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Muscle contractile properties of cancer patients receiving chemotherapy: Assessment of feasibility and exercise effects

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Background: This pilot trial explores the feasibility of measuring muscle contractile properties in patients with cancer, effects of exercise during chemotherapy on muscle contractile properties and the association between changes in contractile muscle properties and perceived fatigue.

Method: Patients who received (neo)adjuvant chemotherapy for breast or colon cancer were randomized to a 9-12 week exercise intervention or a waitlist-control group. At baseline and follow-up, we measured knee extensor strength using maximal voluntary contraction (MVC), contractile muscle properties of the quadriceps muscle using electrical stimulation, and perceived fatigue using the Multidimensional Fatigue Inventory. Feasibility was assessed by the proportion of patients who successfully completed measurements of contractile muscle properties. Exercise effects on muscle contractile properties were explored using linear regression analyses. Between-group differences >10% were considered potentially relevant. Pearson correlation (r_p) of changes in contractile muscle properties and changes in perceived fatigue was calculated.

Results: Twenty two of 30 patients completed baseline and follow-up assessments. Measurements of contractile properties were feasible except for muscle fatigability. We found a potentially relevant between-group difference in the rate of force development favoring the intervention group (1192 N/s, 95% CI = −335; 2739). Change in rate of force development was negatively correlated with change in perceived general ($r_p = -0.54$, $P = .04$) and physical ($r_p = -0.59$, $P = .02$) fatigue.

Conclusion: Chemotherapy induces a decrease in the rate of force development, which may reflect a larger loss in type II muscle fibers. This may be attenuated with (resistance) exercise. The increase in the rate of force development was related to a decrease in perceived fatigue.

KEYWORDS
fatigue, muscle contraction, physical activity, quadriceps muscle, randomized controlled trial

1 | INTRODUCTION

Patients with cancer often experience adverse effects of cancer and cancer treatment, with fatigue as one of the most common and distressing symptoms.[1] Cancer-related fatigue is defined as a distressing, persistent, subjective sense of physical, emotional and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning.[2] Over 80% of patients treated with chemotherapy experience fatigue, and symptoms may persist for months to years in approximately one fourth of the patients.[1,3] Cancer-related fatigue is associated with psychological distress, limited ability to perform daily activities and reduced quality of life (QoL).[1]

The pathogenesis of cancer-related fatigue is complex and multifactorial, including biological, psychological, and physiological factors.[4] Physiological fatigue can be defined as the loss of voluntary force-producing capacity during exercise.[5,6] This loss can both, and simultaneously, have a central or peripheral origin.[7,8] Central muscle fatigue may be caused by a failure of drive from the central nervous system, resulting in a loss of voluntary force production,[8] and can be assessed using a twitch interpolation technique.[9] Peripheral muscle fatigue may be caused by changes in intracellular ion levels that negatively impact contractile force[10,11] and can be assessed by measuring a change in the force in response to electrical stimulation. Besides a decline in force during contractions, peripheral muscle fatigue can also be characterized by a decline in rate of force development and relaxation.[12] Measurements of the above-mentioned muscle contractile properties in patients with cancer can therefore help to understand the origin of cancer-related fatigue.

Prinsen et al[13] examined the role of peripheral and central muscle fatigue in fatigued and non-fatigued patients with cancer post-treatment and found no support of their hypothesis that cancer-related fatigue is characterized by low peripheral and high central muscle fatigue. In contrast, previous studies showed that cancer and its treatment affect both muscle mass and muscle strength,[14,15] which both have been associated with higher cancer-related fatigue.[16,17] Chemotherapy may induce mitochondrial dysfunction contributing to muscle atrophy.[18-20] Muscle atrophy may further be exacerbated by physical inactivity and decreased nutritional intake.[21] To the best of our knowledge, it is yet unclear how cancer and its treatment can affect contractile properties of the muscle and how this relates to cancer-related fatigue. Previous studies showed that exercise interventions during cancer treatment can counteract losses in muscle mass and strength, and limit cancer-related fatigue.[22-24] However, the role of exercise on muscle contractile properties in patients with cancer is currently unknown.

It is currently unknown whether it is feasible to repeatedly measure contractile muscle properties in patients with cancer receiving chemotherapy. Therefore, the first aim of this randomized controlled pilot trial was to evaluate the feasibility of measuring muscle contractile properties with electrical stimulation of the quadriceps muscle in patients with cancer. The second aim was to collect preliminary data on whether (and to which extent) adjuvant chemotherapy results in deterioration of contractile muscle properties, and whether (and to which extent) a combined aerobic and resistance exercise intervention can prevent the expected chemotherapy-induced deteriorations in contractile muscle properties. The final aim was to explore whether changes in muscle contractile properties were associated with changes in perceived fatigue.

2 | METHODS

2.1 | Design and participants

This randomized controlled pilot trial is approved by the medical ethics committee (VUmc: 2012/430) and registered in the Dutch Trial Registry in 2013 (NTR4105). Thirty adult patients with histologically confirmed colon (stage II/III) or breast (stage I/II/III) cancer, scheduled to receive (neo) adjuvant chemotherapy were recruited from the Amsterdam UMC (location VU University Medical Center, both cancer types), Amstelland Hospital (both cancer types), and the Netherlands Cancer Institute/Antoni van Leeuwenhoek Hospital (colon cancer), The Netherlands. Patients were excluded if they: (a) were not able to perform basic activities of daily living such as walking or cycling, (b) showed cognitive disorders or severe emotional instability, (c) suffered from other disabling co-morbidities that hamper physical activity, (d) were unable to read Dutch, (e) received prior or concurrent anticancer therapy, (f) received prednisone up to 6 months before diagnosis, (g) were insulin dependent.

2.2 | Procedure

All patients were screened for eligibility during weekly multidisciplinary meetings at the hospitals. If patients met the inclusion criteria, the treating medical oncologist informed the patient about the study and asked permission to share contact information with the research staff. The researcher discussed participation and answered potential questions by telephone. If the patient agreed to participate, an appointment was made for the baseline assessment before the start of chemotherapy treatment (T0). Participants signed the informed consent form prior to the start of the study assessment. After baseline assessment, patients were randomized into the exercise intervention group or the waitlist-control group. An independent researcher performed the randomization by using a table of random numbers generated from statistical software using

block randomization, which was stratified by cancer type and in case of breast cancer human epidermal growth factor receptor-2 (HER2-receptor) status. Allocation sequence was concealed from the clinical and research staff.

The exercise intervention group received an evidence-based resistance and endurance exercise intervention[22] during the first half of chemotherapy treatment (9-12 weeks), during which the waitlist-control group received usual care that did not include structured exercise training. After the first half of chemotherapy treatment, follow-up assessment was performed (T1). Subsequently, the waitlist-control group was offered the exercise intervention during the second half of chemotherapy treatment. This study design allowed all patients to receive an evidence-based exercise intervention during chemotherapy, as an increasing number of patients show interest in participating in an exercise intervention and prefer not to be randomized to a non-exercise control group. Both visits to the laboratory were synchronized with chemotherapy cycles and consequently, T0 and T1 were planned 1 to 4 days before intravenous chemotherapy administration of the first and third (3-week cycle) or fourth (2-week cycle) administration.

2.3 | Exercise intervention

The exercise intervention included twice weekly, a 60-minute exercise session under supervision of a physiotherapist specifically educated to train patients with cancer.[22] During the first visit to the physiotherapy practice, a steep ramp test[25,26] and indirect 1-repetition maximum (1RM) tests were performed to determine the maximal short exercise capacity and muscle strength, respectively. The steep ramp and 1RM tests were repeated every three weeks to ensure adequate training intensities of the aerobic and resistance exercises. Each exercise session included warming-up exercises for 5 minutes (ie, cycling at low workload and/or light-intensity resistance exercises), followed by resistance exercises of 6 large muscle groups for 20 minutes. These exercises started with 2 series of 12 repetitions at 70% 1RM and increased gradually to 8 repetitions at 80% 1RM. Prescribed exercises were the vertical row (longissimus, biceps brachii, and rhomboideus), leg press (quadriceps, glutei, and gastrocnemius), bench press (pectoralis major and triceps), pull over (pectoralis, triceps brachii, deltoideus, and trapezius), abdominal crunch (rectus abdominis), and lunge (quadriceps, glutei, and hamstrings). Endurance exercises were performed on ergometers (eg, cycling supplemented with walking, rowing, cross-trainer exercise for variation) for 30 minutes (with a minimal duration of 10 minutes per exercise), at an intensity of 50%-80% of the maximal workload as estimated by the steep ramp test,[25,26] and adjusted to a score of 12-15 on the Borg rating of perceived exertion scale (6 to 20). This exercise intervention was shown to be effective in maintaining physical fitness and quality of life and limiting fatigue in women with breast cancer receiving adjuvant chemotherapy.[22] Detailed information on the exercise prescriptions is presented elsewhere.[22,27] Physiotherapists kept an attendance log for each participant. The availability of flexible training hours and the possibility to join a rehabilitation group differed per physiotherapy practice.

2.4 | Assessments

During the visit to the laboratory, height was measured using a SECA scale attached to the wall, rounded up to two decimals (m), body weight was measured using a digital scale, rounded up to one decimal (kg) and Body Mass Index (BMI) was calculated from measured body height and weight. Thickness of skin folds at biceps, triceps, subscapular, and suprailiac was measured at the left side of the body (Harpenden Skinfold Caliper HSK-BI) twice. The average of both measurements was used to estimate fat percentage using the percentage fat estimates table by Durnin and Womersley, providing age and gender-specific fat percentages from sum of skinfolds.[28] Demographic characteristics (age, gender, marital status, education level, smoking status, and employment status), comorbidities (cardiovascular disease, high blood pressure, osteoporosis, asthma, neurological disease, gastrointestinal disease, psychiatric problems, degenerative disease, and migraine), and sports history (dichotomized into "yes" in case of weekly participation and "no" otherwise) were collected using questionnaires and clinical characteristics (cancer type and stage) were collected via medical records.

Muscle contractile properties of the right quadriceps muscle were determined using a custom-built dynamometer, adjustable for upper leg length, and included maximal voluntary contraction (MVC), % voluntary activation, rate of force development and relaxation, and muscle fatigability.[29] For one patient, measures of contractile properties of the quadriceps of the left leg were investigated due to previous injury of the right knee. Patients sat with 90° angles between upper and lower legs and between upper body and legs. The distal part of patients' shank was strapped to a force transducer (KAP-E KL0.2; AST GmbH, Dresden, Germany; 27.5 centimeter below the knee joint), measuring isometric force. Straps were used to restrain the hips and shoulders. Real-time force applied to the force transducer was displayed on a computer monitor and digitally stored on a computer disk.

Following warming-up (several knee extensions against low load), patients were first were asked to maximally exert extension force for 5 seconds to determine MVC. Two attempts were made, separated by 3 minutes rest to avoid muscle fatigue. MVC torque was determined as the peak force from the stable part of the force signal. A third

attempt was made when the MVC force of the two attempts differed by more than 5%. Next, doublets (two electrical pulses, 10 ms in between) were applied using surface electrodes placed on the proximal and distal portions of the quadriceps muscle.[30] Maximal stimulation current was determined by applying doublets to the relaxed muscle and increasing current in steps of 10-50 milli-ampere (mA) until increasing current did not result in additional force enhancement. This current was applied to the fully relaxed muscle and during MVC. The force enhancement due to the superimposed doublet during MVC was expressed as a percentage of the force obtained when the doublet was applied to the relaxed muscle and subsequently subtracted from 100%, resulting in a measure of voluntary activation.[31] The maximal rate of force development (N/s) was determined by the force-time integral during electrically stimulated contractions using doublets with maximal stimulation current. Half-relaxation time (seconds) was defined as the time from peak doublet force until the muscle had relaxed to 50% of the peak force.

To evaluate the fusion effect of the stimulation pulses at different frequencies (stimulation frequency-force relationship), we measured the force in response to a 20, 50, and 150 Hz stimulation that was applied for 1500 ms. Optimal stimulation current was determined using 150 Hz stimulation by increasing the current in steps of 10-50 mA until the force reached 40%-50% MVC. The ratio between the maximum force in response to the 20 Hz and 50 Hz stimulation was calculated because changes in this ration are indicative for different forms of peripheral muscle fatigue. If the muscle is fatigued, there is a slower muscle relaxation, which may counteract the fatigue-induced force decline at lower stimulation frequencies (20 Hz), due to an increased force fusion.[32] This is expected to lead to an increase in the 20/50 Hz ratio. In contrast, as a result of low-frequency fatigue, force losses could also be relatively higher at low stimulation frequencies. This would result in a decrease of the 20/50 Hz ratio. Low-frequency fatigue may be dependent on fiber type composition, with fast muscles being more susceptible.[33] Finally, muscle fatigability (ie, a loss of maximum or potential performance of the muscle[32]) was assessed by fatiguing the muscle by a 3 minute-series of muscle contraction evoked by electrical stimulations (50 Hz; 1-second pulse-train followed by 1-second rest). Maximal force of the last contraction was expressed as a percentage of the maximal force response of the first contraction. Muscle force recovery was assessed 6 minutes after the fatigue protocol by means of a MVC, which was compared to the MVC response of the unfatigued muscle.

Perceived fatigue was measured using the Multidimensional Fatigue Inventory (MFI). The MFI is a valid 20-item questionnaire measuring 5 dimensions of fatigue: general fatigue, physical fatigue, reduced activity, reduced motivation, and mental fatigue.[34] Participants were asked to indicate, on a 1-5 scale, to what extent the particular item applied to them, with a maximum sum score of 20 points per subscale. For this study, we investigated the effects on general and physical fatigue as these are most responsive to exercise.[1,35]

2.5 | Analyses of feasibility

We evaluated the feasibility of assessing muscle contractile properties in patients undergoing chemotherapy by describing the number of patients that completed the different assessments, as well as the reasons for not willing or being able to proceed with the assessments. Furthermore, we will show typical examples of force-time signals, to illustrate specific problems experienced during force assessments.

2.6 | Statistical analyses of preliminary effects

Demographic and clinical characteristics of patients who completed T0 and T1 assessments were summarized by means and standard deviations or percentages. Linear regression analyses were used to evaluate within-group change and between-group differences in muscle contractile properties and perceived fatigue, represented by the regression coefficients and corresponding 95% confidence intervals (CI). We used a threshold of 10% as indicator a potential relevant difference. For perceived fatigue, a change of two points is considered clinically relevant.[36]

Subsequently, we calculated the Pearson correlation coefficient (r_p) to study the association of changes in muscle contractile properties (of those potentially relevant) with changes in perceived fatigue. For this analysis, we used residual change scores representing change scores adjusted for baseline values. Positive and negative correlations between 0.5 and 0.69 were considered moderate and correlations $\geq$0.7 were considered strong.[37] All analyses were based on complete cases and were conducted in SPSS (IBM SPSS Statistics 22).

3 | RESULTS

3.1 | Participants

Between September 2014 and May 2017, 30 of 103 eligible patients were recruited (response rate 29%; Figure 1). Thirteen participants randomized to the intervention group (81%) and nine participants randomized to the control group (64%) completed follow-up assessment. Reasons for discontinuation included complications of the cancer treatment (n = 3), disliking being randomized to the

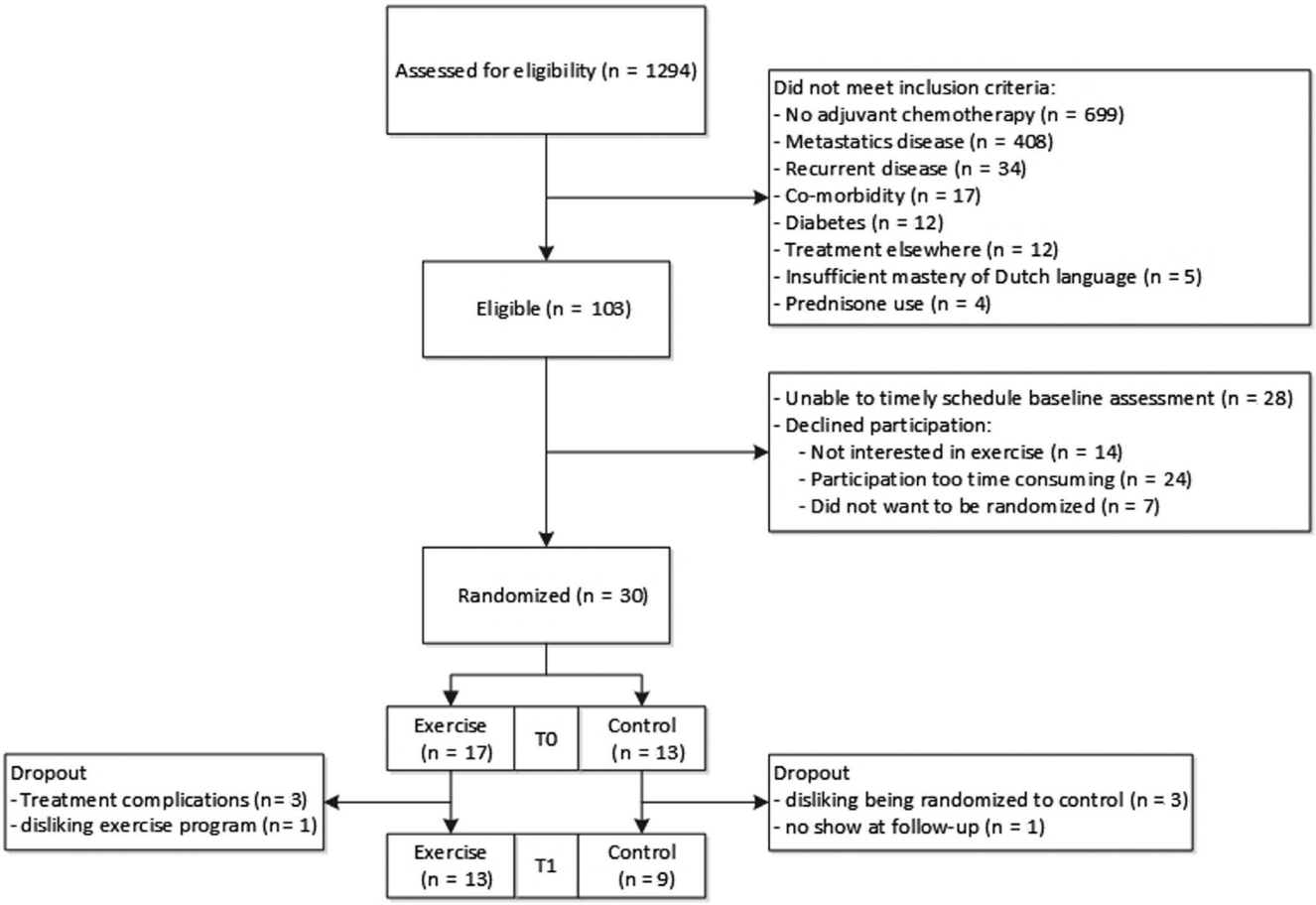

FIGURE 1 Flowchart of patient inclusion

waitlist-control group (n = 3), and disliking the exercise program (n = 1). One patient did not show up for follow-up assessment and the research team was not able to contact the patient before the next intravenous chemotherapy session was scheduled. Patients were on average 56 (standard deviation [SD] = 13) years old and 82% of participants were female (Table 1). On average, patients attended 74% of prescribed exercise sessions with comparable average attendance rates for patients with colon (72%) and breast cancer (75%).

3.2 | Feasibility of assessing muscle contractile properties

3.2.1 | Completion of assessments

We were not able to assess muscle contractile properties for two out of 30 patients at baseline and two out of 22 at follow-up, due to technical problems. Another follow-up assessment could not be performed because the patient felt too tired. Consequently, data from 19 patients were available at follow-up.

Maximal voluntary contraction was determined for 28 patients at baseline and 19 at follow-up. All patients obtained their MVC within three attempts. During the process of determining the maximal stimulation current for assessing % voluntary activation, two patients at baseline and four at follow-up did not want to proceed because they perceived the stimulation as uncomfortable. As a consequence, rate of force development and halve relaxation time could be determined for 26 and 17 patients at baseline and follow-up, respectively. At follow-up, we could not determine the force enhancement in response to the superimposed doublet in two patients (fainting [n = 1] and stimulation uncomfortable [n = 1]). As a consequence, % voluntary activation was calculated for 26 at baseline and 15 patients at follow-up.

During the process of determining the optimal stimulation current for assessing the fusion effect of different stimulation pulses (ie, 150 Hz stimulation), six patients at baseline and nine at follow-up did not want to proceed due to discomfort of the stimulation. Additionally, six patients at baseline and four at follow-up did not want to proceed with the 50 and 20 Hz stimulations. As a consequence, the 20/50 Hz ratio could be calculated for 14 patients at baseline and four at follow-up.

TABLE 1 Demographic and clinical characteristics of patients who completed the study (n = 22)

	Intervention (n = 13)	Control (n = 9)
Age, mean (SD)	56.2 (13.3)	56.9 (13.8)
Gender, n (%) female	11 (84.6)	7 (77.8)
BMI, mean (SD)	25.9 (6.7)	27.1 (4.4)
% body fat, mean (SD)	37.5 (6.3)	38.5 (9.2)
Marital status, n (%) married	8 (61.5)	7 (77.8)
Education level, n (%)		
Low	1 (7.7)	4 (44.4)
Middle	6 (46.2)	2 (22.2)
High	5 (38.5)	3 (33.3)
Missing	1 (7.7)	—
Employment status, n (%) working	8 (61.5)	4 (44.4)
Smoking status, n (%) non-smoking	12 (92.3)	9 (100)
Sports history, n (%) yes	8 (61.5)	7 (77.8)
Co-morbidities, n (%) yes	6 (46.2)	5 (55.6)
Cancer type, n (%)		
Breast cancer	7 (53.8)	5 (55.6)
Colon cancer	5 (46.2)	4 (44.4)

Abbreviations: BMI, body mass index; SD, standard deviation.

Finally, six patients at baseline did not want to proceed with the muscle fatigability assessment. As a result, muscle fatigability and muscle force recovery could only be assessed for eight patients at baseline and four patients at follow-up.

3.2.2 | Description of force signals

Figure 2A shows a typical force signal in response to a doublet, demonstrating a clear peak in force and a complete muscle relaxation. In some patients, the force signal showed two peaks (Figure 2B), which may have resulted in an underestimation of the peak force in response to a doublet. Other patients had difficulties with fully relaxing their muscle after the stimulation, which may have resulted in a longer half-relaxation time.

For the assessment of the voluntary activation, it is important that the MVC is stable before the superimposed stimulus is applied (Figure 2C). Sixty percent of patients were able to reach a force corresponding to 90% of their MVC directly before applying the stimulation, however, this force often fluctuated (Figure 2D). As a result, the voluntary force calculation may be overestimated or underestimated, depending on the exact timing of the doublet.

Figure 2E shows a typical example of the muscle force in response to a series of fatiguing 50 Hz stimulations, with the patient fully relaxing the muscle during the 1-second rest intervals. Some patients were not able to fully relax during and between stimulation-trains (Figure 2F), resulting in invalid estimations of muscle fatigability.

3.3 | Effects of exercise on muscle contractile properties and perceived fatigue

The rate of force development showed an average increase of 935 (95% confidence interval [CI] = −665; 2535) N/s in the exercise intervention group and an average decrease of −393 (95% CI = −1185; 397) N/s in the control group, resulting in a between-group difference of 1192 (95% CI = −335; 2739) N/s (Table 2). Within- and between-group differences in MVC, % voluntary activation, and half-relaxation time did not show potential relevance (Table 2).

Both the intervention and the control group showed significant and clinically relevant increases in perceived fatigue, but there were no significant or clinically relevant differences in effect between the exercise intervention and the control group on general fatigue (β = 1.3, 95% CI = −1.7; 4.4) and physical fatigue (β = −0.3, 95% CI = −3.8; 3.2, Table 2).

3.4 | Relationship between contractile muscle properties and perceived fatigue

A larger increase in the rate of force development was moderately correlated with larger decreases in perceived general (r_p = −0.54, P = .04) and physical (r_p = −0.59, P = .02) fatigue (Figure 3).

4 | DISCUSSION

The current study investigating muscle contractile properties of the quadriceps muscle of patients with cancer had three important findings. First, maximal electrical stimulations with a short duration (10 ms; doublets) were feasible in patients with cancer, allowing the assessment of % voluntary activation, and rate of force development and relaxation. However, maximal electrical stimulations with a longer duration (1500 ms) were generally not feasible, hampering the assessments of the 20/50 Hz ratio and muscle fatigability. Second, the rate of force development of the quadriceps muscle decreased during (neo)adjuvant chemotherapy, while it seems increased by a combined

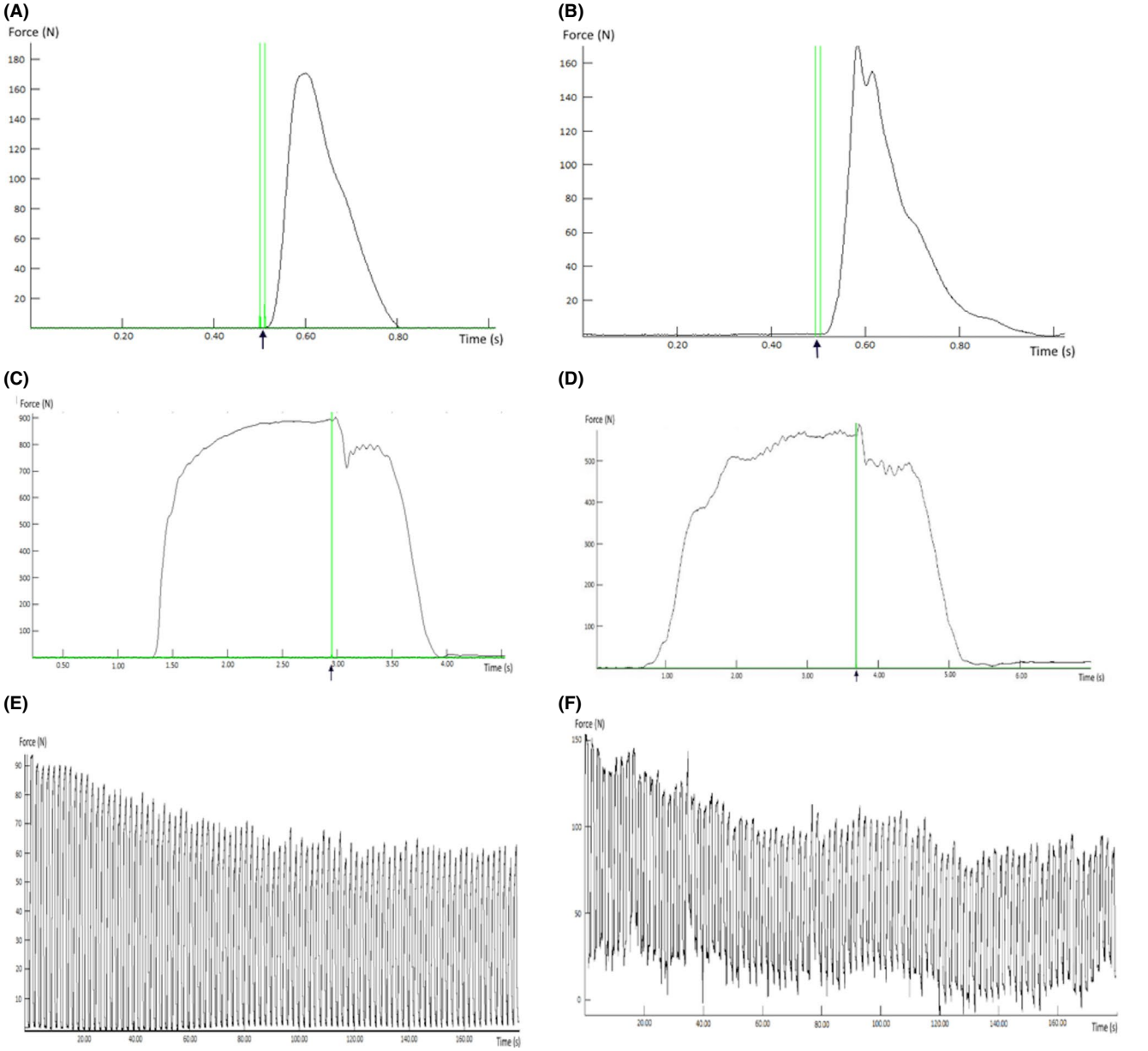

FIGURE 2 Examples of force signals. Arrows indicate timing of stimulation (A-D). A, force signal in response to a doublet for the assessments of rate of force development and relaxation; B, force signal in response to a doublet, showing two peaks and irregular relaxation; C, force signal in response to superimposed stimulation (doublet) for the assessment of % voluntary activation; D, force signal in response to superimposed stimulation, showing fluctuations in force before applying the superimposed stimulation; E, force signal in response to a series of fatiguing electrical contractions with 1-second rest intervals; F, force signal in response to a series of fatiguing electrical contractions, showing incomplete relaxation during and between electrical stimulation trains

resistance and endurance exercise intervention. Third, we found that changes in the rate of force development were moderately, inversely correlated with changes in perceived fatigue. Due to the small sample size and the explorative character of this pilot study, our findings should be viewed more as hypothesis-generating than hypothesis-testing. Therefore, we would like to emphasize the effect sizes rather than statistical significance.

4.1 | Feasibility

All patients were able to deliver their MVC within three attempts, and most patients tolerated the process of determining the maximal stimulation current when doublets were applied to their fully relaxed muscle, as well as absorbing a doublet during their MVC. Therefore, it was feasible to assess patients' MVC, % voluntary activation, rate

TABLE 2 Baseline and follow-up values of fatigue and contractile muscle properties of patients who completed the study

	Intervention				Control				
	Number of patients	Baseline, Mean (SD)	Follow-up, Mean (SD)	Within group change (95% CI)	Number of patients	Baseline, Mean (SD)	Follow-up Mean (SD)	Within-group change (95% CI)	Between-group difference (95% CI)
MFI general fatigue[a](points)	11	9.6 (4.5)	13.6 (4.1)	4.2 (1.7; 6.7)*	9	11.0 (5.1)	13.4 (5.3)	2.4 (0.4; 4.5)*	1.3 (−1.7; 4.4)
MFI physical fatigue[a](points)	11	9.6 (4.2)	12.6 (4.6)	3.0 (0.3; 5.7)*	9	10.3 (4.9)	13.4 (5.1)	3.1 (−5.8; 0.4)*	−0.3 (−3.8; 3.2)
MVC (N)	10	459.9 (224.4)	474.6 (179.0)	14.7 (−38.6; 68.1)	9	506.2 (234.9)	511.3 (240.9)	5.1 (−56.6; 66.8)	3.4 (−68.0; 47.8)
Voluntary activation (%)	7	92.3 (5.8)	90.5 (12.4)	−1.9 (−11.9; 8.2)	8	90.5(6.5)	86.3 (9.7)	−4.2 (−10.6; 2.2)	2.4 (−8.6; 13.4)
Rate of force development (N/s)	8	3920.8 (2243.8)	4855.9 (2638.5)	935.1 (−664.7; 2534.8)	9	4532.3 (2286.8)	4138.2 (1868.5)	−393.0 (−1185.1; 397.0)	1192.2 (−355; 2739.5)
Half relaxation time (ms)	8	94.0 (12.8)	88.3(18.4)	−5.7 (−15.2; 3.7)	9	90.0 (15.2)	83.9 (20.8)	−6.1 (−16.3; 4.1)	2.4 (−10.9; 15.7)
20/50 Hz ratio	3	0.76 (0.05)	0.76 (0.03)	0.005 (−0.12; 0.13)	2	0.80 (0.06)	0.76 (0.03)	−0.04 (−0.37; 0.28)	0.02 (−0.12; 0.15)
Muscle fatigability[b](%)	3	54.7 (7.2)	57.8 (18.7)	N/A	1[d]	53.8	57.4	3.6	N/A
MVC 6 min after fatigue protocol[c](%)	3	89.4 (5.4)	90.4 (8.4)	0.98 (−31.5; 44.3)	1[d]	96.5	95.6	−0.9	N/A

Abbreviations: CI, confidence interval; Hz, Hertz; MFI, multidimensional fatigue inventory; ms, seconds; MVC, maximal voluntary contraction; N, newton; N/A, not assessed; SD, standard deviation. [a]Higher score is more fatigued. [b]Force in response to the last stimulation as proportion of the force in response to the first stimulation. [c]Force as proportion of MVC at the start of the protocol. [d]Not possible to calculate SD due to number of patients = 1. *P < .05.

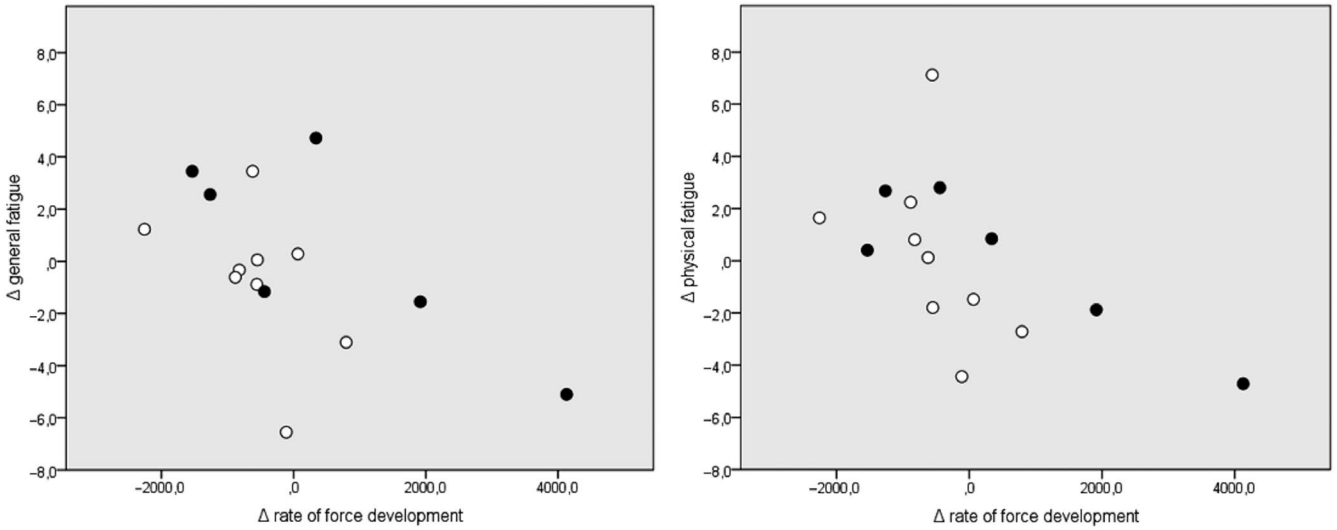

FIGURE 3 F Relationship between changes in rate of force development and changes in perceived fatigue. Black dots = exercise intervention group, white dots = control group; r_p = Pearson correlation coefficient; * $P < .05$

of force development, and half-relaxation time. However, when increasing the duration of the electrical stimulation to 1500 ms to assess the fusion effect of stimulation pulses at different frequencies as well as muscle fatigability, the majority of the patients could not tolerate the process of determining the optimal stimulation current (150 Hz stimulation) to reach 40%-50% MVC. In contrast, previous studies have successfully completed comparable assessments in healthy young adults,[38,39] patients with post-polio syndrome[40] and patients after stroke.[41] It is unclear why these assessments were not feasible in patients with cancer. The assessments may be too burdensome in the precarious period of recent diagnosis and treatment of cancer. It is difficult to disentangle whether patients could not tolerate the electrical stimulations of 1500 ms at 150 Hz (optimal current determination) due to the stimulations itself or due to the accumulation of all measurement in the full protocol. Therefore, we recommend that future studies limit the number of electrically induced muscle assessments.

4.2 | Muscle contractile properties

The average voluntary activation of 91% (range 82%-98%) was somewhat lower than the 94% previously found in a healthy untrained population, while healthy trained individuals can fully activate most muscle groups.[29] The present results indicate that patients in the control group lose on average 4.2% of their capacity for maximal muscle activation during 9-12 weeks of chemotherapy, while patients in the intervention group lose on average 1.9%. This may suggest an increase in central muscle fatigue during cancer treatment which may (partly) be counteracted by exercise. The clinical relevance of these changes in % voluntary activation needs to be addressed in future studies. It should be noted that the assessment of % voluntary activation is difficult, as it is challenging for untrained individuals and patients to generate maximal force and keep this force stable while knowing that a stimulus will be applied.

Notably, we found that the rate of force development, indicative for peripheral muscle fatigue, may reduce during chemotherapy, which may reflect a change in fiber-type distribution toward type I (slow-twitch and oxidative) muscle fibers. This finding is in line with previous studies showing that cancer and cancer treatment result in greater atrophy in type II (fast-twitch and glycolytic) muscle fibers than in type I muscle fibers,[42] although a recent study showed that chemotherapy also affects the cross-sectional area of type I muscle fibers in addition to type II fibers most likely as a consequence of deconditioning.[43] Our preliminary data on force development during electrical stimulation suggest that a combined resistance and endurance exercise intervention may preserve, or even improve, the contractile properties of type II muscle fibers. The finding of a faster force development is not reflected in the muscle relaxation time. One explanation may be potential measurement bias caused by involuntary (electrical) activity when patients have difficulties in fully relaxing the muscle.[29]

The rate of force development, but not % voluntary activation, was correlated with perceived fatigue. The finding that an increase in the rate of force development was associated with a decrease in perceived fatigue indicates that maintaining contractile properties of type II muscle fibers may be important to prevent fatigue during chemotherapy. This can be achieved by high-intensity and high velocity exercise programs, such as resistance and sprint exercises.[44] Accordingly, a recent study among patients receiving chemotherapy for breast cancer showed that a 16-week exercise intervention including resistance exercises

and high-intensity interval training maintained or increased cross-sectional area of type II muscle fibers compared to usual care, while both aerobic and resistance exercise combined with high-intensity interval training preserved type I muscle fibers.[43] Additionally, the association between muscle mass and perceived fatigue has been shown previously,[16,43] highlighting the potential of muscle mass as intervention target.

The exercise intervention effect on perceived fatigue was smaller than previously reported in patients with breast and colon cancer undergoing chemotherapy,[22,45-47] which may be related to the shorter intervention period. We chose a shorter intervention period with a waitlist-control group to allow all patients to receive an exercise intervention during chemotherapy, thereby aiming to prevent nonparticipation and dropout. Nevertheless, a few patients in the control group still dropped out due to disliking the randomization outcome. Potential contamination by exercising of patients in the control group may also have underestimated the intervention effects on perceived fatigue. The large interest in exercise was reflected by the high proportion of patients with a history in sports participation, both in the intervention and the control group.

5 | CONCLUSION

With the current measurement protocol, it was feasible to assess % voluntary activation, and rate of force development and relaxation using electrical stimulation. Due to discomfort, it was not feasible to investigate the force-fusion effect of stimulation pulses at different frequencies (the stimulation-frequency force relationship) and muscle fatigability during repetitive stimulation. Based on our preliminary effects of a chemotherapy-induced reduction in the stimulated rate of force development, we hypothesize a change in fiber-type distribution toward type I fibers, which may be attenuated by (resistance) exercise. The increase in the stimulated rate of force development was related to a decrease in perceived fatigue.

6 | PERSPECTIVE

Fatigue is one of the most common and distressing symptoms of cancer and its treatment. The pathogenesis of fatigue is complex and multifactorial. This study focuses on physiological fatigue, defined as the loss of force-producing capacity during exercise. Muscle contractile properties can be examined using electrical stimulation.

The results demonstrate that it was feasible to assess muscle contractile properties using electrical stimulation, except for muscle fatigability which required a 3-minute series of electrical stimulations. Additionally, this study showed that chemotherapy induced a decrease in the rate of force development which may reflect a larger loss in type II muscle fibers relative to type I fibers. This decrease was prevented by a supervised aerobic and resistance exercise program. Moreover, an increase in the rate of force development was related to a decrease in perceived fatigue.

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REFERENCES

1. Hofman M, Ryan JL, Figueroa-Moseley CD, Jean-Pierre P, Morrow GR. Cancer-related fatigue: the scale of the problem. *Oncologist*. 2007;12(Suppl 1):4-10.
2. Berger AM, Mooney K, Alvarez-Perez A, et al. Version 2.2015. *J Natl Compr Canc Netw*. 2015;13(8):1012-1039.
3. Abrahams HJ, Gielissen MF, Schmits IC, Verhagen CA, Rovers MM, Knoop H. Risk factors, prevalence, and course of severe fatigue after breast cancer treatment: a meta-analysis involving 12 327 breast cancer survivors. *Ann Oncol*. 2016;27(6):965-974.
4. O'Higgins CM, Brady B, O'Connor B, Walsh D, Reilly RB. The pathophysiology of cancer-related fatigue: current controversies. *Support Care Cancer*. 2018;26(10):3353-3364.
5. Zwarts MJ, Bleijenberg G, van Engelen BG. Clinical neurophysiology of fatigue. *Clin Neurophysiol*. 2008;119(1):2-10.
6. Bigland-Ritchie B, Jones DA, Hosking GP, Edwards RH. Central and peripheral fatigue in sustained maximum voluntary contractions of human quadriceps muscle. *Clin Sci Mol Med*. 1978;54(6):609-614.
7. Kisiel-Sajewicz K, Davis MP, Siemionow V, et al. Lack of muscle contractile property changes at the time of perceived physical exhaustion suggests central mechanisms contributing to early motor task failure in patients with cancer-related fatigue. *J Pain Symptom Manage*. 2012;44(3):351-361.
8. Van Engelen BG, Kalkman JS, Schillings ML, Van Der Werf SP, Bleijenberg G, Zwarts MJ. Fatigue in neuromuscular disease. *Ned Tijdschr Geneeskd*. 2004;148(27):1336-1341.
9. Gandevia SC. Neural control in human muscle fatigue: changes in muscle afferents, motoneurones and motor cortical drive [corrected]. *Acta Physiol Scand*. 1998;162(3):275-283.
10. Allen DG. Skeletal muscle function: role of ionic changes in fatigue, damage and disease. *Clin Exp Pharmacol Physiol*. 2004;31(8):485-493.
11. Green HJ. Membrane excitability, weakness, and fatigue. *Can J Appl Physiol*. 2004;29(3):291-307.
12. Jones DA, de Ruiter CJ, de Haan A. Change in contractile properties of human muscle in relationship to the loss of power and

slowing of relaxation seen with fatigue. *J Physiol*. 2006;576(Pt 3):913-922.
13. Prinsen H, van Dijk JP, Zwarts MJ, Leer JW, Bleijenberg G, van Laarhoven HW. The role of central and peripheral muscle fatigue in postcancer fatigue: a randomized controlled trial. *J Pain Symptom Manage*. 2015;49(2):173-182.
14. Blauwhoff-Buskermolen S, Versteeg KS, de van der Schueren MAE, et al. Loss of muscle mass during chemotherapy is predictive for poor survival of patients with metastatic colorectal cancer. *J Clin Oncol*. 2016;34(12):1339-1344.
15. Klassen O, Schmidt ME, Ulrich CM, et al. Muscle strength in breast cancer patients receiving different treatment regimes. *J Cachexia Sarcopenia Muscle*. 2017;8(2):305-316.
16. Neefjes ECW, van den Hurk RM, Blauwhoff-Buskermolen S, et al. Muscle mass as a target to reduce fatigue in patients with advanced cancer. *J Cachexia Sarcopenia Muscle*. 2017;8(4):623-629.
17. Kalter J, Kampshoff CS, Chinapaw MJM, et al. Mediators of exercise effects on HRQoL in cancer survivors after chemotherapy. *Med Sci Sports Exerc*. 2016;48(10):1859-1865.
18. Coletti D. Chemotherapy-induced muscle wasting: an update. *Eur J Transl Myol*. 2018;28(2):7587.
19. Barreto R, Waning DL, Gao H, Liu Y, Zimmers TA, Bonetto A. Chemotherapy-related cachexia is associated with mitochondrial depletion and the activation of ERK1/2 and p38 MAPKs. *Oncotarget*. 2016;7(28):43442-43460.
20. Barreto R, Mandili G, Witzmann FA, Novelli F, Zimmers TA, Bonetto A. Cancer and chemotherapy contribute to muscle loss by activating common signaling pathways. *Front Physiol*. 2016;7:472.
21. Al-Majid S, Waters H. The biological mechanisms of cancer-related skeletal muscle wasting: the role of progressive resistance exercise. *Biol Res Nurs*. 2008;10(1):7-20.
22. van Waart H, Stuiver MM, van Harten WH, et al. Effect of low-intensity physical activity and moderate- to high-intensity physical exercise during adjuvant chemotherapy on physical fitness, fatigue, and chemotherapy completion rates: results of the PACES randomized clinical trial. *J Clin Oncol*. 2015;33(17):1918-1927.
23. Stene GB, Helbostad JL, Balstad TR, Riphagen II, Kaasa S, Oldervoll LM. Effect of physical exercise on muscle mass and strength in cancer patients during treatment—a systematic review. *Crit Rev Oncol Hematol*. 2013;88(3):573-593.
24. Buffart LM, Sweegers MG, May AM, et al. Targeting exercise interventions to patients with cancer in need: an individual patient data meta-analysis. *J Natl Cancer Inst*. 2018;110(11):1190-1200.
25. De Backer IC, Schep G, Hoogeveen A, Vreugdenhil G, Kester AD, van Breda E. Exercise testing and training in a cancer rehabilitation program: the advantage of the steep ramp test. *Arch Phys Med Rehabil*. 2007;88(5):610-616.
26. Stuiver MM, Kampshoff CS, Persoon S, et al. Validation and refinement of prediction models to estimate exercise capacity in cancer survivors using the steep ramp test. *Arch Phys Med Rehabil*. 2017;98(11):2167-2173.
27. van Waart H, Stuiver MM, van Harten WH, Sonke GS, Aaronson NK. Design of the Physical exercise during Adjuvant Chemotherapy Effectiveness Study (PACES): a randomized controlled trial to evaluate effectiveness and cost-effectiveness of physical exercise in improving physical fitness and reducing fatigue. *BMC Cancer*. 2010;10:673.
28. Durnin JV, Womersley J. Body fat assessed from total body density and its estimation from skinfold thickness: measurements on 481 men and women aged from 16 to 72 years. *Br J Nutr*. 1974;32(1):77-97.
29. de Haan A, de Ruiter CJ, van Der Woude LH, Jongen PJ. Contractile properties and fatigue of quadriceps muscles in multiple sclerosis. *Muscle Nerve*. 2000;23(10):1534-1541.
30. Behm DG, St-Pierre DM, Perez D. Muscle inactivation: assessment of interpolated twitch technique. *J Appl Physiol (1985)*. 1996;81(5):2267-2273.
31. Altenburg TM, de Ruiter CJ, Verdijk PW, van Mechelen W, de Haan A. Vastus lateralis surface and single motor unit electromyography during shortening, lengthening and isometric contractions corrected for mode-dependent differences in force-generating capacity. *Acta Physiol (Oxf)*. 2009;196(3):315-328.
32. Jones D, Round J, de Haan A. *Skeletal Muscle from Molecules to Movement*. London, UK: Churchill Livingstone Elsevier; 2004.
33. Rijkelijkhuizen JM, de Ruiter CJ, Huijing PA, de Haan A. Low-frequency fatigue is fibre type related and most pronounced after eccentric activity in rat medial gastrocnemius muscle. *Pflugers Arch*. 2003;447(2):239-246.
34. Smets EM, Garssen B, Bonke B, De Haes JC. The Multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. *J Psychosom Res*. 1995;39(3):315-325.
35. van Vulpen JK, Peeters PH, Velthuis MJ, van der Wall E, May AM. Effects of physical exercise during adjuvant breast cancer treatment on physical and psychosocial dimensions of cancer-related fatigue: a meta-analysis. *Maturitas*. 2016;85:104-111.
36. Purcell A, Fleming J, Bennett S, Burmeister B, Haines T. Determining the minimal clinically important difference criteria for the Multidimensional Fatigue Inventory in a radiotherapy population. *Support Care Cancer*. 2010;18(3):307-315.
37. Mukaka MM. Statistics corner: a guide to appropriate use of correlation coefficient in medical research. *Malawi Medical Journal*. 2012;24(3):69-71.
38. Morse CI, Wust RC, Jones DA, de Haan A, Degens H. Muscle fatigue resistance during stimulated contractions is reduced in young male smokers. *Acta Physiol (Oxf)*. 2007;191(2):123-129.
39. Wust RC, Morse CI, de Haan A, Rittweger J, Jones DA, Degens H. Skeletal muscle properties and fatigue resistance in relation to smoking history. *Eur J Appl Physiol*. 2008;104(1):103-110.
40. Voorn EL, Beelen A, Gerrits KH, Nollet F, de Haan A. Fatigue resistance of the knee extensor muscles is not reduced in post-polio syndrome. *Neuromuscul Disord*. 2013;23(11):892-898.
41. Horstman AM, Gerrits KH, Beltman MJ, Koppe PA, Janssen TW, de Haan A. Intrinsic properties of the knee extensor muscles after subacute stroke. *Arch Phys Med Rehabil*. 2010;91(1):123-128.
42. Toth MJ, Callahan DM, Miller MS, et al. Skeletal muscle fiber size and fiber type distribution in human cancer: effects of weight loss and relationship to physical function. *Clin Nutr*. 2016;35(6):1359-1365.
43. Mijwel S, Cardinale DA, Norrbom J, et al. Exercise training during chemotherapy preserves skeletal muscle fiber area, capillarization, and mitochondrial content in patients with breast cancer. *FASEB J*. 2018;32(10):5495-5505.
44. Wilson JM, Loenneke JP, Jo E, Wilson GJ, Zourdos MC, Kim JS. The effects of endurance, strength, and power training on muscle fiber type shifting. *J Strength Cond Res*. 2012;26(6):1724-1729.

45. van Waart H, Stuiver MM, van Harten WH, et al. Recruitment to and pilot results of the PACES randomized trial of physical exercise during adjuvant chemotherapy for colon cancer. *Int J Colorectal Dis*. 2018;33(1):29-40.
46. Van vulpen JK, Velthuis MJ, Steins bisschop CN, et al. Effects of an exercise program in colon cancer patients undergoing chemotherapy. *Med Sci Sports Exerc*. 2016;48(5):767-775.
47. Travier N, Velthuis MJ, Steins Bisschop CN, et al. Effects of an 18-week exercise programme started early during breast cancer treatment: a randomised controlled trial. *BMC Med*. 2015;13:121.

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