heckler CE, et al. YOCAS(c)(R) Yoga Reduces Self-reported Memory Difficulty in Cancer Survivors in a Nationwide Randomized Clinical Trial: Investigating Relationships Between Memory and Sleep. *Integr Cancer Ther.* 2015
47. Sprod LK, Mohile SG, Demark-Wahnefried W, et al. Exercise and Cancer Treatment Symptoms in 408 Newly Diagnosed Older Cancer Patients. *J Geriatr Oncol.* 2012; 3:90–97. [PubMed: 22712028]

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