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Late effects of adjuvant chemotherapy for breast cancer on fine motor function

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Abstract

***Background*: Adjuvant chemotherapy for breast cancer has been associated with deterioration of fine motor skill. Which aspects of motor performance are underlying this problem is unclear but important because manual motor deterioration could affect quality of life. The current study aims to investigate late effects of adjuvant chemotherapy for breast cancer on fine motor function, using both speed and accuracy measures.**

***Method*: We compared fine motor function of 174 women who had received adjuvant Cyclophosphamide Methotrexate 5-Fluorouracil chemotherapy for breast cancer on average 20 years ago with that of a population sample of 195 women without a history of cancer. Fine motor function was measured with the Purdue Pegboard Test and the Archimedes spiral test.**

***Results*: The group of chemotherapy-exposed breast cancer survivors was slower in drawing an Archimedes spiral than the reference group. Furthermore, in the chemotherapy-exposed subjects, we found that older age is related to more crossings of the spiral template, more return movements, and more deviations from the template. Such relationships were not observed within the reference group. No significant between-group differences were found for any of the Purdue Pegboard measures.**

***Conclusions*: Compared with a population-based reference group, Cyclophosphamide Methotrexate 5-Fluorouracil chemotherapy-exposed breast cancer survivors demonstrated motor slowing while drawing an Archimedes spiral, on average 20 years after completion of primary treatment. Furthermore, the Archimedes spiral test is a more sensitive measure than the Purdue Pegboard Test to assess fine manual motor performance in long-term breast cancer survivors following chemotherapy.**

Introduction

Adjuvant chemotherapy for breast cancer has been associated with cognitive problems [1] up to decades of post-treatment [2], and has been related to structural as well as functional brain changes [3]. The most prominent cognitive sequelae of adjuvant chemotherapy are observed in the domains of learning and memory, processing speed, and executive functioning [1]. Besides cognitive problems, chemotherapy has also been associated with worse psychomotor speed and dexterity. We previously found that chemotherapy-exposed long-term (i.e., ~20 years post-treatment) breast cancer survivors performed worse with their nondominant hand on the Purdue Pegboard Test [4]. Moreover, out of 13 [4–16] studies investigating the adverse effects of chemotherapy that included a measure of motor function in their test battery, eight reported worse performance in the group of chemotherapy-exposed breast cancer survivors compared with either baseline (i.e., pre-chemotherapy) measurements [8,9,12,14,16] or non-cancer control subjects [4,10,13]. The other five studies of these 13 reported no differences in motor skills between

groups, or from baseline in the chemotherapy-exposed subjects. Motor skill tests that were used in these studies were either finger-tapping tests [17] or versions of the pegboard test [18]. The finger-tapping test measures motor speed and is an indirect measure of the integrity of the cortical motor areas and efferent motor pathways [17]. Pegboard tests assess eye–hand coordination, dexterity, and motor speed and thus require sensorimotor integration and a high level of motor processing [18]. Nevertheless, these measures only provide insight into a small spectrum of fine motor functioning and are not able to distinguish between speed and accuracy. Because fine motor skill can be associated with quality of life, it is important to investigate a broad spectrum of manual motor skill measures [19,20].

A motor test that does allow separation of different aspects of motor skills is the computerized version of the Archimedes spiral drawing test [21]. Different outcomes can be derived from this test, including movement time, speed variability, and spatial deviation from the spiral template. These outcome measures can provide insight into both speed and accuracy aspects of fine motor skills.

The number of long-term chemotherapy survivors is rapidly increasing [22], and impairment of manual fine motor skills may interfere with daily life functioning [23]. Therefore, it is increasingly relevant to report effects of adjuvant chemotherapy on fine motor skills. The aim of this study was to investigate effects of adjuvant chemotherapy for breast cancer on speed and accuracy measures of fine motor skills. We compared performance on the Archimedes spiral drawing test of 174 women who had received adjuvant chemotherapy for breast cancer on average 20 years before with that of 195 women who had never been diagnosed with cancer. In addition, we looked if results from the spiral test corroborated with those of the Purdue Pegboard Test and if the spiral test is a more sensitive measure of motor (dys)function.

Methods

Participants

We compared chemotherapy-exposed breast cancer survivors with a reference group of non-cancer reference subjects. The reference group was selected from the Rotterdam Study: an ongoing population study in the Netherlands [24]. The review boards of the participating institutes (the Netherlands Cancer Institute and the Erasmus University Medical Center) approved this study. All participants gave written informed consent.

Chemotherapy-exposed subjects

From the registries of the Netherlands Cancer Institute and the Erasmus University Medical Center—Daniel den Hoed Cancer Center, we identified consecutive female breast cancer patients who, as part of their primary treatment, had received six cycles of adjuvant Cyclophosphamide Methotrexate 5-Fluorouracil (CMF) chemotherapy (cyclophosphamide 100 mg/m^2, taken orally, on days 1–14; methotrexate 40 mg/m^2, given intravenously, on days 1 and 8; 5-fluorouracil 600 mg/m^2, given intravenously, on days 1 and 8) between 1976 and 1995. Eligibility criteria included age between 50 and 80 years at recruitment time in 2008 and sufficient command of the Dutch language. Only women with unilateral breast cancer who never had had a relapse, secondary primary tumor, or distant metastasis were selected. Exclusion criteria were ever use of adjuvant endocrine therapy and contraindications for magnetic resonance imaging (magnetic resonance imaging results have been presented elsewhere [25]). Subjects completed all examinations during a one-test session, which took place between October 2008 and October 2009. Of 196 subjects that participated in our previously published cognitive study [2], 174 completed the Archimedes spiral test. Data on the Purdue Pegboard Test was available in 165 persons (Table 1).

Reference group

The study was embedded in the Rotterdam Study, a prospective, population-based cohort study that started in 1990 and investigates causes and consequences of age-related disease [24]. The initial cohort was expanded in 2000 and 2005 and currently totals 14,926 persons. From 1126 female participants of the Rotterdam Study who were never diagnosed with cancer on the basis of self-report, and who completed the Archimedes spiral drawing test between October 2008 and December 2010, we randomly selected subjects within the same age range as the chemotherapy-exposed breast cancer survivors and matched the sample on age (Table 1). This yielded a reference group of 195 subjects, of which 187 also completed the Purdue Pegboard Test.

Fine motor skill assessment

Fine motor skill was assessed using (a) the Purdue Pegboard Test and (b) a computerized version of the Archimedes spiral drawing test. (a) The Purdue Pegboard Test [26] is a test of dexterity and fine motor skill. Participants are asked to use their dominant hand, nondominant hand, and both hands to place as many metal pins as possible within 30 s in vertical rows of holes on a wooden board. In case of physical limitations, or deviation from instruction, data were excluded from analysis. (b) The computerized version of the Archimedes spiral test—consisting of a spiral template that was printed on a piece of paper attached to an electronic drawing board (WACOM Graphire Wireless Pen Tablet, model CTE-630BT)—measures speed and accuracy functions of fine motor skills (discussed later in the text). Participants were

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Table 1. Sample characteristics

	Statistic	Chemotherapy-exposed breast cancer survivors	Reference group	*p*-value			
Age (years)	M, SD	63.9 ± 6.3	64.9 ± 6.1	0.10			
Left handedness	%	4.6	5.8	0.61			
Primary education only	%	8.6	11.3	0.40			
Antihypertensive drugs	%	17.8	27.3	0.030			
Lipid-lowering drugs	%	35.6	12.9	<0.001			
Tumor location: left	%	50.0	—	—			
				Model 1		Model 2	
				Effect size (95% CI)	*p*	Effect size (95% CI)	*p*
Spiral drawing, no. of participants	*N*	174	195				
Clinical score				OR: 0.98 (0.62–1.57)	0.94*	OR: 0.87 (0.53–1.45)	0.60*
0A	%	70.7	67.2				
0B	%	20.7	23.6				
1	%	8.1	8.7				
2	%	0.6	0.5				
Quantitative data							
Length of drawing (cm)	Md, IQR	56.8 (56.0–57.7)	56.5 (55.9–57.2)	η^2: 0.015	0.018	η^2: 0.018	0.010
Movement time (s)	Md, IQR	18.3 (11.7–24.5)	15.7 (11.6–21.2)	η^2: 0.015	0.018	η^2: 0.014	0.027
Average speed (cm/s)	Md, IQR	3.2 (2.3–4.8)	3.6 (2.7–4.9)	η^2: 0.017	0.014	η^2: 0.015	0.021
Speed variability	Md, IQR	1.5 (1.1–2.2)	1.6 (1.3–2.2)	η^2: 0.011	0.049	η^2: 0.010	0.054
Deviation from template (cm^2)	Md, IQR	5.0 (3.9–6.6)	4.9 (4.1–6.5)	η^2: <0.001	0.72*	η^2: 0.001	0.52*
No. of template crossings	Md, IQR	5 (4–6)	5 (4–6)	IRR: 1.06 (0.97–1.17)	0.22*	IRR: 1.05 (0.95–1.16)	0.34*
No. of return movements	Md, IQR	0 (0–1)	0 (0–1)	IRR: 1.50 (1.01–2.23)	0.047*	IRR: 1.44 (0.94–2.22)	0.10*
Purdue Pegboard, no. of participants	N	165	187				
Both hands (no. of pints)	M, SE	10.9 ± 0.12	10.8 ± 0.11	η^2: 0.001	0.78	η^2: 0.001	0.55
Dominant hand (no. of pins)	M, SE	13.6 ± 0.13	13.4 ± 0.13	η^2: 0.005	0.20	η^2: 0.005	0.15
Nondominant hand (no. of pins)	M, SE	12.8 ± 0.13	13.1 ± 0.12	η^2: 0.002	0.15	η^2: 0.002	0.36

OR, odds ratio; IRR, incidence rate ratio; M, mean; SD, standard deviation; no., number; 95% CI, 95% confidence interval; Md, median; IQR, interquartile range; SE, standard error.
Model 1: adjusted for age.
Model 2: adjusted for age and use of lipid-lowering and antihypertensive medication.
*Additionally adjusted for educational level.

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instructed to place the pen in the middle of the spiral before the tracing started (Figure 1a). They were not allowed to lean on the drawing board with their hand or arm. Participants were asked to trace the spiral as accurately and as fast as possible using their dominant hand.

Clinical scoring of spiral drawing

Pen position was recorded at a rate of 60 Hz and stored for off-line quantitative analysis. Drawings of participants were evaluated visually to ensure proper data collection. Drawings were analyzed visually by a trained observer (YYH) for qualitative analyses. First, suspected tremors were noted; these drawings were later re-evaluated by an experienced neurologist (P.J.K.; Acknowledgements). Two persons from the reference group with a tremor were excluded from any further analyses, because of the fact that these persons show very different scores on the spiral drawing variables. No tremors were observed in the chemotherapy-exposed subjects. Second, each drawing was rated with a clinical score ranging from 0 to 4, according to the Archimedes spiral drawing test of the International Cooperative Ataxia Rating Scale (ICARS) [27]. This rating scale is developed for patients with movement difficulties, and thereby not very suitable to detect minor deviations from normal motor performance. Therefore, we subdivided the original score 0 into two subscores: score 0A was given to drawings without any disturbances and score 0B was given to drawings with minor disturbances. ICARS score 1 is reserved for drawings with impairment and decomposition; score 2 was given to drawings with a line completely drawn outside of the pattern and/or hypermetric swerves. Persons with a score over 2 (i.e., one in each group), were excluded, because quantitative measures could not be reliably obtained from these drawings. Example of spiral drawings and associated ratings are shown in Figure 1b.

Quantitative analysis of spiral drawing

Automatic quantitative analyses were performed using custom-made software written in MATLAB (version 8.1; The Mathworks, Natick, MA, USA). This yielded the following outcome measures: movement time (s), defined by the time it took the participant to trace the spiral; length of drawing (cm), defined as the length of the drawn spiral; average speed, defined by the ratio of length of drawing and movement time; speed variability (cm/s), defined as the standard deviation of the instantaneous speed; deviation from template (cm^2), defined as the area between the template and the drawn spiral; number of crossings, defined as the number of times the drawn spiral crossed the template; and return movements, defined as the absence or presence of one or more return movements (i.e., brief movements in the opposite direction; Figure 1a). A smoothly drawn spiral with a clinical score of 0A would have a length of drawing of about 56 cm (the length of the template) with little deviation from the template, a low variability in speed, and no crossings or return movements (Figure 1b).

Statistical analysis

Between-group differences in age were tested using one-way analysis of variance. Differences in the proportion of left-handed subjects, subjects who only attained primary education, and subjects that used antihypertensive drugs, or lipid-lowering medication were tested with a

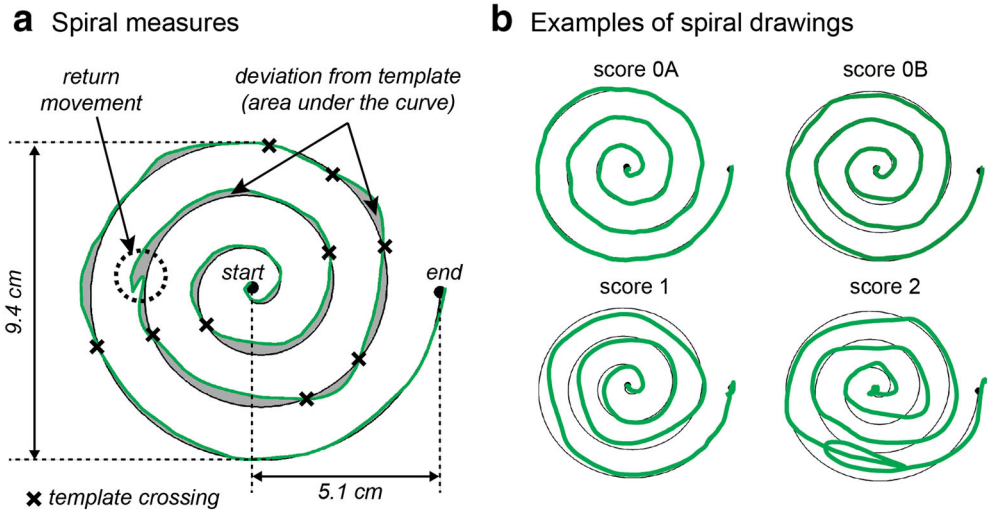

Figure 1. Examples of spiral drawing quantification and clinical scores. (a) An example of the calculation of quantitative measures of fine motor skills. The start and endpoint are indicated by a dot, and the green line represents the drawing made by the participant. The figure explains how deviation from template, crossings, and return movements are defined. (b) Examples of clinical scores of the spiral drawings with scores 0A, 0B, 1, and 2

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chi-square test. Between-group differences in the qualitative ICARS score were tested with ordered logistic regression after verification of proportional odds assumption. The continuous spiral test variables length of drawing, movement time, average speed, speed variability, and deviation from template were log-transformed because of skewness of the untransformed measure. Outliers of the continuous spiral test measures and Purdue Pegboard measures were defined as values ±2.58 standard deviation from the mean. For all continuous variables, the number of outliers never exceeded eight observations (i.e., 2.17%) of the total sample. Between-group differences for all continuous outcome measures were tested using analysis of covariance with age as a covariate and excluding outliers. Median and interquartile range are presented for skewed variables. Count variables (i.e., number of template crossings and number of return movements) were analyzed using negative binomial regression analysis with age as covariate and with robust standard errors. To explore the possibility that level of education would confound the relation between differences in motor functions between groups, we studied the relation between level of education and our outcome variables (Purdue Pegboard scores and spiral test measures). We found that higher level of education related to a better clinical score, less deviation from the template, and fewer number of crossings and return movements. No relationships were found between level of education and any of the other seven outcome measures. Because a variable can only be considered a confounder if it relates to both exposure and outcome [28], we added level of education as a covariate in analyses regarding variables that were associated with educational level. Because motor performance can be related to blood pressure and serum cholesterol, all models were additionally adjusted for use of antihypertensive medication and lipid-lowering medication. Results for models with and without these potential confounders are presented separately.

In order to test whether movement time influenced the quality of the drawn spiral in the Archimedes spiral drawing test, we added movement time as a covariate to test for group differences on the other outcome parameters including deviation from template, and number of crossings and return movements. However, this adjustment did not significantly change any of the results and is therefore not reported.

Finally, we related age and fine motor skills. First, all log-transformed continuous variables were standardized using z-scores to enable mutual comparison of variables. The coefficient of age was tested per group using linear regression analysis. Linear regression analysis with group, age, and a group-by-age interaction term within the whole sample were then used to test the interaction of group-by-age. For the clinical ICARS score, an ordered logistic regression model with age and a group-by-age interaction term was used, whereas for number of template crossings and number of return movements, negative binomial regression analysis with age and an age-cohort interaction term was used to investigate the effect of age on these outcomes. Results are presented with 95% confidence intervals. Analyses were run both with and without adjusting for antihypertensive and lipid-lowering medication.

Breast cancer surgery can cause lymphedema, although the number of affected survivors after 5 years has been estimated to be only about 10% [29]. Because breast cancer surgery-induced lymphedema could potentially affect spiral drawing performance, we compared breast cancer survivors who had breast cancer on their dominant hand body side with those who had breast cancer on their nondominant hand body side. We used the same statistical models as those used to compare the breast cancer survivors and the reference group (discussed in the preceding text). All analyses were performed using Stata 13.1 for Mac OSX.

Results

Table 1 shows the characteristics of the chemotherapy-exposed breast cancer survivors and the reference subjects. No significant differences in age, handedness, or the proportion of subjects who only completed primary education were found between groups. Breast cancer survivors significantly more often used lipid-lowering medication, whereas women from the reference group more often used antihypertensive drugs. Within the breast cancer survivors, left-side and right-side breast cancer occurred evenly frequently (50.0% for both left and right side). In the Archimedes spiral drawing test, no group differences were observed in a clinical score (i.e., ICARS score), deviation from template, and number of return movements. However, after adjusting for age and use of antihypertensive and lipid-lowering medication, we found that breast cancer survivors' median length of drawing was 0.3-cm longer ($p=0.010$), their median movement time was 2.6-s longer ($p=0.027$), and their median speed was lower ($p=0.021$) compared with the that of the reference group. Age-adjusted analyses showed that the speed with which the chemotherapy-exposed breast cancer survivors drew their spirals was more variable ($p=0.049$) and that they made more return movements ($p=0.047$) than the subjects from the reference group, although these results were no longer significant after additional adjustment for use of antihypertensive and lipid-lowering medication. Performance on the Purdue Pegboard task was not different between the two groups.

Table 2 shows effects of age on fine motor skills for chemotherapy-exposed breast cancer survivors and the reference group. Older age was not significantly related to a spiral drawing performance in the sample of reference subjects, but was significantly related to a worse clinical score, longer drawings, increased deviation from the template, increased number of crossings, and an increased

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Table 2. Effects of age on chemotherapy-exposed breast cancer survivors and reference subjects

	N = 174 Chemotherapy-exposed breast cancer survivors	*N* = 195 Reference group	*p*-value interaction*
Clinical score, OR	**1.145** (**1.079**; **1.214**)	0.987 (0.941; 1.036)	<0.001
Length of the drawing, SD	**0.018** (**0.002**; **0.034**)	0.006 (−0.007; 0.018)	0.242
Movement time, SD	0.002 (−0.023; 0.027)	−0.002 (−0.019; 0.018)	0.873
Speed variability, SD	0.013 (−0.011; 0.037)	0.002 (−0.019; 0.022)	0.477
Deviation from template, SD	**0.032** (**0.010**; **0.054**)	0.002 (−0.018; 0.022)	0.044
Number of crossings, IRR	**1.017** (**1.006**; **1.029**)	0.998 (0.998; 1.009)	0.015
Return movements, IRR	**1.160** (**1.103**; **1.220**)	1.024 (0.981; 1.069)	<0.001
Purdue Pegboard both hands, SD	**−0.041** (**−0.061**; **−0.021**)	**−0.056** (**−0.077**; **−0.035**)	0.334
Purdue Pegboard dominant hand, SD	**−0.060** (**−0.081**; **−0.039**)	**−0.043** (**−0.064**; **−0.023**)	0.262
Purdue Pegboard nondominant hand, SD	**−0.049** (**−0.070**; **−0.028**)	**−0.028** (**−0.048**; **−0.007**)	0.147

Values represent differences in odds ratio (OR) obtained using ordered logistic regression analysis, *z*-score (standard deviation (SD)) obtained using linear regression analysis, and incidence rate ratio (IRR) obtained using negative binomial regression analysis per year increase in age (95% confidence interval). Bold printed values indicate significant within-group effects of age at $p < 0.05$.

*p-value of interaction between group and age.

number of return movements in the sample of chemotherapy-exposed breast cancer survivors. The significant age by cohort interaction term in the analysis of clinical score ($p < 0.001$), length of drawing ($p = 0.044$), number of template crossings ($p = 0.015$), and number of return movements ($p < 0.001$) further highlights the differential effect of age on these two groups. In the reference group, age was not related to these variables. For both groups, similar effects of age were found for Purdue Pegboard Test scores. Except for the significant group-by-age interaction for deviation from template, none of the significant within-group effects of age, or the interaction terms, changed after additionally adjusting for antihypertensive or lipid-lowering medication (results not shown). Breast cancer survivors with cancer on their nondominant hand side did not outperform the breast cancer survivors with cancer on their dominant hand side on any of the spiral drawing measures (results not shown).

Discussion

Our aim was to investigate long-term effects of adjuvant chemotherapy for breast cancer on fine motor skills. We compared women who received adjuvant CMF chemotherapy for breast cancer on average more than 20 years before to a group of age-matched women from the general population who had never been diagnosed with cancer. We found that the group of chemotherapy-exposed breast cancer survivors drew longer Archimedes spirals, needed more time to draw the spirals, and had an overall slower drawing speed than the population-based reference group. While reference subjects on average needed 15.7 s to complete the drawing, breast cancer survivors needed 18.3 s on average, which is a 17% increase. No significant differences in other measures of the Archimedes spiral test, such as deviation from the template and number of crossings were observed. The proportion of chemotherapy-exposed breast cancer survivors who made one or more return movements was marginally significantly larger than the proportion of those subjects from the reference group.

Our findings show that the chemotherapy-exposed breast cancer survivors are slower in the execution of fine motor movements than subjects without a history of cancer. The well-documented chemotherapy-related changes in cognitive functioning, specifically in executive functioning, could explain the relation between motor performance and chemotherapy that we observed [4]. Motor coordination correlates with executive functioning [30] that has been found impaired in chemotherapy-exposed breast cancer survivors, including those in the current study [2].

Our results show a differential effect of age on motor performance (Table 2); with increasing age, the chemotherapy-exposed subjects had higher clinical scores, deviated more from the template, more often crossed the spiral template, and made more return movements. Such relationships were not observed within the reference group. These differential associations with aging could indicate chemotherapy-induced accelerated cognitive aging, a phenomena where the effects of aging and the detrimental effects of chemotherapy on the central nervous system interact, leading to larger cognitive function decline earlier in life [31]. Considering the cognitive component of fine motor functioning, accelerated aging could be one of the underlying mechanisms of the worse motor performance in the group of breast cancer survivors. Chemotherapy-related cognitive dysfunction has been linked to structural brain changes. Potentially, chemotherapy-related brain changes, which have been observed in widespread brain regions including areas important for motor functioning such as the cerebellum [32,33], could also partially account for the association between motor slowing and chemotherapy that we observed in the current study. Because motor function and cognition are closely related and because their dysfunction potentially shares underlying mechanisms, it is important to consider these adverse

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effects of cytotoxic treatment together. Performance of instrumental activities of daily living that requires intact fine manual motor skill has been associated with quality of life. Hence, the small to moderate effects of chemotherapy on motor skill that we observed could therefore affect the quality of life.

We observed no differences between the chemotherapy-exposed breast cancer survivors and the population-based reference group in performance on the Purdue Pegboard Test measuring unimanual and bimanual dexterity and psychomotor speed. Previously, we reported that chemotherapy-exposed breast cancer survivors had significantly worse scores than population-based reference subjects on the Purdue Pegboard Test performed with their nondominant hand, but not with their dominant hand or both hands [4]. Despite the large overlap of the samples of reference subjects (i.e., 48.7% ($n=95$)) in the current study who were also part of the reference group of the previously reported data [4]), results from the current study do not show significant performance differences on the Purdue Pegboard between the chemotherapy-exposed breast cancer survivors and the reference group. However, the group mean scores are very similar to the ones we reported previously [4]. Our previous study had a much larger reference group (i.e., 1509 subjects) than the current study, and thus, it had more power to detect differences between groups. We conclude that there is a very small difference in psychomotor speed for the nondominant hand, but that this difference is not reliably detectable with our current sample. In this light, it is of interest to see that the Archimedes spiral drawing test was able to detect significant differences between the groups, despite the relatively small number of participants. This suggests that the computerized Archimedes spiral test is a more sensitive measure to detect adjuvant chemotherapy-related changes in motor performance.

The here reported eta-squared effect sizes of the significant effects of the fully adjusted models range from 0.014 to 0.018 indicating small to moderate effects [34]. Considering the large and growing number of breast cancer survivors, small to moderate effects of chemotherapy on motor skill could significantly affect the quality of life [23] of a substantial group of breast cancer survivors. Future studies investigating the effects of chemotherapy on motor performance should additionally include quality of life measures to verify this relationship.

Breast cancer survivors with cancer on their nondominant hand side never outperformed the breast cancer survivors with cancer on their dominant hand side. Therefore, our data does not support the idea that lymphedema affected spiral drawing performance. Furthermore, some cytotoxic agents have been associated with peripheral polyneuropathy. Peripheral polyneuropathy could adversely affect spiral drawing performance. However, of the agents of the CMF regimen (cyclophosphamide, methotrexate, and 5-fluorouracil) under study, only a high dose of 5-fluorouracil has been associated with peripheral neuropathy that showed to be reversible [35,36]. The CMF regimen does not incorporate high dosage of 5-fluorouracil. Thus, we believe that breast cancer treatment-related lymphedema and potentially neuropathy can only partially explain the observed group differences in fine motor performance. Future longitudinal studies that record and quantify information on lymphedema and polyneuropathy as well as measures of manual skill and executive functioning are warranted to disentangle the different mechanisms underlying the poorer motor skill that we observed in our sample of chemotherapy-exposed breast cancer survivors in comparison with a population-based reference group.

CMF chemotherapy is no longer the main adjuvant treatment regimen for breast cancer. However, we think our results may still apply to contemporary regimens considering that these regimens still include cyclophosphamide and 5-fluorouracil, considering that the currently incorporated taxanes are associated with neuropathy, and considering that the (less frequently prescribed) contemporary cisplatin-based chemotherapy has also been associated with worse fine motor skills [37].

Some drawbacks of the present study need to be addressed. First, its cross-sectional design prevents us to make causal inferences about the relationship between adjuvant chemotherapy for breast cancer and motor performance. Prospective longitudinal studies that include motor assessment could give more insight in the nature of the observed association. Second, we compared chemotherapy-exposed breast cancer survivors to subjects who were never diagnosed with cancer. Therefore, we cannot separate the effects of cancer and cancer treatment.

Strengths of our study include the large number of chemotherapy-exposed breast cancer survivors and the large number of control subjects. In addition, we looked at the effects of chemotherapy on motor performance on average more than two decades of post-treatment, and therefore, we are able to report on the very late symptoms associated with a breast cancer history plus chemotherapy exposure. This is the first study that specifically investigates the relation between adjuvant chemotherapy and motor performance, and the first study that combines different measures of motor behavior to parcel out the different aspects of fine motor functioning.

Conclusions

Compared with a population-based reference group, and on average more than 20 years post-treatment, chemotherapy-exposed breast cancer survivors demonstrated motor slowing while drawing an Archimedes spiral. This suggests that adjuvant CMF chemotherapy

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for breast cancer can be associated with long-term worse motor functioning.

Up until now, most behavioral studies on the effects of adjuvant chemotherapy have focused on the adverse cognitive effects of this treatment. Future studies should include motor performance tests to further investigate the adverse effect of chemotherapy on motor functioning, shortly and at longer times post-treatment, and to assess the clinical relevance of this lower-than-expected motor performance, given the observed small effect size. Investigating cognitive and motor performance together could furthermore help in determining the motor and cognitive components that underlie the cytotoxic effects on motor skill. To gain more insight in the neural mechanisms of chemotherapy-induced motor dysfunction, studies in chemotherapy-exposed cancer patients that combine neuroimaging and motor behavioral outcome measures are warranted.

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Conflict of interest

The authors have declared no conflicts of interest.

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