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Review

Neuropsychological functioning following systemic treatment in women treated for breast cancer: a review

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Abstract

The aim of this review was to evaluate the effect of treatment and illness-related factors on neuropsychological functioning in women treated for breast cancer. Eight studies were identified examining neuropsychological test performance following systemic treatment. Six of the eight studies suggest that neuropsychological functioning may be impaired following treatment. However, there are a number of important methodological issues which limit interpretation of these results. Therefore, it is unclear whether neuropsychological outcome differs according to a range of treatment, biomedical and psychological factors. Larger samples with longitudinal follow-up are required in order to examine the treatment-related factors that best predict cognitive deficits.

Keywords: Breast cancer; Adjuvant chemotherapy; Tamoxifen; Cognitive deficits

1. Introduction

Although the ultimate goal of cancer treatment is improved survival, increasing emphasis is placed on reducing morbidity associated with treatments and improving quality of life. The physical side-effects of chemotherapy such as myelosuppression, hair loss, nausea, fatigue, mucositis, diarrhoea, weight gain and constipation are well known [1]. Less clear is the effect that cancer treatment may have on cognitive functioning. Cognition is an aspect of quality of life that has rarely been explored systematically in adult patients with cancer, particularly when treatment does not appear to directly involve the central nervous system [2–4].

Assessment of cognitive functioning in breast cancer patients is important for a number of reasons. The number of anecdotal reports concerning changes in cognition following adjuvant treatment necessitates further investigation. Accurate information about side-effects must be disclosed to patients in order to enable informed treatment decisions to be made [5]. Information concerning late effects of treatment will enable health care professionals to help prepare patients to expect and cope with any changes in cognition that may occur [6]. Further research in this area will also lead to an understanding of whether all women undergoing adjuvant treatment are at risk, or what the risk factors for subsequent cognitive impairment might be. In addition, an integrated account of the neural, psychophysiological and cognitive changes that might result from treatment will enable an understanding of the aetiology and mechanisms underlying cognitive deficits.

Systemic treatment for breast cancer involves chemotherapy or hormone therapy, either alone or in combination. Breast cancer cells that are endocrine-dependent need oestrogen in order to proliferate. Treatment with Selective Oestrogen Receptor Modulators (SERMs), such as tamoxifen, have been shown to improve survival for these patients [7]. At present, tamoxifen is the 'gold standard' in adjuvant hormonal therapy [7]; however, it is associated with a number of side-effects, including an increased risk of endometrial cancer and thromboembolic disorders. Tamoxifen is generally administered to women for 5 years (20 mg daily). In contrast, chemotherapy is administered over a much shorter duration, typically 3–6 months.

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This review examines the evidence for deficits in neuropsychological functioning following systemic treatment for breast cancer. Potential explanations for observed deficits will also be discussed. A total of eight studies were identified, which examined neuropsychological functioning following systemic treatment for breast cancer (see Table 1). Of these, five focused on women who had received adjuvant chemotherapy [8–12]. One [13] was a follow-up study of cohorts of women previously assessed [9,10], and the remaining two studies [14,15] examined tamoxifen-treated populations. Table 2 presents an overview of the range of cognitive functions assessed in these studies.

2. Incidence of cognitive deficits

The proportion of women shown to exhibit a cognitive deficit varies across studies, and is a function of the instruments used to measure cognitive status, and the cut-off point used to define impairment. Wieneke and Dienst [8] reported that 75% of women in their sample scored greater than 2 standard deviations below the norm on at least one of the neuropsychological tests they administered. However, clinical samples often vary systematically from 'healthy' controls, which may lead to an overestimation of the differences [5]. Four studies have demonstrated that approximately one-third of women have mild to moderate cognitive impairment [9–12]. For example, Schagen and colleagues [10] found impairment in cognitive function in 28% of women treated with chemotherapy compared with 12% of women in the control group. Similarly, Ahles and colleagues [12] reported that 39% of women who had received adjuvant chemotherapy 5 years previously had cognitive impairments compared with 14% of women who had received local therapy, some of whom had also taken tamoxifen.

3. Profile of neuropsychological deficits

Five studies found impairment on overall neuropsychological function as reported in an 'overall' score [8–12]. Insufficient statistical power due to small sample sizes has meant that an examination of performance across individual sub-tests is limited. However, where performance on cognitive sub-tests has been explored deficits have been observed in verbal and visual memory, attention and motor speed.

Wieneke and Dienst [8] identified deficits in non-verbal long-term memory, but not in verbal long-term memory. van Dam and colleagues [9] found women treated with high-dose myeloablative chemotherapy and autologous bone marrow or peripheral blood stem cell rescue had lower scores than controls on seven of the 19 tests they administered. However, when correcting for multiple comparisons, none of these differences remained significant and the relevance of this study is compromised by a lack of evidence for the efficacy of high-dose chemotherapy in randomised controlled trials to date [16]. In a subsequent study, Schagen and colleagues [10] adopted the same test battery with the addition of a visual reproduction sub-test (immediate and delayed recall). The pattern of results was similar to that obtained previously [9]. Performance on 12 of the 21 sub-tests was significantly poorer for the standard chemotherapy group when compared with the control group ($P < 0.05$). Deficits were observed for a range of cognitive skills, including, attention, mental flexibility, reaction time, visuo-spatial memory, motor function and verbal function [10].

Brezden and colleagues [11] carried out an exploratory analysis of six cognitive domains (memory; language; visual-motor; spatial; attention and concentration; and self-regulation and planning) measured by the High Sensitivity Cognitive Screen. The memory and language domain revealed impairment for women who were on-treatment compared with healthy controls. Language and visual motor skills were impaired for women who were off-treatment compared with healthy controls. No correction was made for confounding factors (e.g. age, and education) or multiple comparisons [11]. Ahles and colleagues [12] found that patients who had completed adjuvant chemotherapy treatment scored lower than those who had received local treatment in the domains of verbal memory and psychomotor functioning.

Interpretation of the pattern of deficits observed needs to be made with caution. A greater deficit for one or more particular sub-tests could mean either that the neural systems which underly the domains tested are more susceptible to chemotherapy-related disruption, or that findings may be an artefact of the assessments used. Such that certain sub-tests may be more reliable and/or more sensitive to the detection of cognitive deficits in this population.

Adjustment for confounding factors (e.g. age, education, socio-economic status, menopausal status, premorbid intelligence quotient (IQ)) is essential. The estimation of premorbid IQ has only been used in a few studies [8–10]. The lack of adequate controls and/or comparison groups presents a further challenge. The use of a disease-specific comparison group goes some way to act as a control for the impact of the diagnosis of cancer. However, the lack of pretreatment assessment of cognitive functioning does limit interpretation of post-treatment cognitive performance.

4. Adjuvant chemotherapy and cognitive function

In order to examine the cognitive effects of chemotherapy, attention should be directed to the

Table 1
Summary of studies examining neuropsychological functioning following adjuvant treatment for breast cancer

Study [Ref.]	Participants	Chemotherapy/ time since treatment	Tamoxifen use	Results
Wieneke and Dienst [8]	28 Stage I and II breast cancer patients (mean age 42 years; S.D. 6.7)	CMF ($n=17$) CMF+CAF ($n=7$) CAF ($n=4$)	11 current 17 never	• Comparisons made with test norms. • Demographic variables were not related to overall cognition.
		Duration of therapy: 3–18 months (time since therapy: from 0.5 to 12 months)		• Cognitive impairment was related to duration of chemotherapy.
van Dam and colleagues [9]	34 High-risk breast cancer patients (stage II or III) (mean age: 45.5 years; S.D.: 6.2).	CTC (time since therapy: mean: 1.6 years; S.D.: 0.8)	29 current 5 past	• Each volunteer was scored as impaired if 3 or more test scores were 2 or more standard deviations below the mean.
	36 High-risk breast cancer patients (stage II or III) (mean age: 48.1 years; S.D.: 6.8)	FEC (time since therapy: mean: 1.9 years; S.D.: 1.1)	28 current 8 past	• Impaired performance reported for 32% of women treated with high-dose chemotherapy, compared with 17% with standard dose, and 9% of the control group ($P=0.043$).
	34 breast cancer (control) patients (stage I) (mean age: 46.1 years; S.D.: 5.2)	No chemotherapy (time since local therapy: mean: 2.4 years; S.D.: 1.0)	34 never	
Schagen and colleagues [10]	39 Breast cancer patients (mean age 47.1 years; S.D.: 6.5).	CMF (6 courses) (time since therapy: mean 1.9; S.D.: 1.0)	18 current 2 past 19 never	• Calculated an overall impairment score (see above). • Hormonal treatment had no influence on patients self-reports of symptoms or cognitive function.
	34 controls consisting of age-matched axillary lymph node negative breast cancer patients (mean age: 46.1 years; S.D.: 5.2)	No chemotherapy (time since local therapy: mean 2.4; S.D.: 1.0)	34 never	
Schagen and colleagues [13]	23 High-risk breast cancer patients (stage II or III). (mean age: 50.4 years, S.D.: 6.3)	FEC (time since therapy: mean: 3.4 years; S.D.: 1.2)	4 current 19 past	• Follow-up study of cohorts previously assessed [8,9] • No significant differences in cognitive performance between the four groups.
	22 High-risk breast cancer patients (stage II or III) (mean age: 47.0 years; S.D.: 4.8)	CTC (time since therapy: mean: 3.3 years; S.D.: 1.1)	7 current 15 past	• CTC: fewer women classified as impaired at T2 ($n=3$) versus T1 ($n=5$) • FEC: appeared to be stable over time. (T1: $n=3$; T2 = 2)
	31 Breast cancer patients (mean age 50.3 years; S.D.: 4.5).	CMF (6 courses) (time since therapy: mean 3.7 years; S.D.: 1.1)	11 current 9 past 11 never	• CMF: fewer women classified as impaired at T2 ($n=4$) versus T1 ($n=8$). • Control: more women classified as impaired on T2 ($n=3$) versus T1 ($n=1$).
	27 stage I breast cancer patients (mean age 48.8 years; S.D.: 5.0)	N/A (time since local therapy. mean: 4.6 years; S.D.: 1.1)	27 never	

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Table 1 (*continued*)

Study [Ref.]	Participants	Chemotherapy/ time since treatment	Tamoxifen use	Results
Brezden and colleagues [11]	31 breast cancer patients (stage I or II) (median age: 49 years; range: 34–70).	CMF ($n=12$); CEF ($n=19$) (on-treatment)	31 never	• HSCS scores were poorer in patients receiving chemotherapy compared with controls. • Included the covariates: age, education, menopausal status.
	40 Breast cancer patients (stage I or II) (median age: 46 years; range: 26–61).	CMF ($n=21$); CEF ($n=17$) (completed treatment median of 2 years previously).	16 current 2 past 22 never	• No trends to suggest differences between more aggressive chemotherapy with CEF and those receiving CMF.
	36 Healthy controls (Median age: 41.5 years ; Range: 24–61).	N/A	36 never	
Ahles and colleagues [12]	35 breast cancer patients (mean age: 59.1 years; S.D.: 10.7).	CMF ($n=14$) CAF ($n=14$) Other ($n=5$) (time since therapy: mean: 9.4, S.D.: 4.5)	13 at some time 22 never	• Calculated Neuropsychological Performance Index: (lower quartile versus upper three quartiles). • When compared with treatment with local therapy, those treated with adjuvant chemotherapy scored significantly lower on the verbal memory, and psychomotor components.
	36 Lymphoma patients (mean age: 55.9 years; S.D.: 12.1)	CAVP ($n=10$) MVPrP ($n=8$) Other ($n=18$) (time since therapy: 9.5; S.D.: 4.8)	N/A	
	35 breast cancer patients treated with local therapy only (mean age: 60.6 years; S.D.: 10.5)	N/A (time since therapy: 9.9; S.D.: 5.8).	5 at some time 30 never	
	22 lymphoma patients treated with local therapy only. (Mean age: 48.7 years; S.D.: 11.7).	N/A (time since local therapy: 14.4; S.D.: 6.3)	N/A	
Paganini-Hill and Clark [14]	1163 women treated for primary breast cancer. (age range: 57–75 years)	Approximately 20% of patients	453 never 231 < 4 years 333 > 4 years 146 unknown duration 428 past 241 current 4 not reported	• No differences between those who had not taken tamoxifen and those who had used tamoxifen for the standard 5 years on the cognitive assessments. • Assessments sent by post, therefore, question the validity of this approach.
Ernst and colleagues [15]	16 Women diagnosed with localised breast cancer and given local treatment	N/A	All for at least 2 years (mean 4.4; S.D. 1.7 years).	• Measured myo-inositol (MI) levels. • Women in tamoxifen and HRT group had lower levels of MI than controls.
	27 women who were on HRT (no history of breast cancer); received HRT for at least 2 years (mean 20.8; S.D. 10.5 years)	N/A	N/A	
	33 control women with no history of breast cancer or HRT use		N/A	

C, cyclophosphamide; M, methotrexate; F, fluorouracil; E, epirubicin; A, doxorubicin (Adriamycin); V, vincristine; P, prednisone; Pr, procarbazine; S.D., standard deviation; N/A, not applicable; HRT, hormone replacement therapy; CTC, cyclophosphamide, thiotepa and carboplatin; T, time; HSCS, High sensitivity cognitive screen.

Table 2
List of sub-tests used to assess neuropsychological functioning in breast cancer patients

Function measured	Sub-test administered	Study
Verbal skills	Word Fluency sub-test (Dutch Aphasia Society Test)	van Dam and colleagues [9]
		Schagen and colleagues [10]
		Schagen and colleagues [13]
	Narrative writing to describe a pictured scene	Paganini-Hill & Clark [14]
	Vocabulary (WAIS-II)	Ahles and colleagues [12]
	Reading (WRAT-3)	Ahles and colleagues [12]
	Boston Naming Test	Ahles and colleagues [12]
	Controlled Oral Word Association	Ahles and colleagues [12]
Abstract concepts	Categories: short booklet	Wieneke & Dienst [8]
Memory skills	Digit span (WAIS-R)	Wieneke & Dienst [8]
		van Dam and colleagues [9]
		Schagen and colleagues [10]
		Schagen and colleagues [13]
	California Verbal Learning Test	Wieneke & Dienst [8]
	Short delay; Long delay	Ahles and colleagues [12]
	Rey Auditory Verbal Learning Test	van Dam and colleagues [9]
		Schagen and colleagues [10]
		Schagen and colleagues [13]
Visuo-spatial memory	Rey Osterrieth Complex Figure Test: Direct copy; Recall	Wieneke & Dienst [8]
		van Dam and colleagues [9]
		Schagen and colleagues [10]
		Schagen and colleagues [13]
	Visual Reproduction Sub-test:	Schagen and colleagues [10]
	Copy and Recall (Wechsler Memory Scale)	Ahles and colleagues [12]
Visuo-spatial construction	Clock Drawing	Paganini-Hill & Clark [14]
	Box Drawing: Copy task	Paganini-Hill & Clark [14]
	Block Design (WAIS-R)	Wieneke & Dienst [8]
		Ahles and colleagues [12]
Attention	Digit symbol (WAIS-R)	Wieneke & Dienst [8]
		van Dam and colleagues [9]
		Schagen and colleagues [10]
		Schagen and colleagues [13]
		Ahles and colleagues [12]
		Ernst and colleagues [15]
	Fepsy Visual Searching Test	van Dam and colleagues [9]
		Schagen and colleagues [10]
		Schagen and colleagues [13]
	D2 Test	van Dam and colleagues [9]
		Schagen and colleagues [10]
		Schagen and colleagues [13]
	Vigilience and Distractability	Ahles and colleagues [12]
	(Continuous Performance Test)	
	Vigilence and Distractability reaction time scores	Ahles and colleagues [12]
	(Continuous Performance Test)	
Mental flexibility	Stroop Test	van Dam and colleagues [9]
		Schagen and colleagues [10]
		Schagen and colleagues [13]
	Paced Auditory Serial Addition Test	Wieneke & Dienst [8]
	Trail making A and B	Wieneke & Dienst [8]
		van Dam and colleagues [9]
		Schagen and colleagues [10]
		Schagen and colleagues [13]
		Ahles and colleagues [12]
	Trail Making A	Ernst and colleagues [15]

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Table 2 (*continued*)

Function measured	Sub-test administered		Study
Perceptuo-motor	Fepsy Visual Reaction Task		van Dam and colleagues [9] Schagen and colleagues [10] Schagen and colleagues [13]
	Fepsy Finger Tapping Task		van Dam and colleagues [9] Schagen and colleagues [10] Schagen and colleagues [13]
	Finger Tapping;	Thumb Finger Sequencing	Ahles and colleagues [12]
	Grooved Peg Board:	Dominant; non-dominant	Wieneke & Dienst [8]
	Fepsy Binary Choice Test		van Dam and colleagues [9] Schagen and colleagues [13]
General	High Sensitivity Cognitive Screen		Brezden and colleagues [11]
	Mini-Mental State Examination		Ernst and colleagues [15]
Premorbid IQ	Dutch Adult Reading Test		van Dam and colleagues [9] Schagen and colleagues [10]
	National Adult Reading Test		Wieneke & Dienst [8]

chemotherapeutic agents used, their doses, duration and intensity of treatment, and potential drug interactions. The main adjuvant chemotherapeutic combinations used in the treatment of breast cancer are CMF (cyclophosphamide, methotrexate and 5-fluorouracil) or regimens based on an anthracyclines, such as doxorubicin or epirubicin [17].

Cognitive impairment in women treated with adjuvant chemotherapy has been reported when compared with women treated with local therapy [9,10,12], and when performance is compared with test norms [8]. Patients who were undergoing adjuvant chemotherapy at the time of assessment have been found to show cognitive impairment when compared with healthy controls [11].

Only one study has compared different doses of chemotherapy as part of a randomised controlled trial [9]. Patients treated with myeloablative high-dose chemotherapy (FEC: 5-fluorouracil 500 mg/m^2 intravenously (i.v.), epirubicin 90 mg/m^2 i.v. and cyclophosphamide 500 mg/m^2 i.v. for four cycles with a fifth cycle of CTC: cyclophosphamide 6 g/m^2 i.v., thiotepa 480 mg/m^2 i.v., and carboplatin 1.6 g/m^2 i.v.) were found to show deficits in cognitive function compared with patients treated with FEC for four cycles [9]. However, high-dose chemotherapy with autologous haematopoietic progenitor support is inevitably associated with significant morbidity, and it is unclear whether the physical and emotional effects of this procedure may have contributed to changes in cognition.

Ahles and colleagues [12] report a significant, but low, correlation between the number of treatment cycles and mean neuropsychological domain scores, suggesting that more cycles of chemotherapy were associated with a lower neuropsychological performance.

The timing of cognitive assessments may also be crucial, since deficits may manifest themselves during specific treatment phases or may only emerge with time. At present, research suggests that cognitive deficits are associated with cancer chemotherapy regimens during treatment [11], approximately 1–2 years following treatment [8–10], and 5 years following treatment [12]. Schagen and colleagues [13] re-administered a neuropsychological battery 2 years following the initial neuropsychological assessments [9,10]. The results showed no statistically reliable differences between the treatment groups and control group at Time 2. There were some fluctuations in the number of women classified as cognitively impaired at Time 2 when compared with Time 1 (see Table 1), however, the interpretation was limited due to the small sample, and loss to follow-up.

It is not known if chemotherapy-associated neurotoxicity is caused by the combination of chemotherapy drugs or by one drug in particular. Increased risk of cognitive impairment has been shown for patients who received conventional CMF chemotherapy (cyclophosphamide 100 mg/m^2 orally on days 1–14, methotrexate 40 mg/m^2 i.v. on days 1 and 8, and 5-fluorouracil 600 mg/m^2 i.v. on days 1 and 8) when compared with controls [10] and test norms [8]. No increased risk was found for standard dose FEC (fluorouracil at 500 mg/m^2 i.v., epirubicin at 90–120 mg/m^2 i.v., and cyclophosphamide at 500 mg/m^2 i.v.; cycles repeated every 21 days) when compared with controls [9]. Brezden and colleagues [11] found no difference between patients who had undergone CMF or CEF chemotherapy. However, the small number of volunteers within each treatment group precludes any reliable conclusions

concerning likely agents associated with an increased risk of cognitive deficits. An intact blood–brain barrier is assumed to limit entry of chemotherapeutic agents to the brain; however, higher doses are associated with penetration of chemotherapeutic agents across the blood–brain barrier, leading to neurotoxicity [5]. Ahles and colleagues [12] report that cognitive deficits may also be caused by a physiological reaction (e.g. immunological response), which may be more closely associated with certain side-effects profiles. However, this has yet to be explored.

Adjuvant chemotherapy is also known to affect ovarian function leading to temporary or permanent amenorrhoea in premenopausal women. For these women, the drop in oestrogen occurs more rapidly than in natural menopause [18]. Oestrogen receptors are located throughout the brain, especially in regions that are involved in learning and memory, such as the hippocampus and amygdala [19]. Oestrogen deficiency has been related to memory loss and poorer cognitive function in postmenopausal women [20]. However, findings are equivocal and not all studies have found beneficial effects of oestrogen on cognition [21]. The relationship between oestrogen levels following adjuvant treatment and cognitive function has not been explored.

5. Adjuvant hormonal therapy and cognitive function

Approximately 45% of patients taking tamoxifen experience hot flashes [22]. Hot flashes may be related to an antagonistic effect on the hypothalamic–pituitary axis [23]. This has led to the suggestion that tamoxifen may act as an oestrogen-antagonist in the brain. Experimental animal studies [24] have shown that tamoxifen led to impaired memory consolidation and retrieval processes in mice. Tamoxifen impacts upon a number of pharmacological activities which may be directly or indirectly related to cognitive function [24]. However, the mechanism by which tamoxifen may impair learning and memory has not been clearly evaluated.

A small proportion of the studies identified included a sub-sample of patients who had been prescribed tamoxifen in addition to undergoing adjuvant chemotherapy. Schagen and colleagues [10] found no detectable differences between patients treated with both chemotherapy and tamoxifen ($n=20$) and those treated by chemotherapy alone ($n=19$). Ahles and colleagues [12] identified 18 women who had taken tamoxifen at some time, 13 of whom had also undergone chemotherapy. Comparisons of tamoxifen users ($n=18$) and non-users ($n=52$) revealed no significant differences on any of the neuropsychological domain scores. However, the number of patients who had taken tamoxifen in both of these studies was small, so the results may lack the statistical power to detect subtle differences in cognition.

Two studies [14,15] have set out to explicitly assess cognitive function in breast cancer patients treated with tamoxifen. Paganini and Clark [14] examined performance on three cognitive tests (clock drawing, copying a box drawing, and narrative writing to describe a pictured scene) in a sample of patients who had taken tamoxifen for a period of 5 years. Performance was not significantly different to that of 'never users'. However, current users had a significantly lower mean complexity score on the narrative writing task when compared with 'never users'. More women who had used tamoxifen for the standard term (5 years) reported seeing their physician for memory problems than 'never-users' (3.8% versus 1.5%, $P=0.04$).

A study examining the effects of tamoxifen on brain chemistry suggests that tamoxifen may offer some degree of neuroprotection [15]. The prediction was that an oestrogen-antagonistic effect of tamoxifen might be associated with elevated myo-inositol (MI) levels. Proton magnetic resonance spectroscopy (MRS) was employed to measure brain metabolite concentrations in the frontal white matter, basal ganglia and hippocampus of women aged 65 years and over (mean age 70.4 years). In this cross-sectional study, 16 women had taken tamoxifen following localised breast cancer which was not treated with chemotherapy, and 27 women with no history of breast cancer had received HRT. The control group consisted of 33 healthy women who had not received any hormone treatment. Women treated with tamoxifen and HRT had lower levels of myo-inositol in the brain than untreated women. Performance on a modified version of the Mini-Mental State Examination and two cognitive tests that are sensitive to psychomotor speed did not differ across the three groups. It was concluded that tamoxifen has a similar effect to oestrogen. However, findings may not be generalisable to younger age groups. This is the first published study to look at chemical markers and results should be interpreted with caution due to the small number of patients who were on tamoxifen [25]. In addition, it is important to eliminate alternative explanations for the lower MI levels. For example, older women who develop breast cancer may have higher circulating levels of oestrogen following the menopause than healthy women who do not have breast cancer [25].

Recently, research has examined the impact of Raloxifene, a SERM, on cognitive function in postmenopausal women. Yaffe and colleagues [26] found no significant differences in overall cognitive scores in postmenopausal women with osteoarthritis randomly assigned to treatment with raloxifene (60 mg or 120 mg orally per day) or placebo for 3 years ($N=7478$). However, there was a trend towards less decline in the combined raloxifene group on two tests of verbal memory. Bernstein and colleagues [27] report similar findings from a randomised

double-blind placebo-controlled study examining the short-term effects of raloxifene (60 mg/day), tamoxifen (20 mg/day), and conjugated equine oestrogen (0.625 mg/day) on cognitive function in 103 healthy postmenopausal women. There were no significant differences between treatment groups over time on cognitive measures. However, there was a trend towards a slightly enhanced performance for the raloxifene group on the word recall test.

An understanding of cognitive function in women treated with tamoxifen is important, particularly with the emergence of aromatase inhibitors, such as anastrozole ('Arimidex'), which substantially reduces oestrogen concentrations in postmenopausal women. A large randomised efficacy study of anastrozole as an adjuvant treatment suggests a disease-free survival advantage compared with tamoxifen [28], but before these results can be applied to clinical practice, the effect of chronic oestrogen deprivation on cognition needs to be explored. Shilling and colleagues [29] assessed cognitive function in 103 women participating in the ATAC trial (a double-blind comparison of tamoxifen and anastrozole alone and in combination for early breast cancer) and 85 non-cancer controls. There was no difference between the patient and control groups on measures of working memory, attention and visual memory. However, performance in the patient group on measures of verbal memory were significantly poorer ($P = 0.035$) than the performance by the control population.

6. Objective measures versus subjective perceptions of cognitive function

Four studies used subjective measures of cognitive function to supplement measures of neuropsychological performance. van Dam and colleagues [9] used the Cognitive Problems in Daily Life Checklist; a semi-structured interview designed to tap into problems with memory, attention, thinking, and language that occur in daily life. The results showed that patients who had received high-dose and standard-dose chemotherapy reported more problems than the no chemotherapy control group, in the domains of memory, attention, and thinking. However, there was no relationship between self-reported cognitive problems and neuropsychological tests [9]. In a subsequent study using the same measure, Schagen and colleagues [10] found a greater prevalence of self-reported cognitive problems in the domains of concentration and memory. However, there were no significant differences between the groups on self-reported problems of thinking or language. Once again, there was no relationship between cognitive test scores and self-reports of cognitive problems [10]. In a follow-up study, Schagen and colleagues [13] also found that the correlation between objective test results and subjective measures was low. Ahles and colleagues [12] used the Squire Memory Self-Rating Scale, an 18-item measure which assesses perceived changes in a range of memory functions. It is composed of three factors: learning of new information; working memory; and retrieval of information from long-term memory. The only factor that differentiated the treatment groups was working memory, which was rated as poorer in a group which had received adjuvant chemotherapy compared with a local therapy group. Correlations between the Squire subscales and the neuropsychological test scores were not significant [12].

There are a number of reasons for the finding that patients may complain of memory deficits despite achieving scores within the normal range on tests of memory functioning. First, subjective measures and neuropsychological test batteries may not be measuring the same construct. Most clinical memory tests are extensions of laboratory tests, therefore, they do not necessarily map directly onto memory problems encountered by patients in their everyday lives. As a result, they may be poor predictors of such problems [30]. Secondly, cognitive impairment is most prominent in conditions like dementia, learning disability and acquired brain injuries. A number of the tools that have been used to assess cognitive functioning in patients treated for cancer are those which are routinely used with these groups (e.g. Rey Osterrieth Complex Figure), and thus may be insufficiently sensitive to detect mild deficits. Therefore, subtle differences in cognition may go undetected.

7. The effect of biomedical and psychological factors on cognitive function

Eighty per cent of breast cancers occur in postmenopausal women. Cessation of ovarian oestrogen production with menopause has been associated with changes in cognitive processes, including memory and attention [31]. Cognitive performance may be improved in these groups after Oestrogen Replacement Therapy, although this issue remains controversial [32]. Women with oestrogen receptor-positive breast cancer are advised not to take hormone replacement therapy and therefore would be unable to benefit from potential cognitive gains.

The cognitive changes noted by postmenopausal women may be related not only to the loss of oestrogen, but to other factors including advancing age. Cognitive effects of old age vary in frequency, direction and extent. For example, slowing of information processing is ubiquitous among people over 60 years, but there is a fair chance of reaching the age of 90 years with no memory problems [33]. There is very little data available on the influence of age on cognitive functioning in

breast cancer patients following adjuvant treatment. Schagen and colleagues [13] found that age, IQ and depression contributed to risk of impairment at Time 2 of their follow-up study in participants who had undergone CTC/FEC chemotherapy. For the CMF group, age was the sole predictor of risk of impairment. However, in an earlier study, Schagen and colleagues [10] found that age did not influence the risk of neuropsychological impairment.

The psychological experience of having had breast cancer may contribute to a decline in cognitive performance. It is generally accepted that both depression and anxiety are more commonly found amongst cancer patients than in the general population, and that the prevalence of clinically significant morbidity following treatment is in the region of 25–35% [34]. For many breast cancer patients, much of their anxiety is generated by their perceived risk of recurrence. Patients selected for adjuvant chemotherapy are generally in the groups with the highest risk of recurrence and this difference may account for some of the cognitive deficits reported in patients receiving chemotherapy. Memory functions in anxious and depressed people have been investigated quite extensively. It has been shown that anxiety produces worry and other intrusive thoughts that compete for resources in short-term working memory [35].

Two studies [9,10], which explored the effect of psychological constructs on cognition, found a relationship between self-reported cognitive function and anxiety and depression. Schagen and colleagues [10] found an association between the self-reported cognitive problems reported at interview and the scores on the cognitive and emotional subscales of the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-C30. The problems reported at the interview and the scores on the anxiety and depression subscales of the Hopkins Symptom Checklist were also related. The lack of further associations between psychological morbidity and cognitive deficits may be due to the fact that survivors experiencing major psychological difficulties were screened out [11], or chose not to take part.

8. Conclusions

The relationship between adjuvant treatment for breast cancer and cognitive function is complicated. There are a number of factors which may influence cognitive performance, and, as yet, it is difficult to ascertain which of these factors play a central role. Six [8–12,14] of the eight studies identified suggest that adjuvant breast cancer treatment reduces cognitive function to some extent. However, methodological weaknesses in the research published thus far have impeded an understanding of the characteristics of women who are shown to have cognitive deficits.

The range of approaches used to define and measure cognitive performance in cancer patients contributes to the inconsistent findings. With two exceptions [11,15], studies have involved extensive neuropsychological testing, often relying heavily on general IQ assessments, which may not be sensitive to subtle changes. Whilst this enables a comprehensive assessment of neuropsychological functioning, small sample sizes and the large number of variables entered into the analysis contribute to the lack of statistical power. Hence, despite the range of neuropsychological assessment tools used, there is a lack of specificity, such that no distinct neuropsychological profile for women treated for breast cancer has been identified. As a result, there is limited evidence to indicate the most suitable cognitive assessment strategy. In all the studies reviewed, effect sizes have not been reported, so despite these studies reporting statistically significant differences in the cognitive function of patients treated with chemotherapy when compared with controls, the effect size may be so small as to make the difference negligible, in terms of the likely impact on the daily cognitive functioning of patients.

It is important to identify the effects of cognitive deficits in terms of everyday living. This is especially pertinent given the lack of concordance between objective measures and subjective reports of cognitive function. There are a number of ways in which cognitive deficits may impact upon quality of life. A greater understanding of the implication of adjuvant treatment on cognitive function is needed. Such an understanding will also be important for the development and implementation of suitable intervention strategies, which also take into account the social and emotional consequences of cognitive deficits [36].

Research that delineates processes that affect cognitive functioning over time would provide a much stronger basis for inference regarding the influence of treatment on cognition. In addition, it remains unclear whether the profile of deficits differs according to a range of variables, for example, chemotherapy, tamoxifen, time since treatment, and socio-demographic factors. However, there is a clear need for measures that are sensitive to change in women with mild-to-moderate cognitive impairment. Both the assessment of premorbid cognitive ability and the impact of conventional treatment protocols such as CMF or anthracycline-based chemotherapies is also important. This will enable a greater understanding of any additional effects upon cognition of chemotherapy regimens with longer duration, increased dose intensity or the inclusion of newer cytotoxics, for example, the taxanes and of the use of adjuvant aromotase inhibitors in place of tamoxifen.

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