Risk factors for cognitive problems in breast cancer patients: the role of brain white matter

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As only a subgroup of breast cancer patients experience long-term cognitive decline after adjuvant chemotherapy, it is critical to identify risk factors for this decline. Some risk factor like higher age, lower cognitive reserve (either defined as...

Ethical review	Approved WMO
Status	Pending
Health condition type	Cognitive and attention disorders and disturbances
Study type	Observational invasive

Summary

ID

NL-OMON38553

Source
ToetsingOnline

Brief title
DINAMO

Condition

- Cognitive and attention disorders and disturbances

Synonym
cognitive decline, memory and concentration problems

Research involving
Human

Sponsors and support

Primary sponsor: Antoni van Leeuwenhoek Ziekenhuis
Source(s) of monetary or material Support: KWF Kankerbestrijding

Intervention

Keyword: chemotherapy, cognitive functioning, MRI, risk factors

Outcome measures

Primary outcome

1) Cognitive decline 3 years after chemotherapy (dependent variable)

Cognitive decline 3 years after chemotherapy completion is evaluated with standardised neurocognitive tests. These are well-known tests that are often used at the department of Psychosocial Research and Epidemiology of the Netherlands Cancer Institute.

Overall cognitive decline can range from 0 to 18 based on cognitive decline on the number of individual outcome measures (for details see Statistical Analysis section).

The following tests are administered: Flanker test, Digit Span and Digit Symbol of the Wechsler Adult Intelligence Scale III, Behavioural Assessment of the Dysexecutive Syndrome (BADS) Zoo map test, Controlled oral word association test (COWAT), Hopkins Verbal Learning Test Revised (HVLT-R,Trail making test, Visual Reproduction of the Wechsler Memory Scale, Fepsy Finger Tapping Task, Fepsy Visual Reaction Time Task. The official Dutch versions of the tests are used.

For each of the 18 outcome measures cognitive decline is calculated with the reliable change index corrected for practice effects. When a patients score drops below a 90% confidence interval of the baseline score (assessed at

baseline before chemotherapy exposure in the PROSPECT study) this is considered significant cognitive decline. When a patients declines on all outcome measures she scores 18, when she doesn*t decline on any outcomes measure she scores 0.

2) White matter reserve (independent variable)

White matter reserve (premorbid microstructural white matter integrity before chemotherapy exposure) is measured with diffusion MRI scans. These scans are collected in an ongoing study (PROSPECT, NL32148.031.10).

Secondary outcome

(*) Cognitive decline 2 years after chemotherapy (dependent variable)

Cognitive decline 2 years after chemotherapy is measured in the same way as the 3 year measurement (see above).

(*)Early decline of white matter integrity

Early decline of white matter integrity (6 months after chemotherapy) is measured with diffusion MRI scans (difference baseline measurement and measurement 6 months after chemotherapy). These scans have been acquired in an ongoing study (PROSPECT, NL32148.031.10).

(*) Late decline of white matter integrity as measured with diffusion MRI and other MRI markers for late decline of the brain

MRI scans are acquired on a Philips 3 Tesla scanner with an 8 channel SENSE head coil. MRI scan sequences: 1. Diffusion tensor imaging (DTI) is used to measure late decline of white matter integrity (3 years after chemotherapy). 2.

3-dimsional inversion recovery T1 weighted sequence for (automated) volumetrics as a global marker for tissue injury. 3. FLAIR sequence for rating of white matter lesions. 4. Proton MR spectroscopy for evaluation of brain chemistry. Metabolites that can be measured are N-acetyl aspartate (NAA), choline (Cho) and myo-inositol (MI). NAA is a marker for neuronal function. Choline is a marker for demyelination. MI is a glia marker. 5. Functional MRI (fMRI): 3 fMRI scans will be acquired that are sensitive to the BOLD signal (blood oxygenation level dependent) and are a proxy for local brain activation. One scan is acquired while participants perform an fMRI version of the Tower of London, an executive functioning test to measure activation of the prefrontal lobe, 1 scan during performance of a paired associates test, a memory test (encoding and retrieval) to measure activation of (para)hippocampal structures, 1 resting state scan to measure activity of neural network during rest.

The following data will be collected for all participants 2 and 3 years after chemotherapy (or matched intervals for cancer patients who did not receive chemotherapy and healthy controls): age, educational status, smoking habits, alcohol intake, body mass index, age at menopause (if applicable), type of menopause (natural or artificial), psychological distress (Hopkins Symptom Checklist), health related quality of life (EORTC QLQ-C30), self-reported cognitive problems (MOS questionnaire), self-reported medical history and medication use. For all cancer patients the following additional information will be obtained through the medical records: kind of cytotoxic treatment, radiotherapy yes/no, endocrine therapy yes/no. For the breast cancer patients

not treated with chemotherapy, the following information will be obtained through the medical records: radiotherapy yes/no, endocrine therapy yes/no, type and dose of chemotherapy (if applicable). To study potential effects of stress on brain and cognition, cortisol levels will be measured in hair samples (only at 3 year measurement). Blood samples will be collected in all participants to allow for analyses of hormonal levels and cytokines (only at 3 year measurement). Previous studies have shown that fluctuations and changes of sex hormones, such as LH, FSH, estradiol and progesterone, correlate with decreased cognitive performance. Deregulation of cytokines, such as IL1, IL6, TNFα, has been associated with cognitive dysfunction following chemotherapy. All parameters that will be measured have also been measured in the ongoing PROSPECT study (NL32148.031.10).

Study description

Background summary

Improvements in cancer therapy have increased survival in breast cancer patients. Therefore, psychosocial aspects of breast cancer and its treatment have become increasingly important. About half of the breast cancer survivors report cognitive problems at some stage of their disease. The problems include forgetfulness and lack of concentration and sometimes also occur long after treatment (> 1 year), without signs of disease recurrence. Cognitive decline can negatively impact quality of life after cancer and is one of the most frequently reported problems in breast cancer survivors who are back at work.

At the level of self-report cognitive problems usually co-occur with psychological problems like fatigue, anxiety and depression. However, when cognitive functioning is evaluated with standardized neurocognitive tests, cognitive decline, to some extent appears to be the result of the specific type of treatment that breast cancer patients received. Particularly after adjuvant chemotherapy cognitive decline occurs, in 19 -78 % of patients. Who are the breast cancer patients that show cognitive decline after chemotherapy?

At the level of self-report cognitive problems usually co-occur with psychological problems like fatigue, anxiety and depression. However, when cognitive functioning is evaluated with standardized neurocognitive tests, cognitive decline, to some extent appears to be the result of the specific type of treatment that breast cancer patients received. Particularly after adjuvant chemotherapy cognitive decline occurs, in about 30% of patients.

Animal studies and neuroimaging studies in humans, some conducted by our group, point to measurable alterations in brain structure and function after chemotherapy. Recent advanced neuroimaging techniques like diffusion MRI indicate that particularly brain white matter is susceptible to neurotoxic side effects of chemotherapy. This technique shows a reduction in white matter integrity on a microstructural level. White matter consists of nerve tracts that connect brain regions. Intact nerve tracts are essential for cognitive functioning, which is supported by extensive neural networks. Injury to white matter, therefore, is potentially very detrimental for cognitive functioning.

Study objective

As only a subgroup of breast cancer patients experience long-term cognitive decline after adjuvant chemotherapy, it is critical to identify risk factors for this decline. Some risk factor like higher age, lower cognitive reserve (either defined as lower IQ, education or cognitive performance at baseline), low levels of hemoglobin and high levels of anxiety have been identified but none of them consistently. Because brain white matter is sensitive to toxic effects of chemotherapy, and essential for cognitive functioning, our objective in this study is to evaluate whether a low *white matter reserve* (before chemotherapy is administered) is a risk factor for developing late cognitive decline, 3 years after chemotherapy exposure.
White matter reserve is measured with diffusion MRI scans that have been collected in the PROSPECT study (P10CDC/NL32148.031.10).

The identification of a low white matter reserve before treatment might ultimately guide treatment strategies. For instance, when the administration of a particular kind of chemotherapy is already questionable (in the case of an elderly patient with a weak constitution, and/or a particular type of breast cancer for which the added value of chemotherapy is unclear).

Secondary Objectives:
In addition to cognitive decline after 3 year, we also aim to investigate whether a low white matter reserve (before chemotherapy administration) is a risk factor for cognitive decline 2 years after chemotherapy.

In addition we aim to evaluate whether early decline of white matter integrity after chemotherapy (6 months after chemotherapy exposure) is a risk factor for late cognitive decline (2 and 3 years after chemotherapy).

Identifying early decline of white matter integrity after chemotherapy might serve to inform the patient about potential side effects of chemotherapy and early interventions after treatment (e.g., neurorehabilitation). Also the patient might be advised to adapt their lifestyle in a way that is beneficial to the quality of brain white matter (e.g., quit smoking and start exercising).

We also aim to investigate whether other aspects of brain structure and function as measured with state of the art MRI scan sequences (before chemotherapy and 6 months after chemotherapy) are predictive of late cognitive decline, 2 and 3 years after chemotherapy. Finally we also aim to assess various aspect of late brain decline 3 years after chemotherapy by repeating the MRI sequences from the PROSPECT study (P10CDC/NL32148.031.10).

Study design

This prospective observational study is a collaboration between the departments of Psychosocial Research and Epidemiology and Neuro-oncology of the Netherlands Cancer Institute and the department of Radiology of the Academic Medical Center of the University of Amsterdam. In this study, patients will participate who were treated at the Netherlands Cancer Institute, VU University medical center, Flevo Hospital and Reiner de Graaf Hospital. The current study recruits patients from the ongoing PROSPECT study (NL32148.031.10) on brain function and structure in breast cancer patients.

Study burden and risks

Participants will be assessed twice, 2 and 3 years after chemotherapy completion, or matched intervals for breast cancer patients for whom chemotherapy was not indicated en healthy controls. The assessment after 2 years lasts 1.5 hours and the assessment after 3 years lasts 3 to 3.5 hours. The assessment after 2 years comprises the neurocognitive test administration and several questionnaires. At the assessment after 3 years these data are also collected. In addition the cortisol hairsample and a venipuncture will be collected and the MRI scans will be acquired.

Burden of undergoing MRI scans (only the 3 year after chemotherapy assessment or comparable intervals for patients who did not undergo chemotherapy and healhy controls). About half of the total duration of MRI scan acquisition the participant is actively involved in performing the fMRI tests. The remainder of the MRI scan acquisition no active involvement of the participant is required. De participant has to lie still in the scanner which is sometimes experienced as unpleasant. In addition the scanner makes noise, but this is effectively reduced by using earplugs and headphones. When standard safety rules are applied (eg., no ferromagnetic objects inside the scanner room) no risks exist for the participant. In our ongoing PROSPECT studie,
die identieke metingen heeft, weten we dat patiënten het onderzoek als niet te

belastend ervaren. Dat blijkt ook uit het lage percentage patiënten dat niet aan de tweede meting van deze studie deelneemt om andere redenen dan dat zij inmiddels voldoen aan de exclusiecriteria (<3%).

Only 3 year after chemotherapy (or comparable intervals for patients who did not undergo chemotherapy and healhy controls), a small hair sample will be collected to measure cortisol levels. The collected sample is very small. It is not visible that this hair strand has been taken from the back of the head. We also collect hair samples in the ongoing PROSPECT study that participants in the present study are recruited from. In the PROSPECT study participants have not expressed problems with collection of the sample. Venipuncture (also only after 3 years) is performed by a certified research assistant to limit patient burden to the minimum.

No information on individual test results and other outcomes measures will be communicated to participants (except for serious incidental MRI findings), in accordance with the approved PROSPECT protocol.

The measurement after 2 years takes place at the Antoni van Leeuwenhoek Hospital or at home, if the participant prefers that.
The measurement after 3 years takes place at the Spinoza Centre for Neuroimaging at the University of Amsterdam (Roeterseiland).

Travel and parking expenses will be reimbursed. Patients will also be paid an additional 20 euros (2 year measurement) and 40 euros (3 year measurement) for compensation. Participants will be given a short break during the assessment and will receive a lunch voucher.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

-participation in study PROSPECT, NL32148.031.10;Inclusion criteria PROSPECT study (all groups):
-female
-age < 70 (to allow for the use of the same neuropsychological test battery in all participants)
-sufficient proficiency in the Dutch language;Experimental group:
-newly diagnosed breast cancer patients without distant metastases who will receive anthracycline-based adjuvant chemotherapy;Breast cancer control group:
-newly diagnosed breast cancer patients without distant metastases who do not require chemotherapy;Healthy control group:
-healthy females, matched for age

Exclusion criteria

All groups:
-new malignancies, except for basal cell carcinoma
-excessive use of alcohol of drugs
-use of psychotropic medication
-neurologic or psychiatric disorders that may influence cognitive functioning
-conditions that preclude MRI examination (e.g., pacemaker);Experimental group and breast cancer control group:
-relapse and/or metastases
-treatment with trastuzumab (Herceptin)

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Other

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-10-2013
Enrollment:	114
Type:	Anticipated

Ethics review

Approved WMO

Date:	17-10-2013
Application type:	First submission
Review commission:	METC NedMec

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL44466.031.13