

# Cancer-related cognitive impairment in adult cancer survivors: A review of the literature

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## Abstract

Cognitive symptoms are commonly reported by cancer patients. Qualitative research has shown that up to 70% of cancer patients experience symptoms of varying magnitude. Several studies have demonstrated only a weak association between self-reported cognitive symptoms and objective cognitive impairment on formal neuropsychological testing. Conversely, cognitive symptoms have been consistently shown to be associated with other patient reported outcomes, including anxiety/depression, fatigue and quality of life. Cognitive symptoms can have a major impact on individual's personal and professional lives. Initially, the terms 'chemo brain' or 'chemo fog' were used, as it was believed that cognitive changes were a direct result of chemotherapy treatment. It is now clear that the aetiology of cognitive change is more complex, with several studies showing presence of impairment in patients with a new cancer diagnosis, prior to commencement of systemic therapy. The exact aetiology of cognitive impairment is unknown, but it is likely multifactorial. There has been interest in the evaluation of pharmacological and cognitive training strategies for the management of cognitive impairment in cancer patients. Most recently, a large randomised study of a home-based, online cognitive rehabilitation program showed improvements in cognitive symptoms and patient reported outcomes. However, there remains no universally accepted treatment.

In the last two decades, there has been a growing body of research focused on the evaluation of cognitive symptoms in cancer patients. The incident rate varies, but studies in breast cancer patients suggest that up to 70% of patients receiving chemotherapy will self-report some cognitive impairment.<sup>1</sup> The cognitive domains most commonly affected are memory, concentration, information processing speed and executive function.<sup>2,3</sup>

For some patients, their cognitive impairment may be transient, but for a subgroup, these symptoms can be long-standing and have a major impact on quality of life and function.<sup>4,5</sup> Cognition has been recognised as an important component of cancer survivorship, particularly with the improvement in cancer treatments, leading to increased survival times.<sup>6</sup> It is therefore imperative that we better understand these symptoms and how best to treat or prevent them, to ensure that cancer patients are not only living, but are 'living well' after their cancer diagnosis and treatment.

## History of early research

Initial reports of cognitive changes associated with chemotherapy date back to 1980, in a small study of ten cancer patients.<sup>7</sup> A study by Wieneke et al in 1995 in early stage breast cancer patients, <55 years of age, who had completed adjuvant chemotherapy, found that 75% of patients met the investigators' definition of moderate cognitive impairment on neuropsychological testing. The impairment was not associated with depression, type of chemotherapy, or time since treatment, but there was a positive association with the number of cycles of chemotherapy.<sup>8</sup>

In 1998, Van Dam et al published a cross-sectional study assessing the prevalence of cognitive deficits in high-risk breast cancer patients, <55 years of age, randomised to high (n=34) or standard-dose (n=36) adjuvant chemotherapy, followed by hormonal therapy. They included a

control group comprising patients with stage I breast cancer who had not received systemic therapy (n=34). Cognitive impairment on formal neuropsychological testing was seen in 32% undergoing high-dose treatment and 17% receiving standard-dose treatment compared to 9% of controls ( $P=.043$ ). Patients receiving high-dose chemotherapy reported significantly more symptoms than controls ( $P=.014$ ). However, no association was seen between cognitive symptoms and neuropsychological testing (Spearman correlation 0.03).<sup>9</sup>

A series of cross-sectional studies followed; the majority confirmed findings of early studies, although reassuringly the rates of cognitive impairment post-chemotherapy were lower than that first reported by Wieneke et al.<sup>10-13</sup> However, there remains wide variability in the frequency of cognitive impairment across studies. There are multiple reasons for this including diverse patient populations and cancer treatments, time from treatment, instruments used to assess cognition, lack of a standardised definition of what constitutes cognitive impairment and methodological issues in earlier studies.<sup>14</sup>

The lack of association between self-reported cognitive symptoms and objective cognitive function on neuropsychological testing emerged during these early studies. It was noted that many participants reported cognitive symptoms, but were scoring within normal range on neuropsychological tests. Several factors may contribute including: 1) patients' functioning above the normal range of cognitive performance prior to their cancer diagnosis or systemic treatment, and while their cognition may have declined, it remained within normal range, albeit at a lower level; 2) lack of 'ecological validity' of the neuropsychological testing, i.e. the artificial conditions in which testing is performed is not representative of real life situations in which individuals are most likely to experience cognitive symptoms; 3) the neuropsychological tests are not sensitive enough to detect the subtle cognitive changes typically seen in cancer patients; and 4) self-reported and objective measures of cognitive function are measuring different constructs.

### *Recommendations for future research*

There were a number of methodological limitations with earlier studies. Most used cross-sectional designs, with small sample sizes, and were restricted to young women with breast cancer. Little was known about cognitive function in men or in patients with tumour types other than breast cancer.

The International Cognition and Cancer Task Force made the following recommendations for future studies: 1) longitudinal study design; 2) inclusion of different primary tumour types with no gender restrictions; 3) incorporation of baseline assessment of cognition function prior to initiation of chemotherapy; 4) inclusion of a control group; 5) evaluation of potential underlying mechanisms e.g. imaging, blood parameters; 6) use of neuropsychological tests sensitive to the types of cognitive change reported in cancer studies; and 7) development and validation of self-reported questionnaires specific to cancer patients.<sup>15-17</sup>

## **Newer generation of studies**

### *Longitudinal studies*

A series of longitudinal studies have confirmed the findings of earlier cross-sectional studies demonstrating that a subgroup of patients experience cognitive issues following administration of chemotherapy.<sup>4,18,19</sup> Hermelink et al completed a longitudinal study in 101 breast cancer patients reviewing cognitive function before and immediately prior to completion of neoadjuvant chemotherapy. At baseline, 31% of patients scored within the lower 5% range on neuropsychological testing. On follow-up, deterioration in performance was seen in 27%, with improvement in 28%. There was a significant increase in self-reported cognitive symptoms at the follow-up evaluation.<sup>19</sup>

Kopplemans et al performed a case-cohort study comparing cognitive performance of 196 breast cancers patients who had received chemotherapy (mean of 21 years following diagnosis), with 1509 healthy females. They found that women who had received chemotherapy performed worse on all neuropsychological tests compared to controls. Interestingly, patients experienced less symptoms of depression than controls ( $P=.001$ ), but had more self-reported cognitive symptoms.<sup>4</sup>

Of note, there have been a small number of studies that have not found impairment associated with cancer treatment.<sup>20-23</sup> Jenkins et al performed a prospective longitudinal study evaluating neuropsychological performance in 128 women diagnosed with early stage breast cancer (chemotherapy n=85; endocrine therapy +/- radiotherapy n=43) and healthy controls (n=49). There were no significant differences in cognition between the groups on assessments post-chemotherapy or 12 months later, with no associations between objective neuropsychological testing and self-reported cognitive function, quality of life and distress. However, the latter were significantly associated with one another.<sup>20</sup>

Deboss et al examined self-reported and objective cognitive function in 120 women who had received treatment for early breast cancer (chemotherapy n=75, hormone therapy n=26, no adjuvant treatment n=19) in comparison to 208 aged-matched women with no history of malignancy. There were no significant differences in neuropsychological testing between the three patient groups and the healthy controls at baseline or post-chemotherapy. All patients improved on most measures of self-reported cognitive function and psychological distress at six months and patients who did not receive adjuvant treatment, reached a level similar to controls at six months.<sup>21</sup>

Overall, the majority of cognitive studies in women with breast cancer show that approximately 30% have cognitive impairment on objective testing which is frequently sustained up to at least 10 years, with one study suggesting impairment still at 20 years.<sup>4</sup> Most studies found a lack of association between neuropsychological test results and cognitive symptoms.

### *Studies conducted in non-breast cancer populations*

More recent studies have evaluated cognitive function in non-breast cancer populations with a particular focus on colorectal, testicular and gynaecological malignancies.<sup>24-32</sup> These studies confirm that cognitive changes occur in a number of other tumour types, and in both men and women. This is important as it was initially postulated that the cognitive changes in women may be related to abrupt changes in the hormonal milieu induced by chemotherapy, leading to an early menopause.

The largest study reported by Vardy et al was a longitudinal study in 289 patients with localised colorectal cancer: 173 received adjuvant chemotherapy, and 116 did not. There were two additional groups: 72 patients with recurrent/metastatic colorectal cancer, and 73 healthy controls. The rates of cognitive impairment were significantly higher in localised colorectal patients than healthy controls at baseline, six and 12 months (43%, 39% and 46% compared to 15%, 6% and 13%). There was no significant effect from chemotherapy. Self-reported cognitive impairment was more common at six months in participants who received chemotherapy (32%) than those who did not (16%;  $P=.007$ ) or in healthy controls (12.5%), with no significant differences between groups at 12 months.<sup>29</sup>

There is a growing body of work highlighting the presence of cognitive changes in cancer patients before they have commenced systemic treatment.<sup>33-35</sup> Ahles et al compared neuropsychological function of breast cancer patients (n=132) with invasive cancer and non-invasive cancer following surgery, but prior to any adjuvant treatment, with matched healthy controls (n=45). They found 22% of patients with breast cancer had lower than expected cognitive performance, compared to 4% of healthy controls ( $P=.002$ ).<sup>34</sup> As described previously, Vardy et al's study in patients with localised colorectal cancer found more objective cognitive impairment in patients than healthy controls at baseline (45 vs 15%,  $P<0.001$ ).<sup>33</sup>

Potential explanations for the presence of cognitive changes prior to initiation of systemic treatment include the presence of a common risk factor for both the development of cancer and cognitive changes. Additionally, there may be some intrinsic property of the cancer driving cognitive changes.

### *Influence of age and comorbidities on cognition*

Age is a known risk factor for cognitive decline in the general population. This is particularly relevant in today's oncological practice, with an ageing population and an increase in older patients receiving chemotherapy.

Hurria et al studied an older population in a longitudinal study enrolling 45 patients with early stage breast cancer with a mean age of 70 years. Half (51%) reported a decline in memory from baseline to six months post-chemotherapy. Patients who reported a below average memory prior to chemotherapy were more likely to report further memory deterioration after chemotherapy (63%) compared to those reporting their memory to be average or better prior to chemotherapy (27%).<sup>36</sup>

Mandelblatt et al evaluated whether older patients with breast cancer have cognitive impairment prior to systemic therapy.<sup>37</sup> They recruited 164 newly diagnosed early stage breast cancer patients, ≥60 years, together with 182 community controls. The age range was 60-94 years. They found that the breast cancer patients and controls had similar neuropsychological scores. However, those patients with stage II–III cancers had lower executive function compared to those with stage 0–I disease ( $P=.05$ ), with significantly higher impairment among older, non-white, less educated women and those with greater comorbidity.<sup>37</sup>

Ahles et al evaluated age and baseline cognitive reserve in 132 patients diagnosed with early stage breast cancer prior to adjuvant therapy (chemotherapy  $n=60$ , no chemotherapy  $n=72$ ), and 45 healthy controls. A three-way interaction among treatment group, age and baseline cognitive reserve ( $P<.001$ ) revealed older patients with lower baseline cognitive reserve who received chemotherapy had significantly lower cognitive performance compared to the other two groups ( $P<.003$ ).<sup>38</sup>

These results highlight the need for collection of data relating to comorbidities and pre-morbid function in future cognitive studies. While these data may not be practice changing for the oncology community, it should be carefully considered when reviewing patients with multiple comorbidities and borderline functional status, prior to proceeding with adjuvant therapy that may confer minimal benefits.

There has been a consistent lack of association between self-reported cognitive symptoms and objective cognitive function measured by neuropsychological testing.<sup>9,10,20,39,40</sup> A meta-analysis by Hutchinson et al of 24 studies, found eight reported a significant association between self-reported and objective cognitive function, and often the correlation was weak.<sup>41</sup> This was more likely in studies of breast cancer patients and when the relationship between memory (rather than global cognitive function) and self-reported symptoms was explored. However, both self-reported cognitive symptoms and objective cognitive impairment are important to patients and where possible both measures should be incorporated in to trial designs. Finally, self-reported symptoms are frequently linked to fatigue, worse quality of life and symptoms of anxiety and depression.

## **Potential mechanisms**

The aetiology of cognitive change in cancer patients is not known, but is likely to be multifactorial. Postulated mechanisms include: direct neurotoxic effects of therapy, genetic factors, oxidative stress and immune dysregulation.

### *Direct neurotoxicity*

Traditionally chemotherapy agents, with the exception of methotrexate and 5-fluorouracil, were thought to have minimal penetration through the 'blood brain barrier.' However, a variety of neurotoxicities have been described with many chemotherapy agents.<sup>42-44</sup> Imaging studies using positron emission tomography have shown that detectable levels of certain chemotherapeutic agents can be found in the brain following intravenous administration. While these levels are low, and are not at a level sufficient to cause an anti-cancer therapeutic response, there remains uncertainty whether they are sufficient to alter cognitive function.

Animal studies have suggested that neural progenitor cells and oligodendrocytes are the cell populations most vulnerable to multiple chemotherapeutic agents. Furthermore, repetitive drug exposure resulted in long-term suppression of cell division and prolonged cell death in the subventricular zone, the hippocampus, and major white matter tracts.<sup>45-47</sup>

### *Genetic factors*

One potential candidate marker is the apolipoprotein (APO) Eε4 gene, a known risk factor for

Alzheimer's disease and other forms of cognitive impairment. Preliminary support for this came from Ahles et al who demonstrated that long term cancer survivors with at least one APOEε4 allele scored significantly lower in multiple neuropsychological domains ( $P < .03-.05$ ).<sup>48</sup> By contrast, the larger colorectal study by Vardy et al found no association with APOEε4 and cognitive function.<sup>29</sup>

There has been recent interest in the catechol-O-methyltransferase (COMT) genotype, which is associated with levels of dopamine in the prefrontal cortex of the brain. The COMT valine-158 methionine-158 single-nucleotide polymorphism is associated with increased enzymatic activity resulting in greater degradation of dopamine and less availability of dopamine at the synaptic receptor. Small et al studied breast cancer survivors treated with radiotherapy (n=58), chemotherapy (n=72) and healthy controls (n=204). The COMT valine carriers performed worse on neuropsychological tests ( $P < .009-.033$ ) compared to those without the polymorphism, as did COMT valine carriers treated with chemotherapy compared to healthy control COMT valine carriers ( $P < .001$ ).<sup>49</sup>

### *Immune dysregulation*

Cytokines have an important role in normal brain function, including the modulation of neuronal and glial cell functioning, neural repair and metabolism of a number of important neurotransmitters. Cancer and/or chemotherapy causes activation of the immune system with release of proinflammatory cytokines, many of which have been shown to cross the blood-brain barrier (e.g. interleukin(IL)-1, IL-6, tumour necrosis factor-alpha (TNF-α)) and have been associated with cognitive impairment in other diseases.

Some breast cancer studies have found an association between cognitive impairment and elevation of interleukin IL-6 and TNF.<sup>50,51</sup> By comparison the much larger colorectal study, Vardy et al found no association between global cognitive function and cytokines in blood.<sup>29</sup>

### *Neuroimaging findings*

Recent developments in the field of cognition and cancer include the use of functional magnetic resonance imaging to determine which areas of the brain are activated both at rest and while doing a memory task. Cross-sectional studies in breast cancer survivors who received chemotherapy have found hypoactivation in prefrontal and parietal brain regions.<sup>52-56</sup>

## **Intervention studies**

There are an increasing number of studies focusing on both pharmacological and non-pharmacological interventions for the management of cognitive symptoms in cancer patients. The majority are small and while some have shown promising results, no treatment has as yet been established in main stream practice.

### *Pharmacological interventions*

A number of medications have been of interest in this area and the most commonly evaluated agents include erythropoietin, dexamethylphenidate and modafinil. Results from trials have largely been disappointing. Vardy et al are currently evaluating the Chinese herb, *Ginkgo biloba*, in a randomised controlled trial in breast cancer survivors. Its mechanisms of actions are reported to include anti-oxidant properties, increasing cerebral blood flow, improving glucose utilisation and stimulation of neurotransmitters.

### *Non-pharmacological intervention studies*

Treanor et al recently published a Cochrane systematic review of non-pharmacological interventions for cognitive impairment related to systemic cancer treatment.<sup>57</sup> Their selection criteria included randomised controlled trial of non-pharmacological interventions in survivors of adult-onset cancers who had completed systemic cancer therapy. They identified five randomised controlled trials of six interventions (n=235) in breast cancer patients. Of these, two used computer-assisted cognitive training interventions (n=100); two compensatory strategy training interventions (n=95) and one each meditation (n=47) and physical activity (n=19).<sup>58-62</sup> They found that use of cognitive and compensatory strategy training had beneficial effects on objective cognitive function, self-reported cognitive function, well-being and spiritual quality of life. The evidence for the assessed studies was graded as low quality for physical and mental health outcomes and did not

permit firm recommendations to be made.

Our group recently reported the results of a large longitudinal randomised controlled trial of a web-based cognitive rehabilitation program in cancer patients reporting cognitive symptoms 6-60 months following completion of adjuvant chemotherapy. All participants received a 30-minute telephone consultation outlining cognitive training strategies and were then randomised to the 15-week, home-based intervention or standard care. The study met its primary outcome with improvements in self-reported cognitive function post intervention and these changes were sustained at six months. Importantly, symptoms of anxiety and depression, fatigue and stress were lower in the intervention group upon completion of the program and quality of life was improved at six months. There were no major differences found in objective neuropsychological test results between the groups.<sup>63</sup> Three other small intervention studies have also shown provisional efficacy of cognitive rehabilitation programs.<sup>64-66</sup>

There remain a number of unanswered questions with regards to cognitive interventions in the cancer population, including: the best method of delivering cognitive training; the optimal dose, frequency, and duration of training; how to improve adherence to training; whether benefits translate to real world situations; and, the long-term durability of cognitive training. Similarly, we need to better understand which patients are most at risk of persistent cognitive symptoms with the aim of selecting patients who may benefit from earlier implementation of an intervention.

## Conclusion

Cancer-related cognitive symptoms are an issue for many cancer survivors and can have a significant impact on their daily life. As we make advances towards the implementation of effective management strategies for cancer patients reporting cognitive symptoms, it is vital that both health professionals and patients are educated about this important issue. Patients need to be informed about the potential risk of cognitive symptoms, in context of the benefits of treatment, to enable them to make informed choices about their treatment and recovery.

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