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Adjuvant ovarian function suppression and cognitive function in women with breast cancer

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Background: To examine the effect on cognitive function of adjuvant ovarian function suppression (OFS) for breast cancer.

Methods: The Suppression of Ovarian Function (SOFT) trial randomised premenopausal women with hormone receptor-positive breast cancer to 5 years adjuvant endocrine therapy with tamoxifen + OFS, exemestane + OFS or tamoxifen alone. The Co-SOFT substudy assessed objective cognitive function and patient reported outcomes at randomisation (T0), and 1 year later (T1); the primary endpoint was change in global cognitive function, measured by the composite objective cognitive function score. Data were compared for the pooled tamoxifen + OFS and exemestane + OFS groups *vs* the tamoxifen alone group using the Wilcoxon rank-sum test.

Results: Of 86 participants, 74 underwent both T0 and T1 cognitive testing; 54 randomised to OFS + either tamoxifen (28) or exemestane (26) and 20 randomised to tamoxifen alone. There was no significant difference in the changes in the composite cognitive function scores between the OFS + tamoxifen or exemestane groups and the tamoxifen group (mean ± s.d., -0.21 ± 0.92 *vs* -0.04 ± 0.49, respectively, $P = 0.71$, effect size $= -0.20$), regardless of prior chemotherapy status, and adjusting for baseline characteristics.

Conclusions: The Co-SOFT study, although limited by small samples size, provides no evidence that adding OFS to adjuvant oral endocrine therapy substantially affects global cognitive function.

Adjuvant endocrine therapy with the selective oestrogen receptor modulator tamoxifen reduces mortality and has long been a standard of care for premenopausal women with potentially curable hormone receptor-positive breast cancer (Early Breast Cancer Trialists' Collaborative Group, 2005; Burstein *et al*, 2014). Two recent randomised trials, TEXT and Suppression of Ovarian Function Trial (SOFT), have shown that ovarian function suppression (OFS), in combination with either the aromatase inhibitor exemestane or tamoxifen, provides additional benefit over tamoxifen alone (Pagani *et al*, 2014; Francis *et al*, 2015). On the basis of these results, OFS will be increasingly used as part of the adjuvant treatment of premenopausal women with hormone receptor-positive breast cancer (Coates *et al*, 2015).

In choosing the most appropriate adjuvant endocrine therapy for an individual woman, side-effect profile is a major consideration (Hershman, 2015). It has been shown that women who experienced more side-effects required a greater survival benefit to accept adjuvant endocrine therapy (Thewes *et al*, 2005). Cognitive dysfunction is a much feared potential side-effect of breast cancer treatment (Haiken, 2015). Studies suggest that all components of

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cancer treatment may impair cognition (Janelsins *et al*, 2014) and that impairment may also be present in some women prior to cancer treatment (Scherling *et al*, 2012). It is clear that oestrogen has an important role in cognitive functioning (Sherwin, 2012) but few studies have examined the effect of adjuvant endocrine therapy for breast cancer on cognitive function (Phillips *et al*, 2010, 2011a, b; Schilder *et al*, 2010; Ganz *et al*, 2014) and none has assessed the impact of OFS. OFS results in very-low circulating oestrogen levels and some (Varney *et al*, 1993; Grigorova *et al*, 2006; Craig *et al*, 2007), but not all (Owens *et al*, 2002; Schmidt *et al*, 2013) data from non-oncological settings suggest that OFS with gonadotropin-releasing hormone agonists (GnRH) agents impair cognition and that this impairment can be reversed with add-back oestrogen (Sherwin and Tulandi, 1996). It has also been reported that surgical menopause adversely affects cognition (Rocca *et al*, 2007; Ryan *et al*, 2014).

We conducted a cognitive function substudy of the SOFT. The primary objective of this Co-SOFT substudy was to compare changes in cognitive function, measured objectively over 1 year in premenopausal patients with breast cancer who received adjuvant endocrine therapy with OFS (either tamoxifen + OFS or exemestane + OFS) against those who received tamoxifen alone. It was hypothesised that, because of greater oestrogen deprivation, women who received OFS would have greater deterioration in cognitive function than those who received tamoxifen alone.

MATERIALS AND METHODS

The SOFT trial was an international, three-arm, non-blinded, randomised trial in premenopausal women with hormone receptor-positive breast cancer (Francis *et al*, 2015). It evaluated the efficacy of 5 years of adjuvant hormonal therapy using OFS plus tamoxifen or OFS plus exemestane or tamoxifen alone. Prior chemotherapy was allowed, provided women had premenopausal oestradiol levels after completing all chemotherapy and before enroling in the SOFT study. Women were stratified at randomisation according to whether they received adjuvant chemotherapy prior to randomisation, axillary lymph node status and intended initial method of OFS (women could choose between the GnRH agonist triptorelin, surgical oophorectomy or ovarian irradiation). Patients were enrolled within 12 weeks of their definitive breast cancer surgery or, for those who received chemotherapy, within 8 months of completing chemotherapy. Between November 2003 and January 2011, 3066 women were randomised on the SOFT trial.

Patients. To be eligible for the Co-SOFT substudy, women must have been registered for the SOFT study but not yet received any adjuvant endocrine therapy, and they must have been able to speak and write the local language fluently and have provided written informed consent. To minimise the potential for sampling bias, participating centres were to enrol all eligible patients. The substudy protocol was approved by the local and International Breast Cancer Study Group (IBCSG) ethics committees and the required health authorities of each participating centre.

Measures. At baseline before the start of protocol therapy (T0) and at ~1 year after randomisation to the SOFT study (T1) objective cognitive function was tested and patients provided self-reported data on cognitive function, psychological distress, fatigue, insomnia and quality of life.

Objective cognitive function. Objective cognitive function was measured with the CogState computerised test battery (CogState Ltd; http://www.cogstate.com); a brief test designed specifically for repeated application and free from practice effects (Falleti *et al*, 2003; Silbert *et al*, 2004; Vardy *et al*, 2006). Testing consisted of five non-verbal tasks, measuring the speed of psychomotor function, visual attention, attention and working memory, and visual learning and memory. In addition, two verbal learning and memory tasks required subjects to learn a 12-word shopping list, and then to recall this list after 20 minutes (Table 1). Details of the test battery have been described elsewhere (Phillips *et al*, 2010). For the seven tasks, a composite score, representing the age-adjusted average standardised score of each task for each individual, was calculated (Phillips *et al*, 2010). This provides a measure of global cognitive function that has been validated psychometrically (Maruff *et al*, 2009) and empirically in studies of pharmacological agents (Snyder *et al*, 2005; Maruff *et al*, 2006), head injury (Collie *et al*, 2001), fatigue (Falleti *et al*, 2003) and surgery (Silbert *et al*, 2004).

Patient reported outcomes. After cognitive testing, women completed several questionnaires. Self-reported cognitive function was assessed by the Cognitive Failures Questionnaire (CFQ) (Broadbent *et al*, 1982), a 25-item questionnaire that assesses the frequency of failures in memory, perception and motor function over the past 6 months. To measure psychological distress, a 12-item version of the General Health Questionnaire (Goldberg and Williams, 2000) was used. In addition, the Brief Fatigue Inventory (Mendoza *et al*, 1999), a nine-item instrument to assess severity of fatigue and its inference with daily living in a 24 h period, was administered. Global quality of life domains (physical well-being, mood, coping effort, subjective health estimation) as well as symptom-specific quality of life domains (nausea and vomiting, appetite, tiredness, hot flushes, restriction in arm movements and insomnia) were measured by linear analogue self-assessment indicators (Bernhard *et al*, 2015). Validated language versions were used where available, otherwise a standard translation procedure was performed (forward-backward).

Statistical considerations. The protocol-specified primary comparison was the change in the composite score of the CogState tasks over 1 year for women randomised to tamoxifen + OFS *vs* tamoxifen alone. Due to low accrual to the substudy, this was modified, prior to any analysis, to compare the pooled tamoxifen

Table 1. Tasks and cognitive domains assessed by the CogState battery

Task	Cognitive Domain Assessed	Type of test	Unit of measurement
Detection	Speed of psychomotor function	Performance speed	Log_{10} milliseconds
Identification	Visual attention	Performance speed	Log_{10} milliseconds
Monitoring	Visual attention	Performance speed	Log_{10} milliseconds
Memory	Attention and working memory	Performance accuracy	Arcsine proportion correct
Learning	Visual learning and memory	Performance accuracy	Arcsine proportion correct
ISLT	Verbal learning and memory	Performance accuracy	Total number correct
Delayed ISLT	Verbal learning and memory	Performance accuracy	Total number correct

Abbreviation: ISLT = International Shopping List Test.

+OFS and exemestane+OFS groups with the tamoxifen alone group. The observed sample size provided 80% power to detect an effect size of 0.76 with two-sided $\alpha = 0.05$. Cognitive test scores were transformed (Phillips *et al*, 2010), standardised according to age-specific norms, and the resulting *Z*-scores averaged to calculate the composite score (Maruff *et al*, 2009). Individual *Z*-scores more than 1.96 s.d. below the norm were defined as 'impaired.' The change in composite scores between T0 and T1 were calculated; a negative change in composite score indicated deterioration in cognitive function. Changes in composite score and individual tasks were compared between treatment groups using Wilcoxon rank-sum tests. Effect sizes for the comparison of treatments were calculated as mean change in OFS groups minus mean change in tamoxifen alone group divided by the pooled s.d. of the change (Cohen, 1988) for the composite score and each task. According to convention, effect sizes of +0.2 was considered small, +0.5 moderate and +0.8 large (Cohen, 1988). Sensitivity analyses compared treatment groups using regression modelling, adjusting for patient, disease and treatment characteristics at baseline: language and treatment assignment, age, family history of breast cancer, body mass index, menstruation status, history and/or treatment of anxiety/depression, nodal status and prior chemotherapy and use of HER2-targeted treatment. Characteristics were compared between treatment groups using Fisher's exact tests. Spearman's correlation coefficients were calculated between composite score and patient-reported outcome measures.

RESULTS

Co-SOFT commenced recruitment in October 2007 and after 26 Co-SOFT centres were activated, 86 of 102 (84%) eligible women enrolled in SOFT and with no prior endocrine therapy were recruited. Planned accrual was 321 patients but Co-SOFT was closed in January 2011 because the SOFT trial had completed accrual. Patient, demographic, medical, disease and treatment characteristics were similar between those eligible women at participating centres who did and those eligible women who did not participate in Co-SOFT (data not shown). Of 86 Co-SOFT participants, 74 underwent both T0 and T1 cognitive function testing and were included in the primary analysis (8 withdrew consent or declined assessment, 4 missed testing for administrative reasons). Of the 74 evaluable patients, 54 were randomised to OFS + oral endocrine therapy (OFS + tamoxifen $n = 28$ or OFS + exemestane $n = 26$) and 20 were randomised to tamoxifen alone (Figure 1).

As shown in Table 2, baseline characteristics were well-balanced between the two groups. During the first year 49 women had GnRH agonist alone for OFS, 4 had GnRH followed by oophorectomy and 1 had oophorectomy.

Figure 2 shows the change in objective cognitive function between T0 and T1 by study treatment assignment. There was no significant difference in the changes in the CogState composite scores from T0 to T1 for patients randomised to OFS + oral endocrine therapy compared with tamoxifen alone (mean ± s.d., -0.21 ± 0.92 *vs* -0.04 ± 0.49, respectively, $P = 0.71$, effect size = -0.20). This was true regardless of whether women had received prior chemotherapy, and adjusting for baseline characteristics. Women who received OFS showed greater deterioration in the International Shopping List Task (ISLT) than those who received tamoxifen alone (mean ± s.d. -0.20 ± 0.68 *vs* 0.29 ± 0.73 respectively, $P = 0.02$, effect size = -0.68). For the other six tasks there were small effect sizes and no statistically significant difference between the two treatment groups.

Table 3 shows the number of women that met the definition for impairment on each cognitive task at each timepoint. The task for which the largest proportion of women changed from normal to

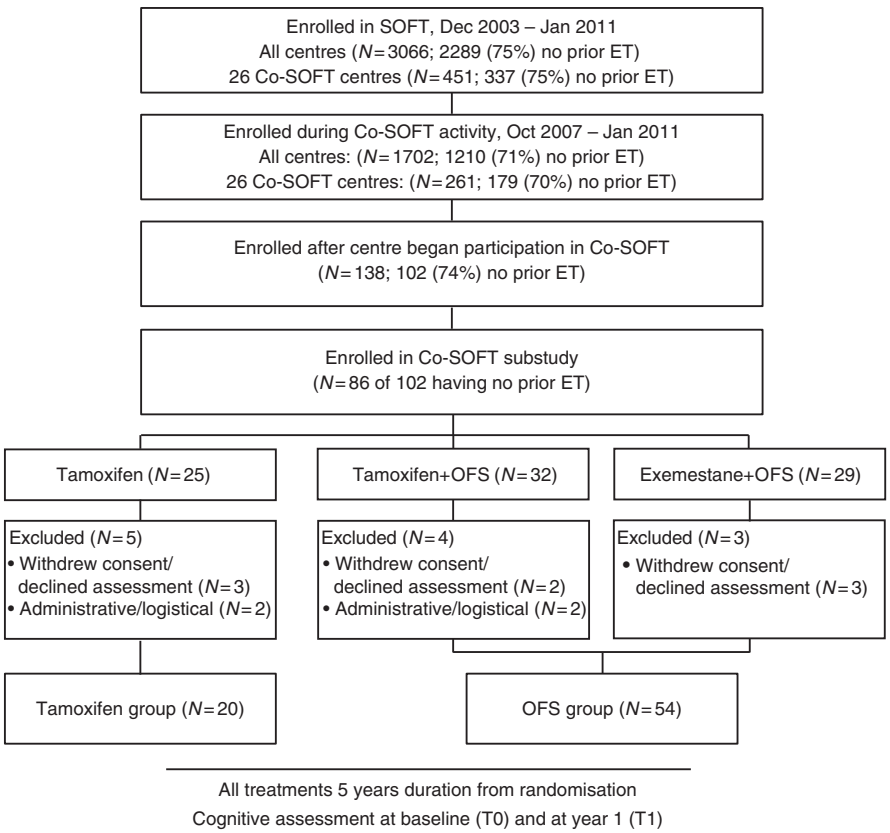


Figure 1. CONSORT Flow Diagram showing the design and enrolment to the Co-SOFT substudy. Eligible patients were enrolled in the substudy at the time of randomisation to SOFT. ET = endocrine therapy.

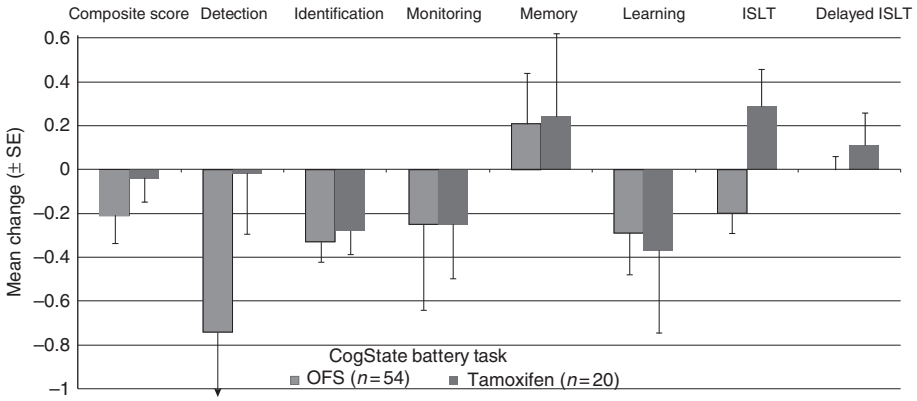
Table 2. Patient, disease and treatment characteristics at T0

	OFS		Tam		All		
Characteristic	***N***	**%**	***N***	**%**	***N***	**%**	***P*-value[a]**
***N* patients**	54		20		74		—
Age at randomisation							0.56
Mean (range)	44	(28–58)	46	(38–53)	45	(28–58)	
<35	5	9.3	—	—	5	6.8	
35–39	4	7.4	2	10.0	6	8.1	
40–44	15	27.8	5	25.0	20	27.0	
45–49	21	38.9	7	35.0	28	37.8	
50+	9	16.7	6	30.0	15	20.3	
Education							1.00
Primary/secondary education	9	16.7	3	15.0	12	16.2	
Additional education	31	57.4	12	60.0	43	58.1	
Academic education	14	25.9	5	25.0	19	25.7	
Body mass index							0.94
Normal (<25)	30	55.6	11	55.0	41	55.4	
Overweight (25–<30)	13	24.1	4	20.0	17	23.0	
Obese (⩾30)	9	16.7	4	20.0	13	17.6	
Unknown	2	3.7	1	5.0	3	4.1	
Menstruation							0.79
Normal	36	66.7	13	65.0	49	66.2	
Irregular (but cycles continuing)	7	13	4	20.0	11	14.9	
Persistent amenorrhoea	11	20.4	3	15.0	14	18.9	
Performance status							1.00
Fully active (K90–100)	48	88.9	18	90.0	66	89.2	
Restricted (K70–80)	6	11.1	2	10.0	8	10.8	
History and/or treatment of depression/anxiety							0.41
No	33	61.1	15	75.0	48	64.9	
Yes	21	38.9	5	25.0	26	35.1	
Nodal status							0.75
Negative	42	77.8	17	85.0	59	79.7	
Positive	12	22.2	3	15.0	15	20.3	
Local-regional treatment							0.92
Mastectomy, no radiation	13	24.1	4	20.0	17	23.0	
Mastectomy with radiation	6	11.1	2	10.0	8	10.8	
Breast-conserving with radiation	35	64.8	14	70.0	49	66.2	
Weeks from randomisation to completion of radiation if received, median (interquartile range)	7.4	(1.9–9.7)	7	(2.1–13.4)	7.4	(1.9–10.0)	
Prior chemotherapy							0.78
No	38	70.4	15	75.0	53	71.6	
Yes	16	29.6	5	25.0	21	28.4	
Months from last dose of chemotherapy, median (interquartile range)	2.1	(1.7–2.8)	2.1	(1.9–2.4)	2.1	(1.8–2.7)	
HER2 status and therapy							1.00
Not HER2+	51	94.4	19	95.0	70	94.6	
HER2+/HER2-directed therapy	3	5.6	1	5.0	4	5.4	
Type of OFS during year 1							NA
GnRH agonist only	49	90.7	NA		—		
GnRH agonist followed by oophorectomy	4	7.4	NA		—		
Oophorectomy only	1	1.9	NA		—		

Abbreviations: NA = not applicable; OFS = ovarian function suppression.
[a]Patient, disease and prior treatment characteristics were compared between groups using Fisher's exact tests for categorical variables.

impaired status between T0 and T1 was the learning task; for which 22% of those on OFS and 15% of those on tamoxifen went from normal to impaired and conversely 7% of those on OFS and 20% of those on tamoxifen went from impaired to normal. It has to be noted that the numbers in the various subgroups are too small for a conclusive interpretation.

Table 4 shows the patient reported outcome data. The change in self-reported cognitive function between T0 and T1 indicated greater decline in patients receiving OFS *vs* those receiving tamoxifen alone (mean ± s.d., 7.8 ± 13.1 *vs* 1.1 ± 9.7, effect size = 0.53). Note that higher CFQ scores indicate worse self-reported cognitive function, thus a positive change score indicates deterioration. No correlation was observed between objective cognitive function (CogState composite cognitive function score) and self-reported cognitive function ($r = -0.12$), fatigue ($r = -0.05$), psychologic distress ($r = 0.06$) or quality of life indicators (range, $r = -0.09$ to 0.16) including insomnia ($r = 0.11$), at year 1. However, self-reported cognitive function was moderately and positively correlated with fatigue ($r = 0.55$) and psychologic distress ($r = 0.53$) and was low to moderately correlated with quality of life indicators (range, $r = -0.13$ to -0.45), including insomnia ($r = -0.31$), at year 1.



Effect Size	–0.20	–0.24	–0.08	0	–0.02	0.06	–0.68	–0.22
P-value	0.71	0.64	0.99	0.35	0.86	0.59	0.02	0.49

Figure 2. Mean change in CogState test performance between T0 (baseline) and T1 (one year) according to treatment assignment for the composite score and the seven cognitive tasks assessed by the CogState battery. A negative change in individual task or composite score indicates deterioration in cognitive function. ISLT, international shopping list test.

Table 3. Normal/Impaired CogState task scores according to treatment assignment

	Normal T0 & Normal T1		Impaired T0 & Impaired T1		Normal T0→Impaired T1		Impaired T0→Normal T1	
	N (%)		*N* (%)		*N* (%)		*N* (%)	
Task	**Tam**	**OFS**	**Tam**	**OFS**	**Tam**	**OFS**	**Tam**	**OFS**
Detection	16(80)	50(93)	1(5)	1(2)	0(0)	1(2)	3(15)	2(4)
Identification	18(90)	53(98)	0(0)	0(0)	2(10)	0(0)	0 (0)	1(2)
Monitoring	18(90)	45(83)	0(0)	3(6)	2(10)	2(4)	0(0)	4(7)
Memory	16(80)	48(89)	1(5)	0(0)	1(5)	3(6)	2(10)	3(6)
Learning	7(35)	28(52)	6(30)	10(19)	3(15)	12(22)	4(20)	4(7)
ISLT	19(95)	52(96)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
Delayed ISLT	20(100)	53(98)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)

Abbreviations: ISLT = International Shopping List Test; OFS = ovarian function suppression. Impairment was defined as a score more than 1.96 s.d. below the age-adjusted norm. Note % may not add to 100 due to missing data (for ISLT and delayed ISLT).

Table 4. Patient reported outcomes data

	T0		T1		Change from T0 to T1	
	Mean (s.d.)		Mean (s.d.)		Mean (s.d.)	
Patient Reported Outcome	**Tam**	**OFS**	**Tam**	**OFS**	**Tam**	**OFS**
Cognitive Failures Questionnaire[a]	32.1 (12.0)	32.7 (14.5)	32.3 (12.4)	40.2 (18.0)	1.1 (9.7)	7.8 (13.1)
General Health Questionnaire – 12	25.7 (5.1)	24.5 (4.8)	23.7 (4.9)	25.3 (6.6)	– 2.1 (5.2)	0.9 (5.9)
Brief Fatigue Inventory	3.2 (2.3)	2.9 (1.8)	3.0 (2.2)	3.7 (2.2)	– 0.1 (1.9)	0.7 (2.3)
Physical Well-Being	71 (25)	74 (25)	71 (25)	69 (23)	0 (37)	– 5 (30)
Mood	70 (23)	69 (26)	72 (25)	68 (24)	2 (35)	0 (29)
Tiredness	62 (26)	59 (31)	57 (28)	50 (29)	– 5 (37)	– 9 (33)
Appetite	75 (25)	81 (21)	85 (17)	80 (21)	10 (32)	– 2 (24)
Hot Flushes	83 (23)	84 (27)	62 (29)	41 (30)	– 21 (32)	– 42 (37)
Nausea and Vomiting	89 (21)	94 (14)	82 (25)	91 (17)	– 6 (37)	– 3 (19)
Coping Efforts	66 (29)	69 (28)	80 (23)	72 (26)	14 (31)	3 (29)
Arm Restricted	79 (28)	76 (29)	79 (28)	84 (22)	0 (25)	9 (26)
Subjective Health Estimation	71 (26)	70 (24)	80 (22)	70 (23)	8 (28)	0 (26)
Insomnia	67 (25)	70 (29)	65 (27)	56 (29)	– 1 (32)	– 13 (33)

Abbreviations: CFQ = Cognitive Failures Questionnaire; OFS = ovarian function suppression.
[a]Note-higher CFQ scores indicate worse self-reported cognitive function.

DISCUSSION

The study results do not provide evidence that the addition of OFS to oral adjuvant endocrine therapy for breast cancer affects objective global cognitive function in a clinically meaningful way over 1 year of endocrine treatment. However, the study did not have adequate power to detect a small to moderate effect on cognitive function. The only cognitive task for which performance of women randomised to OFS deteriorated significantly more than those randomised to tamoxifen alone was a test of verbal learning and memory, the ISLT. Some studies have suggested that verbal memory is particularly affected by OFS in non-oncological settings (Craig *et al*, 2007); however, we did not find a difference between the OFS and tamoxifen alone groups in terms of amount of deterioration in another measure of verbal memory, the delayed ISLT.

Previous studies in this field have focussed on tamoxifen and the aromatase inhibitors, nevertheless the impact of these drugs on cognitive function remains poorly understood (Buwalda and Schagen, 2013). Most studies have been observational, with important differences between treatment groups that limits the interpretation of associations of particular endocrine treatments with cognitive changes. One randomised study tested postmenopausal patients before and 1 year after commencing endocrine therapy and compared those randomised to tamoxifen treatment with those randomised to the aromatase inhibitor exemestane and also included a healthy control group (Schilder *et al*, 2010). It revealed that women randomised to tamoxifen had worse information processing speed after one year compared with those randomised to exemestane. In the non-randomised comparison with healthy controls exemestane did not seem to impact cognitive function adversely. The lack of impact of aromatase inhibitors on cognitive function is also supported by the results of the cognitive function substudy of the randomised IBIS II chemoprevention trial, which showed that postmenopausal women randomised to the aromatase inhibitor anastrozole had similar cognitive function after 2 years compared with those randomised to placebo (Jenkins *et al*, 2008). Similarly in the randomised BIG 1–98 study, postmenopausal women taking the aromatase inhibitor letrozole during year 5 of adjuvant endocrine therapy had better global cognitive function than those taking tamoxifen (Phillips *et al*, 2010) and cognitive function in both groups improved after cessation of adjuvant endocrine therapy (Phillips *et al*, 2011a).

Although no previous study has examined the impact of adjuvant OFS on cognitive function, several studies have attempted to assess the impact of chemotherapy-induced premature ovarian insufficiency with mixed results (Jenkins *et al*, 2006; Schagen *et al*, 2006; Hermelink *et al*, 2008; Vearncombe *et al*, 2011). Recently a longitudinal neuroimaging study showed that women who had chemotherapy-induced amenorrhoea showed increases in brain activation from pre to post-chemotherapy, suggesting compensatory neural activation; no increases were seen in women who did not have chemotherapy-induced amenorrhoea or healthy controls (Conroy *et al*, 2013).

In our study, there was greater deterioration in self-reported cognitive function in the OFS group compared with the group that received tamoxifen alone. This was an unplanned exploratory analysis and needs further prospective evaluation; however, many previous studies have found that subjective cognitive complaints are often worse than would be expected from objective cognitive function testing (Hutchinson *et al*, 2012). There are several possible explanations for this discrepancy, but studies that have incorporated functional brain imaging suggest that patients that complain of cognitive dysfunction may reach normal performance on objective cognitive function tests by activating other brain areas not usually directly related to the cognitive task, and this may be perceived as greater effort (Hutchinson *et al*, 2012). Our finding that self-reported cognitive function was moderately correlated with fatigue and psychologic distress is consistent with most previous studies (Hutchinson *et al*, 2012).

The strengths of our study include the longitudinal design with a well-defined and homogenous sample of SOFT patients who had not commenced endocrine therapy, defined type and duration of endocrine therapy that was randomly assigned and the ability to control for potential confounding factors. Small sample size is the main limitation of our study, which resulted in limited power to detect a small, but potentially meaningful, effect, as might be anticipated when comparing two groups of patients receiving endocrine therapies. There is potential for sampling bias, as substudy centres enrolled only 84% of eligible patients, and the possibility that the treatment assignment was part of the decision cannot be excluded. In the future, consideration perhaps should be given to incorporating measures of cognitive function in the main study protocol, as is often done for quality of life measures, in order to avoid having uninformative data on the effects of new treatments on cognition. Other limitations include the absence of a control group not treated with any endocrine therapy and the lack of hormone testing to confirm the functional gonadal status of the women, particularly those in the tamoxifen arm, some of whom may have had chemotherapy-induced hypogonadism at T1. Also, our cognitive function test battery did not include a measure of verbal fluency and cognitive function was assessed only over the first year of adjuvant endocrine therapy, which perhaps allowed time for development of some compensation for any cognitive dysfunction related to the endocrine therapy.

Given the importance of this clinical question for women, the strong biological basis for a potential effect of OFS on cognitive function, and the limitations of our study, we believe further study of the impact of adjuvant OFS on cognitive function in breast cancer patients is warranted.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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APPENDIX

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