Cancer-related cognitive impairment in non-CNS cancer patients

European Cancer and Cognition Consortium (ECCC); Sleurs, Charlotte; Amidi, Ali; Wu, Lisa M; Kiesl, David; Zimmer, Philipp; Lange, Marie; Rogiers, Anne; Giffard, Benedicte; Binarelli, Giulia; Borghgraef, Cindy; Deprez, Sabine; Duivon, Mylène; De Ruiter, Michiel; Schagen, Sanne; Ahmed-Lecheheb, Djihane; Castel, Hélène; Buskbjerg, Cecilie R; Dos Santos, Mélanie; Joly, Florence; Perrier, Joy

Published in:
Critical Reviews in Oncology/Hematology

DOI:
10.1016/j.critrevonc.2022.103859

Publication date:
2022

Document Version
Early version, also known as pre-print

Cancer-related cognitive impairment in non-CNS cancer patients: Targeted review and future action plans in Europe

On behalf of the European Cancer and Cognition Consortium (ECCC): Charlotte Sleurs [1,15*,#], Ali Amidi [2,#], Lisa M. Wu [3,4,5,#], David Kiesl [6,#], Philipp Zimmer [7,#], Marie Lange [8,9,10,#], Anne Rogiers [11,#], Benedicte Giffard [10,12,#], Giulia Binarelli [8,9,#], Cindy Borghgraef [13,#], Sabine Deprez [14,15,#], Mylène Duivon [8,9,10,#], Michiel De Ruiter [16,#], Sanne Schagen [16,17,#], Djihane Ahmed-Lecheheb [8,9,#], Hélène Castel [18,19,#], Cecilie R Buskbjerg [2,#], Mélanie Dos Santos [8,9,#], Florence Joly [8,9,10,#], Joy Perrier [12,*,#]

[1] Department of Cognitive Neuropsychology, Tilburg University, Tilburg, The Netherlands

[2] Department of Psychology and Behavioural Sciences, Aarhus University, Aarhus, Denmark

[3] Department of Medical Social Sciences, Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA

[4] Aarhus Institute of Advanced Studies, Aarhus University, Aarhus, Denmark

[5] Department of Population Health Science and Policy, Icahn School of Medicine at Mount Sinai, New York City, New York, USA

[6] Department for Internal Medicine III, Kepler University Hospital, Linz, Austria

[7] Divison of Performance and Health (Sports Medicine), Institute for Sport and Sport Science, TU Dortmund University, Dortmund, Germany

[8] Clinical Research Department, Centre François Baclesse, 14000 Caen, France

[9] ANTICIPE, INSERM, UNICAEN, Normandie University, 14000 Caen, France

[10] Cancer and Cognition Platform, Ligue Nationale Contre le Cancer, 14000 Caen, France

[11] Department of Psychiatry, Brugmann University Hospital, Brussels, Belgium

[12] Normandie Univ, UNICAEN, PSL Université, EPHE, INSERM, U1077, CHU de Caen, GIP Cyceron, Neuropsychologie et Imagerie de la Mémoire Humaine, 14000 Caen, France

[13] Université Libre de Bruxelles, Faculté des Sciences Psychologiques et de l'Éducation, Brussels, Belgium.

[14] Department of Imaging and Pathology, KU Leuven, Leuven, Belgium

[15] Leuven Cancer Institute, KU Leuven, 3000 Leuven, Belgium

[16] Division of Psychosocial Research and Epidemiology, The Netherlands Cancer Institute, Amsterdam, The Netherlands

[17] Brain and Cognition, Department of Psychology, University of Amsterdam, Amsterdam, The Netherlands

[18] Normandie University, UNIROUEN, INSERM, DC2N, Team Astrocyte and Vascular Niche, Place Emile Blondel, CEDEX, 76821 Mont-Saint-Aignan, France

[19] Institute for Research and Innovation in Biomedicine (IRIB), 76000 Rouen, France

[#]All authors equally contributed to this manuscript

Corresponding author: Joy Perrier, Neuropsychologie & Imagerie de la Mémoire Humaine Unité de recherche 1077 INSERM-EPHE-UNICAEN, Pôle des Formations et de Recherche en Santé (PFRS), 2 rue des Rochambelles F-14032 Caen Cedex CS 14032

Phone: +33(0) 2 31 56 83 83; E-mail: joy.perrier@unicaen.fr

Authors' biographies

Charlotte Sleurs

Charlotte Sleurs, PhD, is assistant professor at the Department of Cognitive Neuropsychology, Tilburg University (TIU) in the Netherlands. She investigated chemotherapy-related neurotoxicity in pediatric oncology during her PhD. In her post-doc career, she mainly focused on cranial radiotherapy-induced neurotoxicity in neuro-oncology patients. She continues to coordinate research in both topics at TIU and as visiting professor at KU Leuven, Belgium.

Ali Amidi

Ali Amidi, PhD, is an Associate Professor in Behavioural Neuroscience at the Department of Psychology and Behavioural Sciences, Aarhus University, Aarhus, Denmark and a member of the Unit for Psychooncology & Health Psychology. His research has been dedicated to the investigation of the onset, development, prevention, and treatment of various cancer-related symptoms such as neurocognitive impairment, fatigue, and sleep disturbances in both CNS- and non-CNS cancer populations. He has a particular interest in exploring the neural substrate underlying these symptoms. He is the founder of The Sleep and Circadian Psychology Research Group at Aarhus University.

Lisa M. Wu

Lisa Wu, PhD, is Associate Professor in the Aarhus Institute of Advanced Studies, Aarhus University in Denmark. She is a clinical psychologist and neuropsychologist who has investigated the nature, severity and mechanistic underpinnings of side- and late-effects of cancer and its treatment, with a particular interest in cognitive impairment, sleep and circadian rhythm dysfunction. She has also undertaken non-pharmacological intervention studies to ameliorate cancer side- and late-effects, including light therapy.

David Kiesl

David Kiesl, MD, is a medical Oncologist and Hematologist, at the department for hematology and internal oncology of the Kepler University Hospital in Linz, Austria. He is the head of the institute for sports medicine, the Sportmed-Cardiomed GmbH in Linz In his role as research team leader he coordinates the exercise and cognition study group – Austria and is involved in the oncological care and clinical research in patients with solid and hematooncological cancers.

Philipp Zimmer

Philipp Zimmer, PhD, is Full Professor at TU Dortmund University. He is working at the Institute for Sport and Sport Science and chair of the division of Performance and Health. He holds two PhDs, one in exercise science and one in Neuroscience. His main research interest is exercise (neuro-) immunology, with a special focus on persons with cancer and multiple sclerosis. In this context his group is conducting translational clinical trials, combining mechanistic research and patient reported outcomes.

Marie Lange

Marie Lange is neuropsychologist at the Clinical Research department of Comprehensive Cancer Center of Caen and INSERM U1086 Anticipe, in France. During her PhD, she investigated cancer-related cognitive impairment in elderly breast cancer patients treated by chemotherapy. She coordinates several studies of the French Cancer and Cognition platform mainly focused on the impact of cancer treatments on cognition, including new cancer therapies, and interventional studies to improve cancer-related cognitive impairment.

Anne Rogiers

Anne Rogiers, MD, PhD is a clinical professor at the Faculty of Medicine and Pharmacie of the Vrije Universiteit Brussel (VUB). She obtained her medical degree in 1994 from the VUB and her specialist degree as a psychiatrist in 2001. Since 2018, she has been the head of the Neurocognitive Remediation Clinic at the Department of Psychiatry of the Centre Hospitalier Universitair (CHU) Brugmann, Brussels, Belgium. She works as a scientific collaborator at the Universitair Ziekenhuis Brussel and the Oncology Research Center of the VUB. Prof. Rogiers is also a member of the EORTC Quality of Life Group. During the last 15 years, she has gained clinical and scientific experience in the fields of neuroscience, psycho-oncology, and neuro-oncology. Since 2016, she has focused her research on cancer survivorship, cognition and quality of life in the field of immunotherapy.

Benedicte Giffard

Bénédicte Giffard, PhD, is Full Professor of neuropsychology at the University of Caen Normandy in France where she is the head of university educations (master of

neuropsychology, continuing education…). She is member of the Executive Committee of the Research Unit 1077 Inserm-EPHE-UNICAEN "Neuropsychology and Imaging of Human Memory", where she funded and leads a research team on the impact of non-CNS cancers on memory functioning. She is co-leader of the Cancer and Cognition clinical research platform within the Cancéropôle Nord-Ouest.

Giulia Binarelli

Giulia Binarelli is a psychologist PhD candidate in public health at the University of Caen (research Unit INSERM U-1086) in France. She is investigating the use of digital interventions for cancer-related cognitive impairments in women with breast cancer. She also collaborates in projects aiming to improve patients' support concerning cancer-related cognitive impairment at Centre François Baclesse.

Cindy Borghgraef

Cindy Borghgraef is neuropsychologist at the Psycho-Oncology and Geriatric Oncology departments of the Jules Bordet Institute in Brussels, Belgium. During her PhD, she investigated cancer-related cognitive impairment in elderly patients with hematological malignancies treated by chemotherapy. She has also interest in exploring the impact of cognitive impairment on psychological distress and especially sense of being a burden in elderly patients.

Sabine Deprez

Sabine Deprez, PhD, is senior research at the University of KU Leuven, Department of Imaging and Pathology, Translational MRI, KU Leuven in Belgium. Her research focuses on the investigation of the neural correlates of cognitive impairment after cancer treatment in a multidisciplinary set-up, combining multimodal imaging, neuropsychological evaluation and other biomarkers and possible therapeutic interventions.

Mylène Duivon

Mylène Duivon, PhD, is a postdoctoral fellow at the University of Caen (research Unit INSERM U-1086) in France. She investigated the impact of endocrine therapy and sleep on cognitive functioning of breast cancer patients during her Ph.D. Her current research interests focus on the biological predictors of cancer-related cognitive impairment and non-pharmacological interventions to improve cognitive functioning.

Michiel De Ruiter

Michiel de Ruiter, PhD, worked as an associate staff scientist at the Netherlands Cancer Institute till June 2022. He is trained in cognitive neuroscience. He contributed to neuroimaging and neuropsychological studies focusing on cognitive problems in cancer patients for 15 years. He pursued a career outside academia and now works at the Dutch Federation of Cancer Patient Organizations, where he is involved in a project to improve transparency of oncology care.

Sanne Schagen

Sanne Schagen, PhD, is Group leader and head of the Division of the Psychosocial Research and Epidemiology and coordinator of the Cognition and Cancer research group at the Antoni van Leeuwenhoek (AVL), where she works since 1996. She combines clinical work and research in the fields of cognitive consequences of cancer and cancer treatments. Using neuropsychological research, 'imaging' but also animal experiments, she looks at the presence and causes of cognitive problems (such as memory and concentration problems) in various tumor types and treatments. In addition, we investigate how we can reduce these cognitive complaints and how patients can best deal with them in daily life.

Djihane Ahmed-Lecheheb

Djihane Ahmed-Lecheheb, PhD Science and health, Project manager of the Platform "Cancer and Cognition", Research Unit INSERM U1086 ANTICIPE, Center for the fight against

cancer, Caen, France. During her postdoctoral fellow, she investigated side effects of chemotherapy in cancer patients and post-cancer follow-up.

Hélène Castel

Hélène Castel, PhD, is senior researcher at Inserm, University of Rouen Normandie, head of the Team "Genetics, Biology and Plasticity of Brain Tumors" in the researhc Unit 1245 Inserm. She is specialized in Neuro-oncology in i) cancer, biomarkers and cancer treatments on cognition/brain functions in preclinical models and in translational programs, and brain tumor development and remodeling the cerebral microenvironment. The team develops preclinical mouse models of PDX-GBM resection, local treatments and immunotherapy and collaborate with the in a recent sSelected PAIR Tumeurs Cérébrales, the start-up Hippoxis to test a macrophage-regulating compound on GBM (RIN Normandie Neuroncochimie, AMI Oncochimie). The team is an active member of the ERNEST COST action, and GoPa networks of ANOCEF. Recently H. Castel organized and currently coordinates a Working Group on Brain Tumours within the NorthWest Canceropole and has been awarded for a Structuring Program (CNO) on GBM heterogeneity and recurrence, involving at least in part Partner 1 for proteomics of GBM cells during invasion.

Cecilie Buskbjerg

Cecilie Buskbjerg is a postdoctoral fellow at Department of Oncology, Aarhus University Hospital, and Department of Psychology and Behavioral Science, Aarhus University, in Denmark. During her PhD, Cecilie investigated cancer-related cognitive impairment in men undergoing treatment for testicular or prostate cancer with a particular focus on the role of endocrine status, structural brain networks, and risk genotypes. Her current research is mainly concerned with neuropsychological rehabilitation of children and adults treated for CNS tumors and online neuropsychological testing of cancer-related cognitive impairment.

Mélanie Dos Santos

Dr Mélanie DOS SANTOS, MD, PhD is a medical Oncologist who also works in the Clinical Research Department in the Comprehensive Cancer Centre Francois Baclesse in Caen, FRANCE. She has recently finished her work on the subject of cognition in oncology as a doctoral student in the research Unit INSERM U-1086, Anticipe (Lower Normandy University). She continues to coordinate research studies on this topic.

Florence Joly

Florence Joly, MD, PhD, is a medical Oncologist in the Francois Baclesse Comprehensive Cancer Centre in Caen, Normandy, France. She is at the head of the Clinical Research Department of the François Baclesse Centre. She has coordinated for 6 years the "Symptom Benefit" group of the international intergroup in Onco-gynecology (GCIG). She is a member of the research Unit INSERM U-1086, Anticipe. She developed a large multidisciplinary research program on quality of life with two main topics: long term quality of life among survivors and impact of cancer treatments on cognition. She is at the origin of the French Cancer platform dedicated to Cancer and Cognition and labeled by the French League Against Cancer.

Joy Perrier

Joy Perrier, PhD, is a post-doctorate working in the field of insomnia, cognition and cancer. Through a multidisciplinary approach, her research aims at studying the modifications of sleep and their consequences on the quality of life, in particular memory, in cancer patients. For this purpose, sleep analyses, physiological measures, but also neuroimaging analyses (fMRI and aMRI) and cognitive performance measures are performed and put into relationship. Thanks to the collaboration with the clinical services of the Centre François Baclesse (Prof. Florence Joly and her team), the results of this research can be taken into account by the clinicians as soon as possible. Joy Perrier is currently holding a Chair of

Excellence from the Normandy Region for the ICANSLEEP project (Cancer, Sleep and Memory - 2021-2024).

Abstract

Cancer-related cognitive impairment (CRCI) has increasingly been identified over the last two decades in non-CNS system cancer patients. Across Europe, researchers have contributed to this effort by developing preclinical models, exploring underlying mechanisms and assessing cognitive and quality of life changes. The ultimate goal is to develop interventions to treat patients experiencing CRCI. To do so, new challenges need to be addressed requiring the implementation of multidisciplinary research groups. In this consensus paper, we summarize the state of the art in the field of CRCI combined with the future challenges and action plans in Europe. These challenges include data sharing/pooling, standardization of assessments as well as assessing additional biomarkers and neuroimaging investigations, notably through translational studies. We conclude this position paper with specific actions for Europe based on shared scientific expert opinion and stakeholders involved in the Innovative Partnership for Action Against Cancer, with a particular focus on cognitive intervention programs.

Keywords: Cancer-related cognitive impairment (CRCI), rehabilitation, European consortium, risk factors, neuroimaging, biomarkers, clinical, preclinical

1. Context

Across Europe, survival rates in non-central nervous system (non-CNS) cancer patients have dramatically increased over the last decades (Crocetti et al., 2017; De Angelis et al., 2014). However, there has also led to a concomitant increase in the number of survivors living with potential late effects of cancer and its treatments. As a result, increased attention has been devoted to psychosocial outcomes associated with cancer and cancer treatments and patient quality of life (Aaronson et al., 1993; Joly et al., 1996). Among the psychosocial concerns, cancer-related cognitive impairment (CRCI) has increasingly been identified over the last two decades in non-CNS cancer patients (Vitali et al., 2017; Wefel et al., 2015). In Europe, the first study that included cognitive assessments was published in 1998 by van Dam in Netherlands (van Dam et al., 1998) and showed the presence of cognitive impairment in 32% of breast cancer patients receiving high doses of chemotherapy. Since then, a considerable international research effort has been undertaken, including among European researchers, to develop preclinical models to explore the pathophysiology of CRCI (Seigers et al., 2013), to examine pathophysiological changes in cancer patients themselves (Amidi et al., 2017), to assess cognitive and quality of life changes (e.g., Wu et al., 2016;) and to develop interventions to treat patients experiencing CRCI (Binarelli et al., 2021; Oberste et al., 2018; Van der Gucht et al., 2020). This research domain has expanded from breast cancer only to other non-CNS cancer diagnoses, as well as to other treatments than chemotherapy only. Furthermore, European researchers aimed to harmonize the evaluation and interpretation of CRCI in clinical studies.

In recent years, the focus of research within this field has broadened to the role of biopsychosocial factors in neurocognitive outcomes (including sedentarity, physical activity, sleep, psychological distress and aging) (de Ruiter et al., 2021; Lange et al., 2019a; Menning et al., 2015). In order to provide new insights into potential mechanisms and predictive

models, innovative biomarkers (Dubois et al., 2014) and human neuroimaging techniques have been developed by different European teams (Amidi et al., 2017; de Ruiter et al., 2011; Deprez et al., 2012; Kreukels et al., 2008; Perrier et al., 2022). These studies have helped to increase knowledge about CRCI and their determinants with the potential to inform better cancer treatments and cognitive intervention programs. Nonetheless, new challenges need to be addressed, requiring the implementation of multidisciplinary research groups.

The European scientific community have had a strong presence in the CRCI research community. After the initial work in 1998 by van Dam et al. (van Dam et al., 1998), multiple research programs have been installed in multiple European countries. In the Netherlands, The Netherlands Cancer Institute has led several research programs focusing on CRCI, using diverse methodologies such as neuroimaging and the development of online cognitive assessment tools. Similarly, in Denmark, the Danish Cancer Society has continuously supported research to investigate CRCI and the development of National Late Effect Clinics since 1999 (Mehlsen et al., 2009). In France, research programs began in the early 2010s and have culminated, which resulted in the development of a platform that provides the scientific/medical community and pharmaceutical companies in 2015. In the same decade, also projects were launched in breast cancer in Belgium (Deprez et al., 2011).

In this consensus paper, we summarize the state of the art in the field of CRCI in Europe, the most recent trends, as well as future research challenges. In addition, we propose specific actions for European authorities to take up based on a recent report issued by the Innovative Partnership for Action Against Cancer (iPAAC) Joint Action, with a particular focus on cognitive intervention programs.

2. Detection of CRCI

a. Detection of cognitive complaints

Cognitive complaints are prevalent (40-75%) in non-CNS cancer patients (Lange et al., 2019a) and are important to detect, due to their significant negative impact on quality of life (Bray et al., 2018; Giffard et al., 2020; Hardy-Leger et al., 2021). Currently, cognitive complaints, for the most part, are assessed using cancer-specific quality of life questionnaires that are limited in scope. For instance, the European Organization for Research and Treatment of Cancer (EORTC) created the Quality-of life Questionnaire C30 (EORTC-QLQ-30) (Aaronson et al., 1993) which focuses on the assessment of general quality of life and only two items pertain to cognitive complaints. A few specific questionnaires have been developed outside Europe that have focused on cognitive complaints and impacts on quality of life (e.g., the Functional Assessment of Cancer Therapy – Cognitive Function [FACT-Cog]) and have been standardized in selected European populations (Jacobs et al., 2007; Lange et al., 2016), but there is still a need for improvements in the standardization and implementation of these cognitive questionnaires across Europe with a focus on validation in multiple languages with country-specific normative data and established clinical cut-offs.

b. Neuropsychological assessments

Neuropsychological test batteries remain the gold standard for objective assessment of cognitive functioning. The assessment of CRCI is often limited by several methodological issues, such as small samples and effect sizes (Cohen's $d<0.30$), as well as practice effects that occur over time (Bernstein et al., 2017). Consequently, the estimated prevalence of CRCI varies widely between studies thus necessitating the need for standardization of assessments to facilitate international studies and meta-analyses. In a first attempt, the International Cognition and Cancer Taskforce (ICCTF) recommended a core test battery in 2011 that included tests available in alternate forms with adequate psychometric properties (Wefel et

al., 2011). Subsequent studies have generally attempted to implement these criteria. However, it still remains to be seen as to whether these tests are sensitive enough for cognitive changes in non-CNS cancer populations. Furthermore, the test assessments are often language- and culture-dependent, and normative data are not available for all countries. This is a particular challenge in Europe, a continent of linguistic and cultural diversity, and indeed, multinational European studies are scarce. Another more general issue relates to a lack of available alternate test forms necessary to minimize practice effects in longitudinal studies, with few exceptions (e.g. the Hopkins Verbal Learning Test (HVLT) (Uchiyama et al., 1995)). Furthermore, when alternate forms do exist, there may only be two of them (e.g. HVLT), threatening the validity of longitudinal studies. As a result of these aforementioned problems, the Cognition and Cancer group in the Netherlands has developed a cognitive test battery through online assessments (Amsterdam Cognition Scan - ACS). The ACS permits repeated cognitive testing in clinical settings and is available in several languages (Feenstra et al., 2017). This work intends to improve cognitive measurements in cancer patients and to create large normative datasets.

3. Direct and indirect risk factors contributing to CRCI

In addition to the appropriate detection of CRCI, it is also crucial to understand potential risk factors, over and above treatment factors. A few of the potential significant risk factors being investigated are described below.

a. (In-)direct effects of cancer treatments

Cancer treatments can either directly or indirectly induce damage of the brain tissue, potentially leading to cognitive impairments in cancer patients. Previous neuroimaging research has consistently shown reductions in white and gray matter volume of brain areas important for memory (Apple et al., 2019) and executive functioning after chemotherapy for

non-CNS cancer patients (Deprez et al., 2011; Stouten-Kemperman et al., 2015). Among other mechanisms, it is known that the blood-brain barrier allows the non-selective passage of small quantities of chemotherapy capable of inducing neuronal and glial lesions with a dose-dependent effect of chemotherapy on cognitive functions (van Dam et al., 1998). Moreover, although the majority of chemotherapies not cross the blood-brain barrier in significant doses; the amount that enters the brain could be altered by genetic variability of blood-brain barrier transporters, and in particular Glycoprotein P which is encoded by the Multi-Drug Resistance gene (MDR1) (Ahles and Saykin, 2007). Although the aforementioned effects of chemotherapy are frequently being investigated, the effects of other and more novel treatments have been less of a focus and deserve further attention.

Endocrine therapy, which typically lasts for significantly longer than chemotherapy (at least 5 years), may also affect cognitive functions, especially verbal memory (Kjoe et al., 2022). Such work is supported by animal studies that have highlighted modifications in synaptic plasticity of the neurons of the hippocampus and the prefrontal cortex or in dopaminergic transmission (in nigrostriatal and mesolimbocortical areas) (Liu et al., 2008, Nicola et al., 2021). However, existing results in clinical studies remain mixed.

Finally, there are very few data regarding the direct impact of both targeted therapies and immunotherapies on cognitive functioning, while the latter has become a standard in several cancer treatments (Joly et al., 2020). Targeted therapies mainly rely on the inhibition of the vascular endothelial growth factor (VEGF). Generally, the VEGF has a neuroprotective action due to the inhibition of programmed cell death or apoptosis and the stimulation of neurogenesis (Góra-Kupilas and Jośko, 2005). Furthermore, the VEGF is also known for its crucial role in cognitive functioning and synaptic plasticity. Thus, such targeted therapies may also be responsible for cognitive difficulties in cancer patients. Indeed, a recent in-vivo study has shown that one such type of targeted therapy, Sunitinib, induced memory

disturbances and both hippocampal and cortical neurodegeneration in mice (Abdel-Aziz et al., 2016). Recent findings have also shown microglial activation following immunotherapy in rats (McGinnis et al., 2017). Such microglial activation has been associated with deficits in neural precursor cell population maintenance and neurogenesis, in synaptic structure and function, and in myelin plasticity after both chemo- and radiation therapies (Gibson and Monje, 2021).

b. Physical activity and sleep-related factors

Previous studies have shown that activity level is a significant prognostic and predictive factor for clinically relevant outcomes including quality of life and cognitive performance (Lange et al., 2019b; Salerno et al., 2021). Physical activity is recognized as an important modifiable risk factor for cancer in general (Lahousse et al., 2022). In the European scientific landscape, research has demonstrated that exercise programs are associated with an increase of patients' quality of life during and after treatment (Lahart et al., 2018). More specifically, physical activity is associated with improved cognitive functioning and a reduced risk of neurodegenerative alterations among cancer patients (Furmaniak et al., 2016; Hayes et al., 2019; Zou et al., 2014). Results from preclinical studies suggest positive effects of physical exercise on the expression of neurotrophic factors, the modulation of the blood-brain-barrier and the reduction of inflammatory markers (Erickson et al., 2015; Prakash et al., 2015; Stern et al., 2019; Zimmer et al., 2019). The gold standard to measure physical activity nowadays is actigraphy. However, in the case of financial or practical limitations, subjective measures can be used as a proxy as well, including the Godin's simple questionnaire to assess physical activity during leisure time (Godin and Shephard, 1985). However, as this measure is relatively unspecific, the GPAQ (Global physical activity questionnaire) is advised to use to assess different types of physical activity in daily life (Wanner et al., 2017).

It may also be possible that the beneficial effect of physical activity on cognition could be mediated by positive effects on sleep and fatigue, due to the fact that sleep and fatigue may partly be responsible for cognitive difficulties observed in non-CNS cancer patients (Duivon et al., 2021). Indeed, non-CNS cancer patients frequently complain about sleep difficulties (Leysen et al., 2019; Mogavero et al., 2021; Perrier et al., 2022; Perrier et al., 2021) and fatigue is known as a very prevalent and distressing long-term side effect among cancer survivors (Joly et al., 2019; Castelli et al., 2022; Grayson et al., 2022; Leysen et al., 2019). Moreover, previous reports have shown that physical activity reduce sleep and fatigue complaints in non-CNS cancer patients (de Nys et al., 2022; Sheehan et al., 2020). Sleep can be evaluated using self-report questionnaires, reflecting subjective sleep difficulties. The most well-validated measures include the Insomnia Severity Index (ISI) (Savard et al., 2005) and the Pittsburgh Sleep Quality Index (PSQI) (Akman et al., 2015). In addition, objective measures are available including actigraphy (i.e. accelerometer allowing to quantify sleep/wake cycle) and polysomnography (i.e. multimodal sleep assessment), of which the latter remains to be the most detailed and most recommended measure for sleep quality and quantity evaluation. Future studies will thus need to investigate whether physical activity (and other behavioral therapies) may reduce cognitive difficulties by improving sleep problems in cancer patients. Although interactions between sleep and physical exercise exist in the field of cognitive science, European preclinical and clinical trials in oncology investigating the beneficial effects on cognition remain sparse. Such trials need adequate control groups, sufficient duration and a rigorous protocol that complies with the “Frequency Intensity Type and Time” criteria of exercise interventions. The first large-scaled European interdisciplinary randomized controlled trial in cancer patients is currently ongoing, and will help to elucidate mechanisms associated with physical activity and cognition in cancer

patients (e.g. Physical Activity and Memory – PAM study, Exercise, Cancer and Cognition – ECCO study (Kiesl et al., 2022; Witlox et al., 2019; Zimmer et al., 2016).

c. Psychological factors

Cancer and its treatment can result in emotional distress (i.e., anxiety, depression, and psychological distress) that can interfere with or worsen cognitive functioning through various mechanisms (Boscher et al., 2020; Dias-Carvalho et al., 2021; Eng et al., 2014; Morel et al., 2015). First, from a neurobiological perspective, affective symptoms can influence neural signaling through neuroinflammatory processes, and dysregulation the hypothalamic pituitary axis, which can eventually result in impaired neuroplasticity and impaired cognitive functioning (Miller et al., 2008). Second, from a psychological perspective, intrusive thoughts related to the traumatic experience can monopolize attentional resources, which can have a negative effect on both working and episodic memory (Lau-Zhu et al., 2021). Furthermore, a passive coping style can lead to decreased cognitive performance (Het et al., 2005; Reid-Arndt and Cox, 2012). Although previous studies have shown links between affective factors, coping styles and subjective cognitive complaints, such associations have been scarcely investigated with neuropsychological performance (Lange et al., 2019b; Rogiers et al., 2020; Van Dyk and Ganz, 2021).

Regarding these psychological features, levels of depression and fear of cancer recurrence should be assessed to get more insight into the emotional well-being of the patient. Example measures include the Hospital Anxiety and Depression Scale (HADS) (Castelli et al., 2011) and Fear of Cancer Recurrence Inventory-Short Form (FCRI-SF) (Simard and Savard, 2009), respectively. In case of suspicion of a depressive or anxiety disorder, more specific diagnostic

tools can be used including the State-Anxiety Inventory (STAI) (Spielberger, 1987) and Beck Depression Inventory (BDI) (Beck et al., 1996). In addition, the EORTC QLQ-C30 can be used as this questionnaire measures several cancer-related symptoms and contains subscales of social, emotional and cognitive functioning (Giesinger et al., 2020). However, as questionnaires are a time-dependent and limited measure of daily life functioning, the dynamic character of complaints, their potentially bidirectional nature, and their links with affective factors and coping mechanisms could be addressed more deeply in cancer patients, using ecological momentary (i.e. evaluation in real-time and naturalistic environment) and digital methodology (Kampshoff et al., 2019).

d. The modulating role of aging

Cancer is predominantly a disease of older adults with the highest incidence rates in individuals age 65 and older. Given the general trend toward increased life expectancies, the aging population requires specific consideration (Lange et al., 2014). Age-related changes may occur even in the younger adult brain as a result of cancer and its treatment, which can even persist up to 20 years post-treatment (Koppelmans et al., 2012). Hence, whether such ageing processes occur at an accelerated rate in elderly, remains to be investigated. In addition, polypharmacy is highly prevalent in older cancer patients, with potential deleterious effects on cognitive functioning (Pamoukdjian et al., 2017; Sharma et al., 2016). Nevertheless, these patients are poorly represented in clinical trials (Mandelblatt et al., 2013). Aging itself, in addition to cancer and its treatment, are also associated with cognitive changes through multiple processes (Joly et al., 2019), such as neurodegenerative processes, comorbidities, polymedication and cell senescence, including from inflammation. Research has shown cognitive impairment to be significant in older adults. In one study, 49% of breast cancer patients over 65 years of age were assessed as having objective cognitive decline after treatment (Lange et al., 2016), and women carrying the apolipoprotein E (APOE) ε4 allele

seem to be at particular risk (Mandelblatt et al., 2018). In prostate cancer, cognitive deficits have been observed after androgen deprivation therapy (ADT) as well (Buskbjerg et al., 2021; Wu et al., 2016), although its impact remains inconclusive (Andela et al., 2021). As cognitive impairment may be associated with lower survival (Libert et al., 2016), it is important for older cancer patients to maintain autonomy and their cognitive skills. Moreover, given the strong associations between aging and an increase in the risk factors described above (i.e. sleep difficulties (Li et al., 2018), fatigue (Åkerstedt et al., 2018), sedentary behavior (Rojer et al., 2021) and anxiety disorders (Knight and Durbin, 2015)), one may expect that such factors should be taken into consideration even more in future CRCI studies focused on the older population.

Besides the abovementioned risk factors, many other confounding factors such as cognitive reserve, cancer itself (e.g. type, stage), metabolism, cardiovascular features, but also genetics factors can play an important role in cognitive outcomes in daily life. As older age and cognitive impairment are both related to a higher risk of insufficient management of cancer-related complications (Lund et al., 2022), systematic medical follow-up can be even more important in older cancer patients showing cognitive impairment.

e. Genetic variants

Recently, Sleurs and colleagues (Sleurs et al., 2019) reviewed the genetic variants associated with neurocognitive outcomes in cancer populations. In pediatrics, most genotypes were investigated in leukemia patients (ApoE, GST, NOS3, SLCO2A1, ADORA2A, COMT, MAO-A, MTHFR, MTR, TSER), of which only the neuroinflammation-related genotypes (i.e. GST, NOS3, SLCO2A1) were consistently and significantly associated with cognition. By contrast, fewer genotypes were investigated in adult cancer patients. These studies demonstrated the potential role of the ApoE and COMT genotypes in cognition in breast cancer patients, ApoE, BDNF, COMT, DTNB1 in brain tumor patients, and of a combined

folate pathway risk haplotype for leukoencephalopathy in lymphoma patients. Moreover, genotypes (e.g. ApoE) were more frequently associated with memory in adults and to attention-related outcomes in children. This finding seems to be in line with the hypothesis of age-dependent cancer-related neurotoxic effects.

4. Neurobiological mechanisms and biomarkers

In order to better understand the underlying mechanisms of CRCI, a number of studies have focused on biological as well as neuroimaging markers associated with cognitive difficulties in cancer patients. We summarize the most well-acknowledged findings.

a. Biological markers

Multiple fluid-based biomarkers (i.e. extracted from blood or cerebrospinal fluid) have been investigated in humans in the context of CRCI. Genetic polymorphisms have been associated with cognitive decline in cancer patients (Buskbjerg et al., 2019; Sleurs et al., 2019) and more dynamic measures such as pro-inflammatory cytokines (Castel et al., 2017), number of blood cells and hemoglobin, hormonal levels (e.g. estradiol), neuronal markers and epigenetic changes (Castel et al., 2017) have also been associated with cognitive outcomes. These clinical studies have been able to isolate markers associated with CRCI, but without clear causality yet. Preclinical studies suggest that the cancer itself may induce dysregulation of hormonal levels, inflammation, oxidative stress, architecture of vessels and the blood brain barrier (Winocur et al., 2018), and may be associated with cognitive outcomes (Walker et al., 2018; Yang et al., 2014). In addition, in healthy mice receiving chemotherapy, signs of brain alterations and damage were detected through oxidative balance, neurotransmitter/mono-amine release, or folate deficiency in cerebral spinal fluid (Li et al., 2010; Seigers et al., 2013; Sonis et al., 2004; Winocur et al., 2018). Behavioral models highlighted the cognitive impact of chemotherapy on hippocampal functions, mostly spatial and learning memory but also behavioral flexibility. Decline in these functions was associated with the inhibition of neural precursor proliferation and neurogenesis in the dentate gyrus (Dubois et al., 2014; Winocur et al., 2018). Moreover, reduction in dendritic spines and neuroinflammation through IL-17, IL-1β or the IL-6 receptor gp130 were also associated with hippocampal-mediated CRCI in mice (Groves et al., 2017; John et al., 2021). Interestingly, sex differences

have recently been described in young mice as a combination of chemotherapy induced short memory and executive functions impairment in males but not in females (Konsman et al., 2022). Moreover, this distinct male-related early effect of chemotherapy was supported by increased CCl2 expression in the prefrontal cortex and TNF-α associated intestine chronical inflammation, without excluding a potential impact on hippocampal functions. The interconnection between peripheral and hippocampal inflammation in CRCI was recently confirmed by Parment et al. (2022), showing that chemotherapy 5-fluorouracil (5-FU) caused a significant decrease in exploratory and motivation behaviors and cognitive functions, involving intestinal dysbiosis and intestine -macrophage inflammation, plasma cytokines such as IL-6 and TNF-α, brain hippocampal neuroinflammation and altered neurogenesis (Parment et al., 2022). Besides changes in these neuroinflammatory markers, neurotrophic factors (e.g. NfL, BDNF) can also play an important role in neuroplasticity as well (Ng et al., 2022; Schroyen et al., 2021).

b. Imaging

Besides fluid-based biomarkers, neuroimaging techniques are increasingly applied to disentangle the mechanisms associated with CRCI. The first radiological studies applied conventional anatomical scanning. These often case studies demonstrated chemotherapy-associated leukoencephalopathy (Schroyen et al., 2020). However, more recent imaging techniques permitted the investigation of toxic mechanisms in vivo in greater detail. These studies suggested functional and structural brain changes post-treatment (Mingmei and Caeyenberghs, 2018), including changes to brain activity (Sousa et al., 2020), metabolic changes (De Ruiter et al., 2012; Kahkonen et al., 1999; Schroyen et al., 2021; Stouten-Kemperman et al., 2015), microstructural white matter (Deprez et al., 2012) and grey matter changes (Niu et al., 2020), and recently structural brain networks (Amidi et al., 2017) and microglia-mediated neuroinflammatory changes (Schroyen et al., 2021). Regarding

functional changes, fMRI research has shown alterations in functional network dynamics that underly cognitive domains such as attention, memory and executive functioning, even at rest ('resting state paradigm') (de Ruiter et al., 2011). Furthermore, pre-treatment imaging features have been found to predict long-term cognitive outcomes. suggesting an impact of pre-existing neural reserves. These baseline alterations can be microstructural (de Ruiter et al., 2021), but functional as neural networks can also be affected in non-CNS cancer at baseline (Kesler et al., 2017), and are therefore possible predictive markers for post-treatment CRCI.

5. Future challenges in Europe

a. Moving our understanding of CRCI forward

A European consortium of Cancer and Cognition has recently emerged to integrate multidisciplinary expertise. This consortium has been largely involved in the European guidelines of the iPAAC Joint Action initiative dedicated to public authorities that highlighted guidelines for public actions related to CRCI in Europe (Hernández-García et al., 2022). The iPAAC "Work Package 4 – Integration in National Policies and Sustainability" aimed to collect examples of innovative approaches for implementing cancer control policies through the use of case study methodology focusing on the management of CRCI in Europe. To do so, the points of view of the different stakeholders i.e., researchers, physicians, therapists (e.g., psychologist and speech therapist), patients, members of public authorities, patients' associations and institutions concerning the management of CRCI (e.g., information, screening, interventions, return to work) were collected through interviews. These interviews were completed by a search of the scientific literature on CRCI non-pharmacological management and structures (e.g., clinics and associations) offering cognitive management in Europe. The report is summarized below and in Table 1.

The report's specific recommendations include making the topic of CRCI a priority in multidisciplinary national and European cancer control programs. It recommends that such inclusion be driven by interdisciplinary national and international research networks focused on CRCI that would facilitate the development of identification and assessment tools. Regarding communication to patients and professionals, the report suggests that cognitive impairment be included in supportive care assessment tools, and that multidisciplinary teamwork for post-treatment supportive care be promoted and supported by European funding organizations. The report goes on to encourage experts to raise awareness among public authorities and cancer societies/institutions as increased awareness and recognition of CRCI based on scientific information is a prerequisite for the effective implementation of rehabilitation into health care systems. The importance of including patients and patient organizations as key stakeholders is also emphasized in the report as vital for defining effective action plans into the future. Their perspective and priorities were taken into consideration to develop and implement the most important action plans in the iPAAC joint action.

Overall, research and the iPAAC report indicate that future efforts should focus on supporting research related to CRCI as well as the identification and training of health professionals to manage CRCI in a multidisciplinary manner. Indeed, informing patients and clinicians at an early stage about the potential for CRCI, together with developing systematic standardized and sensitive screening tools (e.g., through the use of apps or other technologies), may facilitate prompt access to appropriate interventions. Most importantly, the report highlights that CRCI and its management is an emerging topic that requires support from public authorities (including funding) in order to develop research and implementation in clinical settings that are still underdeveloped in Europe. Thus, the current European consortium of

Cancer and Cognition aims to support this process by launching future collaborative projects focusing on CRCI prevention and rehabilitation research, starting with this position paper.

Table 1: Summary of the "Guide for practices and recommendations for the management of cognitive impairment after cancer" published in the framework of the iPAAC (Innovative Partnership for Action Against Cancer)

Topics	Main findings of the survey	Recommendations to public authorities*	European countries with existing initiatives
Informing about CRCI	- Lack of information about CRCI by public authorities (e.g. national cancer plan, rehabilitation programs) - Most of health professionals are not aware of CRCI - Lack of information from professional to patients A demand from health professionals and patients to be informed about CRCI	- Promote initiatives of experts to raise awareness among public authorities - Promote the communication about CRCI by public authorities (e.g. in national cancer control programs) - Promote information to professionals and patients	Belgium Denmark Europe France Germany Netherlands Sweden United-Kingdom
Identifying and objectivizing of CRCI	- Underestimation of CRCI by health professionals - No consensus about tools for identification of CRCI - Lack of sensitive and specific tools to assess CRCI - No systematic identification and assessments of CRCI - Lack of organization	- Organize the identification and assessement of CRCI - Use specific assessments - Use available validated tools - Defining professionals' roles - Develop adapted tools	Belgium Denmark France Sweden
Management of CRCI	- Supportive care programs do not include systematically CRCI management - Lack of availability of supportive care for patients - Large inequalities in the access to supportive care - Strong skills in cancer patients leagues and associations to promote CRCI management	- Identify resources available - Set up, develop and facilitate access to supportive care - Develop and promote post cancers care programs for CRCI - Implement management of CRCI in existing organizations	Belgium Denmark Europe France Norway Portugal Sweden
Management of CRCI for return to work	- High socioeconomic burden of work incapacity - Cancer survivors are increasing and want to	- Organize return-to-work consultation with a focus on CRCI - Inform the working environment	Belgium Denmark Europe

	be supported for their return-to-work - Return-to-work is a priority of the European public authorities - Few ressources on return to work after cancer that deal with CRCI	about CRCI - Ensure coordinators of actors involved in the return-to-work	France Germany Netherlands Sweden
Identify and train healthcare professionals for the management of CRCI	- Various healthcare professionals can be involved for the management of CRCI - Few initiatives to promote multidisciplinary work - Lack of training of healthcare professionals about CRCI	- Identify healthcare professionals trained for CRCI management - Train healthcare professionals to CRCI, their identification, assessement and management - Promote multidisciplinary teamwork	Belgium France
Support research related to CRCI	- CRCI is a complex problem requiring a multidisciplinary approach - Research teams already helped developing tools and creating network - Few programs used in clinical routine - CRCI research is under financed - CRCI research is missing from the European agenda	- Support national and international networks on CRCI - Encourage evaluation of the implementation of cognitive management programs in clinical settings - Promote multidisciplinary and interdisciplinary projects on CRCI	Belgium France Netherlands Portugal

*****All recommendations have been voted by experts in the field following the iPAAC consortium meeting; CRCI, cancer-related cognitive impairments

Besides these iPAAC guidelines, the European consortium aims to move towards the development of large European databanks. In addition, translational collaborations between the multidisciplinary teams working on human and preclinical data would allow us to expand our understanding of neurobiological changes associated with cancer and its treatment. This work would be relatively feasible due to the proximity of countries within Europe. Also, Europe has the opportunity to bring together diverse teams of professionals, including (neuro)psychologists, neuroimaging specialists, physiologists, biologists and clinicians, that could facilitate the coalescing of multidisciplinary theoretical knowledge. Such a multidisciplinary approach is crucial to better disentangling the relative contributions of psychological, physiological and biological changes associated with CRCI.

b. Towards adapted cognitive intervention (rehabilitation) programs

Regarding interventions, the iPAAC guidelines state that post-cancer care programs for cognitive impairment should be promoted. For this purpose, the organization and promotion of education of healthcare workers ought to be a priority. The consortium aims to inform professionals and communities on the basis of most recent scientific information. Furthermore, patients would benefit from workplaces being alerted to the impact of CRCI on the ability of patients to return to work, and how return-to-work consultations ought to be developed to facilitate a more effective and health-promoting return to work. Hence, rehabilitation research would benefit from a real-world perspective that more directly translates to patients' ability to function at home and at work (Fernandes et al., 2019). Additionally, given the interdependence of symptoms, cognitive interventions may also benefit from targeting related symptoms such as sleep, fatigue, and mood disorders in addition to targeting CRCI directly.

6. Conclusion

Cognitive impairment is an important side-effect reported by the non-CNS patients during and after treatments. European challenges in the field include the improvement of the integration of this question in practice, as suggested by the iPAAC's report. If health-care providers nowadays recognize this potential side effect, effort should be done to include its screening in routine and to develop strategies to help the patients. These strategies should be supported by European Health Authorities. The development of new technologies is a good opportunity to help the health-care providers to screen and follow cognitive difficulties. However, CRCI is a complex process, as co-occurring symptoms and the physiopathology are not well understood.

Collaborative European multidisciplinary works including preclinical, clinical, imaging and biological aspects to better understand CRCI should be encouraged, particularly with new cancer therapies such as immune therapies or a new generation of hormone therapies. Important challenges are also to develop multimodal interventions to support the patients reporting cognitive impairment and more particularly when there is a project of work return. Targetable parameters such as sleep, fatigue, mood, behavioral risk factors (i.e. diet, physical activities) should be better identified to include them in these future programs. Finally, education of healthcare workers should be also a future priority in order to help them more readily identify individuals who are likely to be vulnerable to CRCI and could benefit from targeted treatment interventions.

Acknowledgments: This work was supported by the *Région Normandie* (*Réseaux d'Intérêts Normands*, RIN) and the *Ligue contre le Cancer – Normandie*. This work was also supported by the *Ligue nationale contre le cancer* (Cancer and Cognition platform), and the *Fonds Européens du Développement Régional* (FEDER, project CancerCOG), Normandy Rouen University and Inserm.

Authors contributions: All authors have equally contributed to this work meaning planned, written and corrected the manuscript. Moreover, both JP and CS led the final version of the manuscript and its submission.

Conflict of interest: None of the authors has conflict of interest related to the content of this paper.

Aaronson, N.K., Ahmedzai, S., Bergman, B., Bullinger, M., Cull, A., Duez, N.J., Filiberti, A., Flechtner, H., Fleishman, S.B., Haes, J.C.J.M.D., Kaasa, S., Klee, M., Osoba, D., Razavi, D., Rofe, P.B., Schraub, S., Sneeuw, K., Sullivan, M., Takeda, F., 1993. The European organization for research and treatment of cancer QLQ-C30: A quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 85. https://doi.org/10.1093/jnci/85.5.365

Abdel-Aziz, A.K., Mantawy, E.M., Said, R.S., Helwa, R., 2016. The tyrosine kinase inhibitor, sunitinib malate, induces cognitive impairment in vivo via dysregulating VEGFR signaling, apoptotic and autophagic machineries. Exp Neurol 283, 129–141. https://doi.org/10.1016/j.expneurol.2016.06.004

Ahles, T., Saykin, A., 2007. Candidate mechanisms for chemotherapy-induced cognitive changes. Nat Rev Cancer 7, 192–201. https://doi.org/10.1038/nrc2073

Åkerstedt, T., Discacciati, A., Miley-Åkerstedt, A., Westerlund, H., 2018. Aging and the change in fatigue and sleep - A longitudinal study across 8 years in three age groups. Front Psychol 9. https://doi.org/10.3389/fpsyg.2018.00234

Akman, T., Yavuzsen, T., Sevgen, Z., Ellidokuz, H., Yilmaz, A.U., 2015. Evaluation of sleep disorders in cancer patients based on Pittsburgh Sleep Quality Index. Eur J Cancer Care (Engl) 24. https://doi.org/10.1111/ecc.12296

Amidi, Ali, Agerbaek, M., Wu, L.M., Pedersen, A.D., Mehlsen, M., Clausen, C.R., Demontis, D., Borglum, A.D., Harboll, A., Zachariae, R., 2017. Changes in cognitive functions and cerebral grey matter and their associations with inflammatory markers, endocrine markers, and APOE genotypes in testicular cancer patients undergoing treatment. Brain Imaging Behav 11, 769–783. https://doi.org/10.1007/s11682-016-9552-3

Amidi, A., Hosseini, S.M.H., Leemans, A., Kesler, S.R., Agerbæk, M., Wu, L.M., Zachariae, R., 2017. Changes in Brain Structural Networks and Cognitive Functions in Testicular Cancer Patients Receiving Cisplatin-Based Chemotherapy. J Natl Cancer Inst 109. https://doi.org/10.1093/jnci/djx085

Andela, C.D., Matte, R., Jazet, I.M., Zonneveld, W.C.G., Schoones, J.W., Meinders, A.E., 2021. Effect of androgen deprivation therapy on cognitive functioning in men with prostate cancer: A systematic review. International Journal of Urology. https://doi.org/10.1111/iju.14596

Beck, A., Steer, R., Brown, G., 1996. Beck Depression Inventory-II. San Antonio 12–15. https://doi.org/10.1037/t00742-000

Bernstein, L.J., McCreath, G.A., Komeylian, Z., Rich, J.B., 2017. Cognitive impairment in breast cancer survivors treated with chemotherapy depends on control group type and cognitive domains assessed: A multilevel meta-analysis. Neurosci Biobehav Rev. https://doi.org/10.1016/j.neubiorev.2017.10.028

Binarelli, G., Lange, M., Dos Santos, M., Grellard, J.M., Lelaidier, A., Tron, L., Lefevre Arbogast, S., Clarisse, B., Joly, F., 2021. Multimodal web-based intervention for cancer-related cognitive impairment in breast cancer patients: Cog-stim feasibility study protocol. Cancers (Basel) 13. https://doi.org/10.3390/cancers13194868

Boscher, C., Joly, F., Clarisse, B., Humbert, X., Grellard, J.M., Binarelli, G., Tron, L., Licaj, I., Lange, M., 2020. Perceived cognitive impairment in breast cancer survivors and its relationships with psychological factors. Cancers (Basel) 12. https://doi.org/10.3390/cancers12103000

Bray, V.J., Dhillon, H.M., Vardy, J.L., 2018. Systematic review of self-reported cognitive function in cancer patients following chemotherapy treatment. Journal of Cancer Survivorship. https://doi.org/10.1007/s11764-018-0692-x

Buskbjerg, C.D.R., Amidi, A., Demontis, D., Nissen, E.R., Zachariae, R., 2019. Genetic risk factors for cancer-related cognitive impairment: a systematic review. Acta Oncol (Madr). https://doi.org/10.1080/0284186X.2019.1578410

Buskbjerg, C.R., Zachariae, R., Agerbæk, M., Gravholt, C.H., Haldbo-Classen, L., Hosseini, S.M.H., Amidi, A., 2021. Cognitive impairment and associations with structural brain networks, endocrine status, and risk genotypes in newly orchiectomized testicular cancer patients. Brain Imaging Behav. https://doi.org/10.1007/s11682-021-00492-x

Castel, H., Denouel, A., Lange, M., Tonon, M.-C., Dubois, M., Joly, F., 2017. Biomarkers Associated with Cognitive Impairment in Treated Cancer Patients: Potential Predisposition and Risk Factors. Front Pharmacol 8, 138. https://doi.org/10.3389/fphar.2017.00138

Castelli, L., Binaschi, L., Caldera, P., Mussa, A., Torta, R., 2011. Fast screening of depression in cancer patients: The effectiveness of the HADS. Eur J Cancer Care (Engl) 20. https://doi.org/10.1111/j.1365-2354.2010.01217.x

Castelli, L., Elter, T., Wolf, F., Watson, M., Schenk, A., Steindorf, K., Bloch, W., Hallek, M., Joisten, N., Zimmer, P., 2022. Sleep problems and their interaction with physical activity and fatigue in hematological cancer patients during onset of high dose chemotherapy. Supportive Care in Cancer 30. https://doi.org/10.1007/s00520-021-06377-5

Crocetti, E., Bossard, N., Uhry, Z., Roche, L., Rossi, S., Capocaccia, R., Faivre, J., Van Eycken, E., Henau, K., Velten, M., Bouvier, V., Launoy, G., Bouvier, A.M., Woronoff, A.S., Robaszkiewicz, M., Tretarre, B., Colonna, M., Molinié, F., Bara, S., Lapôtre-Ledoux, B., Grosclaude, P., Brenner, H., Katalinic, A., Mazzoleni, G., Bulatko, A., Buzzoni, C., Giacomin, A., Ferretti, S., Barchielli, A., Manneschi, G., Gatta, G., Sant, M., Amash, H., Amati, C., Baili, P., Berrino, F., Bonfarnuzzo, S., Botta, L., Di Salvo, F., Foschi, R., Margutti, C., Meneghini, E., Minicozzi, P., Trama, A., Serraino, D., Zucchetto, A., De Angelis, R., Caldora, M., Carrani, E., Francisci, S., Mallone, S., Pierannunzio, D., Roazzi, P., Santaquilani, M., Tavilla, A., Pannozzo, F., Natali, M., Filiberti, R.A., Vercelli, M., Ricci, P., Autelitano, M., Randi, G., Ponz De Leon, M., Spagnoli, G., Cirilli, C., Fusco, M., Vitale, M.F., Michiara, M., Tumino, R., Mangone, L., Di Felice, E., Falcini, F., Iannelli, A., Sechi, O., Cesaraccio, R., Piffer, S., Madeddu, A., Tisano, F., Maspero, S., Fanetti, A.C., Zanetti, R., Rosso, S., Stracci, F., Rocca, A., Tagliabue, G., Contiero, P., Rugge, M., Guzzinati, S., Bielska-Lasota, M., Bento, M.J., Castro, C., Miranda, A., Mayer-Da-silva, A., Primic-Zakelj, M., Almar, E., Mateos, A., Errezola, M., Larrañaga, N., Díaz García, J.M., Marcos-Navarro, A.I., Marcos-Gragera, R., Carmona-Garcia, M.C., Sanchez, M.J., Chang, D.Y.L., Navarro, C., Chirlaque, M.D., Moreno-Iribas, C., Ardanaz, E., Galceran, J., Carulla, M., Lambe, M., Mousavi, M., Bouchardy, C., Usel, M., Ess, S.M., Frick, H., Lorez, M., Herrmann, C., Bordoni, A., Spitale, A., Konzelmann, I., Otter, R., Coleman, M., Allemani, C., Rachet, B., Verne, J., 2017. Trends in net survival from 15 cancers in six European Latin countries: The SUDCAN population-based study material. European Journal of Cancer Prevention 26. https://doi.org/10.1097/CEJ.0000000000000300

De Angelis, R., Sant, M., Coleman, M.P., Francisci, S., Baili, P., Pierannunzio, D., Trama, A., Visser, O., Brenner, H., Ardanaz, E., Bielska-Lasota, M., Engholm, G., Nennecke, A., Siesling, S., Berrino, F., Capocaccia, R., Group, E.-5 W., 2014. Cancer survival in Europe 1999-2007 by country and age: results of EUROCARE-5-a population-based study. Lancet Oncol 15.

de Nys, L., Anderson, K., Ofosu, E.F., Ryde, G.C., Connelly, J., Whittaker, A.C., 2022. The effects of physical activity on cortisol and sleep: a systematic review and meta-analysis. Psychoneuroendocrinology 105843. https://doi.org/10.1016/j.psyneuen.2022.105843

De Ruiter, M.B., Reneman, L., Boogerd, W., Veltman, D.J., Caan, M., Douaud, G., Lavini, C., Linn, S.C., Boven, E., Van Dam, F.S.A.M., Schagen, S.B., 2012. Late effects of high-dose adjuvant chemotherapy on white and gray matter in breast cancer survivors: Converging results from multimodal magnetic resonance imaging. Hum Brain Mapp 33, 2971–2983. https://doi.org/10.1002/hbm.21422

de Ruiter, M.B., Reneman, L., Boogerd, W., Veltman, D.J., van Dam, F.S.A.M.A.M., Nederveen, A.J., Boven, E., Schagen, S.B., 2011. Cerebral hyporesponsiveness and cognitive impairment 10 years after chemotherapy for breast cancer. Hum Brain Mapp 32, 1206–1219. https://doi.org/10.1002/hbm.21102

de Ruiter, M.B., Reneman, L., Kieffer, J.M., Oldenburg, H.S.A., Schagen, S.B., 2021. Brain white matter microstructure as a risk factor for cognitive decline after chemotherapy for breast cancer. Journal of Clinical Oncology in press.

Deprez, S., Amant, F., Smeets, A., Peeters, R., Leemans, A., Van Hecke, W., Verhoeven, J.S., Christiaens, M.-R., Vandenberghe, J., Vandenbulcke, M., Sunaert, S., 2012. Longitudinal assessment of chemotherapy-induced structural changes in cerebral white matter and its correlation with impaired cognitive functioning. J Clin Oncol 30, 274–281. https://doi.org/10.1200/JCO.2011.36.8571

Deprez, S., Amant, F., Yigit, R., Porke, K., Verhoeven, J., Stock, J. van den, Smeets, A., Christiaens, M.R., Leemans, A., Hecke, W. van, Vandenberghe, J., Vandenbulcke, M., Sunaert, S., 2011. Chemotherapy-induced structural changes in cerebral white matter and its correlation with impaired cognitive functioning in breast cancer patients. Hum Brain Mapp 32, 480–493. https://doi.org/10.1002/hbm.21033

Dias-Carvalho, A., Ferreira, M., Ferreira, R., Bastos, M., Sá, S., Capela, J., Carvalho, F., Costa, V., 2021. Four decades of chemotherapy-induced cognitive dysfunction: comprehensive review of clinical, animal and in vitro studies, and insights of key initiating events. Arch Toxicol Epub ahead. https://doi.org/10.1007/s00204-021-03171-4

Dubois, M., Lapinte, N., Villier, V., Lecointre, C., Roy, V., Tonon, M.-C., Gandolfo, P., Joly, F., Hilber, P., Castel, H., 2014. Chemotherapy-induced long-term alteration of executive functions and hippocampal cell proliferation: role of glucose as adjuvant. Neuropharmacology 79, 234–248. https://doi.org/10.1016/j.neuropharm.2013.11.012

Duivon, M., Giffard, B., Desgranges, B., Perrier, J., 2021. Are Sleep Complaints Related to Cognitive Functioning in Non-Central Nervous System Cancer? A Systematic Review. Neuropsychol Rev. https://doi.org/10.1007/s11065-021-09521-4

Eng, J.W.L., Kokolus, K.M., Reed, C.B., Hylander, B.L., Ma, W.W., Repasky, E.A., 2014. A nervous tumor microenvironment: the impact of adrenergic stress on cancer cells, immunosuppression, and immunotherapeutic response. Cancer Immunology, Immunotherapy. https://doi.org/10.1007/s00262-014-1617-9

Erickson, K.I., Hillman, C.H., Kramer, A.F., 2015. Physical activity, brain, and cognition. Curr Opin Behav Sci. https://doi.org/10.1016/j.cobeha.2015.01.005

Feenstra, H.E.M., Murre, J.M.J., Vermeulen, I.E., Kieffer, J.M., Schagen, S.B., 2017. Reliability and validity of a self-administered tool for online neuropsychological testing: The Amsterdam Cognition Scan. J Clin Exp Neuropsychol 1–21. https://doi.org/10.1080/13803395.2017.1339017

Fernandes, H.A., Richard, N.M., Edelstein, K., 2019. Cognitive rehabilitation for cancer-related cognitive dysfunction: a systematic review. Supportive Care in Cancer. https://doi.org/10.1007/s00520-019-04866-2

Furmaniak, A.C., Menig, M., Markes, M.H., 2016. Exercise for women receiving adjuvant therapy for breast cancer. Cochrane Database of Systematic Reviews. https://doi.org/10.1002/14651858.CD005001.pub3

Gibson, E.M., Monje, M., 2021. Microglia in Cancer Therapy-Related Cognitive Impairment. Trends Neurosci. https://doi.org/10.1016/j.tins.2021.02.003

Giesinger, J.M., Loth, F.L.C., Aaronson, N.K., Arraras, J.I., Caocci, G., Efficace, F., Groenvold, M., van Leeuwen, M., Petersen, M.A., Ramage, J., Tomaszewski, K.A., Young, T., Holzner, B., 2020. Thresholds for clinical importance were established to improve interpretation of the EORTC QLQ-C30 in clinical practice and research. J Clin Epidemiol 118. https://doi.org/10.1016/j.jclinepi.2019.10.003

Godin, G., Shephard, R.J., 1985. A simple method to assess exercise behavior in the community. Can J Appl Sport Sci 10.

Góra-Kupilas, K., Jośko, J., 2005. The neuroprotective function of vascular endothelial growth factor (VEGF). Folia Neuropathol.

Grayson, S., Sereika, S., Harpel, C., Diego, E., Steiman, J.G., McAuliffe, P.F., Wesmiller, S., 2022. Factors associated with sleep disturbances in women undergoing treatment for early-stage breast cancer. Supportive Care in Cancer 30. https://doi.org/10.1007/s00520-021-06373-9

Groves, T.R., Farris, R., Anderson, J.E., Alexander, T.C., Kiffer, F., Carter, G., Wang, J., Boerma, M., Allen, A.R., 2017. 5-Fluorouracil chemotherapy upregulates cytokines and alters hippocampal dendritic complexity in aged mice. Behavioural Brain Research 316. https://doi.org/10.1016/j.bbr.2016.08.039

Hardy-Leger, I., Charles, C., Lange, M., Joly, F., Roux, P., Capel, A., Petrucci, J., Rigal, O., Le Fel, J., Vanlemmens, L., Everhard, S., Martin, A.L., Vaz Luis, I., Coutant, C., Cottu, P., Levy, C., Lerebours, F., Andre, F., Licaj, I., Dauchy, S., 2021. Differentiation of groups of patients with cognitive complaints at breast cancer diagnosis: Results from a sub-study of the French CANTO cohort. Psychooncology 30. https://doi.org/10.1002/pon.5572

Hayes, S.C., Newton, R.U., Spence, R.R., Galvão, D.A., 2019. The Exercise and Sports Science Australia position statement: Exercise medicine in cancer management. J Sci Med Sport. https://doi.org/10.1016/j.jsams.2019.05.003

Hernández-García, M., Salas-Trejo, D., Anttila, A., Lipponen, S., Molina-Barceló, A., 2022. Contest of Best Practices tackling social inequalities in cancer prevention: an iPAAC initiative. Eur J Public Health 32. https://doi.org/10.1093/eurpub/ckab206

Het, S., Ramlow, G., Wolf, O.T., 2005. A meta-analytic review of the effects of acute cortisol administration on human memory. Psychoneuroendocrinology 30. https://doi.org/10.1016/j.psyneuen.2005.03.005

Jacobs, S.R., Jacobsen, P.B., Booth-Jones, M., Wagner, L.I., Anasetti, C., 2007. Evaluation of the functional assessment of cancer therapy cognitive scale with hematopoietic stem cell transplant patients. J Pain Symptom Manage 33, 13–23. https://doi.org/10.1016/j.jpainsymman.2006.06.011

John, J., Kinra, M., Mudgal, J., Viswanatha, G.L., Nandakumar, K., 2021. Animal models of chemotherapy-induced cognitive decline in preclinical drug development. Psychopharmacology (Berl). https://doi.org/10.1007/s00213-021-05977-7

Joly, F., Castel, H., Tron, L., Lange, M., Vardy, J., 2020. Potential effect of immunotherapy agents on cognitive function in cancer patients. J Natl Cancer Inst. https://doi.org/10.1093/JNCI/DJZ168

Joly, F., Henry-Amar, M., Arveux, P., Reman, O., Tanguy, A., Peny, A.M., Lebailly, P., Macé-Lesec'h, J., Vié, B., Génot, J.Y., Busson, A., Troussard, X., Leporrier, M., 1996. Late psychosocial sequelae in Hodgkin's disease survivors: A French population-based case-control study. Journal of Clinical Oncology 14. https://doi.org/10.1200/JCO.1996.14.9.2444

Joly, F., Lange, M., Dos Santos, M., Vaz-Luis, I., Di Meglio, A., 2019. Long-term fatigue and cognitive disorders in breast cancer survivors. Cancers (Basel). https://doi.org/10.3390/cancers11121896

Kahkonen, M., Harila-Saari, A., Metsahonkala, L., Korhonen, T., Norvasuo-Heila, M.K., Utriainen, T., Ahonen, A., Bergman, J., Salmi, T.T., Minn, H., 1999. Cerebral blood flow and glucose metabolism in long-term survivors of childhood acute lymphoblastic leukaemia. Eur J Cancer 35, 1102–1108.

Kampshoff, C.S., Verdonck-de Leeuw, I.M., van Oijen, M.G., Sprangers, M.A., Buffart, L.M., 2019. Ecological momentary assessments among patients with cancer: A scoping review. Eur J Cancer Care (Engl). https://doi.org/10.1111/ecc.13095

Kesler, S.R., Adams, M., Packer, M., Rao, V., Henneghan, A.M., Blayney, D.W., Palesh, O., 2017. Disrupted brain network functional dynamics and hyper-correlation of structural and functional connectome topology in patients with breast cancer prior to treatment. Brain Behav 7, e00643. https://doi.org/10.1002/brb3.643

Kiesl, D., Kuzdas-Sallaberger, M., Fuchs, D., Brunner, S., Kommenda, R., Tischler, C., Hornich, H., Akbari, K., Kellermair, J., Blessberger, H., Ocenasek, H., Hofmann, P., Zimmer, P., Vosko, M.R., 2022. Protocol for the Exercise, Cancer and Cognition – The ECCO-Study: A Randomized Controlled Trial of Simultaneous Exercise During Neo-/Adjuvant Chemotherapy in Breast Cancer Patients and Its Effects on Neurocognition. Front Neurol 13. https://doi.org/10.3389/fneur.2022.777808

Kjoe, P.R.L.M., van der Wall, E., Schagen, S.B., 2022. Endocrine Therapy With or Without CDK4/6 Inhibitors in Women With Hormone-receptor Positive Breast Cancer: What do we Know About the Effects on Cognition? Clin Breast Cancer. https://doi.org/10.1016/j.clbc.2021.08.002

Knight, B.G., Durbin, K., 2015. Aging and the effects of emotion on cognition: Implications for psychological interventions for depression and anxiety. Psych J 4. https://doi.org/10.1002/pchj.84

Konsman, J.P., Laaker, C.J., Lloyd, K.R., Hiltz, A., Smith, B.L., Smail, M.A., Reyes, T.M., 2022. Translationally relevant mouse model of early life cancer and chemotherapy exposure results in brain and small intestine cytokine responses: A potential link to cognitive deficits. Brain Behav Immun 99. https://doi.org/10.1016/j.bbi.2021.10.003

Koppelmans, V., Breteler, M.M.B., Boogerd, W., Seynaeve, C., Gundy, C., Schagen, S.B., 2012. Neuropsychological performance in survivors of breast cancer more than 20 years after adjuvant chemotherapy. J Clin Oncol 30, 1080–1086. https://doi.org/10.1200/JCO.2011.37.0189

Kreukels, B.P.C., Hamburger, H.L., de Ruiter, M.B., van Dam, F.S.A.M., Ridderinkhof, K.R., Boogerd, W., Schagen, S.B., 2008. ERP amplitude and latency in breast cancer survivors treated with adjuvant chemotherapy. Clinical Neurophysiology 119. https://doi.org/10.1016/j.clinph.2007.11.011

Lahart, I.M., Metsios, G.S., Nevill, A.M., Carmichael, A.R., 2018. Physical activity for women with breast cancer after adjuvant therapy. Cochrane Database of Systematic Reviews. https://doi.org/10.1002/14651858.CD011292.pub2

Lahousse, A., Roose, E., Leysen, L., Yilmaz, S.T., Mostaqim, K., Reis, F., Rheel, E., Beckwée, D., Nijs, J., 2022. Lifestyle and pain following cancer: State-of-the-art and future directions. J Clin Med 11. https://doi.org/10.3390/jcm11010195

Lange, M., Heutte, N., Rigal, O., Noal, S., Kurtz, J.-E., Levy, C., Allouache, D., Rieux, C., Lefel, J., Clarisse, B., Veyret, C., Barthelemy, P., Longato, N., Castel, H., Eustache, F., Giffard, B., Joly, F., 2016. Decline in Cognitive Function in Older Adults With Early-Stage Breast Cancer After Adjuvant Treatment. Oncologist. https://doi.org/10.1634/theoncologist.2016-0014

Lange, M., Joly, F., Vardy, J., Ahles, T., Dubois, M., Tron, L., Winocur, G., De Ruiter, M.B., Castel, H., 2019a. Cancer-related cognitive impairment: An update on state of the art, detection, and management strategies in cancer survivors. Annals of Oncology. https://doi.org/10.1093/annonc/mdz410

Lange, Marie, Licaj, I., Clarisse, B., Humbert, X., Grellard, J.M., Tron, L., Joly, F., 2019b. Cognitive complaints in cancer survivors and expectations for support: Results from a web–based survey. Cancer Med 8. https://doi.org/10.1002/cam4.2069

Lange, M., Rigal, O., Clarisse, B., Giffard, B., Sevin, E., Barillet, M., Eustache, F., Joly, F., 2014. Cognitive dysfunctions in elderly cancer patients: a new challenge for oncologists. Cancer Treat Rev 40, 810–817. https://doi.org/10.1016/j.ctrv.2014.03.003

Lau-Zhu, A., Henson, R.N., Holmes, E.A., 2021. Selectively Interfering With Intrusive but Not Voluntary Memories of a Trauma Film: Accounting for the Role of Associative Memory. Clinical Psychological Science 9. https://doi.org/10.1177/2167702621998315

Leysen, L., Lahousse, A., Nijs, J., Adriaenssens, N., Mairesse, O., Ivakhnov, S., Bilterys, T., Van Looveren, E., Pas, R., Beckwée, D., 2019. Prevalence and risk factors of sleep disturbances in breast cancersurvivors: systematic review and meta-analyses. Supportive Care in Cancer. https://doi.org/10.1007/s00520-019-04936-5

Li, J., Vitiello, M. V., Gooneratne, N.S., 2018. Sleep in Normal Aging. Sleep Med Clin. https://doi.org/10.1016/j.jsmc.2017.09.001

Li, Y., Vijayanathan, V., Gulinello, M., Cole, P.D., 2010. Intrathecal methotrexate induces focal cognitive deficits and increases cerebrospinal fluid homocysteine. Pharmacol Biochem Behav 95. https://doi.org/10.1016/j.pbb.2010.03.003

Libert, Y., Dubruille, S., Borghgraef, C., Etienne, A.M., Merckaert, I., Paesmans, M., Reynaert, C., Roos, M., Slachmuylder, J.L., Vandenbossche, S., Bron, D., Razavi, D., 2016. Vulnerabilities in older patients when cancer treatment is initiated: Does a cognitive impairment impact the two-year survival? PLoS One 11. https://doi.org/10.1371/journal.pone.0159734

Liu, F., Day, M., Muñiz, L.C., Bitran, D., Arias, R., Revilla-Sanchez, R., Grauer, S., Zhang, G., Kelley, C., Pulito, V., Sung, A., Mervis, R.F., Navarra, R., Hirst, W.D., Reinhart, P.H., Marquis, K.L., Moss, S.J., Pangalos, M.N., Brandon, N.J., 2008. Activation of estrogen receptor-β regulates hippocampal synaptic plasticity and improves memory. Nat Neurosci 11. https://doi.org/10.1038/nn2057

Lund, C.M., Mikkelsen, M.K., Theile, S., Michelsen, H.M., Schultz, M., Sengeløv, L., Nielsen, D.L., 2022. Age-related Differences in Recall of Information and Handling of Chemotherapy-related Side Effects in Cancer Patients: The ReCap Study. Oncologist 27. https://doi.org/10.1093/oncolo/oyab034

Mandelblatt, J.S., Hurria, A., McDonald, B.C., Saykin, A.J., Stern, R.A., VanMeter, J.W., McGuckin, M., Traina, T., Denduluri, N., Turner, S., Howard, D., Jacobsen, P.B., Ahles, T., 2013. Cognitive effects of cancer and its treatments at the intersection of aging: what do we know; what do we need to know? Semin Oncol 40, 709–725. https://doi.org/10.1053/j.seminoncol.2013.09.006

Mandelblatt, J.S., Small, B.J., Luta, G., Hurria, A., Jim, H., McDonald, B.C., Graham, D., Zhou, X., Clapp, J., Zhai, W., Breen, E., Carroll, J.E., Denduluri, N., Dilawari, A., Extermann, M., Isaacs, C., Jacobsen, P.B., Kobayashi, L.C., Holohan Nudelman, K., Root, J., Stern, R.A., Tometich, D., Turner, R., VanMeter, J.W., Saykin, A.J., Ahles, T., 2018. Cancer-related cognitive outcomes among older breast cancer survivors in the thinking and living with cancer study. Journal of Clinical Oncology 36. https://doi.org/10.1200/JCO.18.00140

McGinnis, G.J., Friedman, D., Young, K.H., Torres, E.R.S., Thomas, C.R., Gough, M.J., Raber, J., 2017. Neuroinflammatory and cognitive consequences of combined radiation

and immunotherapy in a novel preclinical model. Oncotarget 8. https://doi.org/10.18632/oncotarget.13551

Mehlsen, M., Pedersen, A.D., Jensen, A.B., Zachariae, R., 2009. No indications of cognitive side-effects in a prospective study of breast cancer patients receiving adjuvant chemotherapy. Psychooncology 18, 248–257. https://doi.org/10.1002/pon.1398

Menning, S., de Ruiter, M.B., Veltman, D.J., Koppelmans, V., Kirschbaum, C., Boogerd, W., Reneman, L., Schagen, S.B., 2015. Multimodal MRI and cognitive function in patients with breast cancer prior to adjuvant treatment--the role of fatigue. Neuroimage Clin 7, 547–554. https://doi.org/10.1016/j.nicl.2015.02.005

Miller, A.H., Ancoli-Israel, S., Bower, J.E., Capuron, L., Irwin, M.R., 2008. Neuroendocrine-immune mechanisms of behavioral comorbidities in patients with cancer. J Clin Oncol 26, 971–982. https://doi.org/10.1200/JCO.2007.10.7805

Mingmei, L., Caeyenberghs, K., 2018. Longitudinal assessment of chemotherapy-induced changes in brain and cognitive functioning: A systematic review. Neurosci Biobehav Rev.

Mogavero, M.P., DelRosso, L.M., Fanfulla, F., Bruni, O., Ferri, R., 2021. Sleep disorders and cancer: State of the art and future perspectives. Sleep Med Rev. https://doi.org/10.1016/j.smrv.2020.101409

Morel, N., Dayan, J., Piolino, P., Viard, A., Allouache, D., Noal, S., Levy, C., Joly, F., Eustache, F., Giffard, B., 2015. Emotional specificities of autobiographical memory after breast cancer diagnosis. Conscious Cogn 35, 42–52. https://doi.org/10.1016/j.concog.2015.04.016

Ng, D.Q., Chan, D., Agrawal, P., Zhao, W., Xu, X., Acharya, M., Chan, A., 2022. Evidence of brain-derived neurotrophic factor in ameliorating cancer-related cognitive impairment: A systematic review of human studies. Crit Rev Oncol Hematol. https://doi.org/10.1016/j.critrevonc.2022.103748

Niu, R., Du, M., Ren, J., Qing, H., Wang, X., Xu, G., Lei, D., Zhou, P., 2020. Chemotherapy-induced grey matter abnormalities in cancer survivors: a voxel-wise neuroimaging meta-analysis. Brain Imaging Behav. https://doi.org/10.1007/s11682-020-00402-7

Oberste, M., Schaffrath, N., Schmidt, K., Bloch, W., Jäger, E., Steindorf, K., Hartig, P., Joisten, N., Zimmer, P., 2018. Protocol for the "chemobrain in Motion - Study" (CIM - Study): A randomized placebo-controlled trial of the impact of a high-intensity interval endurance training on cancer related cognitive impairments in women with breast cancer receiving first-line che. BMC Cancer 18. https://doi.org/10.1186/s12885-018-4992-3

Pamoukdjian, F., Aparicio, T., Zelek, L., Boubaya, M., Caillet, P., François, V., de Decker, L., Lévy, V., Sebbane, G., Paillaud, E., 2017. Impaired mobility, depressed mood, cognitive impairment and polypharmacy are independently associated with disability in older cancer outpatients: The prospective Physical Frailty in Elderly Cancer patients (PF-EC) cohort study. J Geriatr Oncol 8. https://doi.org/10.1016/j.jgo.2017.02.003

Parment, R., Dubois, M., Desrues, L., Mutel, A., Dembélé, K.-P., Belin, N., Tron, L., Guérin, C., Coëffier, M., Compère, V., Féger, C., Joly, F., Hilber, P., Ribet, D., Castel, H., 2022. A Panax quinquefolius-Based Preparation Prevents the Impact of 5-FU on Activity/Exploration Behaviors and Not on Cognitive Functions Mitigating Gut Microbiota and Inflammation in Mice. Cancers (Basel) 14, 4403. https://doi.org/10.3390/cancers14184403

Perrier, J., Duivon, M., Clochon, P., Rehel, S., Doidy, F., Grellard, J.M., Segura-Djezzar, C., Geffrelot, J., Emile, G., Allouache, D., Levy, C., Polvent, S., Viader, F., Eustache, F., Joly, F., Giffard, B., 2022. Sleep macro- and microstructure in breast cancer survivors. Sci Rep 12, 1–8. https://doi.org/10.1038/s41598-022-06664-z

Perrier, J., Duivon, M., Rauchs, G., Giffard, B., 2021. Le sommeil dans les cancers non cérébraux : revue de la littérature, mécanismes potentiels et perspectives pour mieux comprendre les troubles cognitifs associés. Médecine du Sommeil 18. https://doi.org/10.1016/j.msom.2020.12.002

Perrier, Joy, Joue, G., Desgranges, B., Allouache, D., Levy, C., Noal, S., Dayan, J., Eustache, F., Joly, F., Viard, A., Giffard, B., 2022. Self-referential processes and resting-state connectivity in breast cancer patients before and 1 year after chemotherapy. European Journal of Neuroscience 55. https://doi.org/10.1111/ejn.15587

Prakash, R.S., Voss, M.W., Erickson, K.I., Kramer, A.F., 2015. Physical activity and cognitive vitality. Annu Rev Psychol 66. https://doi.org/10.1146/annurev-psych-010814-015249

Reid-Arndt, S.A., Cox, C.R., 2012. Stress, coping and cognitive deficits in women after surgery for breast cancer. J Clin Psychol Med Settings 19, 127–137. https://doi.org/10.1007/s10880-011-9274-z

Rogiers, A., Leys, C., De Cremer, J., Awada, G., Schembri, A., Theuns, P., De Ridder, M., Neyns, B., 2020. Health-related quality of life, emotional burden, and neurocognitive function in the first generation of metastatic melanoma survivors treated with pembrolizumab: a longitudinal pilot study. Supportive Care in Cancer 28. https://doi.org/10.1007/s00520-019-05168-3

Rojer, A.G.M., Ramsey, K.A., Amaral Gomes, E.S., D'Andrea, L., Chen, C., Szoeke, C., Meskers, C.G.M., Reijnierse, E.M., Maier, A.B., 2021. Objectively assessed physical activity and sedentary behavior and global cognitive function in older adults: a systematic review. Mech Ageing Dev. https://doi.org/10.1016/j.mad.2021.111524

Salerno, E.A., Culakova, E., Kleckner, A.S., Heckler, C.E., Lin, P.J., Matthews, C.E., Conlin, A., Weiselberg, L., Mitchell, J., Mustian, K.M., Janelsins, M.C., 2021. Physical Activity Patterns and Relationships With Cognitive Function in Patients With Breast Cancer Before, During, and After Chemotherapy in a Prospective, Nationwide Study. Journal of Clinical Oncology 39. https://doi.org/10.1200/JCO.20.03514

Savard, M.H., Savard, J., Simard, S., Ivers, H., 2005. Empirical validation of the insomnia severity index in cancer patients. Psychooncology 14. https://doi.org/10.1002/pon.860

Schroyen, G., Blommaert, J., van Weehaeghe, D., Sleurs, C., Vandenbulcke, M., Dedoncker, N., Hatse, S., Goris, A., Koole, M., Smeets, A., van Laere, K., Sunaert, S., Sabine, D., 2021. Neuroinflammation and Its Association with Cognition, Neuronal Markers and Peripheral Inflammation after Chemotherapy for Breast Cancer. Cancers (Basel) 13.

Schroyen, G., Meylaers, M., Deprez, S., Blommaert, J., Smeets, A., Jacobs, S., Sunaert, S., Sleurs, C., Uyttebroeck, A., 2020. Prevalence of leukoencephalopathy and its potential cognitive sequelae in cancer patients. J Chemother 0, 1–17. https://doi.org/10.1080/1120009X.2020.1805239

Seigers, R., Schagen, S.B., Van Tellingen, O., Dietrich, J., 2013. Chemotherapy-related cognitive dysfunction: Current animal studies and future directions. Brain Imaging Behav. https://doi.org/10.1007/s11682-013-9250-3

Sharma, M., Loh, K.P., Nightingale, G., Mohile, S.G., Holmes, H.M., 2016. Polypharmacy and potentially inappropriate medication use in geriatric oncology. J Geriatr Oncol. https://doi.org/10.1016/j.jgo.2016.07.010

Sheehan, P., Denieffe, S., Murphy, N.M., Harrison, M., 2020. Exercise is more effective than health education in reducing fatigue in fatigued cancer survivors. Supportive Care in Cancer 28. https://doi.org/10.1007/s00520-020-05328-w

Simard, S., Savard, J., 2009. Fear of Cancer Recurrence Inventory: Development and initial validation of a multidimensional measure of fear of cancer recurrence. Supportive Care in Cancer 17. https://doi.org/10.1007/s00520-008-0444-y

Sleurs, C., Madoe, A., Lagae, L., Jacobs, S., Deprez, S., Lemiere, J., Uyttebroeck, A., 2019. Genetic Modulation of Neurocognitive Development in Cancer Patients throughout the Lifespan: a Systematic Review. Neuropsychol Rev. https://doi.org/10.1007/s11065-019-09399-3

Sonis, S.T., O'Donnell, K.E., Popat, R., Bragdon, C., Phelan, S., Cocks, D., Epstein, J.B., 2004. The relationship between mucosal cyclooxygenase-2 (COX-2) expression and experimental radiation-induced mucositis. Oral Oncol 40. https://doi.org/10.1016/S1368-8375(03)00148-9

Sousa, H., Almeida, S., Bessa, J., Pereira, M.G., 2020. The Developmental Trajectory of Cancer-Related Cognitive Impairment in Breast Cancer Patients: A Systematic Review of Longitudinal Neuroimaging Studies. Neuropsychol Rev. https://doi.org/10.1007/s11065-020-09441-9

Spielberger, C.D., 1987. State-Trait Anxiety Inventory. Anxiety. https://doi.org/10.1037/t06496-000

Stern, Y., Mackay-Brandt, A., Lee, S., McKinley, P., McIntyre, K., Razlighi, Q., Agarunov, E., Bartels, M., Sloan, R.P., 2019. Effect of aerobic exercise on cognition in younger adults: A randomized clinical trial. Neurology 92. https://doi.org/10.1212/WNL.0000000000007003

Stouten-Kemperman, M.M., de Ruiter, M.B., Koppelmans, V., Boogerd, W., Reneman, L., Schagen, S.B., 2015. Neurotoxicity in breast cancer survivors ≥10 years post-treatment is dependent on treatment type. Brain Imaging Behav 9, 275–284. https://doi.org/10.1007/s11682-014-9305-0

Uchiyama, C.L., D'Elia, L.F., Dellinger, A.M., Becker, J.T., Selnes, O.A., Wesch, J.E., Chen, B.B., Satz, P., van Gorp, W., Miller, E.N., 1995. Alternate forms of the auditory-verbal learning test: issues of test comparability, longitudinal reliability, and moderating demographic variables. Archives of Clinical Neuropsychology 10. https://doi.org/10.1016/0887-6177(94)E0034-M

van Dam, F.S., Schagen, S.B., Muller, M.J., Boogerd, W., vd Wall, E., Droogleever Fortuyn, M.E., Rodenhuis, S., 1998. Impairment of cognitive function in women receiving adjuvant treatment for high-risk breast cancer: high-dose versus standard-dose chemotherapy. J Natl Cancer Inst 90, 210–218.

Van der Gucht, K., Ahmadoun, S., Melis, M., de Cloe, E., Sleurs, C., Radwan, A., Blommaert, J., Takano, K., Vandenbulcke, M., Wildiers, H., Neven, P., Kuppens, P., Raes, F., Smeets, A., Sunaert, S., Deprez, S., 2020. Effects of a mindfulness-based intervention on cancer-related cognitive impairment: Results of a randomized controlled functional magnetic resonance imaging pilot study. Cancer 126. https://doi.org/10.1002/cncr.33074

Van Dyk, K., Ganz, P.A., 2021. Cancer-Related Cognitive Impairment in Patients with a History of Breast Cancer. JAMA - Journal of the American Medical Association 326. https://doi.org/10.1001/jama.2021.13309

Vitali, M., Ripamonti, C.I., Roila, F., Proto, C., Signorelli, D., Imbimbo, M., Corrao, G., Brissa, A., Rosaria, G., de Braud, F., Garassino, M.C., lo Russo, G., 2017. Cognitive impairment and chemotherapy: a brief overview. Crit Rev Oncol Hematol. https://doi.org/10.1016/j.critrevonc.2017.08.001

Walker, A.K., Chang, A., Ziegler, A.I., Dhillon, H.M., Vardy, J.L., Sloan, E.K., 2018. Low dose aspirin blocks breast cancer-induced cognitive impairment in mice. PLoS One 13. https://doi.org/10.1371/journal.pone.0208593

Wanner, M., Hartmann, C., Pestoni, G., Martin, B.W., Siegrist, M., Martin-Diener, E., 2017. Validation of the Global Physical Activity Questionnaire for self-administration in a

European context. BMJ Open Sport Exerc Med 3. https://doi.org/10.1136/bmjsem-2016-000206

Wefel, J.S., Kesler, S.R., Noll, K.R., Schagen, S.B., 2015. Clinical characteristics, pathophysiology, and management of noncentral nervous system cancer-related cognitive impairment in adults. CA Cancer J Clin 65, 123–138. https://doi.org/10.3322/caac.21258

Wefel, J.S., Vardy, J., Ahles, T., Schagen, S.B., 2011. International Cognition and Cancer Task Force recommendations to harmonise studies of cognitive function in patients with cancer. Lancet Oncol 12, 703–708. https://doi.org/10.1016/S1470-2045(10)70294-1

Winocur, G., Johnston, I., Castel, H., 2018. Chemotherapy and cognition: International cognition and cancer task force recommendations for harmonising preclinical research. Cancer Treat Rev. https://doi.org/10.1016/j.ctrv.2018.05.017

Witlox, L., Schagen, S.B., de Ruiter, M.B., Geerlings, M.I., Peeters, P.H.M., Koevoets, E.W., van der Wall, E., Stuiver, M., Sonke, G., Velthuis, M.J., Palen, J.A.M.V. der, Jobsen, J.J., May, A.M., Monninkhof, E.M., 2019. Effect of physical exercise on cognitive function and brain measures after chemotherapy in patients with breast cancer (PAM study): Protocol of a randomised controlled trial. BMJ Open 9. https://doi.org/10.1136/bmjopen-2018-028117

Wu, L.M., Tanenbaum, M.L., Dijkers, M.P.J.M., Amidi, A., Hall, S.J., Penedo, F.J., Diefenbach, M.A., 2016. Cognitive and neurobehavioral symptoms in patients with non-metastatic prostate cancer treated with androgen deprivation therapy or observation: A mixed methods study. Soc Sci Med 156, 80–89. https://doi.org/10.1016/j.socscimed.2016.03.016

Yang, M., Kim, J., Kim, J.S., Kim, S.H., Kim, J.C., Kang, M.J., Jung, U., Shin, T., Wang, H., Moon, C., 2014. Hippocampal dysfunctions in tumor-bearing mice. Brain Behav Immun 36. https://doi.org/10.1016/j.bbi.2013.10.022

Zimmer, P., Baumann, F.T., Oberste, M., Wright, P., Garthe, A., Schenk, A., Elter, T., Galvao, D.A., Bloch, W., Hubner, S.T., Wolf, F., 2016. Effects of Exercise Interventions and Physical Activity Behavior on Cancer Related Cognitive Impairments: A Systematic Review. Biomed Res Int 2016, 1820954. https://doi.org/10.1155/2016/1820954

Zimmer, P., Schmidt, M.E., Prentzell, M.T., Berdel, B., Wiskemann, J., Kellner, K.H., Debus, J., Ulrich, C., Opitz, C.A., Steindorf, K., 2019. Resistance exercise reduces kynurenine pathway metabolites in breast cancer patients undergoing radiotherapy. Front Oncol 9. https://doi.org/10.3389/fonc.2019.00962

Zou, L.Y., Yang, L., He, X.L., Sun, M., Xu, J.J., 2014. Effects of aerobic exercise on cancer-related fatigue in breast cancer patients receiving chemotherapy: A meta-analysis. Tumor Biology 35. https://doi.org/10.1007/s13277-014-1749-8