Cédric Hèle instituut VZW
Vlaams Instituut voor Psychosociale Oncologie

NEUROTOXIC AND NEURODEGENERATIVE PROCESSES OF ELDERLY CANCER SURVIVORS

A Systematic Literature Review on the cognitive and neurodegenerative or ageing effects of cancer and its treatment in elderly cancer survivors

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By
Charlotte Kerstens

Promotor: Dr. Charlotte Sleurs
Co-Promotor: Prof. Dr. Hans Wildiers & Prof. Dr. Anne Uyttebroeck

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UNIVERSITEIT GENT
KU LEUVEN
UHASSELT
VUB VRIJE UNIVERSITEIT BRUSSEL

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Abstract

Cancer diagnoses are growing, and cancer is often a disease of the elderly. The elderly population is a complex population to study due to the multimorbidity and natural ageing process. Cancer and its treatment can interact on the natural ageing process of elderly cancer survivors. This makes understanding the impact of cancer and its treatment in elderly complex but essential to understand as these individuals are often already frailer and more at risk for deficits. The objective of this study was to provide an answer to the research question: "*To which extent are elderly (≥ 65 years old) cancer survivors at risk for neurotoxic or neurodegenerative processes?"* In order to answer this research question a systematic literature review was done on the cognitive effects of cancer and treatment. Studies were divided into different categories based on the different measurements used (imaging, neuropsychological testing, interviews/questionnaires). A separate description on neurodegenerative disease following cancer and its treatment was also researched. The results confirm that neurocognitive and neurodegenerative impact of cancer and its treatment is diverse, depending on the individual psychological and physiological risk factors of the patients. Not all biomarkers and mechanisms are well understood. Future studies should help and provide a clearer picture of the interaction between cancer and its treatment and the ageing process. Tools should be developed to identify these patients more at risk for accelerated ageing, neurodegeneration, or cognitive dysfunctions.

INTRODUCTION

Cancer, a Disease of the Elderly

In 2020, the worldwide incidence of cancer was 19,3 million (global cancer observatory, n.d.). As the general population grows, and lives longer, the number of cancer diagnoses is increasing. In Belgium 69% of women and 80% of men diagnosed with cancer are 60 years or older (Belgian Cancer Registry, numbers of 2019). Consequently, most cancer survivors are 65 years or older (Small, Scott, Jim, Jacobsen, 2015). Due to the improvements in treatments, as well as earlier detection, elderly cancer patients can survive longer (Henderson et al. 2014; Lange et al., 2014). Thus, survivorship has become an important topic in cancer research and with that the concern for the long-term effects of cancer and its treatment on neurocognitive functioning of these individuals.

Compared to younger adults, older adults diagnosed with cancer more often have pre-existing medical conditions which can be intensified by the side effects of the cancer or its treatment(s) (Mandelblatt et al., 2013). It is therefore important to understand their short- and long-term effects on the ageing process of this population (Henderson et al., 2014).

The goal of this systematic review is to better understand the effects of cancer and its treatment on the neurological ageing processes of elderly cancer survivors, thus getting a clearer picture of the neurotoxic effects of cancer and its treatment in elderly survivors. This is an important population to study as there is an interaction between cancer and its treatment and the neurological ageing process. First the neurotoxic mechanisms of cancer and its treatment and their link with the neurological ageing processes in general will be discussed. Then a systematic literature review will be performed on neurocognition and neurodegeneration of elderly cancer survivors and the role it had on the neurological ageing process of this specific population.

Neurotoxic Mechanisms of Cancer and its Treatments

There are many different types of cancer (i.e. carcinoma, sarcoma, lymphoma, leukaemia, melanoma,...) being classified in different ways (i.e. benign and malignant, metastasised, primary, secondary). As cancer is defined as abnormal growth of cells it can be found in all parts of the body (Reboux G./WHO/EURO, nd). When discussing the

cognitive side effects of cancer and its treatments, cancer is often classified as either being a central nervous system (CNS) tumor versus a non-central nervous system (non-CNS) tumor. Tumors of the central nervous system are located in the brain or the spinal cord. Non-central nervous system tumors are located outside of the CNS (Hardy et al., 2018). Cognitive impairment can be found in both patients with CNS tumors as well as in patients with non-CNS tumors before or during treatment and in survivorship (Hardy et al., 2018).

As stated earlier, survival rates of cancer have increased due to early detection and new and improved therapies. These include surgery, chemotherapy, radiation, immunotherapy, targeted therapy, hormonal therapy, systemic therapy, or stem-cell transplantation. Cancer is often treated with multiple modalities (Ahles & Root, 2018; Hardy et al., 2018). Different treatment approaches are based on multiple tumor characteristics such as size, location, symptoms, molecular status, histology, etc. (Hardy et al., 2018). All these different types of treatment options have resulted in improved survival rates but can have short- and long-term toxic effects on neurological functioning, which is an important factor for quality of life (QoL) (Lange et al., 2019). These cognitive deficits are defined under the term CRCI (cancer-related cognitive impairment[1]) or often also referred to as 'chemo-brain'. CRCI is described by Janelsins, Kesler, Ahles & Morrow (2014) as immediate or delayed cognitive deficits of a cancer diagnosis or treatment resulting in difficulty in memory, attention, concentration, and executive function.

CRCI is not only attributable to treatment of cancer but can be related to other factors as well, such as; the cancer itself, sociodemographic factors such as age, cognitive reserve, SES, education, genetics, comorbidities, fatigue, frailty, emotional distress, postmenopausal status, allostatic load and lifestyle (Ahles & Hurria, 2018; Ahles & Root, 2018; Hardy et al., 2018). The multifactorial nature causes some people to be more at risk than others and complicates the identification of responsible components for changes in cognition (Ahles & Hurria, 2018). In most people these cognitive complaints tend to

[1] Other terms often used to describe the same Cancer-Related Cognitive Impairment (CRCI) are Cancer-Associated Cognitive Decline (CACD) (Ahles & Root, 2018), Chemotherapy Induced Cognitive Decline (CICD) (Ahles & Root, 2018), Cancer Treatment-Related Cognitive Impairment, Post-Chemotherapy Cognitive Impairment (Cancer.org).

resolve within the first few months after treatment, but in about a third of survivors the cognitive complaints can persist longer or new-onset cognitive dysfunctions can emerge (Vannorsdall et al., 2017).

In CNS tumors CRCI may be directly affected by the cancer itself. Here the impairments are mostly related to the tumor size or neuroanatomical location and local therapy (e.g. surgery, stereotactic/focal radiotherapy), neuroinflammation, host factors (i.e. an individual's traits affecting susceptibility to CRCI such as cognitive reserve) and other related pathways (Hardy et al., 2018). For patients with non-CNS tumors, CRCI mechanisms may be mostly related to the therapy modalities, inflammation, other related pathways, tumor type, stage, and host factors (Hardy et al., 2018). Most of these cognitive deficits include deficits in attention, memory, concentration, processing speed, multi-tasking and executive function and are often associated with alterations in both brain structure and function. These include gray matter volume loss, reduced white matter integrity, overactivation of frontal regions, altered cerebral network organisation (Koppelmans et al. 2012; Vannorsdall et al., 2017). Such imaging finding are also seen in the normal ageing process, providing evidence for the idea that there is a link between cancer survivorship and the ageing process (Ahles & Root, 2018). The clinical manifestation of neurological ageing and cancer treatment effects includes cognitive decline, neurological symptoms, and neurodegenerative diseases (Alzheimers, Parkinson). Neurocognitive changes have been reported and measured in numerous ways, including objective and others subjective assessments (e.g. neurocognitive tests, questionnaires, interviews, neurological symptoms, imaging studies, etc.) (Ahles & Root, 2018).

Different mechanisms for treatment-induced cognitive dysfunction have been identified. These mechanisms are often dependent on the treatment (i.e. radiotherapy, chemotherapy and immunotherapy), but overlap in toxic mechanisms does exist. In 2007, Ahles and Saykin, reviewed the possible mechanisms of chemotherapy-induced cognitive changes. These included decreased integrity of the blood-brain barrier (i.e. cell death and reduced cell division), DNA damage and telomere shortening, neurotoxic effects of inflammation and cytokine deregulation, reduced estrogen and testosterone levels, cardiotoxic effects, alterations in neuroendocrine changes and genetic susceptibility (i.e. variability in blood-brain barrier transporters, DNA -repair mechanisms, rate of telomere

shortening, cytokine dysregulation, neuronal repair and plasticity and neurotransmission). Imaging techniques have also detected structural and functional changes to the brain associated with chemotherapy. These include reduced volume and/or tissue integrity of brain structures (such as the frontal cortex which is important for cognitive functioning) and changes in structural network connectivity of white-matter tracks and reduced grey matter volume/density (Lv, Mao, Dong, Hu, Dong, 2020; Saykin, Ahles & McDonald, 2003; Ahles & Saykin, 2007).

More recently, Makale et al. (2017) reviewed neuroimaging evidence to propose possible mechanisms of brain irradiation. These include changes in white and gray matter (demyelination, inadequate perfusion of white matter tracts due to apoptosis of oligodendrocyte progenitors and damage to microvascular endothelium resulting in structural vascular abnormalities), changes in hippocampus (insufficient production of neurons, loss of hippocampal plasticity, and long-term neuronal loss due to loss of neuronal precursors, inflammation and damage to neuronal dendrite structures), and prefrontal cortex damage (white matter, vessels, and neurons).

Recently, Joly et al. (2020) studied the possible mechanisms of immunotherapy. Higher pro-inflammatory cytokines and growth factors, cytokine dysregulation, increase in T-cell receptor diversity, and white blood cell count could all have an adverse effect on immune-related events affecting all organs of the body. All these processes can cause cognitive changes, or neural degeneration. Hence, there are multiple pathways to cognitive decline depending on the treatment (combinations) and the vulnerabilities of the individual patient. Figure 1 represents a conceptual model of Ahles & Root (2018) in which multiple factors that can contribute to post-treatment cognitive decline are described.

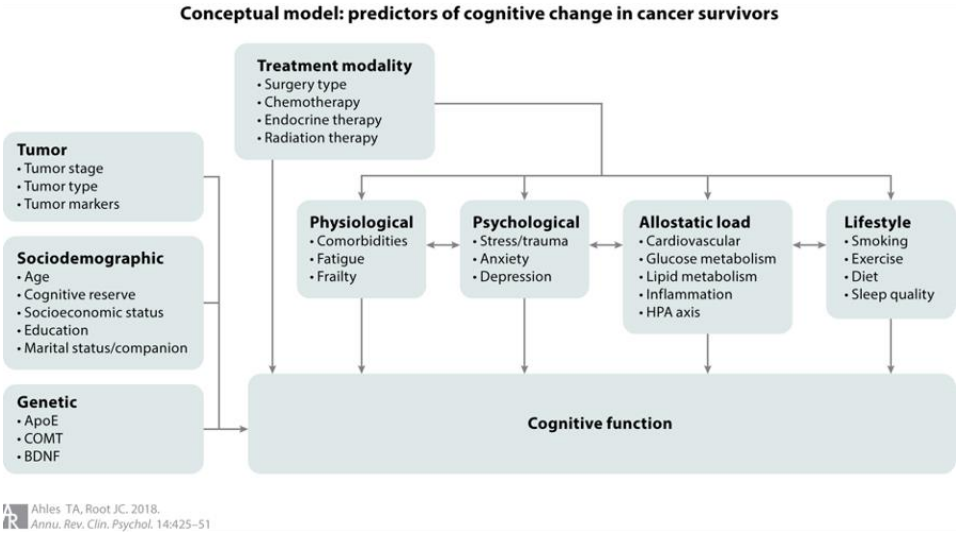

Figure 1: Conceptual model: predictors of cognitive change in cancer survivors (Ahles & Root, 2018).

Ageing, Cognition and Cancer

Ageing occurs throughout an individual's lifespan. Normal biological ageing involves the accumulation of damage on the molecular and cellular level of the body over time, resulting in a deterioration of physical and mental capacities and an increased vulnerability to disease and death (Steverson, 2021). The mechanisms involved in this process includes DNA damage and mutations, epigenetic ageing, stem cell damage (oxidative stress), cellular senescence (telomere shortening) and inflammation. These mechanisms ultimately lead to cognitive decline, frailty, functional decline, chronic disease, and death (Muhandiramge et al., 2021). Some pathways of cancer overlap with some of these ageing processes. More specifically, cancer involves dysregulated cell growth and the accumulation of cellular damage leading to progressive dysfunction (Ahles 2012; Mandelblatt et al., 2013; Muhandiramge et al., 2021). Cancer survivors may be more likely to experience ageing. Muhandiramge et al. (2021) developed a model explaining the mechanisms and outcomes involved in cancer survivorship and accelerated ageing (see figure 2).

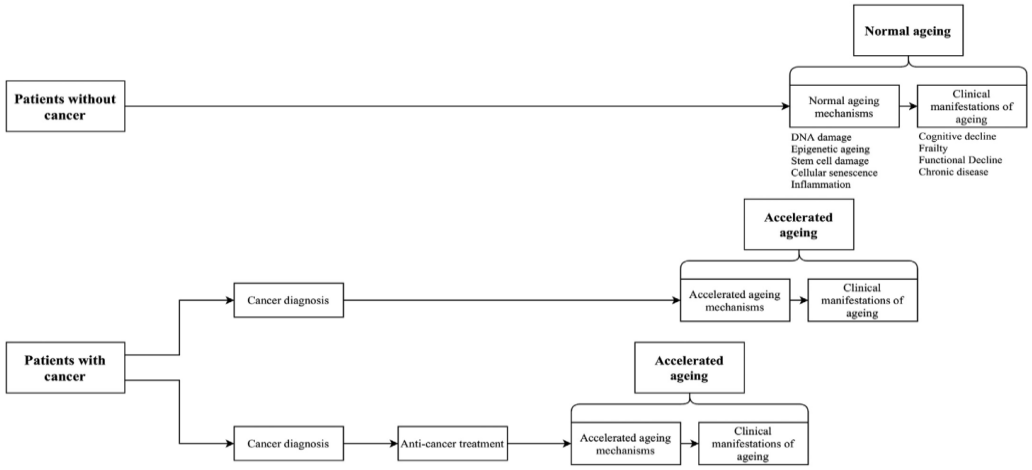

Fig. 1. Potential mechanisms and outcomes of accelerated ageing in cancer survivors.

Figure 2: Potential mechanisms and outcomes of accelerated ageing in cancer survivors (Muhandiramge et al., 2021).

Ageing is considered the rate of progressive accumulation of random damage resulting in failure of the system (Gavrilov & Gavrilova, 1991). This means there is not one specific biological ageing pathway but there are multiple combinations resulting in loss of redundancy and accumulation of damage leading to ageing (Ahles & Root, 2018).

Ahles & Hurria (2018) developed two hypotheses regarding trajectories of neurological ageing in cancer survivors (see figure 3). The "phase shift hypothesis", postulates that cancer and its treatment have an immediate toxic effect on brain regions, thus impacting the trajectory of ageing, but the rate of decline remains constant over time. The "accelerated ageing hypothesis" proposes that cancer and its treatment are accelerating the ageing process, which results in a steeper slope of decline in cancer patients compared to non-cancer patients. These hypotheses are not mutually exclusive. Survivors of cancer with no vulnerability factors or frailty level may follow the phase shift trajectory whereas survivors with more vulnerability of frailty levels (lower reserve) have steeper trajectories of decline compared to normal ageing (accelerated ageing trajectory) (Ahles & Hurria, 2018). Some people are more vulnerable to specific outcomes depending on the frailty level of patients before diagnosis (Ahles & Root, 2018). Higher frailty can result in a steeper decline in functioning (Mandelblatt, Jacobsen & Ahles, 2014).

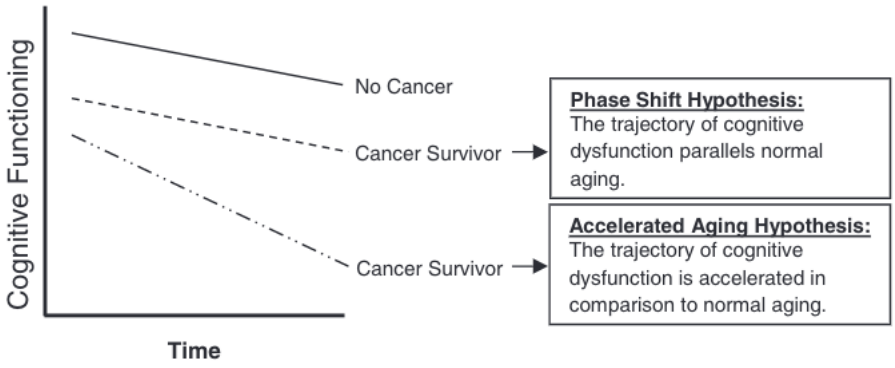

Figure 3: Trajectories of cognitive change (Ahles & Hurria, 2018).

In this systematic literature review we will review to which extent cancer and its treatment can contribute to the neurological ageing process (cognitive decline and neurodegeneration) in elderly survivors of cancer.

METHOD

The focus of this systematic literature review is on neurocognitive and neurodegenerative outcomes of elderly (≥65 years old) cancer survivors. More specifically, the research question is: "To which extent are elderly (≥ 65 years old) cancer survivors at risk for neurotoxic or neurodegenerative processes?" The objective of this review is to provide an answer to the research question above by offering a systematic overview of the research evidence on this topic.

Protocol

A literature search of published papers was conducted in the following databases: *PubMed Central (PMC), Web of Science Core Collection 1955 to present,* and *MEDLINE®.* These databases were consulted through the following two search engines: *PubMed* and *WoS: Web of Science*. Three main key search terms were selected, combined through the Boolean operator *'and'* and entered into the search engines. These general keywords are [Neoplasm] *and* [Neurocognition '*or'* Neurodegeneration] *and* [Elderly]. Each key term consisted of several index terms and the Boolean operator '*or*' connecting all these subterms. MeSH-terms (Medical Subject Headings) were defined by using the tree structure to select all useful MeSH-terms. Subsequently, the engine-specific search strings were entered in the two search engines.

A complete overview of the searches in the two search engines is presented in Annex A. Additionally, reference sections of papers were reviewed to identify additional papers to ensure full coverage of the existing literature.

Inclusion and Exclusion Criteria

After completing the literature search in the different search engines, duplicate articles were removed through EndNote. The finally selected articles were uploaded to Rayyan as a screening measure and were selected based on the following predefined inclusion criteria: (1) Research on cancer survivorship starting 6 months after the last treatment[2] or at least 1 year post-diagnosis; (2) a mean age of at least 65 years old; (3) cognitive, neurotoxic or neurodegenerative outcomes (i.e. not psychiatric problems, sleep, pain, quality of life, etc.); (4) original research articles only (no presentations, posters, conferences or abstract only articles); (5) English language; (6) human studies; (7) publication date between 2000 and June 12th 2021.

Studies were excluded in case of non-original-research articles (case reports, expert opinions, conference summaries), in vitro or animal studies, case studies (i.e. ≤5 patients), studies including a median population <65 years old, pre-treatment or active cancer diagnosis, less than 6 months post-treatment or less than 1 year post-diagnosis, palliative population, studies covering other diagnoses (i.e. non-cancer), studies not focusing on cognitive outcomes, intervention studies, screening tool studies, prevention or predictive studies, reviews or meta-analysis, no full text available.

Studies were categorized according to the measurements used to determine cognitive and neurological functioning (i.e. imaging studies, neuropsychological tests, and questionnaires/interviews). Some studies used a combination of measurements (imaging, cognitive testing, interviews/questionnaires) in their analysis. These studies were categorized in the table based on the measurement focus of the studies. Specific neurodegenerative diseases (i.e. Alzheimer's disease, Parkinson's disease, other types of dementia or cerebrovascular conditions) following cancer or its treatment were separately described in a restricted summary table.

[2] This to allow for neurologic and medical stabilization

Data Extraction

Information of author, publication year, study-design, country, cancer subtype, study-period, treatment type, comparison group, participants, mean age at diagnosis, mean age at baseline, measurement time points, measurements used and the main findings relevant to the current protocol were extracted from the studies and shown in table 1, Appendix D. A restricted summary table on neurodegenerative diseases following cancer is shown in table 2, Appendix E, where information on author, publication year, cancer subtype, neurodegenerative disease and main findings were extracted from the studies.

RESULTS

The search identified a total of 8738 citations of which 2813 in the search engine Pubmed, and 5925 in WoS. The duplicate articles were eliminated using EndNoteDesktop, resulting in 7628 remaining articles. These studies were then uploaded to Rayyan and evaluated based on their title and abstract and 7393 articles were excluded. 235 of the remaining articles were evaluated in detail on their suitability and a divided into categories depending on the measurement used (i.e. imaging studies, cognitive tests, questionnaires/interviews). 4 additional articles were identified by manually searching for studies that have cited these papers. This resulted in a final selection of 49 publications relating to the research question, which met the inclusion criteria. A separate description specifically on neurodegenerative diseases following cancer resulted in 48 separate publications. The complete search process is visualized in a Prisma Flowchart in Appendix C.

Study Characteristics (cognitive function following cancer)

49 articles were eligible according to our inclusion criteria for cognitive function following cancer and its treatment. 5 studies (10%) described primarily the neurological impact of cancer and its treatment through imaging studies. 38 studies (78%) assessed the neurocognitive impact of cancer and its treatment through cognitive testing and 6 (12%) through questionnaires or interviews. 14 studies used a combination of measurements (imaging, cognitive testing, interviews/questionnaires) in their analysis. Studies used a wide range of populations, though most studies took place in the US and included a population of breast or prostate cancer survivors. The studies assessed cognitive function

at different time points (including studies starting 6 months after treatment or 1 year after dianosis) and up to a maximum of 15+ years following diagnosis.

Imaging studies

Of the 5 imaging studies 4 were cross-sectional compared to one prospective study. Cancer and treatment were associated with structural changes in the brain, specifically grey matter loss in areas of the brain such as the basal ganglia, and right superior frontal gyrus (Nudelman et al 2014; Sharma et al. 2020; Simó et al. 2016). White matter changes in the corpus collosum were also found and correlated with cognitive deterioration (Simó et al. 2016). Functional changes in brain metabolism were also found after chemotherapy, chemoradiation or tamoxifen such as hypometabolism in orbital frontal regions in survivors which correlated with neuropsychological test results (Ponto et al. 2015). Lower concentrations of myo-inositol (MI) were also found in the brain when treated with tamoxifen (duration effect) or estrogen (Ernst et al. 2002). No changes were found in the concentration of N-acetyl-containing compounds (NA), Choline-containing compounds (CHO), total creatine (CR) between tamoxifen treatment, no drug treatment or estrogen (Ernst et al. 2002). Most affected regions were the frontal regions and changes in the basal ganglia consistent with changes in cognition, specifically working memory, executive functioning, and information processing (Ernst et al. 2002; Nudelman et al. 2014; Ponto et al, 2015; Simó et al. 2016; Yamada, Denburg, Beglinger & Schultz, 2010).

Neuropsychological Testing

38 studies primarily used neuropsychological testing to research cognitive function after cancer. The studies used a broad spectrum of tests measuring different cognitive domains including attention, memory, processing speed, executive functioning, learning, language, visuospatial abilities, reaction time, psychomotor function, intelligence, and non-verbal function. Older age or ageing related phenotypes were often associated with worse cognition scores and impairment (Cruzado et al. 2014; Kvale et al. 2010; Lombardi et al. 2018; Mandelblatt et al. 2018; Morin & Midlarsky, 2018a; Regier et al. 2019; Schilder et al. 2010). One study found that older individuals who developed cancer had better memory and slower memory decline than cancer free individuals (Ospina-Romero et al. 2019). Another study found that chemotherapy may result faster

decline in memory in late life, thus altering the trajectory of decline in later life (Anstey et al. 2015; Mandelblatt et al. 2018). Depression/anxiety and fatigue was also found to predict worse cognition (Morin & Midlarsky, 2018a; Schilder et al. 2012). Not all studies showed a cognitive deficit after cancer and treatment (Albihai et al 2010; Alibhai et al. 2017; Alonso Quiñones, Stish, Hagen, Petersen & Mielke, 2020; Alonso Quiñones et al. 2021; Buckwalter, Crooks & Petitti, 2005; Deschler, Ihorst, Hüll & Baier, 2019; Keating et al. 2005; Minniti et al. 2013; Moon et al. 2014; Porter, 2013; Tan et al. 2013). Studies analyzing the trajectories of cognitive functioning from pre-diagnosis to a period after diagnosis most often found stable rates and trajectories (Morin & Midlarsky, 2018a, 2018b; Shaffer et al. 2012). Some studies showed no long-term impact on cognition or showed a short-term impact of treatment but improvement in some domains long-term (Cruzado et al. 2014; Mandelblatt et al. 2018; Ospina-Romero et al. 2019; Porter, 2013; Regier et al. 2019). One study found short term cognitive improvements the first year after diagnosis and cognitive decrease in the second year (Legault et al. 2009). Attention, memory, information processing speed, learning and executive functioning seemed to be the most impacted domains (Anstey et al. 2015; Cruzado et al. 2014; Gonzalez et al. 2015; Hurria, Rosen et al., 2006; Jenkins, Bloomfield, Shilling, Edginton, 2005; Kvale et al. 2010; La Carpia et al. 2020; Mandelblatt et al 2018; Schilder et al. 2010; Williams, Janelsins, & van Wijngaarden, 2016; Yamada et al. 2010; Yang, Zhong, Qiu, Cheng & Wang, 2015).

Treatment-specific results were also found. Hormonal therapy (Tamoxifen) often resulted in worse cognition scores, specifically in learning (information processing), verbal memory and executive functioning (Mandelblatt et al. 2018; Schilder et al. 2010; Underwood et al. 2019). Exemestane did not negatively impact cognition (Schilder et al. 2010). ADT in prostate cancer resulted in impaired cognitive performance, specifically executive function attention, memory, and information processing (Jenkins et al. 2005; Gonzalez et al. 2015; Yang et al. 2015). These deficits in hormonal therapy are strongest and most often found in current users and less in past users (Almeida, Waterreus, Spry, Flicker, & Martins, 2004; Paganini-Hill & Clark, 2000). Four studies (Alibhai et al. 2010; Alibhai et al. 2017; Alonso Quiñones et al. 2020; Alonso-Quiñones et al. 2021) did not find a clear association between history of ADT use and cognitive deficits. Hoogland and colleagues (2021) found stable rates of cognitive function in ADT use in the first 12

months while the control group improved. Local therapy such as surgery most often did not have substantial impact on cognition (Deschler et al. 2019; Porter, 2013) or even showed improvements/recovery in cognitive function (Di Cristofori et al. 2018; Konglund et al. 2013). These studies specifically analyzed a population of meningioma patients. Two studies analyzed the impact of radiotherapy in brain metastases or glioblastoma. One study showed no cognitive change after radiotherapy (Minniti et al. 2013), while the other revealed statistically lower cognitive scores 9 months after radiotherapy (Lombardi et al. 2018). One study found an increased risk for cognitive impairment in female survivors due to surgery and/or pelvic radiation (which directly affected ovarian function) compared to chemotherapy (Kurita, Meyerowitz, Hall & Gatz, 2011). Chemotherapy negatively impacted cognitive processing speed, visual and verbal memory, spatial function, and attention (Cruzado et al. 2014; Hurria, Rosen et al., 2006; Kvale et al. 2010). Anstey, Sargent-Cox, Cherbuin & Sachdev (2015) found a short-term impact of chemotherapy on decline in processing speed and a long-term impact on memory. Shaffer et al. (2012) found no difference in the rate of cognitive decline after chemotherapy. One study showed a potential cognitive benefit of exogenous levothyroxine in thyroid cancer on the cognitive function of patients who lack endogenous thyroid hormone (Moon et al. 2014). Morin & Midlarsky (2018b) found that chemotherapy predicted higher recall ability, but this was due to an effect of age on treatment selection (younger people more often received chemotherapy).

Interviews/Questionnaires

The 6 studies focusing on cognitive screening interviews or questionnaires provided more subjective information on cognitive function after cancer or its treatment. Divergent results were found in the studies on subjective cognitive function. There were studies that showed no association between previous cancer diagnosis and poorer self-reported cognitive function (Freedman et al., 2013; Keating, Nørredam, Landrum, Huskamp & Meara, 2005) and where most survivors maintained good long-term self-reported cognition function (Mandelblatt et al. 2016). One study showed the opposite, that long-term survivors most often presented a higher rate of cognitive dysfunction. (Heflin et al. 2005). Memory domains were most likely perceived as affected, specifically the ability to learn new information (Hurria, Goldfarb et al., 2006; Jenkins et al. 2005;

Williams et al. 2016; Paganini-Hill & Clark, 2000). Loss of memory was more often reported in female breast cancer survivors or gynecologic cancers (Kurita et al. 2011; Stava, Weiss & Vassilopoulou-Sellin, 2006), and in patients with preexisting cognitive or memory complaints (Hurria, Goldfarb et al., 2006; Mandelblatt et al. 2016). Most often different results were found depending on the treatment given and changes were seen over time by treatment received. Multiple studies found a specific effects of chemotherapy on more frequently reported loss and decline of memory (Hurria, Goldfarb et al., 2006; Stava et al., 2006) or cognitive decline (Mandelblatt et al. 2016; Mandelblatt et al. 2018). While in one other study chemotherapy did not appear to be associated with long-term subjective changes in cognitive function (Freedman et al. 2013). One study researched hormonal therapy and found that tamoxifen users (but not exemestane users) reported increased attention/concentration complaints (Schilder et al. 2012).

Neurodegenerative diseases following cancer

48 articles were eligible according to our inclusion criteria for a separate description on neurodegenerative disease following cancer and its treatment. These studies explicitly reported on neurodegenerative diseases and met our inclusion criteria. Most studies used a population of prostate or breast cancer studies. The different neurodegenerative diseases or conditions were Parkinson's disease (PD), Amyotrophic lateral sclerosis (ALS), dementia-related events, including cognitive disorder (NOS), Alzheimer's disease (AD), amnestic disorders, transient global amnesia (TGA), vascular dementia (VaD), drug-induced dementia, Lewy body dementia, cerebral degeneration, and cerebrovascular events including cerebral infarction, stroke, stroke death, carotid revascularization, and transient ischemic attack. Divergent results were found.

The majority of studies found that cancer survivors have a lower risk of AD and PD (Bowles et al. 2017; Driver et al. 2012; Frain et al. 2017; Freedman et al. 2016; Ibler et al. 2018; Musicco et al. 2014; Realmuto et al 2012; Roe et al. 2010) or a later age of AD onset (Fowler et al. 2020). While an increased risk of non-AD dementia and stroke were found in cancer survivors (Frain et al. 2017). Some studies found no relevant association between cancer and risk of dementia (AD, Vad, or all-cause dementia) or TGA (Baik, Kury & McDonald, 2017; Elbaz et al. 2002; Hanson et al. 2017; Ording et

al. 2020; Zhu et al. 2015). One study found a lower risk of dementia up to 10 years survival and a higher risk after 10 years (Sun et al. 2020).

Some cancer-specific results were also found. Most studies found a decreased risk for AD or a delay in onset (but not progression) of PD in patients with skin cancer (Ibler et al. 2018; Frain et al. 2017; Mahajan et al. 2020; Nudelman et al. 2014; White, Lipton, Hall, & Steinerman, 2013). Only one study found that skin cancer increased the risk of PD (Olsen, Friis & Frederiksen, 2006). Divergent results were found for smoking-related cancers. Some said that the risk of AD or PD was lowest in smoking-related cancers (Driver et al. 2012; Frain et al. 2017; Olsen et al. 2006) while others stated that risk was higher in smoking-related cancers (lung cancer), or hormonal related tumors (Elbaz et al. 2002; Realmuto et al. 2012; Roderburg et al. 2021). Studies found that survivors of screening-related cancers, such as lung and colorectal cancers, had an increased risk of dementia (specifically AD) or stroke (Chen et al. 2011; Frain et al. 2017; Khan et al. 2011).

Different results based on cancer treatments were also found. Majority of studies found that the use of ADT resulted in increased future AD risk or cognitive dysfunction (Hong et al. 2020; Jayadevappa et al. 2019; Jhan et al. 2017; Khosrow-Khavar et al. 2017; Krasnova et al. 2020; Nead et al. 2015; Nead et al. 2017; Shahinian, Kuo, Freeman, & Goodwin, 2006; Tae, Jeon, Shin et al. 2019). An effect of duration of ADT use was found in one study (Nead et al. 2017) but not in another (Hong et al. 2020). Only three studies found no effect of ADT on AD or PD risk (Chung et al. 2016; Kao, Lin, Chung & Huang, 2015) or on cerebral infarction (Tae, Jeon, Choi et al. 2019). There were studies that looked at the impact of hormonal therapy and found no association with dementia development (Baxter et al. 2009; Bromley et al. 2019) or a decreased risk (Branigan et al. 2020). One study found an effect of antiandrogen monotherapy on increased risk of dementia or AD (Huang et al. 2020). Blanchette et al. (2020) found that aromatase inhibitor therapy was associated with a decreased incidence of dementia as compared to the treatment with tamoxifen. Liao, Lin & Lay (2017) found an association between ever use of tamoxifen and increased odds of AD.

Other treatments such as BCG may show reduced risk of AD and PD (Klinger et al. 2021). An increased risk of cerebrovascular events was found in patients who received

radiotherapy for head or neck cancers (Hong et al. 2013; Smith et al. 2009) while some statin use could reduce this risk (Boulet et al. 2019).

Chemotherapy treatment appeared to have a divergent impact on the different types of dementia. Some studies showed an association between chemotherapy and certain types of dementia for example drug-induced dementia (Du, Cai, & Symanski, 2013; Heck et al. 2008). Other types of dementia such as AD and VaD were lower in patients that received chemotherapy (Du et al. 2013; Frain et al. 2017). Other studies found no association between chemotherapy and development of drug-induced dementia, unspecified cognitive disorders, or dementia (Baxter et al. 2009; Du, Xia, & Hardy, 2010; Raji et al. 2009) while the risk of developing AD, VaD was then again lower (Du et al. 2010).

Not all studies found an effect dependent on the treatment given (Jazzar et al. 2020) but rather found an effect of age and comorbid factors such as SES, depression on increased risk of dementia (Jazzar et al. 2020; Raji et al. 2009).

CONLUSIONS AND DISCUSSION

Given the rising incidence of cancer with age, research on the neurocognitive and neurodegenerative impact of cancer and its treatment in later life is important. A lot of research has been done on the younger population. Only a relatively small number of studies have focused on cancer survivors of advanced biological age. In this systemic literature review the neurocognitive and neurodegenerative effects of cancer and its treatment were investigated to provide an answer to the research question "*To which extent are elderly (≥ 65 years old) cancer survivors at risk for neurotoxic or neurodegenerative processes?"*

In terms of neurocognition, conclusions reflect the use of different measurements (imaging, neuropsychological testing, interviews/questionnaires, or diagnosis of neurodegenerative disease). This systematic literature review demonstrates that neurocognition and neurodegeneration has been studied in various developed countries around the world. Overall, evidence was provided for functional and structural changes in the brain, specifically grey matter loss and white matter changes. The largest impact was found on the frontal regions and changes in the basal ganglia consistent with changes in cognition, specifically working memory, executive functioning, and information

processing. Cognitive test results were not always correlated with subjective cognitive functioning. Memory domains were frequently perceived as affected. Older age or ageing related phenotypes such as frailty were most often related to worse cognition scores or resulted in alterations in the trajectory of decline in later life. Depression/anxiety and fatigue were found to predict worse cognition. Cognitive change after cancer diagnosis and treatment was found in some studies, but not all studies showed these results, and many discrepancies were found. Long-term impacts were found in some studies while in other studies only short-term changes were detected. Treatment specific results were also detected, some reducing and some increasing the neurotoxicity. Hormonal-based therapies could be associated with cognitive changes but the link between hormonal therapies and cognitive impairment remain a matter of debate depending on the type of hormonal treatment. Most studies showed an impact of chemotherapy, and a stronger effect was found in current users of treatment compared to past users. Local therapy such as surgery most often did not have a substantial impact on cognition.

Overall studies report inconsistent results on the relationship between cancer and neurodegeneration and this remains a matter of debate. While some studies found that cancer survivors have a lower risk of developing dementia, or a later age of onset, others found an increased risk of specific types of dementia. Discrepancy in cancer-specific results were also found specifically in smoking related cancers. Skin cancer was often associated with a decreased risk of dementia of PD. A link between screening-related cancers and increased risk of dementia and stroke was also found. Treatment specific results were found. While some hormonal therapies (such as ADT) were related to increased risk of AD others did not show an association. No consistent results were found on studies where patients received chemotherapy. Not all studies showed an impact of treatment, but comorbid factors impacted the risk of dementia such as SES, depression, and age.

The comparison of cognitive effects across studies presented several challenges and limitations as studies were difficult to compare due to different treatments, diagnosis, measurements, outcomes, and measurement times. Taken together these results do not paint a consistent picture as to whether elderly cancer survivors are at greater risk for cognitive decline or neurodegenerative syndromes.

Individual risk factors of neurocognition/neurodegeneration in cancer survivors

As results described above do not paint a consistent picture as to whether cancer and its treatment results in cognitive impairment or neurodegeneration, possible individual risk factors may be important to consider. As older cancer survivors are diverse, many different individual risk factors of neurocognitive decline and neurodegeneration in cancer survivors exists. Occurrence of deficits can be modulated by many different risk factors such as cancer types, treatment types and duration, genetic predisposition, age, comorbidities, psychological and social factors (La Carpia et al. 2020; Országhová, Mego & Chovanec, 2021).

Cancer itself and treatment modalities can induce cognitive impairment or neurodegeneration. Many different treatments for cancer exist including surgery, radiotherapy, chemotherapy, hormonal therapy, targeted therapy, and immunotherapy. All these treatment modalities can have an adverse effect on cognition through different mechanisms (Joly et al. 2015; Országhová et al. 2021). For chemotherapy this adverse state is often referred to as "chemofog" (Joly et al. 2015). The combination between the physiological toxic effects of treatments, in combination with biological and medical factors such as side effects of treatment, fatigue, psychological factors, hormonal changes can also play a role in cognitive impairment (Joly et al. 2015). Different effects on cognition can also be found dependent on the duration or dosage of different treatments (Országhová et al. 2021). The most impacted domains are memory, concentration, information processing speed and executive functioning (Joly et al. 2015). These treatments can have short, as well as long term impact on cognitive functioning and can have a negative impact on the quality of life (Országhová et al. 2021). Besides the cytotoxic drugs used in cancer treatment, other related factors to treatment or cancer itself can have a negative impact on cognition. These include psychological distress related to the life-threatening context of cancer, fatigue, sleep problems, and tumor-related factors (Joly et al. 2015). This is seen in studies where cognitive and brain dysfunction are found prior to starting treatment (Joly et al. 2015; Lange et al. 2014). Cancer itself can have an adverse effect on cognition and is more pronounced in older compared to younger people (Lange et al. 2014).

Genetic predispositions can also form a risk factor in the relationship between cancer and cognition or neurodegenerations. The genetic make-up can predispose a

patient for developing cognitive deficits and have a role in age-related cognitive decline (Mandelblatt et al. 2013). These include genes encoding apolipoprotein E (APOE), catechol-O-methyltransferase (COMT), and brain-derived neurotrophic factor (BDNF) (Országhová et al. 2021). These key genetic polymorphisms can predispose someone to cognitive changes (Castel et al. 2017). APOE has an important role in neuronal plasticity and repair and APOE-E4 gen has been associated with cognitive impairment in Alzheimer's disease, brain trauma and ageing and thus can form a risk factor for cognitive difficulties (Lange et al. 2014; Mandelblatt et al. 2013; Országhová et al. 2021). Polymorphism of the COMT gene is related to oxidative stress/neuroinflammation (Joly et al. 2015). Val Allele of COMT is linked to cognitive impairment through its impact on the metabolic breakdown of catecholamines, resulting in higher enzymatic activity and more degradation of dopamine and decrease of availability at synaptic receptors (Joly et al. 2015; Országhová et al. 2021). BDNF gene is involved in neurogenesis and synaptic plasticity and a functional polymorphism of BDNF is associated with cognitive impairment and hippocampal volume decline (Országhová et al. 2021; Mandelblatt et al. 2013). Other polymorphisms such as single nucleotide polymorphisms (SNPs), multidrug resistance 1 (MDR1) genes can also have an adverse effect on cognition in cancer patients through inflammatory mechanisms in SNP's or effect on the blood-brain barrier directly causing toxicity in MDR1 (Mandelblatt et al. 2013). Lastly miRNA, which plays a major role in regulation gene expression and cell metabolism and may indirectly effect neurogenesis, thus playing an important role in the development neurodegenerative diseases (Mandelblatt et al. 2013; Országhová et al. 2021).

Age- and age-related comorbidities are an important consideration as well in the relationship between cancer (treatment) and cognitive decline or neurodegenerative diseases. Chronological age alone appears to be a poor predictor of tolerance and effects of treatment as the elderly population is heterogenous (Handforth et al. 2015). The combination of chronological age or age-related phenotypes such as frailty or baseline cognitive reserve are an important predictor of cognitive decline and neurodegeneration in cancer survivors (Mandelblatt et al. 2018; Joly et al. 2015). Increasing age also leads to an increase in possible comorbidities, functional decline and cognitive dysfunction that may degenerate into dementia symptoms (Bluethmann, Mariotto & Rowland, 2016; Joly et al. 2015).

Prediagnosis function including comorbidity, frailty and age are related to cognitive trajectories in cancer survivors (Mandelblatt et al. 2016). Treatment of cancer may augment cognitive dysfunction associated with age-related brain changes (Yamada et al., 2010). Cancer and treatment of cancer itself also decreases cognitive reserve. Thus, survivors who are older, have less reserve pre-diagnosis due to frailty or other comorbidities could be more suspectable to reach the threshold of cognitive deficits (Heflin et al. 2005). Prediagnosis health status could be predictive of cognitive trajectory after treatment as worse health status and more comorbidities could result in frailer adults with less reserve (Hurria, Rosen et al. 2006). Several other comorbid factors related to age can also impact cognitive function in older cancer survivors. The prevalence of mood disorders such as depression or anxiety is known to be high in patients aged 65 and above (Lange et al. 2014). Depression and anxiety can have an adverse effect of cognition Depression may represent a risk factor of dementia while anxiety and cognition are more likely to be characteristics of normal ageing (Lange et al. 2014). Ageing is also related to the accumulation of multimorbidity's (such as diabetes and heart disease). These can have a direct or indirect neurovascular impact on cognition which may make certain older survivors more vulnerable to ageing and cognitive impairment (Mandelblatt et al. 2014).

Psychological and social factors can also be a risk factor in cancer-related cognitive impairment or neurodegeneration and are frequent as a reaction to a cancer diagnosis and its treatment (Országhová et al. 2021). Association between cognitive impairment and depression or anxiety, especially in elderly, has been found, as well as post-traumatic stress disorder, sleeping difficulties, distress, and fatigue (Lange et al. 2014; Országhová et al. 2021). Other risk factors that can influence cognitive decline in cancer survivors includes race, ethnicity, socioeconomic status, education, cognitive reserve (influenced by education, occupation, and lifestyle) (Országhová et al. 2021).

These described risk factors (cancer, treatment, genetic predisposition, age, comorbidities, psychological and social factors) lead to physiological toxic effects and impact on the brain (Országhová et al. 2021). While normal ageing has a curvilinear process with most decline in older age, the slope can change due to a variety of individual factors such as cognitive reserve, comorbid conditions, genetic factors, psychological and social factors (Ahles, 2012). Thus, even if cancer treatment has the same impact on the

brain independent of age, the cognitive performance may change depending on the age of the individual and the slope of cognitive ageing (Ahles, 2012).

Physiological features of ageing

Biological ageing is defined as the accumulation of damage over time on a molecular and cellular level, resulting in deterioration of mental and physical capacities and increased risk of disease and death (Steverson, 2021). Linked to that are the phenotypes of ageing such as frailty, can lead to vulnerability by diminished biologic reserve (Mandelblatt et al. 2013). Cancer and ageing could be linked, and the diagnosis of cancer and its treatment can accelerate the ageing process. Ageing in return is again related to neurodegenerative diseases (Mandelblatt et al. 2013). Thus, ageing is a powerful risk factor in both cancer and neurodegeneration (Driver, 2012).

There are many overlapping biological changes involved in both ageing as well as cancer treatment. These changes include hormonal changes, inflammation, DNA damage, increased oxidative stress, decreases in telomere length, disruption of blood brain barrier, and cell senescence (Mandelblatt et al. 2013; Small et al. 2015).

Hormonal levels decrease with age and hormonal replacement therapy which are used in cancer treatment can blocks certain hormonal levels (Mandelblatt et al. 2013). Different effects have been found dependent on the type of hormonal treatment. Tamoxifen generally affects brain estrogen receptors in the frontal lobe and hippocampus but appears to decrease the risk of Alzheimer disease (Mandelblatt et al. 2014). Aromatase inhibitors decrease circulating estrogen and ADT reduces testosterone (Mandelblatt et al. 2014). An overlapping pathway involved in ageing, cancer and treatment are inflammatory responses as they can trigger neurotoxic cytokines (Mandelblatt et al. 2013). Treatment such as chemotherapy can disrupt cellular processes and cell division resulting in increased inflammatory responses (such as pro-inflammatory cytokines and cytokine receptors) (Országhová et al. 2021). Interestingly pro-inflammatory cytokine IL-4 appears to have a protective role against CRCI (Castel et al. 2017). Peripheral amyloid beta and tau are plasma biomarkers and are linked to neurodegeneration through pro-inflammatory cytokine responses (Országhová et al. 2021). Increased Amyloid -AB40 is also known to be associated with normal ageing (Tan

et al.). pNF-H is also a plasma biomarker that can be found in patients treated for cancer as well as in patients who have acute brain ischemic stroke (Országhová et al. 2021). Oxidative DNA damage has also been found in ageing and cancer treatment (Mandelblatt et al. 2013). DNA damage and diminished DNA repair are also a marker of senescence and are found in age-related diseases such as PD, AS, and mild cognitive impairment (Mandelblatt et al. 2013). DNA damage can trigger an inflammatory cytokine release, which in turn increases oxidative stress and further DNA damage (Mandelblatt et al. 2013). Some treatments such as specific chemotherapies (i.e. Cyclofosfamide Methotrexaat Fluorouracil (CMF)) cross the blood-brain barrier. Older patients are more likely to receive CMF treatments, as they are less toxic for the body, but may cause a higher risk of direct neurotoxicity (Mandelblatt et al. 2013). Telomeres shorten with each cycle of replication ultimately leading to senescence and apoptosis. Telomere length is a marker of cellular age and degree of senescence and telomere health is linked to ageing, AD, cancer risk and mortality. Certain cancer treatments influences telomere length, resulting in a common pathway between ageing and cancer related cognitive decline (Mandelblatt et al. 2013). Senescence cells are metabolically active but can no longer replicate. Many of the same pathways between ageing and cancer treatment can be seen as stressors that can lead to cell senescence (Mandelblatt et al. 2013). Treatment of cancer can negatively affect senescence (biological marker of ageing) by evoking an inflammatory response for example or through the P53 pathway which is associated with increased cell senescence (Ahles, 2012). Senescent cells are also a biomarker of the frailty phenotypes that could increase the risk of cognitive decline (Mandelblatt et al. 2013).

These pathways can also result in overlapping brain changes affected by cancer treatment, ageing and neurodegeneration. This includes decreases in brain volume, specifically the frontal cortex and regions around the central sulcus including the hippocampus, and white matter volume and density decreases (Mandeblatt et al. 2013). Changes in brain activation and connectivity such as decreased hypothalamus pituitary-adrenal axis activity, reduced brain vascularization and blood flow have also been found in both ageing and cancer survivors. (Mandelblatt et al. 2013; Mandelblatt et al. 2014). Thus, change in brain structure and function may be an effect of the interaction between cancer treatments and changes associated with ageing (Ahles, 2012). These brain changes are in return related to different self-reported and objectively assessed cognitive

dysfunction (Országhová et al. 2021). Abnormalities in the frontal and subcortical regions are related to abnormalities in working memory, executive functioning, and attention (Ponto et al. 2015; Yamada et al. 2010). Changes in hippocampus volume is related to memory changes (Mandelblatt et al. 2014). Basal ganglia and white matter changes are associated with psychomotor slowing (Yamada et al. 2010). Changes in the integrity of the corpus collosum is crucial for optimal brain function and cognition and changes in corpus collosum contribute to a decline in cognitive function and neurodegenerative disorders in ageing adults (Simó et al. 2016).

Interestingly, not all brain changes are related to cognitive effects measured by neuropsychological testing. Sometime no significant decline in function of elderly cancer patients was found but functional brain changes such as metabolic activity in areas of the brain was found because of treatment (Hurria, Patel et al. 2014). In some areas overactivation is even found in cancer patients which could provide evidence for the idea that the brain recruits compensatory regions of activation (alternate brain structures take over the role of de damaged areas to maintain the performance on neuropsychological testing). This explains why some patients perform within the normal range on neuropsychological testing but report subjective cognitive problems (Mandelblatt et al. 2014). This can also explain how cancer treatment and/ or age-associated changes in the brain ultimately results in the loss of the ability of compensatory activation when pretreatment an overactivation was seen as an attempt to compensate decreased brain resources (Ahles, 2012).

Not all cancer patients develop cognitive effects, a subgroup of patients does dependent on the different risk factors and interactions (such as treatment, age-related phenotypes, cognitive and overall reserve, comorbidities, genes, psychological and social factors, biomarkers and ageing processes) (Mandelblatt et al. 2013). It could be that individual vulnerability to various biological systems may make some people more vulnerable for cognitive deficits than others. Some people may be more susceptible to DNA damage while others may be more influenced by the impact of the hormonal milieu. This would mean that trajectories of cognitive decline are dependent on the individual reserve and susceptibility (Mandelblatt et al. 2013).

Psychological features of ageing

Elderly people are more likely to receive a cancer diagnosis as age is the most significant risk factor for cancer (Small et al., 2015). Dependent on the cancer type and age-related phenotype and genotype different treatments are used to treat these cancers. Younger people for example receive more chemotherapy than older people (Morin & Midlarsky, 2018b), as well as different types of chemotherapy used in the elderly population such as CMF (Mandelblatt et al. 2013).

The risk of cognitive impairment, dementia and delirium increases with age (Soto-Perez-de-Celis, Li, Yuan, Lau & Hurria, 2018). Although the effects of cancer and its treatment can have a larger impact in elderly, not all elderly cancer survivors have cognitive deficits, due to the multi-morbidity of older cancer patients. Therefor it is important that patients are evaluated regarding these comorbidities and physical functioning and psycho-social health to consider treatment options (Given & Given, 2008). When older patients have disabilities in physical function it is often related to loss of functional reserve which can increase the likelihood of toxic effects of treatment (Given & Given, 2008).

Older adults are less likely to receive the optimal dose of treatment due to these toxicities and complications (Given & Given, 2008). Certain treatment plans are not realistic for older people due to a need of home care, incomes, transportation, etc. These factors should also be considered when developing a treatment plan (Given & Given, 2008). Clinically fit older patients are more likely to have altered compensatory strategies (Libert et al. 2017). To evaluate whether elderly cancer patients can benefit from specific treatment plans, a multidimensional assessment must be done such as the Comprehensive Geriatric Assessment (CGA) (Given & Given, 2008; Karuturi et al. 2016). Cognitive function is included as a domain in the CGA and other age-related domains as well including comorbidity, function, physical performance, nutrition, emotional status, polypharmacy, social support and living environment, thus providing an estimate of active life expectancy and functional reserve (Soto-Perez-de-Celis, 2018). Here, special attention should be given to determining the level of frailty of the elderly patient (Given & Given, 2008). Older frailer adults can have more toxic effects of treatment and may recover slower cognitively (Karuturi et al. 2016). GCA includes a domain of cognitive function but does not provide a complete evaluation of cognitive capacities (Karuturi et

al. 2016). A good cognitive evaluation includes cognitive testing, patient observations and caregiver observations and is essential as dementia is often misdiagnosed (Karuturi et al. 2016; Soto-Perez-de-Celis, 2018).

A cancer diagnosis has a large impact on someone's social life. Elderly people are often more isolated and have decreased social activities due to health related or emotional problems. As older compared to younger cancer patients live alone, this provides an additional challenge as these elderly patients face loneliness and challenges such as needs of caregiver support, transportations, and home care (Soto-Perez-de-Celis, 2018). There is a relationship between social isolation and increased cancer mortality as well as poorer treatment tolerance (Soto-Perez-de-Celis, 2018).

Elderly cancer patients may have different psychological needs than younger survivors. Some quality-of-life measures are more appropriate and specifically designed for elderly cancer patients as their needs are different from younger patients (Garman & Cohen, 2002). Older and younger cancer patients perceive cancer and treatment differently as well. Older patients are more concerned with quality-of-life changes while younger patients experience anxiety related to death (Garman & Cohen, 2002). It is therefore very important to focus on maximizing quality of life and not only survival (Garman & Cohen, 2002). First, older patients experience more physical and comorbid conditions which could interfere or complicate treatment and recovery (Stanton, Franco & Scoggins, 2012). Fatigue is more common in elderly cancer patients and their expectations of the effects of cancer treatment may be different from younger patients (Stanton et al. 2012). The recovery goals or concerns may be different for elderly patients. Most concerns in elderly are regarding fatigue (and sleep disturbance) while those younger than 50 were most concerned with sleep disturbances, memory, and body image (Stanton et al. 2012). Depression and anxiety are prevalent in elderly patients with cancer but often remain undiagnosed (Soto-Perez-de-Celis, 2018). Psychological distress and impaired physical function are strongly associated with distress (Soto-Perez-de-Celis, 2018). Older people with cancer experience more depression but less anxiety than younger people. It is important to consider and evaluate the psychological state of elderly cancer patients as it can impact cancer treatment (Soto-Perez-de-Celis, 2018).

Gaps in research and future directions

This systematic literature review demonstrated that cancer diagnosis and treatment could have an adverse effect on cognition or neurodegeneration but is often dependent on individual risk factors. However, several challenges limit the comparison between studies. In evaluating the above conclusions these challenges and limitations should be considered. Not many studies focus specifically on the prevalence of CRCI in older patients with cancer. A common limitation in many studies was the relatively small sample size, raising questions on representativeness of the sample group in the general population. Another limitation was the homogenous populations chosen in some studies resulting in a selection bias. Many different cancer types were studied, and most studies used a population of breast and prostate cancer patients. Many different validated measures of cognitive function were used in different studies making it difficult to make a comparison. Some studies only used a single measure or did not research multiple domains of cognitive function limiting the results. Others only used self-reported measures of cognitive function. A combination of imaging, cognitive testing and subjective cognitive functioning gives the most information on the effects of cancer and treatment on cognition and neurodegeneration as some results may be very subtle. Not all studies described the different cancer treatments used and thus not all could assess the effect of treatment on cognition. Most studies used patients who received multiple treatments making it difficult to conclude which treatment had which effect. Some studies used lacked a control group, making it difficult to compare to the general healthy population. As many studies were prospective, a survival bias also exists is these studies. Different measurement times and treatment durations made it difficult to compare the short- and long-term effects of treatment. No validated or approved tests specifically measured CRCI and some measurement tools lacked sensitivity. Not all studies had the same criteria for cognitive dysfunction and screening tests did not always appear sensitive enough to objectively identify cognitive impairment or self-reported changes. Not all studies made a clear distinction of survivorship. An example of this is studies researching the effects of hormonal therapies. These treatments are given for years and the question remains whether the use of hormonal therapies should be seen as a form of active treatment because this could change the meaning of survivorship. A clearly defined cut-off and definition is an important factor in analyzing the effects of cancer and treatment

in survivorship. In our analysis the cut-off was made at 6 months post-treatment or 1-year post-diagnosis when no information on the end of treatment was available or when hormonal therapies were used.

Future studies on the neurocognitive and neurodegenerative impact of cancer treatment should include sufficient numbers of older patients in order to capture variability in reserve and frailty and to bring to light the effects of different treatments, biological processes and other chronic comorbidities. To do so it will be important to assess baseline cognitive function and other comorbidities by possibly using the GCA and using abbreviated cognitive measures to minimize the impact of fatigue. This could bring to light frailer adults that need closer monitoring and intervention and those who might be at risk for neurotoxic effects of treatment. The batteries used to test cognitive function after treatment, to assess the biomarkers as well as subjective cognitive impact should have a predictive value and should identify subgroups of older patients that are at higher risk for cognitive decline after treatment. Research on treatments that have less toxic impact on elderly patients and provide more quality of life are essential as well. For those patients that do experience cognitive decline and neurodegeneration, rehabilitations and interventions should be created to support these cognitive losses. Through the understanding of specific risk factors for cognitive deficits in elderly cancer patients, and by understanding the link between cancer treatment and the ageing process, tools could be developed to identify patients more at risk for accelerated ageing, neurodegeneration, or cognitive dysfunctions.

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Appendix A

Overview of searches in the search enginges

1. Search engine: Pubmed

- *Databases*: MEDLINE®, PubMed Central (PMC)
- *Replica of the search*:
  [Neoplasm] *and* TITLE
  [Neurocognition OR neurodegeneration] *and* TITLE/ABSTRACT
  [Elderly] TITLE/ABSTRACT
  Limit: "2000 to 2021
  Limit: "languages: English"
  Limit: "Species: Humans"
- *Number of hits from the search*: 2813

2. Search engine: WoS: Web Of Science

- *Databases*: Web of Science Core Collection 1955-present
- *Replica of the search*:
  [Neoplasm] *and* TITLE
  [Neurocognition OR neurodegeneration] *and* TOPIC
  [Elderly] TOPIC
  Limit: "2000-01-01 to 2021-06-12"
  Limit: "document types: Articles"
  Limit: "languages: English"
  Limit: "Not: Web of Science Index: Emerging Sources Citation Index (ESCI) or Book Citation Index - Social Sciences and Humanities (BKCI-SSH) or Book Citation Index - Science (BKCI-S) or Index Chemicus (IC)"
- *Number of hits from the search*: 5925

Appendix B
Detailed Search String Pubmed

Pubmed

(Neoplasms[Mesh] **OR** neoplas*[ti] **OR** cancer[Mesh] **OR** cancer*[ti] **OR** tumor*[ti] **OR** tumour*[ti] **OR** oncolog*[ti] **OR** "cancer survivors"[Mesh] **OR** glioma*[ti] **OR** Psycho-oncology[Mesh] **OR** psycho-oncolog*[ti] **OR** sarcoma*[ti] **OR** osteosarcoma*[ti] **OR** rhabdomyosarcoma*[ti] **OR** meningeoma*[ti] **OR** leukem*[ti] **OR** AML[ti] **OR** CLL[ti] **OR** CML[ti] **OR** lymphoma*[ti] **OR** melanoma*[ti] **OR** carcinoma*[ti] **OR** germinoma*[ti] **OR** blastoma*[ti] **OR** retinoblastoma*[ti] **OR** neuroblastoma*[ti] **OR** medulloblastoma*[ti] **OR** astrocytoma*[ti] **OR** ependymoma*[ti] **OR** craniopharyngioma*[ti] **OR** chordoma*[ti] **OR** ATRT*[ti] **OR** papilloma*[ti] **OR** neurofibroma*[ti] **OR** non-rhabdomyosarcoma*[ti] **OR** leiomyosarcoma*[ti] **OR** liposarcoma*[ti] **OR** angiosarcoma*[ti] **OR** fibrosarcoma*[ti] **OR** neurofibrosarcoma*[ti] **OR** myosarcoma*[ti] **OR** kaposisarcoma*[ti] **OR** dermatofibrosarcoma*[ti] **OR** chondrosarcoma*[ti] **OR** chemotherap*[ti] **OR** "cranial radiotherap*"[ti] **OR** "cranial irradiation*"[ti] **OR** "cranial radiation*"[ti] **OR** "androgen deprivation*"[ti] **OR** "chemical castration*"[ti] **OR** "androgen block*"[ti] **OR** ADT[ti] **OR** "hormone therap*"[ti] **OR** immunotherap*[ti]) **AND** ("Demyelinating diseases"[Mesh:noexp] **OR** demyelinat*[tiab] **OR** leukoencephalopath*[tiab] **OR** "neurobehavioral manifestations"[Mesh] **OR** "neurological symptom*"[tiab] **OR** neurobehavior*[tiab] **OR** agraphia[tiab] **OR** anomia[tiab] **OR** dyslexi*[tiab] **OR** "speech defic*"[tiab] **OR** "speech disorder*"[tiab] **OR** "speech problem*"[tiab] **OR** "speech disabilit*"[tiab] **OR** "speech dysfunction*"[tiab] **OR** "speech function*"[tiab] **OR** dyscalculi*[tiab] **OR** delirium[tiab] **OR** "mental disabilit*"[tiab] **OR** "mental defic*"[tiab] **OR** "mental retard*"[tiab] **OR** amnesia[Mesh] **OR** amnesia[tiab] **OR** agnosia[tiab] **OR** hallucination*[tiab] **OR** "psychomotor defic*"[tiab] **OR** "psychomotor problem*"[tiab] **OR** "psychomotor disabilit*"[tiab] **OR** "psychomotor dysfunction*"[tiab] **OR** "psychomotor symptom*"[tiab] **OR** "psychomotor function*"[tiab] **OR** apraxia[tiab] **OR** "nervous system disorder*"[tiab] **OR** "brain function*"[tiab] **OR** "brain dysfunction*"[tiab] **OR** "brain disorder*"[tiab] **OR** encephalopath*[tiab] **OR** "auditory defic*"[tiab] **OR** "auditory disorder*"[tiab] **OR** "auditory problem*"[tiab] **OR** "auditory disabilit*"[tiab] **OR** "auditory dysfunction*"[tiab] **OR** "auditory function*"[tiab] **OR** "auditory symptom*"[tiab] **OR** "language defic*"[tiab] **OR** "language disorder*"[tiab] **OR** "language problem*"[tiab] **OR** "language disabilit*"[tiab] **OR** "language dysfunction*"[tiab] **OR** "language symptom*"[tiab] **OR** "language function*"[tiab] **OR** aphasia[tiab] **OR** visuoconstruct*[tiab] **OR** visuopercept*[tiab] **OR** neurodegenerat*[tiab] **OR** neurotoxic*[tiab] **OR** neurocognit*[tiab] **OR** neuropsychology[Mesh] **OR** neuropsych*[tiab] **OR** neuro-psych*[tiab] **OR** cognition[Mesh] **OR** cognition*[tiab] **OR** cognitive*[tiab] **OR** "cognition disorder*"[Mesh] **OR** "cognitive reserve"[Mesh] **OR** "executive function*"[tiab] **OR** neurolinguistic*[tiab] **OR** "problem solving"[tiab] **OR** "spatial navigat*"[tiab] **OR** "neurocognitive disorders"[Mesh] **OR** "mental disorder"[tiab] **OR** "mental proces*"[tiab] **OR** "dissociative disorders"[Mesh] **OR** "dissociative disorder*"[tiab] **OR** mental-deterioration*[tiab] **OR** "mental deterioration*"[tiab] **OR** higher-cerebral-function*[tiab] **OR** "cognitive neuroscience"[Mesh] **OR** CRCI[tiab] **OR** "Chemotherapy-Related Cognitive Impairment"[Mesh] **OR** "cognitive dysfunction"[Mesh] **OR** "Chemo Brain"[Tiab]

OR Chemobrain[Tiab] **OR** “Chemo fog”[Tiab] **OR** Chemo-fog[Tiab] **OR** “Postoperative Cognitive Complications”[Mesh] **OR** dementia[Mesh] **OR** dement*[tiab] **OR** memory[Mesh] **OR** memory[tiab] **OR** “memory disorders”[Mesh] **OR** attention[Mesh] **OR** “attention defic*”[tiab] **OR** “attention disorder*”[tiab] **OR** “attention problem*”[tiab] **OR** “attentional disabilit*”[tiab] **OR** “attention dysfunction*”[tiab] **OR** “attention symptom*”[tiab] **OR** “attention function*”[tiab] **OR** “executive defic*”[tiab] **OR** “executive disorder*”[tiab] **OR** “executive problem*”[tiab] **OR** “executive disabilit*”[tiab] **OR** “executive dysfunction*”[tiab] **OR** “executive symptom*”[tiab] **OR** “executive function*”[tiab] **OR** “executive function”[Mesh] **OR** “verbal fluenc*”[tiab] **OR** “processing speed*”[tiab] **OR** “brain damage*”[tiab] **OR** “brain injur*”[tiab] **OR** “neurofibrillary tangle*”[tiab] **OR** tauopathies[Mesh] **OR** tauopath*[tiab] **OR** “amyloid*”[tiab] **OR** “neurofilament*”[tiab] **OR** “cerebrovascular disorder*”[tiab] **OR** “cerebrovascular disease*”[tiab] **OR** “brain ischemia*”[tiab] **OR** “cerebral ischemia*”[tiab] **OR** “brain hypoxia*”[tiab] **OR** “cerebral hypoxia*”[tiab] **OR** “brain infarction*”[tiab] **OR** “ischemic attack”[tiab] **OR** “intracranial embolism*”[tiab] **OR** “intracranial thrombosis”[tiab] **OR** leukomalacia[tiab]) **AND** (elderly[tiab] **OR** ageing[tiab] **OR** aging[tiab] **OR** postmenopausal[tiab] **OR** post-menopausal[tiab] **OR** "older age*"[tiab] **OR** "old age*"[tiab] **OR** "older adult*"[tiab] **OR** "older patient*"[tiab] **OR** "older survivor*"[tiab] **OR** "older participant*"[tiab] **OR** "older population*"[tiab] **OR** "older men"[tiab] **OR** "older women"[tiab] **OR** "older cohort*"[tiab])

Web of Science (WoS)

TI=(Neoplas* **OR** cancer* **OR** tumor* **OR** tumour* **OR** oncolog* **OR** glioma* **OR** psycho-oncolog* **OR** sarcoma* **OR** osteosarcoma* **OR** rhabdomyosarcoma***** **OR** meningeoma* **OR** leukem* **OR** AML **OR** CLL **OR** CML **OR** lymphoma* **OR** melanoma* **OR** carcinoma* **OR** germinoma* **OR** blastoma* **OR** retinoblastoma* **OR** neuroblastoma* **OR** medulloblastoma* **OR** astrocytoma* **OR** ependymoma* **OR** craniopharyngioma* **OR** chordoma* **OR** ATRT* **OR** papilloma* **OR** neurofibroma* **OR** non-rhabdomyosarcoma* **OR** leiomyosarcoma* **OR** liposarcoma* **OR** angiosarcoma* **OR** fibrosarcoma* **OR** neurofibrosarcoma* **OR** myosarcoma* **OR** kaposisarcoma* **OR** dermatofibrosarcoma* **OR** chondrosarcoma* **OR** chemotherap* **OR** “cranial radiotherap*” **OR** “cranial irradiation*” **OR** “cranial radiation*” **OR** “androgen deprivation*” **OR** “chemical castration*” **OR** “androgen block*” **OR** ADT **OR** “hormone therap*” **OR** immunotherap*) AND TS=(demyelinat* **OR** leukoencephalopath***** **OR** “neurological symptom*” **OR** neurobehavior* **OR** agraphia **OR** anomia **OR** dyslexi* **OR** “speech defic*” **OR** “speech disorder*” **OR** “speech problem*” **OR** “speech disabilit*” **OR** “speech dysfunction*” **OR** “speech function*” **OR** dyscalculi* **OR** delirium **OR** “mental disabilit*” **OR** “mental defic*” **OR** “mental retard*” **OR** amnesia **OR** agnosia **OR** hallucination* **OR** “psychomotor defic*” **OR** “psychomotor problem*” **OR** “psychomotor disabilit*” **OR** “psychomotor dysfunction*” **OR** “psychomotor symptom*” **OR** “psychomotor function*” **OR** apraxia **OR** “nervous system disorder*” **OR** “brain function*” **OR** “brain dysfunction*”[tiab] **OR** “brain disorder*” **OR** encephalopath* **OR** “auditory defic*” **OR** “auditory disorder*” **OR** “auditory problem*” **OR** “auditory disabilit*” **OR** “auditory dysfunction*” **OR** “auditory function*” **OR** “auditory symptom*” **OR** “language defic*” **OR** “language disorder*” **OR** “language problem*” **OR** “language disabilit*” **OR** “language

dysfunction*” **OR** “language symptom*” **OR** “language function*” **OR** aphasia **OR** visuoconstruct* **OR** visuopercept* **OR** neurodegenerat* **OR** neurotoxic* **OR** neurocognit* **OR** neuropsych* **OR** neuro-psych* **OR** cognition* **OR** cognitive* **OR** “executive function*” **OR** neurolinguistic* **OR** “problem solving” **OR** “spatial navigat*” **OR** “mental disorder” **OR** “mental proces*” **OR** “dissociative disorder*” **OR** mental-deterioration* **OR** “mental deterioration*” **OR** higher-cerebral-function* **OR** CRCI **OR** “Chemo Brain” **OR** Chemobrain **OR** “Chemo fog” **OR** Chemo-fog **OR** dement* **OR** memory **OR** “attention defic*” **OR** “attention disorder*” **OR** “attention problem*” **OR** “attentional disabilit*” **OR** “attention dysfunction*” **OR** “attention symptom*” **OR** “attention function*” **OR** “executive defic*” **OR** “executive disorder*” **OR** “executive problem*” **OR** “executive disabilit*” **OR** “executive dysfunction*” **OR** “executive symptom*” **OR** “executive function*” **OR** “verbal fluenc*” **OR** “processing speed*” **OR** “brain damage*” **OR** “brain injur*” **OR** “neurofibrillary tangle*” **OR** tauopath* **OR** “amyloid*” **OR** “neurofilament*” **OR** “cerebrovascular disorder*” **OR** “cerebrovascular disease*” **OR** “brain ischemia*” **OR** “cerebral ischemia*” **OR** “brain hypoxia*” **OR** “cerebral hypoxia*” **OR** “brain infarction*” **OR** “ischemic attack” **OR** “intracranial embolism*” **OR** “intracranial thrombosis” **OR** leukomalacia) **AND** TS=(elderly **OR** ageing **OR** aging **OR** postmenopausal **OR** post-menopausal **OR** "older age*" **OR** "old age*" **OR** "older adult*" **OR** "older patient*" **OR** "older survivor*" **OR** "older participant*" **OR** "older population*" **OR** "older men*" **OR** "older women*" **OR** "older cohort*")

Appendix C

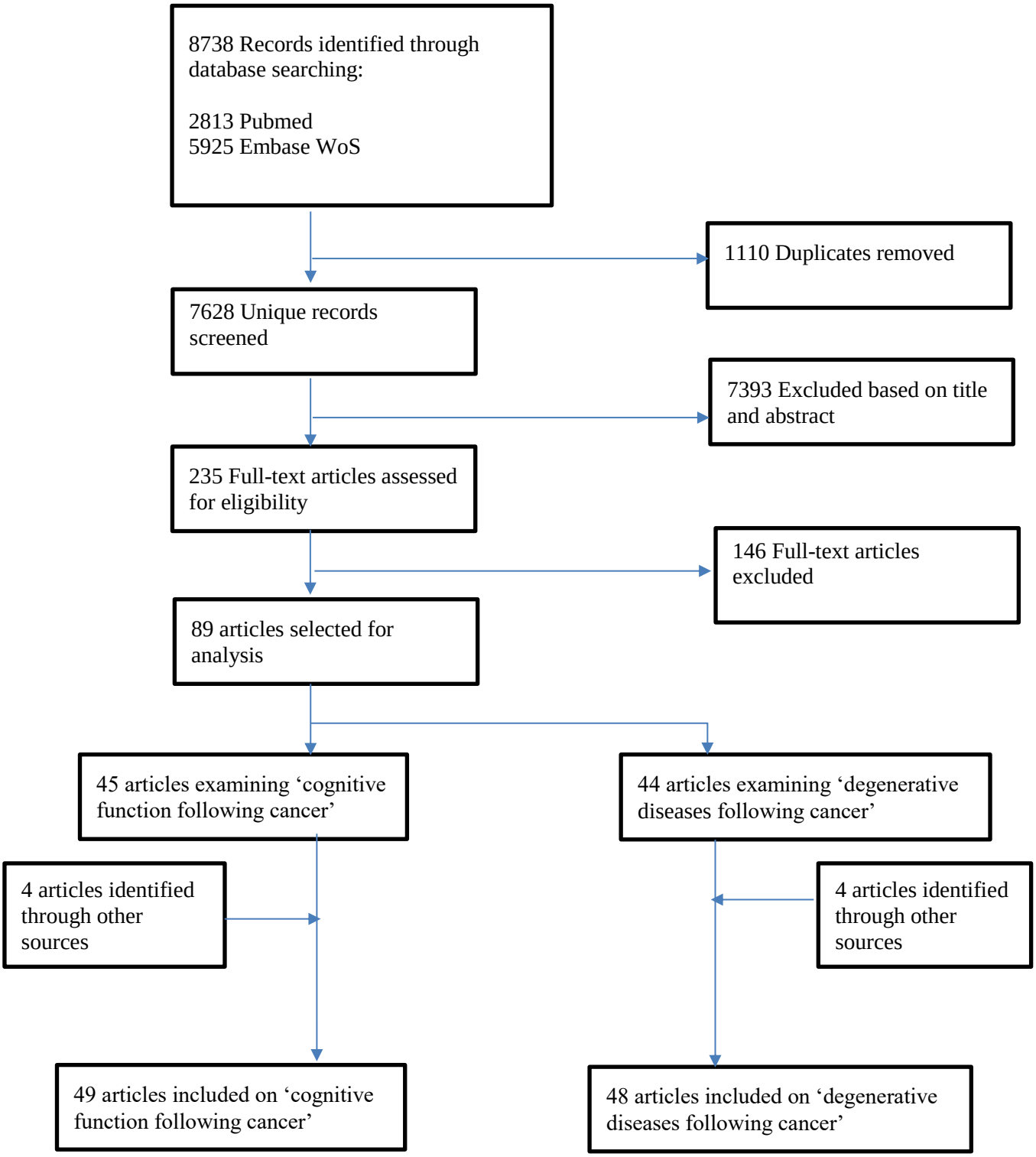

Fig. 3 PRISMA flow chart for study inclusion

Appendix D

Table 1. *Overview of cognitive function in elderly cancer survivors according to the systematic literature review*

Source	Design	Country	Cancer subtype	Study-Period	Treatment types (Tx)	Comparison group	Participants, No	Mean age at Dx (yrs)	Mean age at baseline (yrs)	Measurement times	Measurement	Main findings
IMAGING STUDIES												
Ernst et al. 2002	CS	US	Breast; Other	N.A.	Surgery; Tamoxifen; Estrogen	Tamoxifen; Estrogen; Healthy control	16 Tamoxifen; 27 Estrogen; 33 controls	N.A.	70.4 Tamoxifen; 71.5 Estrogen; 71.8 controls	≥2 years post-Tx	*Imaging* MRI H MRS Cerebral concentration of: -N-acetyl-containing (NA) compounds -Myo-inositol (MI); -Total creatine (CR); -Choline-containing compounds (CHO) *Neuropsychological test* MMSE DSST TMT part A	- Tamoxifen or estrogen use resulted in significantly lower concentrations of MI in the brain, specifically basal ganglia - Longer duration of tamoxifen resulted in lower MI concentrations - No difference in the concentration of NA, CR and CHO between tamoxifen, estrogen or no drug Tx - No differences between groups on the neurocognitive tests
Nudelman et al. 2014	CS	US	All	2003	No Tx information	Cancer; Healthy control	503; 1106 controls	N.A.	71-77	5 years post-Dx	*Imaging* MRI *Subjective measures* Subject, informant & clinician report memory concerns; Cognitive assessment by a physician; CDR *Neuropsychological tests* WMS-R Logic Memory II; MMSE	- Cancer history is associated with a delay in AD onset independent of ApoE ε4 - NMSC was a significant driver effect - Two prior cancers was associated with later mean age of AD onset (additive effect) - Prior cancer was associated with lower GMD in the right superior frontal gyrus, driven by history of cancer types.
Ponto et al. 2015	CS	US	Breast	N.A.	Chemotherapy; Chemo-RT	Cancer; Healthy control	10; 10 controls	>50	73.7; 75.1 controls	≥10 years survival	*Imaging* MRI; FDG PET imaging *Neuropsychological test* WMI-total; TMT part B; ROCF MMSE	- No survivors and one control had a global PET score consistent with AD metabolic pattern - Hypometabolism in orbital frontal regions & hypermetabolism in the left postcentral gyrus in survivors - Lower scores in executive functioning, working memory, and attention in survivors
Sharma et al. 2020	CS	Denmark	Sinonasal	2008-2016	Chemotherapy; RT & dosage; Surgery	No control group	27	N.A.	*67	≥ 1.6 years post-Tx	MRI; Other neuropsychological tests not described	- 11% had structural abnormalities in irradiated areas of the brain - 63% had impaired cognitive function
Simó et al. 2016	PR	Spain	SCLC	2005-2010	Platinum based chemo; PCI	Cancer; Healthy control	11; 11 controls	N.A.	*65	2 - 10 years post-Dx	*Imaging* MRI *Neuropsychological test* MDRS-2; WAIS-III Vocabulary; WAIS-III Digit Span; BNT; VFT (phonemic, semantic); TMT part A & B; ROCF; AVLT	- Decrease in GMD mainly in bilateral basal gangia, (thalamus, right insula) - Decreased white matter integrity in the corpus collosum - Strong association between cognitive deterioration and white matter changes in corpus collosum in survivors - 45% of survivors met the criteria for cognitive impairment - No significant difference in terms of PCI dose or time since Tx
COGNITIVE TESTING												
Alibhai et al. 2010	PR	Canada	Prostate	2004-2007	ADT	Cancer; Healthy control	77 ADT-users; 82 non-ADT users; 82 controls	69.3 ADT-users; 69.6 non-ADT users; 67.9 controls	N.A.	Baseline; 6 months; 12 months	Digit Span forward & backward Spatial Span forward & backward TMT part A & B; COWAT; Animal Fluency; Card Rotations; Judgement of Line Orientation; CVLT; Spatial Working Memory Task Errors; Conditional Associative Learning Test; D-KEFS Color Word Interference Test; NART	- No consistent evidence that 12 months of ADT use had adverse effect on cognitive function

Alibhai et al. 2017	PR	Canada	Prostate	2004-2007	ADT	Cancer; Healthy control	77 ADT users; 82 non-ADT users; 82 controls	69.3 ADT users; 69.6 non-ADT users; 67.9 controls	N.A.	Baseline; 6 months; 12 months; 24 months; 36 months	Digit Span forward & backward Spatial Span forward & backward TMT part A & B; COWAT; Animal Fluency; Card Rotations; Judgement of Line Orientation; CVLT; Spatial Working Memory Task Errors; Conditional Associative Learning Test; D-KEFS Color Word Interference Test	- Ongoing use of ADT for up to 36 months was not associated with cognitive decline
Almeida, Waterreus, Spry, Flicker, & Martins 2004	PR	Australia	Prostate	N.A.	ADT	No control group	40	72.4	N.A.	(Baseline); 4 weeks; 8 weeks; 12 weeks; 24 weeks; 36 weeks (stop-Tx); 42 weeks; 48 weeks; 54 weeks	CAMCO-G; WMS-III Word List; WMS-III Verbal Paired Associated; WMS-III Visual Reproduction; WAIS-III Block Design	- Discontinuation of Tx is associated with better cognitive performance, specifically verbal memory - Chemical castration (hormonal supression & testosterone blockade) is associated with rise in plasma levels of Aβ, and increased depression and anxiety
Alonso Quiñones, Stish, Hagen, Petersen & Mielke 2020	CS	US	Prostate	2004-2018	RT; ADT (& length); Surgery	Cancer; Healthy control	349; 2164 controls	N.A.	73.1	Cancer history	AVLT Delayed Recall; WMS-R logical Memory II; WMS-R Visual Reproduction II; BNT; VFT (Semantic); TMT part B; WAIS-R Digit Symbol; WAIS-R Picture Completion; WAIS-R Block Design	- No association between prostate cancer and odds of mild cognitive impairment - No association between history of ADT use, including length of exposure, and odds of mild cognitive impairment
Alonso-Quiñones et al. 2021	PR	US	Prostate	2004	ADT	ADT use; No ADT use	20 ADT users ≥5; 47 ADT users <5; 174 non-ADT users	*70	*78	Every 15 months, median 4 years	Physician examination; Interview (Participant and informant CDR) Neuropsychological battery (9 tests)	- No association between history of ADT use and risk of mild cognitive impairment. - Potential association between long-term ADT use (5+ years) and risk of mild cognitive impairment
Anstey, Sargent-Cox, Cherbuin & Sachdev 2015	CS	Australia	All	N.A.	Chemotherapy; RT; Surgery	Cancer; Healthy control	81 chemotherapy; 306 no chemo; 1562 controls;	N.A.	70.58 chemotherapy; 70.75 no chemo; 70.58 controls	Tx ≥8 years ago; Tx 1 - 8 years ago	Spot-the-Word; SDMT; CVLT; WMS Digits Backwards; SRT CRT; TMT part B; Name as many words with letter "F" & "C"	- Chemotherapy at least 8 years ago is associated with faster decline in memory in late life - Chemotherapy between 1 and 8 years ago was associated with slower processing speed time
Buckwalter, Crooks & Petitti 2005	CS	US	All (excluded skin)	1998	No Tx information	Cancer; Healthy control	541; 3123 controls	N.A.	≥74	Dx hospitalization ≥5 years; Dx hospitalization <5 years	TICS-m	- No association of cancer history with poorer cognitive function - No differences between women with or without a history of cancer in delayed verbal memory
Cruzado et al. 2014	PR	Spain	Colon	2009-2011	Chemotherapy; Surgery	No control group	81 pre-chemo; 73 post-chemo; 54 6-months post-chemo	66.96	N.A.	Pre-Tx; Post-Tx; 6 months post-Tx	LMWT; WAIS-R Digit Symbol; TMT part A & B; SCWT; Barcelona Test Verbal Memory subtest	- Adjuvant FOLFOX4 can have negative effect on verbal memory => 54% improving, 33% worsening 6 months after Tx - Cognitive impairment was most common in older patients and those with less years of education.
Deschler, Ihorst, Hüll & Baier 2019	PR	Germany	Gastrointestinal; Pancreatic; Retroperitoneal sarcomas	N.A.	Neo-adjuvant Tx; Surgery	No control group	195	N.A.	*75	T1 (pre-surgery); T2 (at discharge); T3 (3 months post-Tx); T4 (6 months post-Tx)	MMSE	- No cognitive decline 6 months post-surgery
Di Cristofori et al. 2018	PR	Italy	Meningioma	2011-2017	Surgery	No control group	41	N.A.	*74	T1 (pre-Tx); T2 (3 months post-Tx); T3 (12 months post-Tx)	Token test; Naming of object; Corsi span; AVLT; Attentional Matrices Test; SCWT; Digit Span Backward; VFT (Phonemic); Weigl Test; RPM; ROCF or MTCF; Ideomotor apraxia	- Global improvement of cognitive function between pre-operative assessment and 12 months post-surgery - 3 patterns: fast recovery, late recovery & progressive recovery - Fast recovery: denomination & non-verbal intelligence - Late recovery: sustained atention & constructional praxis - 50% showed deficit in visuospatal & executive functioning 12 months after surgery => longer recovery needed - At 12 months 27.4% of patients had complete cognitive recovery, 7.7% no recovery, 64.9% partial recovery
Gonzalez et al. 2015	PR	US	Prostate	2008-2013	ADT; Prostatectomy	Cancer; Healthy control	58; 84 Prostatectomy; 88 controls	N.A.	67.31; 67.72 Prostatectomy; 69.10 controls	Baseline (start ADT); After 6 months; 12 months	HVLT-R (total recall & delayed recall); WMS-III Logical Memory II; WMS-III Digit Span; WMS-III Spatial Span; BVMT-R (total recall & delayed recall); SCWT; SDMT Items Completed; COWAT; TIADL; NART Full-Scale IQ	- ADT resulted in impaired cognitive performance within 12 months compaired to control or prostatectomy - ADT performed at an impaired level on executive function

Heflin et al. 2005	CS	Sweden	All (excluded brain)	N.A.	No Tx information	Cancer; Healthy control (Co-twin design)	702; 702 twin controls	N.A.	74.9	<1 year post-Dx; 1-5 years post-Dx; ≥5 years post-Dx	Telephone cognitive screening (unable or poor score on cognitive screening then BDRS); if score 3 Dementia screening using Diagnostic and Statistical Manual-IV criteria	- Long-term survivors presented higher rates of cognitive dysfunction than their respective twin; - Cancer survivors were twice as likely to be diagnosed with dementia as their co-twin (not significant).
Hoogland et al. 2021	PR	US	Prostate	2008-2013	RT; ADT; Brachytherapy	Cancer; Healthy control	47; 82 controls	N.A.	67.6; 68.4 control	Baseline (start ADT); 6 months; 12 months	HVLT-R (total recall & delayed recall); WMS-III Logical Memory II; WMS-III Digit Span; WMS-III Spatial Span; BVMT-R (total recall & delayed recall); Color Trails 1 & 2; SDMT Items Completed; COWAT; TIADL; NART Full-Scale IQ	- ADT resulted in stable rates of cognitive impairment, whereas control group improved over 12 months - IL-6 levels, fatique and depressive symptoms increased significantly in ADT group over 12 months - No relationship between ADT-related inflammation and cognitive impairment or depressive symptomatology
Hurria, Rosen et al. 2006	PR	US	Breast	2001-2003	Chemotherapy (CMF, AC, ACT); Hormonal therapy	No control group	28	71	N.A.	Pre-Tx; 6 months post-Tx	WRAT-III, reading subtest; BNT; COWAT; HVLT-R (total recall & delayed recall); RCFT (copy, immediate, delayed recall); WAIS III Block Design; WAIS III Digit Symbol; SCWT; TMT Part A & B; MMSE	- 39% experiences decline in cognitive function from before to 6 months after chemotherapy - Most affected: visual memory, spatial function, psychomotor function and attention
Jenkins, Bloomfield, Shilling & Edginton 2005	PR	UK	Prostate	N.A.	LHRH agonist; RT	Cancer; Healthy control	32; 18 controls	67.5; 65.4 controls	N.A.	T1 (Baseline, pre-Tx); T2 (Post-Tx, before RT); T3 (9 months after RT)	Semi-structured interviews; NART; VFT (phonetic); AVLT (supraspan & delayed); RCFT (immediate, delayed, processing speed); Mental Rotation (speed & accuracy); WMS III Digit-span task; WMS III Spatial Span-Task; KDCT	- After LHRH therapy declines on tasks of spatial memory and ability were seen most often - No correlation between decrease in bioavailable testosterone and cognitive performance 9 months after Tx - 25% considered that their memory had become worse after 9 months of Tx
Konglund et al. 2013	PR	Norway	Meningioma	2008-2009	Surgery	No control group	47	*70	N.A.	Pre-Tx; 6 months post-Tx	MMSE	- Significant improvement in cognitive function 6 months post surgery
Kurita, Meyerowitz, Hall & Gatz 2011	CS	Sweden	All (excluded skin & brain)	1998-2001	Chemotherapy; Hormone therapy; RT; Surgery	Cancer; Healthy control (Co-twin design)	415; 415 twin controls	61.9	73.3	≥3 years post-Dx & Tx	Telephone cognitive screening (unable or poor score on cognitive screening than BDRS)	- Female but not male cancer survivors were more likely to have cognitive impairment than respective twin; - Female survivors who had RT and/or surgery, had increased risk for cognitive impairment compared to those receiving chemotherapy - Risk was higher among survivors of gynecologic cancers and those with Tx affecting ovarian functioning
Kvale et al. 2010	PR	US	Breast, prostate, colorectal, lymphoma, bladder, uterine, head & neck, ovarian, MM, breast/uterine, breast/colon, breast/cervical/ ovarian	1998-1999	Chemotherapy	Cancer; Healthy control	37; 37 controls	N.A.	76.04; 75.81 controls	Post-Tx around 2 years	UFOV; WAIS Digit Symbol Substitution; RST; TIADL	- Chemotherapy has negative impact on cognitive processing speed. - Poor performance and increased age at baseline were each associated with slow processing speed post-chemotherapy
La Carpia et al. 2020	CS	Italy	NHL	2016-2017	Chemotherapy; RT; Surgery; Human stem cells transplantation	Cancer; Healthy control	63; 61 controls	N.A.	74.2; 74.3 controls	≥5 years post-Tx	MMSE; RAVLT; RPM 47; Digit span; Corsi span; Copying drawings (with landmarks); ROCF; VFT (phonetic, semantic) Nouns naming test; Verbs naming test; SCWT, MFTC; TMT part A & B	- Survivors had lower cognitive performance, especially in executive functioning and attention domains
Legault et al. 2009	PR	US & Canada	Breast	2001-2006	Tamoxifen; Raloxifene	Tamoxifen; Raloxifene	733 Tamoxifen; 765 Raloxifene	70.1 Tamoxifen; 69.7 Raloxifene	N.A.	Baseline; 1 Years; 2 Years	3MS; PMA-V; VFT (phonetic, semantic); BVRT; CVLT; Digits span (forward & backward); Card rotation; Finger tapping	- Tamoxifen and raloxifene are associated with similar patterns of cognitive function.
Lombardi et al. 2018	PR	Italy	Glioblastoma	2013-2015	RT; Temozolomide; Surgery	No control group	35	≥65	N.A.	1 month; 3 months; 6 months; 9 months after RT	MMSE	- Significant lower cognitive score for patients older than 65 years old at 9 months after RT

Mandelblatt et al. 2018	PR	US	Breast	2010-2015	Chemotherapy; Hormonal therapy; Surgery	Cancer; Healthy control	344; 347 controls; 94 chemo +/- hormonal; 237 hormonal only	N.A.	68.1; 67.8 controls	12 months; 24 months post-Dx	TMT Part A & B; NAB Digits (forward & backwards); NAB list A (immediate, short & long delay) COWAT; DSST; Logical memory I & II *Subjective measure* FACT-cog questionnaire	- Survivors (especially with ApoE ε4) exposed to chemotherapy had lower longterm attention, processing speed, and executive function (& self-reported cognition scores) - Hormonal therapy resulted in short-term lower learning & memory, effect confined to those with the ApoE ε4 allele - Self-reported cognition was significantly associated with cognitive tests - Chronological age & aging phenotypes (frailty) were associated with lower baseline attention, processing speed, & executive function & self-reported cognition
Minniti et al. 2013	PR	Italy	Brain metastases	2007-2011	Stereotactic radiosurgery	No control group	102	N.A.	*77	Baseline; 6 months; 12 months post-Tx	MMSE	- No significant decline in neurocognitive function after stereotactic radiosurgery - Neurological complications (seizures, motor & speech deficits, confusion) were reported in 13% of patients
Moon et al. 2014	CS	South Korea	DTC	2003-2008	THS-supressive therapy	Cancer; Healthy control	50; 90 controls	N.A.	70.9 70.5 controls	≥ 5 years post-Tx	*CERAD-K-N* VFT; BNT; MMSE; Word List (memory, recall, recognition); Constructional Praxis Recall Test; TMT part A & B; FAB-K; Digit Span (backward & forward)	- Cognitive function of elderly DTC patients under a long-term TSH suppressive therapy are not impaired - Higher serum free T4 levels resulted in better scores on some cognitive domains => potential benefit of exogenous levothyroxine on cognitive function of patients who lack endogenous thyroid hormone
Morin & Midlarsky 2018a	PR	US	All	1992-2012	Chemotherapy; RT; Surgery	No control group	403	76.15	N.A.	T1 (2 years before Dx); T2 (Dx); T3 (2 year post-Dx); T4 (4 years post-Dx)	Total recall (Immediate & delayed)	- Three classes of cognitive functioning best fit the data: High (18%), Middle (52%) and Low recall (30%) - Fairly stable trajectories from pre-diagnosis to four years after diagnosis - More depressive symptoms after diagnosis significantly predicted membership to the Low Recall Class - Older age, male gender & fewer years of education were predictive of membership to the Low Recall Class
Morin & Midlarsky 2018b	PR	US	All	1992-2012	Chemotherapy; RT; Surgery	No control group	403	76.15	N.A.	T1 (2 years before Dx); T2 (Dx); T3 (2 year post-Dx); T4 (4 years post-Dx)	Total recall (immediate & delayed)	- None of the Tx predicted membership to the low recall class - Tx with chemotherapy predicted likely membership in the high recall class, due to age x Tx interaction - Patients younger than 80 were more likely to receive chemotherapy and have high recall cognition
Ospina-Romero et al. 2019	PR	US	All (excluded NMSC)	1998-2014	No Tx information	Cancer; Healthy control	2250; 12 333 controls	71.7	N.A.	Baseline (before Dx); Follow-up	Immediate & delayed recall of a 10-word list (proxy assessment if individual was too impaired)	- Older individuals who developed cancer had better memory and slower memory decline than cancer free individuals - Possibility of a common pathologic process in opposite directions in cancer and AD
Paganini-Hill & Clark 2000	PR	US	Breast	1987-1996	Chemotherapy; Tamoxifen (& length); RT	Tamoxifen; No tamoxifen	710 tamoxifen; 453 no tamoxifen	*60-64	*69	≥1 year post-Dx	Clock Drawing; Box Copying Task (Necker Cube); Narrative writing Task *Subjective measure* Survey	- Tamoxifen use for standard term or longer resulted in increase physician visits for memory problems. Especially true for current users - Current use of tamoxifen adversely effects cognition
Porter 2013	CS	US	All (excluding skin)	2006	Chemotherapy; RT; Surgery; Other Tx	Cancer; Healthy control	1270; 8312 controls	N.A.	74.8	≥2 years post-Dx	Word list (immediate, delayed recall, recognition) Naming the date, day, (vice)president; Counting backwards; Serial 7s; Vocabulary *Subjective measure* Self-rated memory	- No signifcant differences between cancer survivors and controls in cognitive function in later life - No association between chemotherapy Tx and cognition
Regier et al. 2019	PR	US	Oral-digestive Males	2009-2013	Chemotherapy; RT; Surgery	Cancer; Healthy control	88; 88 control	N.A.	65.93; 72.85 control	6 months; 18 months post-Dx	MoCA	- 40% survivors exhibited cognitive impairment 18 months post-diagnosis, significant compared to controls - At 18 months, cognition improved in comparison to 6 months (improved on phonemic fluency and memory and remained impaired on sustained attention, verbal fluency and memory) - Older age, low hemoglobin, and cancer-related PTSD were associated with worse cognition at 18 months
Shaffer et al. 2012	PR	US	Breast & colorectal	1998-2006	Chemotherapy	Chemotherapy; No chemotherapy	141 breast; 224 colorectal	75.5	N.A.	Every 2 years (max. 9 years)	TICS-m	- No differences in the rates of cognitive decline before and after diagnosis - Cognitive decline after diagnosis did not differ between patients receiving chemotherapy and those who did not
Schilder et al. 2010	PR	Dutch	Breast	N.A.	Tamoxifen; Exemestane; Surgery	Cancer; Healthy control	80 Tamoxifen; , 99 Exemestane; 120 controls	N.A.	68.7 Tamoxifen; 68.3 Exemestane; 66.2 controls	Before Tx (T1); 1 year of Tx (T2)	RAVLT; Visual Association Test; WMS-R Visual Memory; SCWT; TMT A & B; Fepsy Finger Tapping; Fepsy Reaction Times; VFT (Phonetic, Semantic) WAIS-III Letter-Number sequencing	- 1 year of tamoxifen use is associated with significantly lower functioning in verbal memory and executive functioning - 1 year of exemestane use is not associated with negative effects of cognitive functioning - Information processing speed was significantly worse for the tamoxifen group compared to exemestane group - Older age tamoxifen group resulted in worse verbal memory and processing speed compared to healthy controls - Younger age tamoxifen group performed worse on executive functioning compared to healthy controls
Tan et al. 2013	PR	US	Prostate	2003-2008	Leuprolide therapy	No control group	50	*71	N.A.	Baseline (before Tx); 2 months; 4 months; 12 months	MMSE; California Verbal Learning Test-Short Form; Bloodwork (Amyloid Plasma Aβ40)	- No general cognitive decline or change in memory function over time after Tx with leuprolide - No elevated plasma amyloid short term after Tx with leuprolide - Age was correlated with plasma amyloid Aβ40 levels

Underwood et al. 2019	PR	Canada	Breast	2015-2016	Endocrine therapy; RT; Surgery	No control group	42	N.A.	68.38	Tx start (T1); 1 year later (T2)	RAVLT; BVMT-R; TMT Part A & B; WAIS-IV Digit-Symbol Coding; WAIS-IV Symbol Search; WAIS-IV Matrix Reasoning; WAIS-IV Block Design; WAIS-IV Visual Puzzles; VFT (Phonetic)	- Significant decline on verbal memory in older women after 1 year of endocrine therapy (ET); - Performance on other domains did not change significantly after 1 year
van der Willik et al. 2021	PR	Dutch	Non-CNS	1989-2014	Chemotherapy; Hormonal therapy; Local Tx	Cancer; Healthy control	718; 4859 controls	*70.3	N.A.	Every 3 - 6 years	MMSE; LDST; WFT; SCWT; PPT; WLT (immediate, delayed recall & recognition)	- Cognitive trajectories of cancer survivors were largely similar to controls (but most received local therapy only). - After diagnosis the largest decline was found on a memory test
Williams, Janelsins & van Wijngaarden 2016	CS	US	All (excluding skin)	1999-2002	No Tx information	Long term survivors; Short term survivors; Healthy control	408; 2639 controls	N.A.	72.87; 70.67 control	Survivors 5+ years; Survivors <5 years	DSST; Self reported memory or confusion problems	- Cancer survivors suffer more cognitive impairment (processing speed, attention, executive function, learning and working memory) -17% higher odds of self-reported problems with memory or confusion in cancer survivors
Yang, Zhong, Qiu, Cheng & Wang 2015	CS	China	Prostate	2012-2013	ADT; RT; Surgery; Local therapy	Cancer; Healthy control	43 ADT; 35 non-ADT; 40 controls	N.A.	69.28 ADT; 68.83 Non-ADT; 67.80 controls	6 months post-Tx	MoCA; AVLT (immediate, delayed recall, recognition); WAIS III-R Digit Span (forward & backward); TMT A & B; VFT; SCWT	- ADT group had significantly lower scores on cognitive tasks including attention, memory and information processing - Receiving ADT may have selective reductions in EBPM performance but unimpaired TBPM performance - Deficits may result from changes of function and structure of the pre-frontal cortex induced by ADT
Yamada, Denburg, Beglinger & Schultz 2010	CS	US	Breast	1975–2004	Chemotherapy	Cancer; Healthy control	30; 30 controls	>50	72.8; 72.6 controls	≥10 years post-Tx	WASI; WRAT-III, reading subtest MMSE; WAIS-III Digit Span; WAIS-III Letter-Number Sequencing; WAIS-III Arithmetic subtests; COWAT IED Stage 5 Errors; RAVLT; ROCF; TMT parts A & B; Facial Recognition Test; BVRT; BNT; WCST	- In long-term survivors, previous Tx may augment cognitive dysfunction associated with age-related brain changes - Domains affected: global cognition, attention, working memory, psychomotor speed, and executive functioning - Reflects potential dysfunction in frontal-subcortical brain regions
QUESTIONNAIRES/INTERVIEWS												
Freedman et al. 2013	PR	US	Breast	2002-2006	Chemotherapy; Capecitabine; Tamoxifen	No control group	297	*71.5	N.A.	Pre-Tx; Mid-Tx; End of Tx; 12 months; 18 months; 24 months post-Tx	NBF-ADL	- Chemotherapy was not associated with longitudinal changes in self-reported cognitive function - No changes by Tx (standard vs. nonstandard chemotherapy) received - At 24 months, nearly all patients reported normal cognitive function
Hurria, Goldfarb et al. 2006	PR	US	Breast	2001-2004	Chemotherapy	No control group	45	70	N.A.	Baseline; 6 months post-Tx	Squire Memory Self-Rating Questionnaire	- 51% of the patients perceived a decline in memory when comparing to the before chemotherapy - Memory domain most affected: ability to learn new information - Perceived decline was most pronounced in patients with preexisting memory complaints
Keating, Nørredam, Landrum, Huskamp & Meara 2005	CS	US	All	2002	No Tx information	Cancer; Healthy control	964; 14 330 controls	55.0	68.3	≥4 years post-Dx	Survey TICS	- Similar rates of self-reported memory, and among 65+, similar cognition scores between survivors and controls - No difference in cognitive function between cancer survivors and healthy controls
Mandelblatt et al. 2016	PR	US	Breast	2004-2011	Chemotherapy; Hormonal therapy; Surgery	No control group	1280	N.A.	72.7	Baseline; 6 months; Annually (up to 7 years)	EORTC-QLQ-C30	- Majority of older survivors maintained good long-term self-reported cognitive function (42%) - 2.1x higher odds of accelerated decline when exposed to chemotherapy (with or without hormonal therapy) - Comorbidity (or frailty) & low prediagnosis function increased the odds of accelerated cognitive decline - Age was not related to accelerated group - Cognition trajectories were related to physical function trajectories

Schilder et al. 2012	PR	Dutch	Breast	2001-2006	Chemotherapy; Tamoxifen; Exemestane; Surgery	Cancer; Healthy control	80 Tamoxifen; 99 Exemestane; 120 controls	N.A.	68.7 Tamoxifen; 68.3 Exemestane; 66.2 control	T1 (Before start Tx); T2 (1 year of Tx)	CFQ Dutch version; Interview questions "Do you have any complaints with regard to memory & attention/ concentration?" *Neuropsychological tests* RAVLT (immediate & delayed); Visual Association Test; WMS-R Visual Memory (immediate & delayed); SCWT; TMT A & B; Fepsy Finger Tapping; Fepsy Reaction Times; VFT (phonetic, semantic); WAIS-III Letter-Number sequencing; Dutch Adult Reading Test	- Increased attention/concentration complaints in tamoxifen users 1 year after Tx but not in exemestane users - Tamoxifen or exemestane use did not influence self-reported frequency of cognitive failures - Self-reported cognitive function was associated with anxiety/depression, fatigue, & menopausal complaints - Cognitive test was not associated with self-reported cognitive functioning
Stava, Weiss, Vassilopoulou-Sellin 2006	CS	US	Breast; Other	N.A.	Chemotherapy	Breast cancer; Other cancers	814 breast cancer; 1894 other cancers	46.8 breast cancer; 42.7 other cancers	69.4 breast cancer; 66.4 other cancers	≥15 years post-Dx	Survey	- Women who received chemotherapy more frequently reported loss of memory (12.3% vs. 7.2%) - Survivors of cancer who received chemotherapy reported significantly more loss of memory (11.3% vs. 4.8%) - Breast cancer survivors reported loss of memory than other cancers (18.4% vs. 12.5%)

NOTE. * Indicates median. Abbreviations: 3MS, Modified Mini-Mental State Examination; AC, Adriamycine (Doxorubicine) – Cyclofosfamide; ACT, Adriamycin cyclophosphamide Taxol; AD, Alzheimer's Disease; ADT, Androgen Deprivation Therapy; ApoE ε4, Apolipoprotein E; AVLT, Auditory Verbal Learning Test; BDRS, Blessed Dementia Rating Scale; BNT, Boston Naming Test; BVMT-R, Brief Visual-Memory Test-Revised; BVRT, Benton Visual Retention Test; CAMCO-G, Cambridge Cognitive Examination; CDR, Clinical Dementia Rating; CERAD-K-N, Consortium to Establish a Registry for Alzheimer's Disease; CFQ, Cognitive Failure Questionaire; CMF, Cyclofosfamide Methotrexaat Fluorouracil; CNS, Central Nervous System; COWAT, Controlled Oral Word Association Test; CRT, Complex reaction time; CS, Cross-sectional; CVLT, California Verbal Learning Test; D-KEFS, Delis-Kaplan Executive Function System; DSST, Digit Symbol Substitution Test; DTC, differentiated thyroid cancers; Dx, Diagnosis; EBPM, event-based prospective memory; EORTC-QLQ-C30, European Organization for Research and Treatment for Cancer Quality of Life Questionnaire; FAB-K, Frontal Assessment Battery; FACT-cog, Functional Assessment of Cancer Therapy-Cognitive Function; FDG, fluorodeoxyglucose; GMD, grey matter density; H MRS, Proton Magnetic Resonance Spectroscopy; HVLT-R, Hopkins Verbal Learning Test, Revised; IED; Intradimensional/Extradimensional; IL-6, Interleukin 6; KDCT, Kendrick Assessment of Cognitive Ageing battery; LDST, Letter-Digit Substitution Test; LHRH, Luteinizing hormone releasing hormone; LMWT, Luria Memory Word test; MDRS-2, Mattis Dementia Rating Scale-2; MFTC, Multiple Features Target Cancellation Test; MMSE, Mini-Mental State Exam; MoCA, Montreal Cognitive Assessment; MRI, Magnetic Resonance Imaging; MTCF, Modified Taylor Complex Figure Test; NAB, Neuropsychological Assessment Battery; NART, National Adult Reading Test; NBFADL, Neurobehavioral Functioning and Activities of Daily Living Scale; NHL, Non-Hodgkin Lymphoma; NMSC, Non-Melanoma Skin Cancer; No, number; MM, Multiple Melanoma; PCI, prophylactic cranial irradiation; PET, Positron emission tomography; PMA-V, Primary Mental Abilities-Vocabulary; PPT, Purdue Pegboard Test; PR, Prospective; PTSD, Post-Traumatic Stress Disorder; RAVLT, Rey Auditory Verbal Learning Test; RCFT, Rey Complex Figure Test; ROCF, Rey-Osterrieth Complex Figure; RPM, Raven's Progressive Matrices; RST, The Road Sign Test; RT, Radiotherapy; SCLC, Small Cell lung Cancer;; SCWT, Stroop Color Word Test; SDMT, Symbol Digit Modalities Test; SRT, Simple reaction time; TBPM, time-based prospective memory; TIADL, Timed Instrumental Activities of Daily Living; TICS-m, Telephone interview cognitive screening; TMT, Trail Making Test; TSH, Thyroid Stimulating Hormone; Tx, Treatment; UFOV, Useful Field Of Vision; VFT, Verbal Fluency Test; WAIS-III, Wechsler Adult Intelligence Scale III; WASI, Wechsler Abbreviated Scale of Intelligence; WCST, Wisconsin Card Sorting Test; WFT, Word Fluency Test;; WLT, 15-Word Learning Test; WMI, Working Memory Index; WMS, Wechsler Memory Scale; WRAT, Wide Range Achievement Test; Yrs, years.

Appendix E

Table 2. *Overview of neurodegenerative diseases in elderly cancer survivors according to the systematic literature review*

Source	Cancer subtype	Disease outcome	Main findings
Baik, Kury & McDonald 2017	Prostate	AD; Dementia	- No association between ADT use and subsequent AD or dementia
Baxter et al. 2009	Breast	Senile dementia; Presenile dementia; Drug-induced dementia; AD; Pick's disease; Senile degeneration of the brain; Other cerebral degeneration; Toxic encephalopathy; Senility	- Chemotherapy was not associated with greater risk of dementia over time. - Hormone receptor status was not associated with development of dementia or possible dementia
Blanchette et al. 2020	Breast	Dementia	- Aromatase inhibitor therapy was associated with a decreased incidence of dementia as compared to Tx with tamoxifen
Boulet et al. 2019	Thorax, head & neck	Cerebrovascular events: -Transient ischemic attack; -Stroke; -Carotid revascularization; -Stroke death	- Statin use post RT was associated with a significant reduction in stroke, with a trend toward significantly reducing cerebrovascular events
Bowles et al. 2017	All	Dementia; Possible AD; Probable AD	- Prevalent cancer was not associated with decreased risk of dementia or AD - Incident cancer was associated with decreased risk of AD
Branigan et al. 2020	Breast	AD; MS; PD; ALS	- Tamoxifen and steroid-aromatase inhibitors were associated with a decrease in neurodegeneration, specifically AD & dementia
Bromley et al. 2019	Breast	AD; VaD; Dementia with Lewy bodies; Mixed dementia; Unknown type	- No evidence for a difference in dementia, AD or VaD risk between aromatase inhibitors & tamoxifen users
Chen et al. 2011	Lung	Stroke	- Lung cancer is associated with increased risk of subsequent stroke within 1 year after Dx for men and within 2 years after Dx for women - Risk was stronger for hemorrhagic stroke than for ischemic stroke
Chung et al. 2016	Prostate	AD; PD	- Use of ADT was not associated with a higher risk of AD or PD disease during the follow-up period
Driver et al. 2012	All (excluded NMSC)	Any dementia; Possible AD; Probable AD	- Cancer survivors had a lower risk of AD - Risk of AD was lowest in smoking related cancers
Du, Cai, & Symanski 2013	Colorectal	Unspecified cognitive disorder; Amnestic disorder; AD; VaD; Unspecified dementia; Drug-induced dementia; Psychoses	- Chemotherapy use 24% more likely to develop drug-induced dementia - Risk of AD, VaD or other dementias was significantly lower in patients receiving chemotherapy - Cognitive disorder was not significantly different between groups
Du, Xia, & Hardy 2010	Breast	Cognitive disorder NOS; Amnestic disorder; AD; VaD; Dementia; Drug induced dementia; Psychoses	- No significant association between chemotherapy and the risk of drug-induced dementia or unspecified cognitive disorders - Risk of developing AD, VaD, or other dementias was significantly lower in patients receiving chemotherapy - Risk of developing cognitive disorder was not significantly different between groups
Elbaz et al. 2002	All	PD	- No strong association between nonfatal cancer and development of PD - Suggestive trends stratified by sex and age at onset of PD, and for specific cancers related to smoking or hormonal factors
Fowler et al. 2020	Breast, prostate, colorectal, NMSC	Progression of AD	- Cancer history resulted better cognition and later age of AD onset - Progression was similar to participants without cancer history
Frain et al. 2017	All (excluded NMSC)	AD; Non-AD dementia; Stroke; Macular degeneration	- Survivors of non-screening-related cancers have a lower risk of AD - Survivors of screening-related cancers had an increased risk of AD - Cancer survivors have a higher risk of non-AD dementia & stroke - Chemotherapy is associated with decreased risk of AD
Freedman et al. 2016	All	AD	- Risk of AD was 13% lower in cancer patients
Hanson et al. 2017	All	AD	- Cancer is not protective against AD - Under certain model specifications, inverse association between cancer and AD can be replicated
Heck et al. 2008	Breast	Dementia	- Increase in dementia over time (long-term) in subjects who received chemotherapy
Hong et al. 2013	Glottic	Cerebrovascular events	- Patients with early-stage laryngeal cancer post-surgery or RT have a higher burden of cerebrovascular events - RT and surgery are associated with comparable risk of subsequent CVD
Hong et al. 2020	Prostate	Overall cognitive decline; Dementia (including AD and non-AZD); PD	- Significantly higher risk of cognitive dysfunction in patients receiving ADT - Antiandrogen-only ADT was associated with increased risks of cognitive decline, PD & non-AD, but not AD - CAB was associated with higher risks of overall cognitive decline and non-AD - Duration of ADT exposure failed to correlate with cognitive dysfunction
Huang et al. 2020	Prostate	Dementia; AD	- Use of antiandrogen monotherapy was associated with increased risk of dementia or AD - GnRH agonist use and orchiectomy had no significant difference compared to those who did not receive ADT
Ibler et al. 2018	Melanoma & NMSC	AD	- Significantly decreased risk for AD in patients with MM and NMSC
Jayadevappa et al. 2019	Prostate	Dementia; AD	- Use of ADT was associated with subsequent dementia or AD over a follow-up period of 10 years

Jazzar et al. 2020	Bladder	AD; Related dementias (frontotemporal dementia (Pick's disease), Senile degeneration of the brain, VaD, communicating hydrocephalus, obstructive hydrocephalus, cerebral degeneration in other diseases classified elsewhere, Other cerebral degeneration, Unspecified)	- No differences in new-onset AD and related dementias following surgery, RT or chemotherapy (risk was similar regardless of Tx) - Older patients and patients with depression were at increased risk of developing dementia related diseases
Jhan et al. 2017	Prostate	AD	- ADT use is associated with an increased risk of developing AD
Kao, Lin, Chung & Huang 2015	Prostate	Dementia	- No difference in risk of subsequent dementia in ADT receivers versus none ADT receivers - No association between GnRH agonists and subsequent incidence of dementia in prostate cancer patients
Khan et al. 2011	Breast, colorectal & prostate	Dementia	- Increase in incidence of dementia in colorectal cancer survivors compared to controls
Khosrow-Khavar et al. 2017	Prostate	All dementia events, including AD	- Use of ADT was not associated with an increased risk of dementia
Klinger et al. 2021	Bladder	New-onset dementia; New-onset AD; PD; Stroke	- BCG in bladder cancer is associated with significant reduced risk of AD (and PD)
Krasnova et al. 2020	Prostate	AD; All-cause dementia (frontotemporal dementia or Lewy body dementia)	- Association between pharmacologic ADT and higher risk of all-cause dementia, AD, and use of psychiatric services
Liao, Lin & Lay 2017	Breast	AD	- Increased odds of AD associated with ever use tamoxifen - Longer tamoxifen use was associated with increased AD (survival effect)
Mahajan et al. 2020	Skin	PD	- Skin cancer, may delay the onset but not the progression of PD
Musicco et al. 2013	All	AD	- Inverse association between cancer and AD - Olders people with cancer have a reduced risk of AD
Nead et al. 2015	Prostate	New-onset AD	- Use of ADT resulted in an increased future risk of AD
Nead et al. 2017	Prostate	New-onset dementia	- Use of ADT was associated with an increased risk of dementia - Greater duration of ADT use resulted in increased risk of dementia
Olsen, Friis & Frederiksen 2006	All	PD	- Increased prevalence of malignant melanoma and skin carcinoma before PD - Decreased prevalence of smoking-related cancers preceding PD (higher risk of PD among nonsmokers)
Ording et al. 2020	All	Incident dementia -AD; -VaD, -All-cause dementia (including unspecified dementia, Pick's disease, Creutzfeld-Jakob disease, Huntington's disease, HIV dementia, PD, Lewy body dementia, progressive supranuclear palsy, and other specified & unspecified diseases)	- No clinically relevant association between cancer and risk of AD, Vad, or all-cause dementia (as inverse assocation diminishes after 10 years)
Raji et al. 2009	Breast	Dementia	- No association was found between types of adjuvant chemotherapy agents and risk of dementia - Increasing age at cancer diagnosis, black ethnicity, living in a census tract with level of lower education, and increasing number of comorbidities were associated with new claims of dementia
Realmuto et al. 2012	All	AD	- Inverse association between AD and tumors diagnosed before the onset of dementia (limited to endocrine-related tumors)
Roe et al. 2010	All	Any AD; Pure AD; Any VaD; Pure VaD; Mixed AD/VaD	- A history of cancer was associated with reduced risk of any AD or pure AD - No association between cancer history and any VaD, pure VaD, or mixed dementia
Roderburg et al. 2021	All	Dementia; Mild cognitive impairment	- Increased incidence of dementia in patients with different cancer entities (19.7%) than in non-cancer patients (16.7%) - Effect most pronounced in lung cancer patients
Shahinian, Kuo, Freeman, & Goodwin 2006	Prostate	Senile Dementia; Organic or Drug-related memory disturbances; Cerebral degenerations (Ex. AD); Any cognitive disorder	- Cognitive disorders were substantially increased in patients receiving ADT, due to increased age, comorbid conditions and more advanced cancers.
Smith et al. 2009	Head & neck	Cerebrovascular events: -Stroke; -Carotid revascularization; -Stroke death	- RT for head and neck cancer, but not postoperative RT, was associated with cerebrovascular disease risk in older patients - 1/3 of patients who underwent RT alone experienced a cerebrovascular event within 10 years of cancer Dx
Sun et al. 2020	35 types	Dementia	- Overall risk of dementia was significantly lower up to 10 years of follow up - Overall risk of dementia was higher after more than 10 years of survival
Tae, Jeon, Shin et al. 2019	Prostate	Cognitive dysfunction: - Dementia; - AD	- Association between ADT use and increased risk of cognitive dysfunction
Tae, Jeon, Choi et al. 2019	Prostate	Cerebral infarction	- ADT was not associated with cerebral infarction
White, Lipton, Hall & Steinerman 2013	NMSC	Dementia; Possible AD; Probable AD; Mixed VaD	- NMSC have significantly reduced risk of developing AD
Zhu et al. 2015	All	Transient global amnesia (TGA)	- No evidence that patients with cancer have a higher risk of TGA than cancer-free individuals

NOTE. Abbreviations: AD, Alzheimer's Disease; ADT, Androgen Deprivation Therapy; ALS, Lou Gehrig's disease; BCG, Bacillus Calmette-Guérin vaccine; CAB, Combined Androgen Blockage; CVD, Cerebral Vascular Disease; Dx, Diagnosis; GnRH, Gonadotropin-releasing Hormone; MM, Multiple Melanoma; MS, multiple sclerosis; NMSC, Non-Melanoma Skin Cancer; NOS, Not Otherwise Specified; PD, Parkinson's Disease; RT, Radiotherapy; VaD, Vascular Dementia.