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The Effects of Being Informed About Chemotherapy-Related Cognitive Symptoms With And Without Self-Affirmation on Perceived Cognitive Symptoms of Breast Cancer Patients: A Randomized Prospective, Longitudinal Study

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Abstract

Information may increase chemotherapy-related cognitive symptoms (CRCS). This randomized study tested the effects of informing 160 first-time breast cancer patients about CRCS with and without self-affirmation on the perceived frequency and severity of cognitive symptoms at 2.5-months and 6.5-months post-chemotherapy. Pre-treatment information added to experienced side-effects at 6.5-months post-chemotherapy. Self-affirmation attenuated these effects for the perceived severity of symptoms.

Background: Informing patients about chemotherapy-related cognitive symptoms (CRCS) may increase perceived cognitive symptoms. This longitudinal randomized study evaluated this Adverse Information Effect (AIE) in breast cancer patients and examined whether self-affirmation (SA) can reduce AIEs (ClinicalTrials.gov identifier: NCT04813965).

Patients and Methods: Before (neo) adjuvant chemotherapy, 160 newly diagnosed breast cancer patients were randomly allocated to receive: standard information on side-effects (control), standard information with additional information about CRCS (information), or standard and additional information with a subsequent self-affirmative text (information+SA). Online-questionnaires assessed the perceived frequency (MOS-cog) and severity (MDASI-cog) of cognitive symptoms before chemotherapy (baseline, T0), and 2.5-months (T1) and 6.5-months (T2) post-chemotherapy. Higher scores indicate less frequent, and more severe symptoms, respectively. Baseline-to-follow-up analyses using a mixed-effects modeling approach compared groups over time. **Results:** At T0-T2, 148, 140 and 133 patients responded, respectively (attrition rates: 8%, 5%, 5%). Frequency (ES = -0.36, $P = .003$) and severity (ES = 0.54, $P < .001$) of symptoms worsened from baseline to T1, without differences between groups. At T2, symptom frequency remained stable for informed (ES=-0.3, $P = .021$) and self-affirmed (ES=-0.3, $P = .019$) patients, but returned to baseline levels for controls. At T2, symptom severity remained increased for informed patients (ES = 0.3, $P = .006$), but normalized for self-affirmed patients (ES = 0.2, $P = .178$) and controls. **Conclusion:** No AIEs occurred until T2. The initial overall increase in perceived cognitive symptoms recovered at T2 for controls, but not for patients who received additional information about CRCS. Self-affirmation attenuated these longer-term AIEs for the perceived severity but not the frequency of symptoms.

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Keywords: Breast cancer, Chemotherapy-related cognitive symptoms, Self-affirmation, Nocebo, Stereotype threat

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The effects of being informed about chemotherapy-related cognitive symptoms

Introduction

Many cancer patients (17%-75%) experience chemotherapy-related cognitive symptoms (CRCS), sometimes lasting well into the survivorship period.¹⁻³ Although cognitive symptoms have been observed for different cancer types and can be related to various components and combinations of cancer treatments, most studies involve women with breast cancer receiving chemotherapy.^{1,3} Preclinical and neuroimaging studies identified underlying mechanisms of CRCS⁴, but psychological factors may also contribute to their occurrence.⁴ Studies suggest that communicating about CRCS may increase their occurrence.⁵⁻⁷

Although information about their treatment and its side-effects is requested by patients,^{8,9} is vital for informed decision making and can positively impact patients' health outcomes and illness perceptions,^{10,11} this kind of information can also have downsides. Breast cancer patients who were informed about potential CRCS, subsequently indicated more cognitive symptoms in daily life and showed lower verbal memory performance compared to uninformed patients, irrespective of age, education level or negative affect.⁵⁻⁷ Additional reassurance 'that not everyone experiences CRCS' does not seem to reduce such Adverse Information Effects (AIEs).⁵

Previous randomized^{5,7} and quasi-randomized⁶ AIE^b studies in cancer patients assessed cognitive symptoms at one point in time immediately after the experimental manipulation. Moreover, they tested the impact of providing information about CRCS to patient's years after treatment, and not to newly diagnosed patients before chemotherapy. Randomized prospective studies with pre- and post-chemotherapy assessments are lacking. Hence, to what extent AIEs on perceived cognitive symptoms occur before the start and (shortly) after the end of chemotherapy, as well as their duration and trajectory remain unclear. Moreover, if such AIEs indeed occur, it is relevant to investigate possibilities to minimize them.

The observed AIEs on cognitive symptoms in breast cancer patients can be regarded as a subcategory of the so-called nocebo effect. This phenomenon is the counterpart of the placebo response and can be described as an adverse response to an active or inert treatment or drug that cannot be attributed to its specific or active mechanism.¹² Nocebo and placebo research mostly have focused on unravelling the neurobiological mechanisms underlying these effects; far less is known about the contributing psychological factors.¹³ Although nocebo studies suggest that AIEs on perceived cognitive symptoms can be driven by increased expectations of side-effects, suggestion, observational learning and conditioning,¹⁴ research into additional psychological factors involved in nocebo effects is warranted and would help in the development of nondeceptive clinical interventions to minimize nocebo responses.¹³ Stereotype (and diagnosis) threat research outside oncology could provide the necessary insight into potential psychological processes underlying AIEs and possible ways to minimize them.

Stereotype and diagnosis threat occurs when prior to a neuropsychological test or symptom assessment, negative stereotypical information or information about a previous medical diagnosis and its connotations, such as 'many individuals diagnosed with head

injury show cognitive deficits', is provided to individuals who are part of the stigmatized or targeted patient group. Pointing out such information then has a self-fulfilling negative impact on subsequent symptom self-reports and on test performance on tests in the stereotyped domain due to increased concern of confirming, or being judged on the basis of this negative stereotype.¹⁵⁻¹⁹ This phenomenon has been mostly studied for cultural stereotypes regarding race and gender, but could also extend to the oncology domain. Breast cancer patients may experience stigmatization because of their diagnosis and treatment,²⁰ and reading about CRCS may then elicit identity threats or a fear of being stereotyped and devaluated because of one's treatment history or patient status, which in turn adversely impacts test performance and perceived symptoms during a subsequent evaluation.⁵⁻⁷ Research on self-fulfilling prophecies, ie, the idea that false expectations can lead to their own fulfillment,²¹ show that stereotypes and negative self-perceptions can have self-fulfilling effects and can shape the targets' future outcomes and behavior in the predicted or expected direction.^{22,23}

It is largely unknown how to minimize AIEs without having to compromise on informed consent when communicating about possible side-effects. Previous nocebo interventions have mostly changed message content by varying outcome expectancies and prognosis information, emphasizing positive treatment outcomes, and de-emphasizing or omitting negative outcomes to induce positive expectations.^{14,24,25} A potentially fruitful avenue may be stereotype threat- and health promotion-based self-affirmation interventions, because these do not change the message content but merely add an invitation to patients to engage in a self-affirming act. Self-affirmation theory suggests that individuals generally want to maintain a sense of self-integrity, ie, a sense of overall personal adequacy.²⁶ When this sense of self-integrity is threatened in the face of a perceived self-threat, a more expansive self-view and restoration of self-integrity can be obtained by critically reflecting upon personally important actions, characteristics or values unrelated to the threat at hand and on previous occasions in which one has acted in accordance with these values.²⁶⁻³⁰ Restoring self-integrity may become especially important after being confronted with (stereotypical) health information and symptom warnings.²⁸ Such information can act as a self-threat, ie, a threat to an individual's sense of being moral, competent and worthy (self-integrity), triggering negative outcomes such as the resistance of health-risk messages.²⁸ Health promotion and stereotype threat research outside oncology shows that allowing individuals the opportunity for self-affirmation can boost the global sense of self in the face of a specific health threat, thereby improving openness to the information, health-message acceptance, health behavior^{28,31} and subjective health,³² and that self-affirmation can reduce stereotype threat effects, sometimes up until years later.³³⁻³⁷ Moreover, self-affirmation can function as a stress-reduction technique that can improve performance,³⁸ and has also been associated with fewer physical symptoms, and positive (self-reported) cognitive and mental health outcomes in (ex) cancer patients.⁴⁰⁻⁴² Next to the well-known, traditional self-affirmation procedures of writing exercises and value scales²², research suggests that individuals' self-concepts can be affirmed via text-integrated^{43,44} and narrative self-

^a CRCS = chemotherapy-related cognitive symptoms

^b AIE = adverse information effect

affirmations.⁴⁵ Importantly, such novel text-integrated applications of self-affirmation are compatible with the informed consent principle and would be clinically feasible, even more so than traditional self-affirmation procedures.

Previous cancer and non-cancer AIE studies have mostly focused on short-term effects in laboratory situations,⁴⁶ so mostly measured the impact of information and expectancy manipulations during or immediately after the study session up until days afterwards in a cross-sectional^{eg,47} or prospective design.^{eg,48,49} It has not often been assessed whether their initial impact can be maintained for longer after treatment or the study session. Few prospective longitudinal studies suggested that the impact of pre-treatment information on health outcomes can last up until one year in non-cancer patients.^{eg,50-52} Additionally, stereotype threat studies suggest that negative perceptions of aging are associated with reduced cognitive functioning years later.^{eg,53} Cancer patients' pre-treatment expectancies influenced outcomes days up until years post-treatment in several prospective studies,^{eg,54,55} but others did not find support for such lasting expectancy-effects in cancer⁵⁶ or non-cancer patients.⁵⁷ Studies specifically investigating the impact of informing cancer patients about CRCS were cross-sectional in nature.⁵⁻⁷

This randomized prospective study examined the short- and longer-term effects of communication about potential CRCS on perceived cognitive symptoms in newly diagnosed breast cancer patients about to begin (neo) adjuvant chemotherapy. Our first aim was to evaluate the effect over time of providing patients before chemotherapy-initiation with additional written information about CRCS on perceived cognitive symptoms. Building on findings that perceived cognitive symptoms of breast cancer patients increased after receiving cognitive side-effect information,⁵⁻⁷ we hypothesized that communicating about CRCS before chemotherapy-initiation will result in short- and longer-term AIEs on patients' perceived cognitive symptoms after chemotherapy completion. Our second aim was to translate the beneficial effects of self-affirmation to the oncology domain, and to examine the efficacy of a newly developed, text-integrated self-affirmation intervention in reducing such potential AIEs. We hypothesized that adding a textual self-affirmation to pre-treatment information about CRCS would reduce AIEs on patients' perceived cognitive symptoms.

Patients And Methods

Study Design and Procedure

In this randomized, longitudinal, online survey study, patients were accrued in ten hospitals in the Netherlands between March 20, 2014 and September 23, 2016. See [Figure 1](#) for the CONSORT diagram. Prior to chemotherapy, the treating medical oncologist or nurse specialist identified potentially eligible patients and informed them about the study using a standardized research description and information leaflet (see S1). The study coordinator contacted interested patients by telephone to further explain the study and verify in- and exclusion criteria. Patients were informed as much as possible about the study aims, without causing interference with the main research objectives. Hence, the research descriptions did not specifically mention CRCS or the hypotheses, but explained that the trajectory of treatment experiences and the effects of different information conditions on patients' well-being were evaluated.

No further interactions took place, apart from reminding non-responders by telephone. Before chemotherapy (baseline, T0) and at 2.5 months (T1) and 6.5 months (T2) post-chemotherapy, a 30-minute survey was conducted independently online via a standardized email containing a survey link and personal login code. All patients provided written consent.

At baseline, all participants first read a standardized general introduction to the online survey, after which randomization took place by a computer program using an algorithm developed by the University's IT expert that included time of entry, previous allocations, and previous completions. This program was linked to Qualtrics,⁵⁸ where patients completed the online surveys. Outside of the study, all patients received usual medical care and standard treatment information from their clinician, but in order to influence their baseline informational status they were randomly allocated to one of 3 different online experimental manipulations (for details see Textbox 1 and S1):

Control group:

- Received a neutral written introduction to the survey with no reference to CRCS.

Information group:

- Received additional written information about potential CRCS.

Information+SA^c (SA = self-affirmation) group:

- Received the same information about CRCS as the information group.
- Subsequently, received a self-affirming paragraph specifically designed for cancer patients and potential use in clinical practice. This newly developed paragraph was adapted from effective existing interventions^{eg,30,36,43,44} and invited patients to think about their positive characteristics, actions or values beyond cognitive functioning, in order to restore patients' self-integrity.

Patients received these texts only once, directly after randomization at baseline. Next, all groups completed an identical questionnaire. At 2.5 months and 6.5 months post-chemotherapy, all groups received identical general introductions and online surveys, without any experimental manipulations. Health care professionals were blinded to group assignment, but due to the nature of the study patients were not. However, patients were not explicitly informed about the study's main outcomes, experimental conditions, specific aims and hypotheses, and the content of the texts that they did not receive until after T2, when they were debriefed and had the option to withdraw their data (second passive consent; see S1).

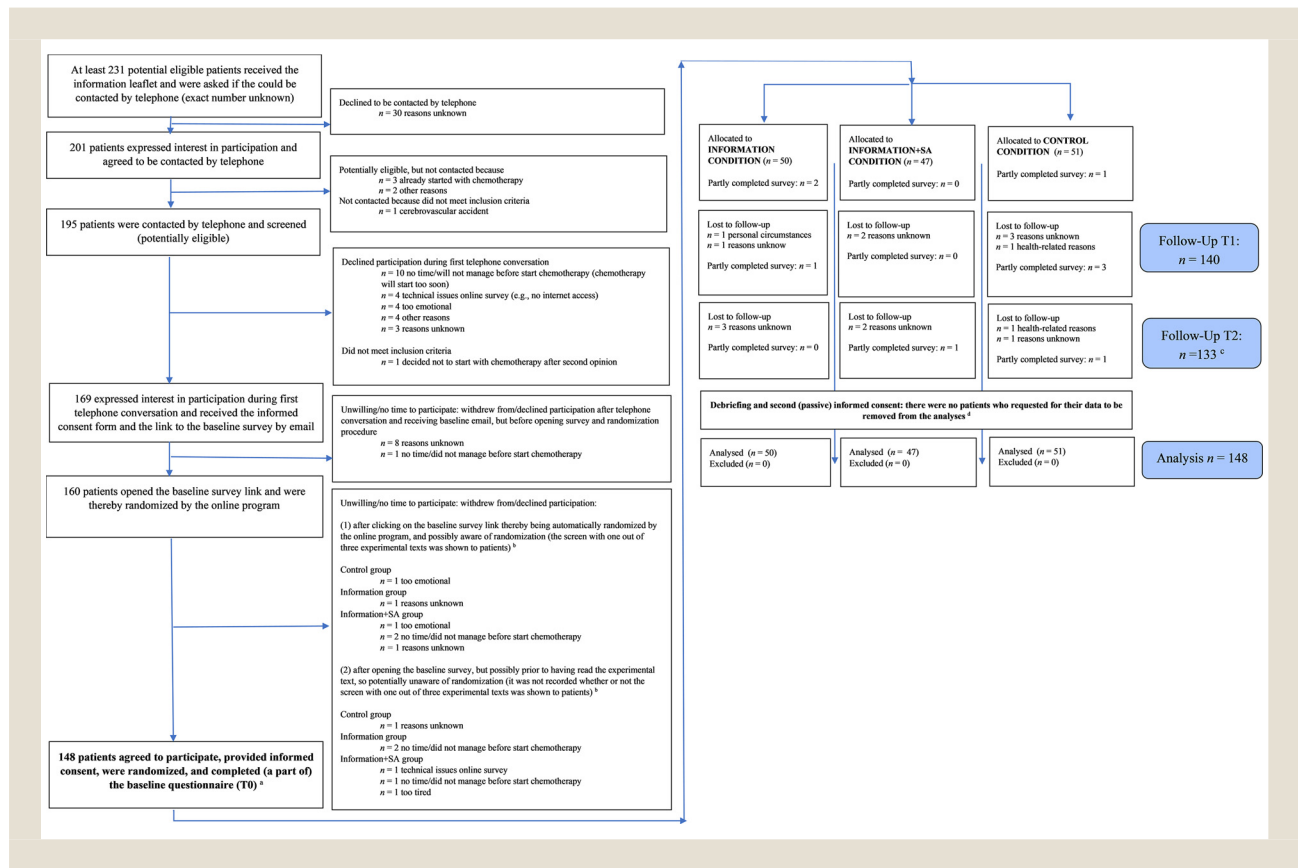
Study Sample

Eligible patients had a primary breast cancer diagnosis stage I-III, were scheduled to receive (neo) adjuvant chemotherapy, were 18 years or older, had sufficient command of the Dutch language, had Internet access, did not have a history of neurological or psychiatric symptoms that influenced cognitive functioning, had not been diagnosed with cancer in the past, did not use drugs, and did not drink more than 3 alcoholic beverages a day. Chemotherapy

^c SA = self-affirmation

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Figure 1 Consort flow diagram.



Notes. (a) Medical records were investigated after T2, which showed that 11 patients did not meet the inclusion criteria of the study at T0 (previous cancer treatment n = 10, alcohol use >3 a day n = 1). The number of participants not meeting the inclusion criteria did not differ across experimental conditions (control n = 5, information n = 1, information+SA n = 5; $\chi^2(2, 148) = 3.26, P = .196$). Following the intention-to-treat principle, all these randomized patients with data on at least one of 3 data waves were included in the analyses (n = 148). (b) Twelve patients withdrew from participation shortly after opening the baseline survey link and consequent randomization, but before providing any post-randomization data (n = 6), and/or having signed consent (n = 10), and/or being exposed to the experimental manipulation (at least 6 patients were exposed to one of the experimental text screens, but for the other 6 this was not recorded by the survey program). These patients were equally distributed across the 3 experimental conditions (n = 12 of n = 160: control n = 2, information n = 3, information+SA n = 7; $\chi^2(2, 160) = 3.64, P = .162$). The proportion of patients who declined after randomization per arm was: 3.77% (2/53) for the control condition, 5.66% (3/53) for the information condition, and 12.96% (7/54) for the information+SA condition. (c) Drop outs after T0 (n = 15 of n = 148: n = 6 control, n = 5 information, n = 4 information+SA) were equally distributed across the 3 experimental groups ($\chi^2(2, 148) = 0.29, P = .867$). (d) Following completion of the third questionnaire, patients were explicitly informed about the specific aims, experimental conditions, and main outcomes of this study. Next, patients were given the option to withdraw their data with a second passive informed consent option. There were no patients who requested for their data to be removed from the analyses.

regimens followed the prevailing guidelines at that time and were mostly anthracycline and taxane based. Patients needed to complete the baseline survey before their first cycle.

Measures

We obtained sociodemographic and medical information through the baseline interview and online surveys, and additional treatment and comorbidity information through the medical records after T2. Primary outcomes were the perceived frequency and severity of cognitive symptoms. Secondary outcomes were other cancer-related symptoms, anxiety, depression and pre-existing knowledge (for details see Table 1). This study was part of a larger project:

results for other primary and secondary outcomes will be described elsewhere (see S2).

Ethical Approval

The Institutional Review Board of the Netherlands Cancer Institute served as the central ethical committee for all participating institutes and approved the study (PTC13.0541-M13WEL-NL43939.031.13). Originally, we wanted to investigate AIEs in 300 patients receiving adjuvant chemotherapy and 300 patients receiving neoadjuvant chemotherapy separately, and to have a 12- instead of 9-month interval between baseline and T2. However, because patient accrual lagged significantly behind expected numbers in the protocol the aimed intervals were shortened, and sample size

Table 1 Study Constructs and Instruments

Construct	Instrument	Number of Items	Possible Score	Cronbach's Alpha (α)/ Pearson's r	Comments	Examples	Assessed at
Perceived cognitive symptom frequency	MOS-cog scale (Medical Outcomes Study – scale) revised, subscale cognitive functioning. ⁸⁴	6	(1) never – (6) always: recoded to (0) always – (100) never ^{cf. 85}	$\alpha = .89$	Participants indicated the frequency of experiencing a range of day-to-day problems in 6 aspects of cognitive functioning during the past week (including today). Scores were reverse coded, transformed to a 0-100 scale and then averaged. ⁸⁵ Higher mean scores indicate better perceived cognitive functioning (range 0-100).	Amount of time in past week (including today) became confused, reacted slowly to things, had difficulty reasoning, was forgetful, had trouble keeping attention, had difficulty concentrating.	T0, T1, T2
Perceived cognitive symptom severity	Two items of the M. D. Anderson Symptom Inventory multiple myeloma module (MDASI-MM, part 1). ^{86,87}	2	(0) symptom has not been present – (10) was as bad as you can imagine it could be	Pearson's $r = .81, P < .001$	Patients reported the severity of 2 cognitive symptoms at their worst in the last 24 hours on a 0-10 scale, with 0 being 'not present' and 10 being 'as bad as you can imagine': difficulty remembering and difficulty paying attention (concentrating). Higher mean scores indicate more severe symptoms.	Difficulty remembering; Difficulty paying attention (concentrating).	T0, T1, T2
Anxiety	Dutch version of the Hospital Anxiety and Depression Scale (HADS). ^{88, 89}	7	4-point scale (range 0-3)	$\alpha = 0.83$	Higher sum scores (range 0-21 per subscale) indicate higher levels of anxiety.	I get sudden feelings of panic.	T0, T1, T2
Depression	Dutch version of the HADS. ^{88,89}	7	4-point scale (range 0-3)	$\alpha = 0.75$	Higher sum scores (range 0-21 per subscale) indicate higher levels of depression.	I still enjoy the things I used to enjoy.	T0, T1, T2
Perceived severity of other cancer-related symptoms	Twelve items of the 13-item core MDASI (part 1). ⁸⁶	12	(0) symptom has not been present – (10) was as bad as you can imagine it could be	$\alpha = 0.85$	Participants reported the severity of 12 symptoms at their worst in the last 24 hours on a 0–10 scale, with 0 being 'not present' and 10 being 'as bad as you can imagine.' Difficulty remembering was excluded. Higher mean scores indicate more severe symptoms.	For example: 'pain'.	T0, T1, T2
Pre-existing knowledge	^{cf. 5-7}	1	(1) Not at all – (5) totally	n.a.	Participants indicated at the end of the third survey, whether they had knowledge about the potential cognitive symptoms of cancer treatment prior to the experiment.	To what extent do you have knowledge about the fact that some people may have memory and concentration problems during and after cancer and cancer treatment?	T2

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calculations were adapted changing the aimed sample size from 300 per treatment group to 300 in total. The trial was retrospectively registered at ClinicalTrials.gov on March 21, 2021 (Identifier: NCT04813965).

Statistical Analysis

Baseline characteristics (eg, education level: low, medium, high; medium is reference) and factors that could potentially influence perceived cognitive symptoms (eg, time between assessments) were compared using chi-square tests for categorical variables, and independent-samples t-tests or univariate analysis of variance for continuous variables. Questionnaire scores were calculated according to published scoring algorithms.

To analyze between-group differences in change over time in symptom frequency and severity, we conducted baseline to follow-up analyses (short-term effect: T0 to T1 and longer-term effect: T0 to T2) using a mixed-effects modelling approach with random intercept, maximum likelihood solution and an autoregressive covariance structure⁵⁹ in R version 3.4.2⁶⁰ using the package *lme4*.⁶¹ The control group served as the reference category.

If despite randomization there were between-group differences in baseline characteristics (see Table 2), or in other potential influencing factors (eg, chemotherapy regimen, see Table 2 and S2), these were corrected for when they significantly correlated with the outcome measure, and were compared with models without adjustment using the Bayesian Information Criterion (BIC)⁶² and the Akaike's Information Criterion (AIC).⁶³ Both are used to compare non-nested models and both penalize the number of model parameters. The BIC also penalizes small sample sizes.⁶⁴ Models with lower BIC or AIC values are considered to be better fitting models. If difference between models were ≤ 2 , we chose the most parsimonious model.^{65,66}

Differences in mean change scores over time between treatment and control groups were accompanied by standardized effect sizes (ES) calculated based on the t-test statistic: $(2 \cdot t) / (\sqrt{\text{degrees of freedom}})$. Effect sizes of 0.2 were considered small, 0.5 moderate, and 0.8 large.⁶⁷ The analyses were conducted on an intention-to-treat (ITT) basis.

Results

Sample Characteristics at Baseline

Figure 1 depicts patient flow and reasons for decline, not meeting inclusion criteria, withdrawal and dropout. Two-hundred-and-one patients were informed about the study and agreed to be contacted, of whom 195 could be reached. One patient did not meet the eligibility criteria and 25 declined after receiving additional information. Another 9 withdrew consent before randomization, resulting in 160 randomized patients. Another 12 withdrew from participation shortly after being randomized, but before providing post-randomization data ($n = 6$), and/or signing consent ($n = 10$), and/or reading the experimental text ($n = 6$ were exposed to the manipulation; $n = 6$ not recorded). Some patients received the survey and consent request simultaneously because of a prompt start with chemotherapy, and could start the survey and the consequent randomization procedure without having consented beforehand. In total, 148 patients agreed to participate and responded at

baseline, 140 responded at T1 and 133 at T2. Table 2 shows baseline clinical and sociodemographic characteristics, as well as relevant treatment-related information and secondary outcomes at follow-ups. Follow-ups took place on average 2.46 (SD = 1.81, range = 0-11.53, median = 1.95) and 6.45 (SD = 2.88, range = 0-21.38, median = 5.68) months after chemotherapy completion, without group differences (see Table 2). Despite randomization, we found baseline group differences for education level ($\chi^2(4,147) = 10.04$, $P = .040$). The control group included more low-educated patients than other groups (see Table 2). Examining correlations between perceived cognitive symptoms and potential influencing factors (see S2) showed that education level was significantly correlated with symptom frequency at T1 (Pearson's $r = -0.19$, $P = .026$; all other P 's $\geq .154$). Here, symptom frequency at T1 increased with higher education levels. All other potential influencing factors were equally distributed across groups and were not added to the analyses (see Table 2 and S2).

Effects Of Group and Time on The Perceived Frequency and Severity of Cognitive Symptoms

Table 3 shows the results from the ITT analysis and shows the difference in mean change in symptom frequency between the information and control group, and between the information + SA and control group from T0 to T1 and from T0 to T2 (see Figure 2 for a graphic representation). Results are described for the model excluding education level, because it had a better fit and effects of education level were not significant. The main effect of time (first contrast) was significant ($P = .003$), indicating that symptom frequency worsened from T0 to T1 for all groups, with a small effect size (ES = -0.36). No significant between-group differences in short-term change (T0-T1) were found, as all groups showed a similar short-term worsening in symptom frequency. Significant differences were found in longer-term change (T0-T2) between the control group and the information and information+SA groups (ES = -0.3, $P = .021$ and ES = -0.3, $P = .019$ respectively), where the increased experience of symptom frequency persisted for patients in both the information and information+SA groups and controls recovered almost to baseline. No other effects were observed.

For symptom severity, we report on the model without education level because of its better fit and because there was no significant correlation with (all P 's $\geq .319$) or effect of education level. Also, for symptom severity the main effect of time (first contrast) was significant (ES = 0.54, $P < .001$), but again no significant between-group differences in short-term change were found, as all groups showed a similar short-term increase in symptom severity. Significant differences were found in longer-term change between controls and informed patients (ES = 0.3, $P = .006$), where informed patients remained increased in their symptom severity and controls recovered towards baseline (Table 3, Figure 2). No significant differences were found in longer-term change between controls and the information+SA group (ES = 0.2, $P = .178$). The level of symptom severity in the information + SA group followed a similar path as in the control group, and the information + SA group partially but significantly recovered towards baseline. No other effects were found.

Table 2 Baseline Clinical and Sociodemographic Characteristics, And Treatment Characteristics and Secondary Outcomes at T1 And T2

	N		Experimental condition			F / χ^2	P
			Control (n = 51)	Information (n = 50)	Information+SA (n = 47)		
Age (M, SD) ^a	148		53.09 (8.49)	50.19 (9.36)	53.65 (8.81)	2.15	0.12
Education level (No. %) ^b	147 (n = 1 not classified)	Low (Verhage 1-3)	7 (14.0%)	2 (4.0%)	1 (2.1%)	10.04	.040*
		Middle (Verhage 4-5)	26 (52.0%)	27 (54.0%)	19 (40.4%)		
		High (Verhage 6-7)	17(34.0%)	21 (42.0%)	27 (57.4%)		
Employment status at T0 (No. %)	148	Yes (full or part-time)	12 (23.5%)	12 (24.0%)	15 (31.9%)	5.44	0.245
		No	21 (41.2%)	12 (24.0%)	12 (25.5%)		
		Temporarily not	18 (35.3%)	26 (52.0%)	20 (42.6%)		
Marital status at T0 (No. %)	148	Single/widowed/divorced	6 (11.8%)	4 (8.0%)	10 (21.3%)	3.86	0.145
		Married/in a relationship	45 (88.2%)	46 (92.0%)	37 (78.7%)		
Days since diagnosis (M, SD)	148		75.10 (29.73)	75.27 (31.61)	83.52 (29.76)	1.21	0.302
Breast cancer subtype (No. %)	148	Triple negative	10 (19.6%)	4 (8.0%)	5 (10.6%)	7.1	0.311
		HER2+ER+ and/or PR+	7 (13.7%)	5 (10.0%)	9 (19.1%)		
		HER2+ER- and PR-	0 (0.0%)	2 (4.0%)	2 (4.3%)		
		HER2- ER+ and/or PR+	34 (66.7%)	39 (78.0%)	31 (66.0%)		
Breast cancer stage (No. %)	147 (n = 1 not classified)	Stage I	16 (31.4%)	14 (28.6%)	20 (42.6%)	3.06	0.548
		Stage II	29 (56.9%)	27 (55.1%)	23 (48.9%)		
		Stage III	6 (11.8%)	8 (16.3%)	4 (8.5%)		
Chemotherapy regimen planned (No. %)	148	FEC/DOC	25 (49.0%)	19 (38.0%)	16 (34.0%)	11.3	0.08
		TAC	9 (17.6%)	16 (32.0%)	13 (27.7%)		
		AC/PAC	11 (21.6%)	15 (30.0%)	11 (23.4%)		
		Other ^c	6 (11.8%)	0 (0.0%)	7 (14.9%)		
Adjuvant or neoadjuvant chemotherapy (No. %)	148	Adjuvant	46 (90.2%)	41 (82.0%)	45 (95.7%)	4.83	0.089
		Neoadjuvant	5 (9.8%)	9 (18.0%)	2 (4.3%)		
Menopausal status (No. %)	148	Pre	22 (43.1%)	27 (54.0%)	21 (44.7%)	4.24	0.375
		Post	26 (51.0%)	21 (42.0%)	26 (55.3%)		
		Unknown ^d	3 (5.9%)	2 (4.0%)	0 (0.0%)		
Age of menopause (M, SD)	69 (n = 4 unknown)		47.15 (5.57)	49.30 (4.46)	48.61 (5.95)	0.96	0.388
Hormonal contraceptive use (eg, pill, Mirena; No. %)	148	Yes	48 (94.1%)	45 (90.0%)	43 (91.5%)	0.59	0.745
		No	3 (5.9%)	5 (10.0%)	4 (8.5%)		
Comorbidity (medical records; No. %)	148	No	23 (45.1%)	24 (48.0%)	23 (48.9%)	0.16	0.923

(continued on next page)

Table 2 (continued)

	N		Experimental condition			F/ χ^2	P		
			Control (n = 51)	Information (n = 50)	Information+SA (n = 47)				
Comorbidity (medical records; No. %)	148	Yes	28 (54.9%)	26 (52.0%)	24 (51.1%)	0.08	0.962		
		Cardiovascular disease							
		Yes	15 (29.4%)	15 (30.0%)	15 (31.9%)				
		No	36 (70.6%)	35 (70.0%)	32 (68.1%)				
		Diabetes Mellitus							
		Yes	3 (5.9%)	3 (6.0%)	3 (6.4%)				
No	48 (94.1%)	47 (94.0%)	44 (93.6%)	0.01	0.994				
Depression		Yes	4 (7.8%)	0 (0.0%)	2 (4.3%)	4	0.135		
		No	47 (92.2%)	50 (100.0%)	45 (95.7%)				
		Other							
		Yes	22 (43.1%)	19 (38.0%)	15 (31.9%)			1.31	0.519
		No	29 (56.9%)	31 (62.0%)	32 (68.1%)				
		Cardiovascular							
Yes	11 (21.6%)	8 (16.0%)	9 (19.1%)	0.51	0.774				
No	40 (78.4%)	42 (84.0%)	38 (80.9%)						
Anti-diabetic									
Yes	2 (3.9%)	2 (4.0%)	2 (2.1%)			0.33	0.848		
No	49 (96.1%)	48 (96.0%)	46 (97.9%)						
Psychotropic									
Yes	6 (11.8%)	6 (12.0%)	7 (14.9%)	0.26	0.877				
No	45 (88.2%)	44 (88.0%)	40 (85.1%)						
Pain medication									
Yes	2 (3.9%)	1 (2.0%)	5 (10.6%)			3.87	0.144		
No	49 (96.1%)	49 (98.0%)	42 (89.4%)						
Perceived severity of other cancer-related symptoms at T0 (M, SD; range 0-10)	146		1.38 (1.19)					1.40 (1.19)	1.12 (1.21)
Pre-existing knowledge at T2 (M, SD; range 1-5)	131		3.61 (1.28)	4.13 (.97)	3.86 (1.03)			2.49	0.087
Anxiety (HADS-A) at T0 (M, SD; range 0-21)	146		4.80 (3.24)	5.84 (3.50)	4.87 (3.36)			1.45	0.239
Depression (HADS-D) at T0 (M, SD; range 0-21)	146		2.20 (2.36)	2.02 (1.92)	2.70 (2.73)			1.08	0.343
Alcohol use at T0 (No. %)	147	Yes (≤ 3 per day)	40 (78.4%)	36 (72.0%)	33 (71.7%)	2.83	0.587		
		Yes (> 3 per day)	0 (0.0%)	0 (0.0%)	1 (2.2%)				
		No	11 (21.6%)	14 (28.0%)	12 (26.1%)				

(continued on next page)

Table 2 (continued)

	N		Experimental condition			F / χ^2	P
			Control (n = 51)	Information (n = 50)	Information+SA (n = 47)		
Time in months between T0 and T1 (M, SD; range 4.10-15.29)	140		6.50 (1.94)	6.37 (1.86)	6.40 (1.42)	0.07	0.934
Time in months between T0 and T2 (M, SD; range 7.56-24.82)	133		10.44 (2.52)	10.10 (1.74)	10.96 (3.36)	1.2	0.306
Time until first chemotherapy cycle in days at T0 (M, SD; range 0-50.12) ^e	148		8.97 (12.53)	5.33 (6.74)	7.65 (11.24)	1.56	0.213
Time in months since chemotherapy completion at T1 (M, SD; range 0-11.53) ^f	140		2.63 (2.18)	2.31 (1.84)	2.44 (1.33)	0.36	0.698
Time in months since chemotherapy completion at T2 (M, SD; range 0-21.38) ^g	133		6.38 (3.14)	6.05 (1.84)	6.95 (3.42)	1.11	0.332
Radiotherapy yes/no (No. %)	147 (n = 1 missing)	Yes	41 (80.4%)	44 (89.8%)	36 (76.6%)	3.07	0.216
		No	10 (19.6%)	5 (10.2%)	11 (23.4%)		
Herceptin yes/no (No. %)	148	Yes	8 (15.7%)	7 (14.0%)	11 (23.4%)	1.67	0.434
		No	43 (84.3%)	43 (86.0%)	36 (76.6%)		
Endocrine treatment yes/no (No. %)	147 (n = 1 missing)	Yes	39 (78.0%)	44 (88.0%)	39 (83.0%)	1.77	0.412
		No	11 (22.0%)	6 (12.0%)	8 (17.0%)		
Type of endocrine treatment received (No. %)	122 (n = 26 no ET or missing)	Tamoxifen	34 (87.2%)	33 (75.0%)	33 (84.6%)	2.65	0.618
		Aromatase inhibitor	1 (2.6%)	3 (6.8%)	1 (2.6%)		
		Tamoxifen and aromatase inhibitor	4 (10.3%)	8 (18.2%)	5 (12.8%)		
Endocrine treatment at T0 yes/no (No. %)	147 (n = 1 missing)	Yes	0 (0.0%)	0 (0.0%)	2 (4.3%)	4.31	0.116
		No	50 (100.0%)	50 (100.0%)	45 (95.7%)		
Endocrine treatment at T1 yes/no (No. %)	142	Yes	28 (58.3%)	31 (64.6%)	34 (73.9%)	2.55	0.28
		No	20 (41.7%)	17 (35.4%)	12 (26.1%)		
Endocrine treatment at T2 yes/no (No. %)	137	Yes	34 (70.8%)	34 (75.6%)	34 (77.3%)	0.54	0.762
		No	14 (29.2%)	11 (24.4%)	10 (22.7%)		
Type of surgery (No. %)	146 (n = 2 missing)	Breast conserving	31 (62.0%)	25 (51.0%)	24 (51.1%)	3.66	0.454
		Mastectomy ^h	18 (36.0%)	22 (44.9%)	23 (48.9%)		
		Axillary/sentinel lymph node dissection	1 (2.0%)	2 (4.1%)	0 (0.0%)		

Notes. (a) M = mean; SD = standard deviation. (b) Education level low: 1 = did not finish primary school, 2 = finished primary school, 3 = did not finish secondary school, middle: 4 = finished secondary school, low level, 5 = finished secondary school, medium level, high: 6 = finished secondary school, highest level, and/or college degree, 7 = university degree.^{90,91} (c) 'Other' includes: PAC, AC, AC/Carboplatin/PAC, FEC/Xeloda(capecitabine)/PAC, DOC, AC/DOC. PAC = Paclitaxel; AC = Doxorubicin/Cyclophosphamide; FEC = 5-Fluorouracil/Epirubicin/Cyclophosphamide, DOC = Docetaxel; TAC = Docetaxel/Doxorubicin/Cyclophosphamide. (d) 'Menopausal status unknown' includes for example no menstruation due to Mirena or continuous use of oral contraceptives. (e) Nineteen patients completed the baseline survey on the same day as they received their first cycle or after receiving their first cycle of chemotherapy. These patients were equally distributed across groups ($\chi^2(2,148) = 0.067, P = .967$). (f) At T1, six patients were not yet finished with chemotherapy. For these patients, time since chemotherapy completion was coded as '0' months. (g) At T2, one patient was not yet finished with chemotherapy. For this patient, time since chemotherapy completion was coded as '0' months. (h) 'Mastectomy' also includes a mastectomy following breast conserving surgery. * < .05. ** < .01. *** < .001.

Table 3 Mean Scores at Baseline, T1 And T2, And Between-Group Differences for Mixed-Effects Models of Primary Study Outcomes

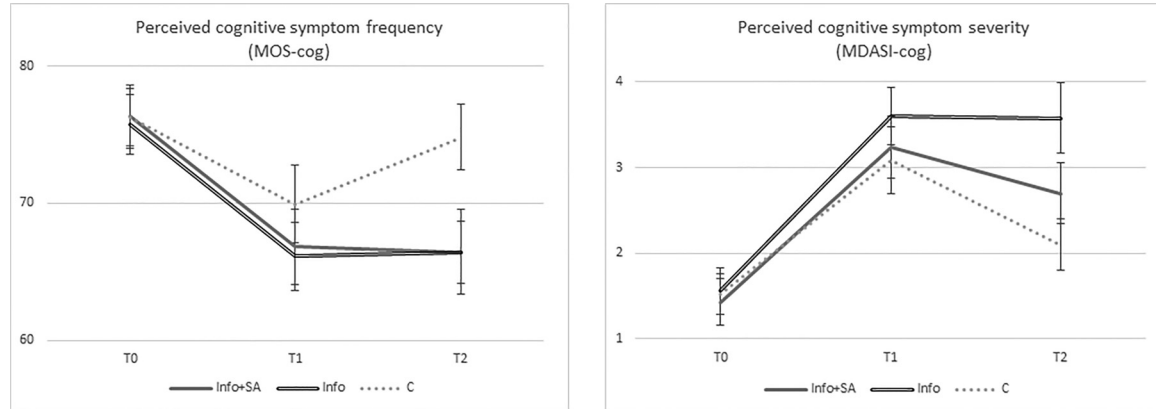
	Assessment									Between-Group Differences								
	T0			T1			T2			T0-T1				T0-T2				
	N	M	SD	N	M	SD	N	M	SD	Mean change	SE	P	ES ^a	Mean change	SE	P	ES	
Symptom frequency																		
MOS-cog total	147			140			133											
Control	50	76.27	14.99	47	69.93	19.52	45	74.81	16.04									
Information	50	75.73	15.50	48	66.11	17.15	45	66.44	20.75	-2.7	3.2	.396	-0.1	-7.6	3.3	.021	-0.3	
Information+SA	47	76.31	15.62	45	66.81	18.41	43	66.43	14.79	-2.5	3.2	.440	-0.1	-7.8	3.3	.019	-0.3	
Symptom severity																		
MDASI-cog total	146			140			132											
Control	50	1.52	1.70	47	3.09	2.67	44	2.10	2.01									
Information	49	1.56	1.91	48	3.60	2.34	45	3.58	2.75	0.5	0.5	.322	0.1	1.4	0.5	.006	0.3	
Information+SA	47	1.43	1.84	45	3.24	2.44	43	2.70	2.33	0.2	0.5	.619	0.1	0.7	0.5	.178	0.2	

Notes. Bold font indicates significant overall interaction effect between group and time and significantly different contrast (T0-T1; T0-T2). Control group is reference group. Reported are the means and standard deviations. Reported are the unadjusted models; education level was not added to the model. MOS-cog scores range from 0-100. MDASI-cog scores range from 0-10. Higher scores on the MOS-cog scale indicate a lower frequency of perceived cognitive symptoms. Higher scores on the MDASI-cog scale indicate a higher severity of perceived cognitive symptoms. * < .05, ** < .01, *** < .001.

Abbreviations: SE= Standard Error; n = number of patients; SA = self-affirmation condition; M = mean; SD = standard deviation; ES = effect size; MOS-cog = revised Medical Outcomes Study – cognitive functioning subscale of Stewart and Ware⁸⁴; MDASI-cog = two items of the M. D. Anderson Symptom Inventory multiple myeloma module^{86,87}; T0 = baseline assessment; T1 = 2.5 months after chemotherapy completion; T2 = 6.5 months after chemotherapy completion.

(a) Effect size was calculated based on the *t* test statistic: (2*t)/sqrt(df).

Figure 2 Interaction between experimental condition and time on (A) the perceived frequency of cognitive symptoms (MOS-cog) and (B) the perceived severity of cognitive symptoms (MDASI-cog).



Notes. Higher frequency scores indicate less frequent cognitive symptoms. Higher severity scores indicate more severe cognitive symptoms. Y-axis for symptom frequency represents the mean of 6 MOS-cog items ranging from 0 to 100. Y-axis for symptom severity represents the mean of two MDASI-cog items ranging from 0 to 10. Bars represent Standard Errors. Abbreviations: SA = self-affirmation; C = control condition; Info = information condition; Info+SA = information+SA condition; T0 = baseline assessment; T1 = 2.5 months after chemotherapy completion; T2 = 6.5 months after chemotherapy completion.

Discussion

This study suggests that no AIEs or self-affirmation effects on perceived cognitive symptoms occurred at 2.5 months after chemotherapy. In line with previous studies^{48,52} the perceived frequency and severity of cognitive symptoms increased shortly after chemotherapy. This short-term worsening of perceived symptoms occurred in all groups, independent of the kind of information patients received before chemotherapy-initiation. Informed and self-affirmed patients showed a similar short-term increase in perceived symptoms as controls. However, at longer-term, this initial increase in perceived symptom frequency and severity persisted for the information group, while controls recovered. This suggests that AIEs on both symptom frequency and severity occurred at 6.5 months post-chemotherapy and that they can develop over time, even when not present initially. This adds to previous cross-sectional studies demonstrating immediate AIEs on (perceived) cognitive symptoms in subgroups of cancer patients years after treatment.⁵⁻⁷ Moreover, it stresses the importance of investigating the course of AIEs over time. Others already suggested that the influence of pre-treatment expectations and placebo/nocebo information on patient-reported outcomes and side-effects can last up until years after treatment,^{49,50,51,55} sometimes with increasing expectation effects over time when negative pre-treatment expectations are confirmed by the experience of high initial side-effects.⁵⁵ Although with much shorter follow-ups, AIEs also developed over time in an 8-day study comparing pain ratings of participants who were informed about increased pain to no-information controls.⁴⁸ Ratings were identical until day 5, but then habituated and reduced for controls, while they remained constant for informed participants.

Against expectations, self-affirmation did not reduce AIEs on the longer-term increased experience of symptom frequency, which persisted for both the informed and self-affirmed patients, while

controls recovered. However, symptom severity followed a similar path from baseline to T2 for self-affirmed patients and controls, indicating that patients who self-affirmed partially, but significantly recovered towards baseline. This suggests that informing patients about CRCS before treatment may elicit a certain self- or identity threat, resulting in a persisted increase in the experience of symptom frequency and severity at 6.5 months post-chemotherapy, that can be partially reduced for symptom severity at T2 by inviting patients to restore their self-integrity at baseline. Future studies should investigate why AIEs and self-affirmation effects only occurred after a significant time delay. In line with our findings, a recent unpublished trial in gastrointestinal cancer patients found positive effects of a nocebo education intervention on the experienced chemotherapy-related adverse events at 12-weeks follow-up, but not yet at 10-days follow-up.^{68,69} It should also be examined why self-affirmation did not reduce the observed AIEs on symptom frequency at T2. Self-affirmation reduces stress,³⁹ and its benefits are thought to mostly occur when the domain under threat is important to the individual⁷⁰ and the threatening information is personally relevant.³⁰ Potentially, symptom severity is a greater indication of the experienced symptom burden or distress and of the extent to which patients value their cognition than the prevalence of symptoms. In symptom research, frequency and severity are generally considered and included as separate but often related components of the symptom experience^{48,71} but empirical study of their distinction,⁷² or the degree to which these and other components contribute to overall distress is limited.⁷³ Hypothetically, some components contribute to distress more than others and are therefore more sensitive to stress-reducing interventions.

Consistent with the suggestion that patients who expect cancer-related stigmatization are vulnerable to AIEs,^{5,74,75} our findings demonstrate that it may be worthwhile to further examine the

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role of identity processes in AIEs, and to translate psychological constructs such as self-affirmation to the clinical context. Others already have suggested to interconnect the separate but overlapping research fields of social expectancies (stereotype threat) and treatment expectations in clinical contexts,⁷⁶ but thus far this integration had not occurred.

Our findings stress the importance of examining the impact of interventions over time, and on various outcomes. Interventions that were effective in laboratory settings need to be translated to actual clinical practice. Further exploration of textual self-affirmations in reducing AIEs seems valuable. They may be more suitable for clinical practice than traditional procedures and can for example be added to patient leaflets. Although beneficial effects of non-textual self-affirmations on health-related variables have been widely established^{38,40,42} studies using text-incorporated self-affirmations are scarce; the best form, timing, target group, and aimed outcomes need to be further explored.

Although effects may be small in magnitude, doctors should be attentive for AIEs when informing patients about side-effects and should be aware that such AIEs may develop after some time. It is too early for specific recommendations about when and how to communicate about CRCS in clinical practice, but inviting patients to self-affirm immediately before or after discussing CRCS may reduce some of the potential AIEs.²⁷ Self-affirmations are brief and could be feasibly implemented in a clinical setting, while maintaining informed consent. Although the translation to clinical practice needs further investigation, clinicians could for example use verbal self-affirmation strategies when discussing symptoms with patients, add written self-affirmations to leaflets, or educate patients about AIEs⁷⁷ and self-affirmation. Patients could self-affirm during doctor-patient interactions, or could request less or more tailored information in trying to minimize AIEs.

Limitations

All patients received standard care by a variety of health care providers. Therefore, information about possible side-effects may have differed between patients, and patients may or may not have been informed about CRCS by their health care provider. However, pre-existing knowledge about CRCS recorded at T2 did not differ across groups.

Patients received the experimental information online, rather than during a medical consultation. Surveys were completed independently online at a self-chosen moment. Consequently, there was limited control over the setting and timing of survey completion and follow-up assessments were regularly delayed, resulting in greater intervals between assessments than planned.

Because patient accrual lagged significantly behind expected numbers in the protocol the aimed intervals between surveys were shortened and sample size calculations were adapted. The adapted power calculation was based on a prior study on AIEs in breast cancer patients with effect sizes of $f = 0.25-0.27$ ($\eta_p^2 = 0.06-0.07$),⁵ an alpha of 0.05, a power of 0.80, and 3 groups, and showed that 132-156 patients were needed for the main effects in the present 3×3 mixed design. Our sample was sufficient to assess main effects of the experimental manipulation, and within-subjects effects of time.

Twelve patients withdrew from participation shortly post-randomization and were excluded. They were equally distributed across conditions. All other available data was analyzed according to the ITT principle.

Further, the occurrence and strength of the self-affirmation effects may have been influenced by the timing of the intervention. Our self-affirmation intervention was presented to patients directly after instead of prior to the threatening information about CRCS. Previous research on the contextual factors that influence the effectiveness of self-affirmation showed that for self-affirmation to be effective, the intervention should be placed in temporal proximity to a psychological threat, that is soon before it occurs or as it takes place,⁷⁸ so before the start of a defensive response.⁷⁹ Affirming after a threat attenuated defensiveness only if the defensive conclusion was not yet reached.⁷⁹ So potentially, affirming before instead of after the information about CRCS will have had a greater effect on symptom severity, and may not have resulted in null-effects for symptom frequency.

Future Directions

Despite our study's shortcomings and small effect sizes, we showed that relatively small variations in the written pre-treatment information presented to patients only once and not even by their own doctor may have a significant effect on patients' perceived cognitive symptoms in the future, and that adding a brief written self-affirmation may partially reduce such longer-term AIEs on symptom severity. Strengths of this study are the longitudinal design, the inclusion of a standard-information control group, and the interdisciplinary approach.

In future, AIEs could be studied in an offline face-to-face setting, more closely resembling the natural procedure of informing patients about side-effects. This will also enable more control over the setting and timing of survey completion. Post-randomization exclusions need to be avoided, although they may be legitimate under certain circumstances even in ITT trials, for example when patients were not exposed to the intervention.⁸⁰ Comparable to other cancer and cognition studies, healthy and no-chemotherapy controls could be included to determine (clinically) significant cognitive impairment, and to clarify previous mixed findings regarding chemotherapy experience as a risk factor for AIEs.^{6,7} It could be worthwhile to compare AIEs and perceived symptoms between neoadjuvant and adjuvant groups. Being informed about CRCS directly after diagnosis, a time known to be especially stressful,⁸¹ may have a different impact on symptom reporting and the occurrence of AIEs than receiving such information at a later time. In addition, patients were assessed during or shortly after the treatment phase. Longer-term post-treatment measurements could indicate whether effects persist or normalize beyond the treatment phase.

Finally, as the effects of self-affirmation depend on the context in which the intervention is introduced, and the intervention will be most (or only) effective when certain key conditions such as 'timeliness' are met,⁷⁸ future studies with optimized designs should further explore under what conditions and at what times self-affirmation is (most) effective in attenuating AIEs on breast cancer patients' perceived cognitive symptoms. For example, it could be explored whether self-affirming *prior* to the information about CRCS can also

attenuate AIEs on longer-term symptom frequency,⁷⁸ and whether repeated self-affirmations throughout the (post) treatment period are more effective than affirming only once before the start of chemotherapy.³³ Also other factors that potentially could influence the effectiveness of the intervention could be studied, such as the form and content of the intervention⁸² and at what times throughout the (post) treatment period they should be delivered to patients, such as at periods of heightened stress or key transition points.³⁵

Conclusion

Providing breast cancer patients with additional written information about potential CRCS before the start of chemotherapy has a small but significant adverse impact on their perceived frequency and severity of cognitive symptoms at 6.5 months after chemotherapy, but not at 2.5 months post-chemotherapy. An additional self-affirming paragraph can attenuate the longer-term AIEs for the perceived severity, but not the frequency of symptoms. AIEs appeared to develop over time and a brief psychological intervention may be useful in reducing some but not all AIEs on breast cancer patients' perceived cognitive symptoms in clinical practice. Randomized prospective studies need to further investigate to what extent pre-treatment information about CRCS has a temporary or longer-lasting influence on patients' future (perceived) symptoms, and how such potential AIEs can be reduced. With the numbers of breast cancer survivors increasing⁸³ and patients expressing the need for pre-treatment information about CRCS,⁹ it will be all the more important for doctors to look for ways to communicate about CRCS without adding to the problem while upholding informed consent.

Textbox 1. Experimental texts at baseline (translated from Dutch).

1. General introduction text, seen by all experimental conditions at baseline

We welcome you to the first questionnaire of the CONTEXT study. This questionnaire is about experiences during the treatment of cancer. We would like to ask you to complete this questionnaire. It will approximately take 30 minutes in total to complete the survey, but you can take as much time as you want. We would like to ask you to complete the survey in one go. In approximately 6 and 12 months, we will contact you again to complete a similar questionnaire. For more information about this study please read the study's patient information leaflet or contact the research coordinator < name, contact details >. Your data will be treated confidentially and anonymously. When you click on the 'next' button, you will first see a short text. Please read this text carefully. After that, the survey will start. Thank you very much for your cooperation.

2a. Information condition

For many people who are treated for cancer, chemotherapy is an important part of their treatment. Chemother-

apy can have several side-effects, such as cognitive problems. Cognitive problems (thinking problems) are for instance memory- or concentration difficulties. We know from experience that some people have cognitive problems during or after chemotherapy. Research shows that chemotherapy can lead to changes in the brain. These changes can cause concentration- and memory problems and can lead to a reduced information processing speed. The goal of this study is to learn more about the relationship between chemotherapy and cognitive problems. This study is important in order to being able to prevent such problems in future.

2b. Patients in the information+SA condition received the exact same first 2 paragraphs as patients in the information condition, but for the information+SA group the following paragraph was added

Not everyone experiences cognitive problems. Many individuals have a good memory- and concentration ability after chemotherapy. In addition, every individual has a unique combination of talents and gains satisfaction from things that are important to him or her, such as spending time with family and children, friends, political involvement, enjoying nature, indulging your passion in hobbies and sports, expanding one's knowledge of art or religion. Every individual is unique.

2c. Control condition

Individuals who are treated for breast cancer have different experiences before, during and after treatment. The goal of this study is to learn more about these experiences. It is important to study which experiences people have and how these experiences change over time, in order to being able to better support and help individuals who are treated for breast cancer in the future.

Note. See S1 for all original texts in Dutch.

Clinical Practice Points

Previous studies showed that breast cancer patients who were informed about potential chemotherapy-related cognitive symptoms (CRCS), subsequently indicated more cognitive symptoms in daily life and showed lower verbal memory performance compared to uninformed patients, irrespective of age, education level or negative affect.⁵⁻⁷ The findings of the current multi-centre, randomized, longitudinal study show how merely informing first-time breast cancer patients about potential cognitive side effects of chemotherapy before treatment may add to the experience of these side effects at 6.5 months after chemotherapy. Moreover, adding a self-affirmation intervention to the information attenuated such longer-term Adverse Information Effects (AIEs) for the perceived severity of symptoms. Although effects were small in magnitude, doctors and patients should be aware of AIEs when informing or being informed about side-effects and should know that such AIEs may develop after some time. It is too early for specific recommendations about when and how to communicate about CRCS in clinical practice, but using self-affirmation techniques when discussing CRCS may be an effective way to

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reduce some of the potential AIEs. Self-affirmation interventions are brief and could be feasibly implemented in a clinical setting while maintaining informed consent. In future, the best form, timing, target group, and aimed outcomes of such interventions need to be further investigated.

Ethics approval and consent to participate

The Institutional Review Board of the Netherlands Cancer Institute served as the central ethical committee for all participating institutes and approved the study (PTC13.0541-M13WEL-NL43939.031.13). The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All participants provided written informed consent.

Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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Disclosure

The authors have stated that they have no conflicts of interest.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.clbc.2022.03.001. S1 shows the study's information leaflets, the informed consent form, patient debriefing information, and experimental materials (in Dutch). S2 shows additional methods and results.

CRedit authorship contribution statement

Wendy Jacobs: Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft, Project administration. **Sanne B. Schagen:** Conceptualization, Methodology, Writing – review & editing, Supervision, Funding acquisition. **Susanne M. Brouwer:** Formal analysis, Writing – review & editing. **Jacobien M. Kieffer:** Formal analysis, Writing – review & editing. **Inge O. Baas:** Resources, Writing – review & editing. **Maartje Los:** Resources, Writing – review & editing. **Gabe S. Sonke:** Conceptualization, Methodology, Resources, Writing – review & editing, Supervision, Funding acquisition. **Enny Das:** Conceptualization, Methodology, Writing – review & editing, Supervision, Funding acquisition.

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