Cancer-Related Cognitive Impairment in Patients With a History of Breast Cancer

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Clinical reports of cognitive difficulties in patients with breast cancer began to appear in the literature in the 1990s, coincident with the increasing use of postoperative adjuvant chemotherapy. Symptoms were more frequently reported in women who received very high-dose chemotherapy, raising concerns that cognitive impairment might become a dose-limiting treatment toxicity. However, this has not occurred, in that over the past 2 decades there has been a deescalation of both the intensity and generalized use of adjuvant chemotherapy in patients with breast cancer. Because of the initial association of cognitive symptoms with chemotherapy treatment, early research focused on what was referred to as chemotherapy. Subsequent studies have documented cognitive changes before any cancer-directed therapies, as well as in association with other common breast cancer treatments (eg, radiation, endocrine therapy).

The evolving body of research on this subject led to a renaming of the condition as cancer-related cognitive impairment (CRCI). Although they are most commonly reported in close proximity to initial breast cancer treatments, for some patients, symptoms of CRCI can persist for years after treatment completion. Importantly, although breast cancer has been the most studied tumor type with CRCI, there is a growing literature on this condition in persons with other types of cancer, including lymphoma, head and neck cancers, and brain tumors, and patients who have received stem cell transplants.

Incidence and Nature of the Problem

CRCI reported by patients with breast cancer is common, although the frequency and nature can vary subject to the population sampled. According to one survey, 885 of 1147 patients (77%) with a history of breast cancer who received chemotherapy with and without endocrine therapy and 371 of 822 (45%) who received only endocrine therapy reported cognitive symptoms during or soon after treatment. A community-based prospective longitudinal cohort study of 503 patients with breast cancer, compared with 334 control participants without cancer, found statistically significant differences after adjuvant treatment in both self-reported clinically meaningful cognitive decline (36.5% vs 13.6% of participants) and neurocognitive decline (effect size 0.2 on the primary outcome as assessed by Janelinsis et al). A meta-analysis of neuropsychological outcomes in patients with breast cancer treated with chemotherapy (n = 2939), compared with healthy control participants (n = 3420), revealed the largest effect sizes in the domains of processing speed and language (Cohen d = −0.39), executive function (Cohen d = −0.34), and memory (Cohen d = −0.30), but no differences compared with patients with breast cancer who were not treated with chemotherapy (n = 1538).

In the current era of more selective chemotherapy use, cognitive symptoms continue to emerge in other contexts, including before any cancer-directed treatments, in association with endocrine therapy, and with radiotherapy and surgery. Patients who develop cognitive difficulties during the acute phase of breast cancer treatment may require several months to a year for recovery and, for some individuals, cognition never fully returns to “baseline,” supported by reports of neuroimaging abnormalities. Although cognitive symptoms rarely reach the level of severe impairment (ie, dementia), symptoms frequently disrupt functioning, work, and quality of life.

Contributing Factors and Mechanisms

Several candidate mechanisms for CRCI have been hypothesized based on clinical and preclinical studies. Increased systemic inflammation occurs in response to cancer, as well as to chemotherapy, radiotherapy, and surgery. Chronically elevated inflammation can lead to neuroinflammation that could result in neurotoxicity and increased oxidative damage. Evidence has also implicated mitochondrial dysfunction in neurons as well as disrupted neurogenesis and neuroplasticity. The potential cognitive effects of immunoendocrine therapy, an emerging breast cancer therapy, will be important to monitor in light of patient reports and earlier studies.

Endocrine therapy is used in the majority of patients with breast cancer and is another important potential risk factor for CRCI. Estrogen has an important role in women’s brain health, and the downregulation of natural estrogen production or blocking of its activity through endocrine therapy is associated with effects on cognition. Although research is still evolving in this area, a 2020 report from a randomized clinical trial involving 552 patients reported clinically meaningful patient-reported cognitive decline 12 months after starting endocrine therapy, with (37.7%) or without (35.3%) chemotherapy, and these difficulties were present in both premenopausal and postmenopausal women.

Patient and context-related vulnerabilities for CRCI may include aging and preexisting medical conditions with known cognitive risk (eg, diabetes, heart disease). Genetic risk for CRCI is an ongoing area of study, with some evidence suggesting particular vulnerability among APOE*E4 carriers, the best-known genetic risk for Alzheimer disease. Preexisting and concurrent psychosocial risks for CRCI include mood symptoms (eg, depression) and trauma symptoms, fatigue, and sleep disturbance. In terms of protective factors, higher cognitive reserve may buffer against the neurotoxicity associated with cancer and its treatment.

The leading model of CRCI suggests the possibility that it represents accelerated aging, given the overlap in mechanisms and vulnerabilities with cognitive aging. Some neuroimaging studies have described brain changes comparable to aging, such as compensatory hyperactivation during cognitive tasks and reduction in
gray matter, as well as a link between markers of biological aging and cognition in patients with a history of cancer.7

Assessment and Treatment of CRCI

The National Comprehensive Cancer Network guidelines for the assessment and management of CRCI suggest that increased patient education regarding CRCI is important. Many patients with breast cancer are unaware of the possibility that they may have cognitive decline after treatment. Screening tools for dementia are insufficient for CRCI evaluation. Screening for mood disturbance and survivorship concerns can identify cognitive symptoms. Careful assessment of cognitive difficulties using validated questionnaires for CRCI can be used to track impairment if clinically suspected. When patients spontaneously report these symptoms to clinicians, they should not be ignored. Acknowledging the patient's symptoms and undertaking a thorough evaluation is important. An initial first step should be examining and addressing potentially manageable associated conditions, such as depression, sleep disturbance, and fatigue, which are all common and frequently co-occurring in this patient population. If CRCI symptoms do not improve, a referral for neuropsychological evaluation should follow, because this can help characterize specific cognitive symptoms and supply targeted recommendations and may provide reassurance and information for patients who may be concerned that they are developing dementia.

There is no established standard care for neuroprotection against CRCI or for managing CRCI in the setting of breast cancer, and more evidence is needed. Cognitive rehabilitation and behavioral therapies are among the most promising interventions for CRCI to date.10 Physical exercise is a promising intervention but has not been adequately evaluated.7 Some pharmacologic agents have been studied (eg, psychostimulants, dementia medications) without conclusive efficacy, and more research is needed.

Summary

CRCI is an important clinical issue that can impair daily function, work productivity, childcare, and other responsibilities in patients with a history of breast cancer. Risk for CRCI includes cancer and cancer treatment, as well as patient-related vulnerabilities. Management recommendations include attending to patient-reported symptoms with a thorough symptom-targeted evaluation. Cognitive and behavioral treatments are the primary recommended intervention. More research is needed to establish a solid evidence base for CRCI that evolves alongside modern cancer treatment practices.

ARTICLE INFORMATION

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REFERENCES