# Change in Cognitive Function After Chemotherapy: a Prospective Longitudinal Study in Breast Cancer Patients

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**Some breast cancer survivors experience cognitive decline following chemotherapy. We prospectively examined changes in cognitive performance among high-risk breast cancer patients who had received high-dose chemotherapy with cyclophosphamide, thiotepa, and carboplatin (CTC group; n = 28) or standard-dose chemotherapy with 5-fluorouracil, epirubicin, and cyclophosphamide (FEC group; n = 39); stage-I breast cancer patients who had received no systemic chemotherapy (no-CT group; n = 57); and healthy control subjects (n = 60). All patients underwent neuropsychologic testing before and 6 months after treatment (12-month interval); control subjects underwent repeated testing over a 6-month interval. No differences in cognitive functioning between the four groups were observed at the first assessment. More of the CTC group than the control subjects experienced a deterioration in cognitive performance over time (25% versus 6.7%; odds ratio [OR] = 5.3, 95% confidence interval [CI] = 1.3 to 21.2, *P* = .02). No such difference was observed for the FEC or the no-CT groups (FEC versus control: OR = 2.2, 95% CI = 0.5 to 9.1, *P* = .27; no-CT versus Control: OR = 2.2, 95% CI = 0.6 to 8.0; *P* = .21). Some cytotoxic treatment for breast cancer affects cognition in a subset of women. [J Natl Cancer Inst 2006;98:1742–5]**

There is growing evidence that some breast cancer patients show impaired cognitive performance on neuropsychologic tests after they receive cytotoxic treatment. For example, a cross-sectional study conducted at The Netherlands Cancer Institute in 1998 *(1)* found that among women who participated in a randomized trial of adjuvant treatment for high-risk breast cancer, those who received adjuvant high-dose chemotherapy had a statistically significantly higher risk of cognitive impairment compared with breast cancer patients who received no chemotherapy (i.e., the control group; odds ratio [OR] = 8.2, 95% confidence interval [CI] = 1.8 to 37.7, *P* = .006), whereas patients who received standard-dose chemotherapy did not show a statistically significantly elevated risk compared with the control group (OR = 2.4, 95% CI = 0.5 to 11.5, *P* = .287). Since then, several cross-sectional studies *(2–7)* have reported that some breast cancer patients have cognitive deficits following chemotherapy treatment and that some of these effects persist for up to 10 years after the completion of therapy.

These findings need to be verified in longitudinal studies in which the cognitive performance of patients is assessed over time and compared with pretreatment performance. An assessment of cognitive performance before treatment is essential because of the possibility of preexisting cognitive deficits in some patients undergoing cytotoxic treatment *(8)*. Few prospective studies of cognitive function among women receiving adjuvant chemotherapy have been published to date *(9–12)*; these studies were limited because of a small sample size *(9,12)* or because they lacked pretreatment cognitive assessment *(10)* or a control group *(12)* or did not correct for the effects of repeated testing *(9,10)*. In addition, none of these studies compared the effects of different cytotoxic regimens. A recently published fifth study *(13)*, which was an extended version of an earlier prospective study *(11)*, addressed some of these limitations. However, because the majority of patients (70%) were treated with low-dose FEC chemotherapy, no comparison between the effects of different regimens could be made *(13)*.

To further investigate the cognitive sequelae of chemotherapy, we conducted a longitudinal study using subjects recruited from the same population of breast cancer patients that was used in our previous cross-sectional study *(1)*. The current study used three groups of breast cancer patients and a control group of healthy women without cancer. Two of the three groups of breast cancer patients were recruited from among high-risk breast cancer patients who had participated in a trial *(14)* in which they were randomly assigned to receive either adjuvant high-dose chemotherapy with cyclophosphamide, thiotepa, and carboplatin (CTC group; n = 28) or

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**Table 1.** Sociodemographic and clinical characteristics of the four study groups*

| Characteristic | FEC (n = 39) | CTC (n = 28) | No CT (n = 57) | Control (n = 60) | P† |
|---|---|---|---|---|---|
| Mean age at first assesssment, y (SD) | 45.5 (6.6) | 45.2 (5.8) | 50.5 (7.7) | 48.8 (6.0) | .00 |
| Mean premorbid IQ score‡ (SD) | 100.8 (15.7) | 100.2 (17.1) | 100.8 (17.2) | 105.1 (14.1) | .38 |
| Postmenopausal§, % | | | | | |
| At first assessment | 28 | 25 | 56 | 38 | .01 |
| At second assessment | 80 | 93 | 63 | 40 | .00 |
| On tamoxifen at second assessment, % | 97 | 100 | 0 | – | .00 |

*FEC = five cycles of fluorouracil, 500 mg/m$^2$ intraveneously (iv); epirubicin, 90 mg/m$^2$ iv; cyclophosphamide, 500 mg/m$^2$ iv; CTC = four cycles of FEC followed by cyclophosphamide, 6 g/m$^2$ iv; thiotepa, 480 mg/m$^2$ iv; and carboplatin, 1.6 g/m$^2$ iv; No CT = no adjuvant chemotherapy; control = healthy subjects; SD = standard deviation; IQ = intelligence quotient; – = not applicable.

†Two-sided *P* value: analysis of variance in case of mean age and IQ score, chi-square in case of menopausal status and tamoxifen use.

‡Assessed by using the Dutch Adult Reading test as a surrogate measure of pretreatment intelligence.

§ Postmenopausal status defined by the absence of (ir)regular menstrual cycles from the time of completion of chemotherapy (for the FEC and CTC groups) until the second neuropsychologic assessment point or by the absence of menstrual cycles for 6 consecutive months (for the no-CT and healthy control groups).

standard-dose chemotherapy with 5-fluorouracil, epirubicin, and cyclophosphamide (FEC group; n = 39), followed by radiotherapy and tamoxifen (40 mg daily for 2–5 years); the third group of breast cancer patients included women with stage I breast cancer who had been treated with radiotherapy but who had not received systemic chemotherapy (no-CT group; n = 57). Women in the control group (n = 60) were recruited from among female friends of the patients in the three groups. The high-risk patients were recruited from seven different hospitals, and the stage I patients were recruited from a single institution. This study was approved by the ethics committees of the participating hospitals, and all subjects provided written informed consent.

All subjects underwent neuropsychologic testing on two separate occasions. Subjects in the CTC and FEC groups were tested before the start of chemotherapy and again 6 months after completion of therapy, i.e., 12 months after the first assessment. Patients in the no-CT group were also tested over a 12-month interval. Subjects in the control group were tested over a 6-month interval. The neuropsychologic examination consisted of 10 tests *(15–21)*, comprising 24 test indices, covering the following domains: focused–sustained attention, working–verbal–visual memory, processing speed, executive function, and verbal/motor function. On the first assessment, the Dutch Adult Reading test *(22)* was used to obtain a measure of verbal premorbid intelligence. Exclusion criteria for neuropsychologic testing were 1) presence of metastatic disease or relapse, 2) a previous or current neurologic or psychiatric disorder [defined according to Diagnostic and Statistical Manual-VI criteria *(23)*] believed to affect performance on cognitive tests, 3) use of medication believed to affect current cognitive functioning (i.e., opioid analgesics, anxiolytics, or antidepressants), and 4) alcohol and/or drug addiction. To assess these exclusion criteria, the medical records of all patients were checked. For the subjects in the healthy control group, a questionnaire was developed to inspect these criteria.

Patients in the FEC, the CTC, and the no-CT groups were treated during the period from September 7, 1998, to January 19, 2002. A total of 52 FEC patients, 36 CTC patients, and 82 no-CT patients were eligible for the first neuropsychologic assessment. Seven FEC patients (13.5%), five CTC patients (13.9%), and 17 no-CT patients (20.7%) refused to participate. At the second neuropsychologic assessment, a total of 17 patients could not be retested; of these, 12 patients (four FEC patients, two CTC patients, and six no-CT patients) no longer met the inclusion criteria and five patients (two FEC patients, one CTC patient and two no-CT patients) refused to participate. Of the 66 healthy women who underwent the baseline neuropsychologic examination, one developed breast cancer, two were diagnosed with a neurologic disorder, and three refused further participation. Nonparticipants at follow-up did not differ from participants with regard to age, premorbid intelligence quotient (IQ), or neuropsychologic performance at the first examination.

We considered a subject to be cognitively impaired on a test index if she scored two standard deviations below the mean of the healthy control group on that test index *(24)*. A patient was classified as cognitively impaired when she scored, on at least three of the 24 test indices, two standard deviations below the mean of the healthy group [the 95th percentile of the healthy group was used as a cutoff score to distinguish between impaired and unimpaired cognitive functioning *(1,5)*]. For all analyses, a two-sided *P* value less than or equal to .05 was considered statistically significant.

Table 1 presents the characteristics of the four groups of subjects. All CTC and FEC patients received the planned courses of chemotherapy (see Table 1 notes for description of regimens).

At the first neuropsychologic assessment, univariate analysis of variance with correction for age and IQ score revealed no statistically significant differences in the raw neuropsychologic test scores among the four groups of subjects (data not shown). A logistic regression model with correction for age and IQ (Table 2) revealed no statistically significant differences between any of the patient groups and the control group in the percentage of subjects who were classified as cognitively impaired at the first neuropsychologic assessment (CTC group versus control group: OR = 2.3, 95% CI = 0.6 to 9.2, *P* = .22; FEC group versus control group: OR = 1.1, 95% CI = 0.3 to 4.4, *P* = .89; no-CT group versus control group: OR = 2.4, 95% CI = 0.7 to 7.7, *P* = .12). A similar analysis revealed no statistically significant differences between any of the patient groups and the control group in the percentage of impaired subjects at the second assessment (Table 2; CTC group versus control group: OR = 3.3, 95% CI = 0.7 to 14.4, *P* = .11; FEC group versus control group: OR = 1.2, 95% CI = 0.3 to 5.8, *P* = .78; no-CT group versus control group: OR = 2.1, 95% CI = 0.5 to 8.4, *P* = .26). In this latter analysis,

**Table 2.** Number of cognitively impaired subjects at first and second assessment and number of subjects classified as having cognitive deterioration over time*

| Study group | n | No. impaired at first assessment (%) | No. impaired at second assessment (%) | No. having cognitive deterioration from first to second assessment (%) |
|---|---|---|---|---|
| FEC | 39 | 5 (12.8) | 4 (10.3) | 5 (12.8) |
| CTC | 28 | 6 (21.4) | 6 (21.4) | 7 (25.0) |
| No CT | 57 | 17 (29.8) | 13 (22.8) | 10 (17.5) |
| Control | 60 | 6 (10.0) | 4 (6.7) | 4 (6.7) |

*Cognitive impairment is defined as a score that was two standard deviations below the mean score of the healthy control group on at least three of the 24 test indices. Cognitive deterioration is defined as a statistically significant decline (based on the reliable change index with correction for practice effects) on at least four of the 24 test indices. FEC = five cycles of fluorouracil, 500 mg/m$^2$ intraveneously (iv); epirubicin, 90 mg/m$^2$ iv; cyclophosphamide 500 mg/m$^2$ iv; CTC = four cycles of FEC followed by cyclophosphamide, 6 g/m$^2$ iv; thiotepa, 480 mg/m$^2$ iv; and carboplatin, 1.6 g/m$^2$ iv; No CT = no adjuvant chemotherapy; control = healthy subjects.

however, no correction was made for practice effects. In neuropsychology, practice effects refer to the impact of repeated assessments on a subject's performance. With repetition of the same neuropsychologic test, systematic changes in test scores can be observed without the occurrence of a true change in cognitive performance. Therefore, we also evaluated, for all subjects, the magnitude of cognitive changes from the first neuropsychologic assessment to the second, while taking into account repeated testing effects by using the reliable change index with correction for practice effects *(11,12,25,26)*, which was based on the differences between the neuropsychologic scores of the first and the second assessment of the healthy control group. Using this index, participants were classified per test as having either cognitive performance that statistically significantly improved or deteriorated or remained stable over time. The 95th percentile of the healthy reference group was used as a cutoff to define deterioration; we considered a subject to have deteriorated in cognitive functioning only when she showed a statistically significant decline in performance on at least four of the 24 tests (Table 2). A logistic regression model with adjustment for age and IQ score revealed that the percentage of patients in the CTC group whose cognitive performance had deteriorated was statistically significantly higher than the percentage of healthy subjects in the control group whose cognitive performance had deteriorated (25% versus 6.7%; OR = 5.3, 95% CI = 1.3 to 21.2, $P$ = .02). For the FEC and the no-CT groups, no such decline in performance compared with the control group was observed (FEC group versus control group: OR = 2.2, 95% CI = 0.5 to 9.1, $P$ = .27; no-CT group versus control group: OR = 2.2, 95% CI = 0.6 to 8.0, $P$ = .21). Repeated-measures multiple analysis of covariance showed that deterioration in cognitive performance over time occurred across a variety of tests that measured several cognitive functions. However, the neuropsychologic measures that were sensitive to so-called executive function exhibited the strongest effects. Executive functions include skills such as planning, inhibiting or delaying responding, initiating behavior, and the ability to shifting between activities in a flexible way, all of which are aspects of behavior that patients who are treated with chemotherapy frequently complain about *(27)*.

For all groups, cognitive performance at baseline and follow-up, and change in performance over time, was not statistically significantly associated with subjects' reports of anxiety, depression [as assessed with the Hopkins Symptom Checklist *(28)*], or fatigue [as assessed with the Multidimensional Fatigue Index *(29)*] (data not shown). Menopausal status was also not associated with changes in cognitive performance. We tested this association by comparing the change in cognitive performance between patients whose menopausal status did not change following chemotherapy and patients who became postmenopausal after treatment (defined as the absence of regular menstrual cycles, from the time of completion of chemotherapy until the second neuropsychologic assessment point).

The strengths of our study include the pre- and posttreatment assessment, the testing of patients who were randomly assigned to different chemotherapy regimens, and the comparisons with breast cancer patients who were not treated with systemic therapy as well as with healthy control subjects. Our study has several limitations. First, because all chemotherapy patients and none of the no-chemotherapy patients received tamoxifen, we cannot determine the potential contributory role of tamoxifen on the cognitive test performance. However, even though both the CTC and the FEC treatments were followed by tamoxifen, a difference in cognitive function was found between the CTC and FEC groups. Second, we retested our three patient groups after a 12-month interval, whereas the control group was retested after 6 months. Because our correction for practice effects was based on the retest data of the healthy control group, this difference in retesting interval might have led to an underestimation of the prevalence of cognitive impairment or decline in our patient groups.

Our results confirm the findings of our earlier cross-sectional study *(1)*; that is, more patients treated with high-dose CTC chemotherapy than patients treated with standard-dose FEC chemotherapy showed a decline in cognitive performance compared with healthy control subjects. Our results also show that analyses of cognitive change that correct for the effects of repeated testing are essential for an accurate interpretation of cognitive performance in studies with a longitudinal design.

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## NOTES

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