How may exercise reduce fatigue in patients with cancer. A pilot study examining the role of muscular, immune and endocrine systems.

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Primary Objective(s): 1. To obtain preliminary data on whether (and to which extend) adjuvant chemotherapy for colon cancer results in (a) deterioration of contractile muscle properties and increased muscle fatigability, (b) increased inflammation...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Gastrointestinal neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON43997

Source
ToetsingOnline

Brief title
MEchanisms of TRaining In patients with Cancer (METRIC)

Condition

- Gastrointestinal neoplasms malignant and unspecified

Synonym
breast cancer, colorectal cancer

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum

Source(s) of monetary or material Support: Sponsorgeld van de Zuidasrun

Intervention

Keyword: Cancer, Exercise, Fatigue, Quality of life

Outcome measures

Primary outcome

The main outcome of measures of this pilot study are:

a) Measurements of muscles contractile properties, i.e. muscle force, speed of force development and relaxation, and fatigability.

b) Measures of inflammation (CRP, IL-6, TNF-alpha)

c) Measures of the insulin pathway (insulin, IGF, C-peptide).

Secondary outcome

Secondary outcome measures are perceived fatigue, assessed with the Multidimensional Fatigue Inventory (MFI) (60), and health-related quality of life, assessed with the European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire C30 (EORTC QL-C30).

Sociodemographic factors (e.g. age, gender) will be assessed with questionnaires. Physical activity will also be measured by questionnaire. Cardiorespiratory fitness will be measured using a submaximal exercise test (Chester step test). Upper and lower extremity strength will be measured using a handgrip dynamometer and 30s sit to stand test. Body composition will be assessed by measuring height, weight, hip and waist circumference, and thickness of four skinfolds. These assessments correspond to those used in the Alpe d*HuZes Cancer Rehabilitation (A-CaRe) research programme .

Information on clinical variables (e.g. diagnose, tumour stage, treatment and

follow-up data including progression free survival (PFS) and overall survival

(OS) up to 5 years after diagnosis) will be obtained by medical records.

Study description

Background summary

Survival after cancer has substantially improved due to advances in early detection and treatment. In the Netherlands, the current 5-year survival rate of patients with colon cancer is 94% for patients with stage I, 78% for stage II and 59% for stage III. For stage IV, 5-year survival rates are only 7%. Cancer and its treatment are often associated with prolonged adverse psychosocial and physical symptoms, including decreased physical fitness, reduced lean body mass, bone loss, increased risk for anxiety and depression and fatigue. Particularly fatigue has been identified as one of the most common and distressing symptoms of patients with cancer affecting quality of life (QoL). Approximately 70% of patients with cancer report fatigue complaints during chemotherapy and/or radiotherapy. Even years after the end of treatment, fatigue is still a major problem for at least 30% of cancer survivors. In a previous study in a large group of colorectal cancer (CRC) survivors (n= 1371) we showed that fatigue was present in 42%. This number is considerably higher than in the general population; results from the Maastricht Cohort Study showed that prolonged fatigue is present in 22% of the general Dutch working population.
Reducing fatigue is a key component in optimising daily functioning and QoL of patients with cancer and survivors. However, a main barrier to effective management of fatigue is the inadequate understanding of its aetiology. To date, specific mechanisms that cause and maintain fatigue are not yet known. Fatigue is a multidimensional concept covering physiological, biological and psychological aspects. Psychological aspects of fatigue include anxiety and depressive symptoms. In addition perceived fatigue may be influenced by concentration, physical activity, and social functioning. Physiological fatigue is usually defined as the loss of voluntary force-producing capacity during exercise, and can both (and simultaneously) have a peripheral and central origin. Peripheral fatigue refers to the loss of force in the muscle tissue after constant activation. Central fatigue refers to a decrease of voluntary activation of the muscle by the nervous system, leading to a suboptimal input from the nervous system to the muscle. As a consequence, the muscle is not able to develop its maximal force capacity. Central and peripheral fatigue can be assessed by measuring contractile muscle properties (e.g. force production, speed of force development and speed of relaxation),

and muscle fatigability after/during repeated contractions.
The muscular system is the body*s largest metabolic organ system, and therefore has an important role in human functioning. Interestingly, skeletal muscle has been shown to have great adaptability with appropriate training stimuli even in cases of severe muscle atrophy and fatigue. Exercise in patients with cancer, and particularly resistance training can counteract the reduced muscle mass and strength, and bone mass. Previous studies showed that exercise may improve muscle mass and strength, reduce fatigue and improve the QoL in cancer patients during and after treatment. Epidemiological studies further showed that physical activity after the diagnosis of stages I to III CRC may reduce the risk of CRC-specific and overall mortality. In patients with metastatic breast cancer treated with capecetabine, Prado et al. showed that sarcopenia (severe atrophy of skeletal muscle) was an important predictor of toxicity and time to tumour progression. Therefore, exercise may even be more important in patients with metastatic disease in which sarcopenia and fatigue is more present. So far, little is known about the effects of exercise on health outcomes and survival in patients with stage III CRC.

Biological aspects include the function of the immune and endocrine systems. Cancer and its treatments may alter immune system function. C-reactive protein (CRP) is a sensitive marker of low-grade systemic inflammation. In cancer survivors, elevated concentrations of CRP have been found to be associated with fatigue and reduced overall and disease-free survival. Exercise can have a beneficial effect on the immune system of cancer survivors. Reductions in CRP after exercise were found in an observational study among breast cancer survivors and randomised controlled trials (RCTs) among survivors of breast, lung, and prostate cancer.
Pro-inflammatory cytokines (e.g. tumour necrosis factor-alpha (TNF-*) and Interleukin (IL)-6) may be released in response to the tumour or cancer treatment, and may promote tumour growth and angiogenesis. TNF-* and IL-6 have been associated with cancer-related anaemia, cachexia, loss of muscle mass, and cancer-related fatigue. Exercise may have an anti-inflammatory effect in cancer survivors, as cytokines may be expressed and released by muscle fibres. However, no change in IL-6 levels after exercise was found in 20 patients with breast cancer. Comparably, a study in 10 patients with prostate cancer did not find changes in resting serum concentrations of IL-6 and TNF-* after a 20-week resistance exercise program, but increased IL-6 levels were found after acute resistance exercise. Exercise has been shown to improve Natural Killer cell cytotoxity among cancer survivors, indicating improved immune function. Other beneficial effects included increased lymphocyte proliferation and granulocyte cell counts. Although evidence is still preliminary, exercise may be associated with beneficial changes in inflammation and immunity. However, the effect of chemotherapy on the immune system responses, and the potential preventive effect of exercise in patients with colon cancer, and the mediating role in reducing fatigue, improving QoL and survival is unclear.
Insulin, Insulin-like growth factor (IGF), and IGF binding proteins (IGFBP) are important regulators of energy metabolism and growth, and may also

be involved in tumour development and progression. High insulin levels have been associated with increased risk of tumour recurrence or death in survivors of breast and colon cancer. In addition, there is increasing evidence suggesting that insulin, IGF and IGFBP may have an important mediating role in the effect of exercise on cancer risk and prognosis. Recently, Ballard-Barbash et al. systematically reviewed studies among cancer survivors examining associations between exercise and biomarkers. One observational study and four RCTs evaluated effects of exercise on insulin, IGF and IGFBP among breast cancer survivors. Higher levels of exercise were found to be associated with lower levels of C-peptide (marker of insulin secretion) and leptin, and higher levels of IGF-1, but no association was found for IGFBP-III. Results from RCTs provide preliminary evidence that exercise may result in beneficial changes in the circulating levels of insulin and insulin-related pathways, which may be more pronounced for obese or sedentary women who generally have higher serum insulin levels at baseline, and for women who are not taking Tamoxifen. Weighted-mean effect size of the effect of post-treatment exercise on IGF-1 was found to be significant but small-to-moderate. No changes were reported for insulin and IGFBP-III, and evidence was insufficient for IGF-II and IGFBP-I. The number of studies on the effects of exercise on insulin, IGF and IGFBPs during treatment was too small to draw conclusions. Therefore, more insight in the effect of cancer treatment on the endocrine system function and the potential beneficial effects of exercise is necessary.

More insight into the mechanisms through which exercise exerts its effect on fatigue should provide information for more potent and effective interventions. Exercise during chemotherapy may prevent deterioration or improve function of the muscular, immune and endocrine systems.

Study objective

Primary Objective(s):
1. To obtain preliminary data on whether (and to which extend) adjuvant chemotherapy for colon cancer results in (a) deterioration of contractile muscle properties and increased muscle fatigability, (b) increased inflammation, (c) deterioration of the insulin pathway (within group differences in group A).
2. To obtain preliminary data on whether (and to which extend) resistance and endurance exercise can prevent adjuvant chemotherapy-induced deterioration of or improve (a) contractile muscle properties and muscle fatigability, (b) immune system function (i.e. reduced inflammation), (c) endocrine system function (i.e. improved insulin pathway) in patients after surgery for colon cancer (differences between group A and B).

Secondary Objective(s):
1. To obtain preliminary data on whether improvement in function of the muscular, immune and endocrine systems are associated with:
a. Reduced perceived fatigue

b. Improved health-related quality of life (HRQoL)

Study design

This prospective pilot randomized controlled trial (RCT) will compare a nine or twelve weeks resistance and endurance exercise program to a usual care control group. All potentially eligible patients will be identified and informed of the study by their treating medical oncologist. They will receive written information of the study to take home. If the patient decides to participate in the study, he or she will sign the informed consent.
Following consent, the baseline measurements will take place. Subsequently, the participating patients will be randomized into one of the two study groups and will be informed of the result of randomization. Prior to randomization, patients will be stratified by gender.
Group A will receive a 9 or 12-week (depending on the duration of chemotherapy treatment) resistance and endurance exercise intervention in the first half of chemotherapy treatment. Group B will receive usual care in the first half of chemotherapy treatment. Current usual care does not contain a structured exercise training. However, since usual care for patients with cancer is rapidly changing towards the inclusion of physical activity and exercise programs, we will also offer the same exercise intervention to group B, but starting mid-chemotherapy treatment (after 9 or 12 weeks). This allows us to examine the effects of chemotherapy on muscular, immune and endocrine systems and the potential beneficial effects of exercise.
Function of the muscular, immune and endocrine system, as well as perceived fatigue and QoL are measured at baseline (T0), mid-chemotherapy treatment (T1), and after chemotherapy treatment (T2).

Intervention

Resistance and endurance exercise: the CytoFys program.
Patients will participate in a 9 or 12-week resistance and endurance exercise intervention during chemotherapy. They will be randomly assigned into two groups. Patients in the first group (group A) will start the exercise program immediately, e.g. at start of the chemotherapy, and patients in the second group (group B) will start 9 or 12 weeks after they started chemotherapy (mid-chemotherapy treatment). In the CytoFys program, resistance and endurance exercise and will be performed twice a week under supervision of a physiotherapist.

Laboratory visits: measurement of contractile properties and fatigability of muscles and blood samples
Patients will visit the laboratory on three occasions (see figure 1): at baseline (T0), mid-chemotherapy treatment (T1) and after completing chemotherapy treatment (T2).
During these visits, contractile properties of the muscle and fatigability will

be determined, using electro stimulation of the muscles of the upper leg (m. quadriceps) (see methods). In addition, during each visit patients will fill out questionnaires to assess perceived fatigue and HRQoL, and their physical activity and fitness levels will be assessed. At the start of each visit, a venous blood sample (ca 43 ml) will be drawn. Each visit will last approximately 120 minutes.
Participants are requested to avoid any moderate and/or vigorous intensity activity or to consume any alcohol for at least 48 hours prior to the laboratory visits, and to refrain from eating or drinking sugar-containing beverages 2 hours prior to the visit.

Study burden and risks

We expect the risk associated with participation to be negligible. The only burden for the patients is the time investment, and not being able to consume alcohol or conduct vigorous exercise 48 hours prior to the measurement and eating or drinking suger-containing beverages 2 hours prior to the measurements. In clinical practice, it has been shown that CytoFys is feasible for cancer patients. At baseline, mid-chemotherapy treatment and after chemotherapy treatment, patients will visit the laboratory (VU University, Faculty of Human Movement Sciences) for approximately 120 minutes. During these sessions, muscle properties and fatigability will be assessed, and venous blood samples will be drawn to assess inflammation and insulin-pathway. Both measurements of muscle properties and fatigue have been shown to be feasible in various groups of patients.
The effect of physical exercise on muscle properties, inflammation and the insulin-pathway, and the relationship with fatigue and HRQoL in CRC and breast cancer patients stage II/III is still unclear. We expect exercise to have beneficial effects on these outcomes.

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

Patients with histological confirmed primary colorectal cancer or breast cancer stage II/III aged * 18 years, who will be treated with (neo-)adjuvant or first line chemotherapy.

Exclusion criteria

Patients who are not able to perform basic activities such as walking or biking, who show cognitive disorders or severe emotional instability, who are suffering from other disabling co-morbidity that might hamper physical exercise (e.g. heart failure, chronic obstructive pulmonary disease (COPD), orthopaedic conditions and neurological disorders), and patients who are unable to understand and read the Dutch language will be excluded from the study

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Single blinded (masking used)

Primary purpose: Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-09-2014
Enrollment:	30
Type:	Actual

Ethics review

Approved WMO Date:	18-03-2013
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-04-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-06-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-02-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-04-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

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

ID: 24982
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
CCMO	NL41283.029.12
OMON	NL-OMON24982