

Cognition and early menopause in breast cancer patients: an update

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ABSTRACT

Background and Purpose: Many breast cancer patients are premenopausal at diagnosis and they subsequently suffer from symptoms of iatrogenic menopause, including cognitive impairment. In this review, we analyzed the neurological diseases and cognitive impairment associated with early menopause in breast cancer patients with the aim of identifying the possibilities for their prevention and treatment.

Material and methods: This is a narrative review that summarizes the evidence on cognitive dysfunction and early menopause in breast cancer patients and analyzes the prevention and treatment possibilities.

Results: About 40% of healthy women in the menopausal transition complain of forgetfulness and difficulties with concentration, attention and other cognitive abilities. Many studies have demonstrated that sex hormones, especially estrogen, play a crucial role in the modulation of brain functions through many different mechanisms; in iatrogenic early menopause, the abrupt depletion of these hormones may contribute to causing brain lesions, leading to cognitive impairment. In breast cancer patients an important role is played by chemotherapy and endocrine therapy, which seem to be involved in the onset of structural and functional brain changes.

Conclusions: In breast cancer patients, who are premenopausal at diagnosis, the onset of early menopause due to chemotherapy and endocrine therapy is related to cognitive impairment, memory dysfunction, depression and anxiety. Although the prevention and treatment of these problems are not yet established the treatment of vasomotor symptoms and rehabilitation programs may play an important role.

KEYWORDS

Breast Cancer; Menopause; Climacteric Symptoms; Cognitive Impairment; Estrogen; Endocrine Therapy; Chemotherapy.

Introduction

Breast cancer affects up to one in eight women in developed countries, with a median age of 61 years at diagnosis. Approximately 2% of breast cancer occurs between 20 and 34 years of age and 11% between 35 and 44 years of age^[1]. Young women often present aggressive breast cancer, which means higher proportions of late stage cases (stages II, III and IV), high grade tumors, positive lymph nodes, negative estrogen receptors and progesterone receptors, and HER2/neu overexpression^[2-4]; it follows that most of these women receive systemic treatment with adjuvant endocrine therapy, chemotherapy, or both^[5].

In recent years, breast cancer survival rates have significantly improved thanks to advances in diagnosis and treatment, but potential late side effects of the treatment itself can negatively impact the quality of life of patients^[1]. Many breast cancer survivors suffer from climacteric symptoms, such as vasomotor symptoms (hot flashes, night sweats, palpitations), vaginal dryness, sexual dysfunction, poor sleep and tiredness, osteoporosis, fertility problems and neurological diseases, including cognitive dysfunction. In particular, young women diagnosed with breast cancer have several issues and concerns, and are strongly affected by symptoms of premature menopause and cognitive deterioration^[6].

Breast cancer treatment depends on the stage at diagnosis, and the size, location, and characteristics of the tumor. Women

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who have stage II or III disease at diagnosis may receive stronger cancer treatments, which can result in a greater likelihood, and greater severity, of an impact of the treatment itself^[7]. In premenopausal women with hormone receptor-positive breast cancer, the most effective adjuvant endocrine therapy is the aromatase inhibitor exemestane in addition to ovarian suppression, as shown by the TEXT and SOFT trials, which represent a milestone in the field of endocrine therapy in breast cancer^[8,9]. In cases of hormone receptor-negative tumor or other negative prognostic factors, breast cancer patients can also receive chemotherapy, which may affect ovarian function via several mechanisms, including cortical fibrosis, vascular damage and follicular depletion, leading to premature ovarian failure and permanent amenorrhea with an incidence of 40-85% depending on the patient's age and chemotherapy regimen^[10,11]. The association of cyclophosphamide, methotrexate and 5-fluorouracil (CMF schedule) carries a 61% risk of amenorrhea in patients

under 40 years of age and a 95% risk in women older than 40 years ^[12]. With anthracycline-based associations, the incidence of menopause was higher when compared with the CMF schedule (from 35 to 59%). Conflicting results have been found by studies on taxane-based regimens ^[13-16]. Moreover, the literature reports that the association of chemotherapy and endocrine therapy in premenopausal breast cancer patients results in higher rates of amenorrhea and early menopause than the same treatments considered individually ^[17]. Up to 75% of breast cancer patients on treatment and 35% after treatment report cognitive impairment, including problems with concentration, executive function, verbal fluency and memory ^[18].

In this review, we analyzed the impact on neurological functions and cognition associated with early menopause in breast cancer patients and the possibilities for prevention and treatment.

Material and methods

This is a narrative review that focuses on the analysis of cognitive impairment associated with early menopause in breast cancer patients; it is aimed at providing an update on the most common cognitive symptoms experienced by breast cancer patients and their biological pathways. We searched the PubMed database using the following keywords: breast cancer, premenopausal women, early menopause, climacteric symptoms, cognitive dysfunction, neurological dysfunction, endocrine therapy, chemotherapy. Only publications written in English included. We summarized evidence from studies about cognitive dysfunction and early menopause in breast cancer patients, their correlation, and the possibilities for prevention and treatment.

Results

About 40% of healthy women in the menopausal transition complain of forgetfulness, “brain fog” and difficulty concentrating, and there is evidence of a decrease in attention, memory, processing speed and other cognitive abilities interfering with their daily activities ^[19]. Many studies have demonstrated that sex hormones such as estrogen, progesterone and androgens play an important role in the modulation of brain functions and synaptic organization and plasticity, affecting neurons, glia and microglia in many areas of the brain, including the hippocampus and limbic system, where cognition, mood and dementia originate ^[20].

In premenopausal women the effect of estradiol on specific brain areas (hippocampus and temporal lobes) contributes to memory performance, improving verbal fluency, with differences observed between the follicular and luteal phase of the menstrual cycle, following the changes in estradiol circulating levels ^[21,22]. The decline in sex steroids, particularly estrogen, during the menopausal transition is associated with changes in eating behavior, metabolism and sleep, mood, sexuality, locomotor activity, immune response, memory and cognitive function. Although these brain changes originate in the central

nervous system, sex hormone changes have also been reported to influence peripheral nervous system functions, such as sensory function, fine-touch perception, two-point discrimination, hearing, smell and vision ^[20]. Estrogen receptor beta has been found to be widely distributed in the female brain, being found especially in the hippocampus, amygdala and dorsal raphe nucleus, and to have multiple functions, for example regulation of the protein expression of genes involved in neurological functions, promotion of neurogenesis, modulation of stress response, neuroendocrine regulation, neuroprotection against ischemia and inflammation, and reduction of anxiety and depression ^[23]. Current evidence suggests that estrogen improves the formation of synapses on dendritic spines in the hippocampus, increases cerebral blood flow and glucose metabolism, and acts as an antioxidant. Moreover, estrogen increases choline acetyltransferase activity in the basal forebrain and hippocampus, reduces deposition of amyloid in the brain, and prevents cellular mitochondrial damage ^[24].

Important observations from studies in women who underwent oophorectomy before the onset of menopause for a non-cancer indication, show that both unilateral and bilateral oophorectomy before the onset of natural menopause are associated with an increased risk of cognitive impairment or dementia, with an age-dependent effect ^[25]. The hormonal changes occurring after oophorectomy in premenopausal women are different from those occurring during natural menopause. Bilateral oophorectomy before menopause causes an abrupt depletion of estrogen, progesterone and testosterone, and a disruption of the hypothalamic-pituitary-ovarian axis, which is associated with an abrupt increase in gonadotropins (luteinizing hormone and follicle-stimulating hormone) ^[26].

This endocrine disruption and estrogen deficiency, associated with genetic variants (in the apolipoprotein E, estrogen receptor 1, and estrogen receptor 2 genes) and non-genetic factors (smoking, alcohol consumption, obesity, education and diabetes mellitus), contribute to causing brain lesions, such as plaques, tangles, deposition of Lewy bodies and vascular lesions, that lead to cognitive impairment, declines in global cognition, episodic memory and semantic memory, and an increased risk of dementia and Alzheimer’s disease ^[27,28]. Moreover, a recent trial demonstrated that women who underwent bilateral oophorectomy have an increased risk of several chronic diseases, including depression and anxiety ^[29]. Studies of premature menopause in animal models revealed that the most affected cerebral area is the hippocampus, which becomes hypersensitive to ischemic injury and is involved in the induction of Alzheimer’s disease-related proteins, in the increase of amyloidogenesis, and in worsening of cognitive outcome after ischemic stress ^[30-32].

Hippocampal CA1 neurons of surgically menopausal rats show basal up-regulation of the neurodegenerative protein DKK1, basal antagonism of pro-survival Wnt/ β -catenin signaling, and basal acetylation/stabilization of the stress sensor p53, which sensitizes cells to stress ^[33,34]. Additional studies revealed that hippocampal CA3 region hypersensitivity, Alzheimer’s disease-related protein induction, and enhanced amyloidogenesis might also depend on activation of NADPH oxidase/superoxide/C-Jun N-terminal kinase/c-Jun signaling pathway,

a stress-activated intracellular signaling cascade that further enhances oxidative stress and promotes apoptosis in neurons^[31]. A recent study demonstrated that women who underwent bilateral oophorectomy show increased β -amyloid deposition (detected by PET) in the medial temporal lobe, leading to cognitive impairment and dementia^[35].

Moreover, estrogen plays an additional, critical, role in sustaining the brain's bioenergetic capacity by preserving glucose metabolism and mitochondrial function^[36-38]. The literature reports that the relationship between low levels of estrogen and cognitive changes is mediated by inflammation, which compromises the integrity of the blood-brain barrier (BBB), increasing its permeability and allowing the passage of inflammatory cells and molecules, for example cytokines (IL-1, IL-6, TNF- α), which can degrade the BBB itself^[39]. Therefore, there is evidence suggesting that surgical induction of early menopause enhances the risk of ischemic stroke, doubles the lifetime risk of dementia, and increases the risk of mortality from neurological disorders five-fold, and that these detrimental effects increase as the age of menopausal onset decreases^[25,26]. Furthermore, both premature surgical menopause and premature ovarian failure before the age of 40 years are associated with a more than a two-fold risk of poor verbal fluency and visual memory, in comparison with women who experienced menopause after the age of 50^[40].

In breast cancer patients, systemic therapies (chemotherapy and endocrine therapy) contribute, through different mechanisms, to the onset of early menopause and the abrupt reduction of circulating estrogen levels, causing menopausal symptoms similar to those analyzed in women who undergo bilateral oophorectomy.

These women experience vasomotor symptoms, vulvo-vaginal atrophy, sexual dysfunction and dyspareunia, musculoskeletal symptoms, neuropathy, and fatigue, in addition to cognitive impairment, distress, depression and anxiety^[7,41].

The role of adjuvant chemotherapy

Many premenopausal women diagnosed with breast cancer who received adjuvant chemotherapy complain of impaired memory, attention, speed of processing, word-finding, and other basic cognitive functions, in other words, "chemo fog" or "chemo brain"^[42,43].

During the last 30 years, many studies have been carried out on this subject, and the evidence has changed over time. In the 1990s many cross-sectional studies assessed the cognitive function in breast cancer patients receiving chemotherapy and consistently found that these patients showed lower than-expected cognitive performance on the neuropsychological tests, thus demonstrating the detrimental effects of chemotherapy on cognitive functioning. Around the year 2004, when data from prospective studies began to emerge, the concept of "chemo brain" was surprisingly changed.

Many studies discovered that cognitive deficits were already present in breast cancer patients before adjuvant chemotherapy, and suggested that they had presumably been misinterpreted as chemotherapy effects in previous investigations. Moreover, in several prospective studies, including methodologically sound large-scale studies, only subtle cognitive change has been ob-

served, usually in a limited subset of cognitive domains. Generally, a minority of patients (15–25%) seemed to be affected, with higher rates (up to 61%) sporadically reported^[42]. Recently, a meta-analysis of neuropsychological studies concluded that six months after the end of a standard chemotherapy regimen for breast cancer, cognitive deficits are, on average, small in magnitude and limited to the domains of verbal ability and visuospatial ability^[44].

Several studies using neuroimaging techniques (mostly MRI) documented both structural and functional brain differences between breast cancer patients treated with chemotherapy and control groups. Structural differences in breast cancer survivors include reductions in gray matter volume, primarily in frontal structures and the hippocampus, and white matter integrity. Functional differences are represented by regional hypoactivation as well as more widespread brain activation during cognitive tasks, which may indicate that affected patients compensate for the dysfunction of areas relevant to the task by activation of additional brain areas^[45-47].

To date, the role of chemotherapy neurotoxicity in the onset of cognitive disease is still unclear because many other factors may potentially affect the breast cancer patient's brain; these factors include endocrine therapy, surgery, radiotherapy and biological factors, such as high cytokine levels^[48]. Also, psychological factors play an important role since women who receive chemotherapy have a more advanced cancer stage at diagnosis, worse prognosis and a greater psychological burden^[42].

In particular, women with chemotherapy-induced menopause not only experience the chemotherapy-related cognitive, neurological and psychological disorders previously mentioned, but also have to deal with various menopausal symptoms associated with the chemotherapy-induced drop in estrogen level, such as cognitive function decline, physical and psychological symptoms, vasomotor symptoms, reproductive and sexual function problems, and body weight change^[49].

The role of adjuvant endocrine therapy

Given that the literature suggests a positive effect of estrogen on brain functioning, it is possible that endocrine therapy in breast cancer patients, whose aim is to bring about estrogen deprivation, might influence brain functioning and cognition.

In recent years, several studies have evaluated the impact of endocrine therapy on cognitive function in breast cancer patients and small prospective studies have found that initiation of endocrine therapy is associated with significant changes in neuropsychological performance^[50,51].

The TEAM (Tamoxifen and Exemestane Multicenter) trial assessed neuropsychological performance in breast cancer patients approximately two years after they started either tamoxifen or aromatase inhibitors. Significantly greater memory complaints were observed among breast cancer patients than healthy control participants, with no significant differences between tamoxifen or aromatase inhibitor; both groups performed significantly worse than healthy controls on verbal fluency and information processing speed.

The trial also showed that after one year of treatment, women randomized to tamoxifen showed statistically significantly lower functioning in verbal memory and information process-

ing speed compared with those randomized to exemestane. In the non-randomized comparison with healthy women, the study also showed that exemestane did not seem to impact cognitive function adversely [52,53].

The lack of impact of aromatase inhibitors on cognitive function is also supported by a trial showing that postmenopausal women taking anastrozole have similar cognitive function after 2 years compared with those taking placebo [54] and by another one demonstrating that postmenopausal women taking letrozole during 5 years of adjuvant endocrine therapy have better global cognitive function than those taking tamoxifen [55]. A recent study, dealing specifically with premenopausal women treated with tamoxifen, demonstrated that these women exhibited an impairment in executive control of the attention network and executive function performance deficit on neuropsychological tests, associated with a reduction in performance on executive function tests [56].

Moreover, the Co-SOFT study, although limited by a small sample size, provided no evidence that the addition of ovarian function suppression to adjuvant endocrine therapy (both tamoxifen and exemestane) in premenopausal woman substantially affects global cognitive function [57].

What can we do?

To date, the cognitive impairment experienced by many breast cancer patients during and after treatments is thought to be multifactorial and related to chemotherapy, surgery, anesthesia, endocrine therapy, psychological factors, and the cancer itself, and its prevention and treatment are not yet clearly established.

Guidelines have recommended that primary care clinicians ask breast cancer patients if they are experiencing cognitive difficulties, assess for reversible contributing factors of cognitive impairment, optimally treat when possible and refer patients with signs of cognitive impairment for neurocognitive assessment and cognitive rehabilitation programs [7].

There is evidence that memory problems in healthy menopausal women can be due to, or worsened by, vasomotor symptoms, as demonstrated by a few studies directly addressing the relationship between hot flashes and cognitive performance. Although inflammation is one of the main mediators between menopausal low levels of estrogen and cognitive function, it has recently been proposed that cortisol might mediate the relationship between hot flashes and cognitive performance, with higher urinary levels found in highly symptomatic women [7,58,59]. The relationship between vasomotor symptoms and cognitive impairment in breast cancer patients has not yet been demonstrated, but a correlation is likely to exist, as in healthy menopausal women.

For this reason, many non-hormonal treatments of vasomotor symptoms have been proposed as methods that can contribute to improving cognition in breast cancer patients. Several medical treatments may be effective in decreasing the intensity and severity of menopausal symptoms: selective serotonin reuptake inhibitors (SSRIs) and selective serotonin-norepinephrine reuptake inhibitors (SSNRIs) reduce the intensity and frequency of hot flashes by 20% to 65% [60-62]. Moreover, depressive disorders, which are quite common during the men-

opausal transition and are frequently reported by breast cancer patients, are also associated with memory problems; treatment of depressive symptoms might help to improve cognition in these women [22].

Anticonvulsant drugs, such as gabapentin and pregabalin, decrease the frequency of climacteric symptoms by modulating thermoregulatory activity both in healthy menopausal women and in breast cancer survivors; the anti-hypertensive alpha-adrenergic agonist clonidine inhibits flushing by reducing peripheral vascular reactivity [63-65].

Purified pollen extract showed beneficial effects on vasomotor symptoms and insomnia in healthy women, probably deriving from the inhibition of serotonin uptake at the synaptosomal junction, with an SSRI-like mode of action; unfortunately, no data are available in women with breast cancer [66]. Extract of black cohosh (*Actae racemosa* or *Cimicifugae racemosae*) has been used for centuries as a phytotherapeutic treatment for many conditions, including the management of climacteric symptoms. Today, its use in breast cancer patients is still controversial due to its selective modulation of estrogen receptors (SERM)-like mechanism of action [67-70].

Non-pharmacological methods, such as acupuncture, yoga, breathing, hypnosis, diet and stellate ganglion block, can reduce climacteric symptoms both in healthy women and in breast cancer survivors [69].

As regards cognitive impairment related to early menopause in breast cancer patients, rehabilitation strategies play an important role and include group cognitive training, based on structured tasks or activities with the aim of improving cognition through practice by strengthening neural pathways and training compensatory strategies, such as interventions geared at improving, restoring or maintaining mental function through structured, repetitive practice of tasks posing a mental challenge or requiring the person to problem solve [71-73].

Conclusions

In breast cancer patients, who are premenopausal at diagnosis, the onset of early menopause due to chemotherapy and endocrine therapy is related to cognitive impairment, memory dysfunction, depression and anxiety. Frequently underdiagnosed and undertreated, it represents an important issue, negatively impacting on patients' quality of life, with detrimental effects on their role within the family, in the workplace and in society.

Although the correlation between vasomotor symptoms and cognitive impairment in breast cancer patients has not yet been demonstrated, it seems likely that the treatment of hot flashes may improve cognition and memory, as shown in healthy menopausal women.

Primary care clinicians play an important role in identifying breast cancer patients suffering from early menopause and cognitive impairment and referring them for specific treatments and rehabilitation programs [52].

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