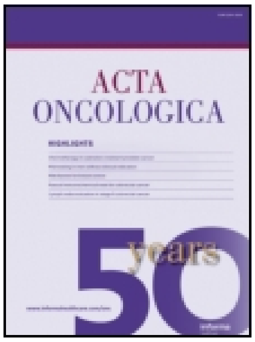

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ORIGINAL ARTICLE

Lean body mass and muscle function in head and neck cancer patients and healthy individuals – results from the DAHANCA 25 study

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Abstract

Introduction. Loss of lean body mass is common following radiotherapy in patients with head and neck squamous cell carcinoma (HNSCC) and may reduce maximal muscle strength and functional performance. However, the associations between lean body mass, muscle strength and functional performance are unclear and no studies in HNSCC patients have compared the levels of these variables to the levels seen in healthy individuals. *Purpose.* The purpose of the present study was to investigate the associations between lean body mass, maximal muscle strength and functional performance in HNSCC patients and to compare the levels of these variables after radiotherapy and after progressive resistance training with the levels in healthy individuals. *Material and methods.* Lean body mass (dual energy X-ray absorptiometry), maximal muscle strength (isokinetic dynamometry) and functional performance (10 m max gait speed, 30 s chair rise, 30 s arm curl, stair climb) from HNSCC patients from the DAHANCA 25 trials and data from 24 healthy individuals were included. *Results.* Lean body mass and maximal muscle strength were significantly associated according to the gender and age-adjusted linear regression model ($p < 0.0001$). In addition, maximal muscle strength were associated with 30 s arm curl performance, 10 m max gait speed and 30 s chair rise ($p < 0.0001$). Multiple regression analyses showed that HNSCC patients expressed significant lower levels of the investigated variables after radiotherapy than healthy individuals ($p < 0.0001$), and that all differences were evened out after training. *Conclusions.* Significant associations were found between lean body mass, maximal muscle strength and functional performance in HNSCC patients. Patients expressed lower levels of these variables compared with healthy individuals, suggesting that lean body mass is a clinically relevant health factor in HNSCC patients.

Following radiotherapy, patients with head and neck squamous cell carcinoma (HNSCC) experience considerable side effects such as dysphagia, xerostomia and mucositis. Consequently, the majority of patients experience a weight loss of 6–12% of pre-treatment body weight [1–3]. This weight loss may persist for more than two years post-treatment [4,5] and has been shown to negatively impact survival in HNSCC patients [6,7]. Moreover, studies show that up to 72% of the weight loss following radiotherapy in HNSCC patients is lean body mass [1,8].

In the healthy elderly population loss of lean body mass (sarcopenia) is strongly associated with decreased muscle strength and further associations are reported between sarcopenia and functional impairment, disability, increased risk of falls and all-cause mortality [9–13]. This strongly emphasizes the clinical relevance of building or maintaining lean body mass in elderly individuals.

The loss of lean body mass in HNSCC patients may be considered to be of clinical relevance if it can be documented that loss of lean body mass leads

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to a loss of physical function. Only few studies on the consequences of reduced lean body mass in HNSCC patients have been published [1,14,15] and they report contradictory findings on the associations between lean body mass, hand grip strength and functional performance [1,14]. In addition, most trials in HNSCC patients assess functional (or physical) performance by patient reported questionnaires [16], while the association between outcomes of such questionnaires and objectively assessed functional performance in HNSCC patients remains uninvestigated.

Previously, we found that progressive resistance training significantly increased lean body mass, maximal muscle strength and functional performance following radiotherapy in HNSCC patients [2,17]. However, it is undefined how the levels of lean body mass, strength and functional performance in patients before or after training, compare to the levels of a healthy population. Thus, to understand the clinical relevance of lean body mass in HNSCC patients, it is evident to study both the associations between lean body mass, maximal muscle strength and functional performance in the same cohort of HNSCC patients as well as compare the levels of these variables to the levels of healthy individuals. Consequently, the purpose of the present study was to: 1) investigate the associations between lean body mass, maximal muscle strength and functional performance; and 2) and compare baseline and post-training values of these variables of HNSCC patients to values of healthy individuals.

It was hypothesized that lean body mass, maximal muscle strength and functional performance would be positively associated in HNSCC patients. Furthermore, HNSCC patients were expected to express significantly lower levels of these variables at baseline following radiotherapy than healthy individuals, and that increased levels post-training would counterbalance this difference. Thus, lean body mass was expected to be a highly clinically relevant factor.

Material and methods

Setting and patients

HNSCC patients. Data from patients enrolled in DAHANCA 25A and 25B trials were included in this study. The DAHANCA 25A is a single center, randomized, non-controlled trial, investigating the feasibility of 12 weeks of progressive resistance training in HNSCC patients. The DAHANCA 25B is a multicenter, randomized trial investigating the effect of 12 weeks of progressive resistance training on lean body mass in HNSCC patients. All patients had received primary radiotherapy prescribed with curative intent according to the DAHANCA guidelines (www.dahanca.dk). Full details on both trials are presented elsewhere [2,17].

Baseline data on body composition, maximal muscle strength and functional performance from 66 patients from the DAHANCA 25A ($n = 25$) and 25B ($n = 41$) trials were included. The two groups of the 25A trial (training with dietary supplementation vs. training with placebo supplementation) and the two groups of the 25B trial (early vs. delayed onset of training following radiotherapy) all engaged in the same 12-week progressive resistance training protocol, and post-training data of the 55 patients completing the entire training intervention were included in the present study. Due to the designs of the 25A and 25B trials, the intervention was not entirely identical between groups with regards to nutritional intake (25A) and timing of training post-treatment (25B). However, the same training intervention was completed by all patients regardless of group assignment and both studies found no significant differences between different training groups on changes in lean body mass, muscle strength and functional performance.

Healthy individuals. Twenty-four healthy individuals were included in the study. The recruitment procedure was conducted to match the healthy control group with the population of HNSCC patients of the DAHANCA 25 trials with respect to age, gender and socio-economic status. Thus, asking all patients from the DAHANCA 25 trials to find family members, friends or colleagues interested in participating, provided a total of 24 individuals. Participants fulfilled the following inclusion criteria: 1) No current or previous malignancies, psychological, social or geographical conditions that could prevent participation; 2) No self-reported excessive alcohol intake (men > 21 and women > 14 units/wk); 3) No participation in resistance training of more than one hour per week; and 4) written consent. All interested individuals were contacted by telephone and if they fulfilled the inclusion criteria received both written and oral information before giving written consent. One of the interested individuals was excluded due to knee problems.

Endpoint evaluation

Within four weeks after the two month post-treatment follow-up at the clinic, all HNSCC patients underwent a comprehensive assessment protocol, where all endpoints were evaluated. The methodological details have been described previously [2,17]. Whole body lean body mass was determined using dual energy x-ray absorptiometry (DEXA).

Maximal knee extensor (KE) and flexor (KF) strength were determined using isokinetic dynamometry. From six maximal attempts of both isokinetic ($60° \times s^{-1}$ KE and KF) and isometric (70° KE and 20° KF) contractions, the best attempt in terms of peak torque (Newton-meters) from each contraction type was used for further analysis. Functional performance was assessed by the following test battery: 10 m maximal gait speed test (m/s); 30 s maximal chair rise test (maximal number of chair rises recorded); 30 s maximal arm curl test (maximal number of repetitions recorded); maximal stair climbing test (steps/second).

As a secondary explorative analysis, we investigated the association between functional performance and patient reported physical function. The latter was evaluated by the sub-scale "Physical Function" from the European Organisation for Research and Treatment of Cancer (EORTC) questionnaire QLQ-C30.

The level of leisure time physical activity (PA) of the HNSCC patients post-treatment and of the healthy individuals was categorized by the Saltin & Grimby questionnaire [18].

Statistics

Associations between lean body mass, muscle strength and functional performance. Owing to physiological differences between genders we assumed that gender would act as a confounder to the association between lean body mass and maximal muscle strength and between maximal muscle strength and functional performance. Accordingly, gender was included as a confounder in the linear regression models. To account for the possibility that the associations could be different within different age groups, we included age dichotomized as below or above the median age (56 and 59 years for HNSCC patients and healthy individuals, respectively) in the model as an effect modifier. Consequently, we made two models; the *crude* linear regression model and the *adjusted* model that included gender as a confounder and age as an effect modifier. Only crude linear regression models were performed on associations between functional performance and patient-reported physical function.

The results from the crude and adjusted linear regression models are presented as R^2 indicating the degree to which the variation of the dependent variable can be explained by the variation of the independent variable. In addition, the regression coefficients are presented to describe the magnitude of change in the dependent variable, when the independent variable changes.

To compare the associations between lean body mass, muscle strength and functional performance between patients and healthy individuals, further linear regression analyses were performed.

Comparisons between HNSCC patients and healthy individuals. Endpoint values of HNSCC patients at baseline and post-treatment were compared statistically with values of the healthy individuals using multiple regression analyses. All analyses and results are based upon regression models adjusted for gender, as both body composition and physical performance in general are influenced by gender.

All analyses were performed using STATA version 11.2. and all data followed a normal distribution (tested using Q-plots and histograms). Endpoints were tested statistically using a 5% level of significance. Results from the multivariate analyses are expressed as mean values $\pm$ standard error unless otherwise stated and patient characteristics as mean $\pm$ standard deviation. Bonferroni corrections were employed to correct for type I errors due to multiple testing (0.05/72 tests) and consequently $p < 0.0006$ was considered statistically significant.

Results

Characteristics of HNSCC patients and healthy individuals are presented in Table I. The two groups were similar regarding age, gender and socio-economic status. With regard to the baseline variables presented in Table I, the 11 patients that did not complete the 12 weeks of progressive resistance training and thus had no post-training values were not different to the 55 patients that completed the training ($p > 0.05$; student's t-tests). HNSCC patients had a significant lower body weight and body mass index (BMI) than the healthy individuals, however after Bonferroni correction this did not reach statistical significance ($p < 0.05$).

Of the 66 HNSCC patients, two were excluded from all analyses that included muscle strength or functional performance due to a meniscus injury and unspecified knee problems negatively affecting their performance. Further two patients felt uncomfortable during the muscle strength test, why the data sets from these two patients are incomplete.

Associations between lean body mass, muscle strength and functional performance in HNSCC patients

Lean body mass and all measures of maximal muscle strength were significant associated with R^2 values ranging from 0.59–0.67 ($p < 0.0001$) (adjusted models) (Table II and Figure 1). The coefficients of the adjusted linear regression models on the association between lean body mass and KE strength ranged from 4.8–5.5 Nm/kg lean body mass. In the

Table I. Characteristics of HNSCC patients and healthy individuals.

	HNSCC patients (n = 66)	Healthy individuals (n = 24)
Median age (range), years	56 ± 8 (27–72)	59 ± 9 (25–69)
Body weight, (at time of inclusion), kg	71.7 ± 12.4	79.5 ± 13.7
Weight loss during treatment (range), kg	−8.5 ± 6.5 (−30.0–8.0)	–
Weight loss during treatment (range),%	−9.6 ± 6.4 (−26.1–11.9)	–
Height (m)	1.76 ± 0.08	1.77 ± 0.08
Body mass index	23.0 ± 3.4	25.5 ± 3.6
Relative weight loss		
> 8.5%	34 (52%)	–
< 8.5%	31 (48%)	–
Gender		
Female	12 (18%)	7 (29%)
Male	54 (82%)	17 (71%)
Physical activity level (leisure time)		
I	6 (17%)	1 (5%)
II	21 (60%)	7 (35%)
III	8 (23%)	9 (45%)
IV	0 (0%)	3 (15%)

Values presented as mean ± SD unless stated otherwise. *Group difference (unpaired t-test, $p < 0.05$). Physical activity level measured by the Saltin and Grimby questionnaire [18]: Level I (almost completely inactive, 0–2 hours of light PA per week), II (at least 4 hours of light PA per week), III (light PA of > 4 hours per week or 2–4 hours of vigorous PA per week) and IV (vigorous PA > 4 hours per week or strenuous exercise several times per week).

association between lean body mass and KF strength the coefficients ranged from 2.0–2.2 Nm/kg lean body mass. The associations between total body weight and muscle strength were also significant, albeit with lower R^2-values ranging from 0.50–0.57 ($p < 0.0001$) in the adjusted models. Maximal isometric KE strength was associated with 30 s arm curl ($R^2 = 0.44$, $p < 0.0001$), 10 m max gait speed ($R^2 = 0.31$, $p = 0.0001$) and 30 s chair rise ($R^2 = 0.34$, $p < 0.0001$), whereas the association with stair climb did not reach statistical significance after the Bonferroni correction ($R^2 = 0.21$, $p = 0.007$). None of the functional performance tests were associated with the physical function dimension of the EORTC QLQ-C30 questionnaire after the Bonferroni correction (R^2 ranging from 0.06–0.14, $p < 0.05$).

The results from the adjusted linear regression analyses in healthy individuals revealed associations similar to those of HNSCC patients. However, the associations between isometric muscle strength and functional performance did not reach statistical significance. As illustrated in Figure 1, the linear regression coefficients of the crude models were not significantly different between healthy controls and HNSCC patients for any of the analyses performed (Figure 1).

See Table II for all results from both adjusted and crude linear regression models.

HNSCC patients compared with healthy individuals

At baseline lean body mass adjusted for gender was 10% lower in HNSCC patients compared with the healthy individuals (5.6 ± 1.5 kg; $p < 0.0001$; 95% CI -8.6;-2.7). After 12 weeks of progressive resistance training in the patient group the difference was no longer significant (2.1 ± 1.5 kg; $p > 0.05$; 95% CI -5.1;0.9). Maximal muscle strength was consistently lower in HNSCC at baseline than healthy individuals. Overall maximal muscle strength adjusted for gender based on values from all four muscle strength tests was 15% lower in HNSCC patients at baseline, however the difference was only significant for isometric muscle strength ($p < 0.0001$). After training there were no significant differences between patients and controls in maximal muscle strength. In all four functional performance tests at baseline, HNSCC patients scored significantly lower than healthy individuals. Overall functional performance based on all four tests adjusted for gender was 18% lower in HNSCC patients at baseline. Again, the training period eliminated the differences between patients and healthy individuals (Table III).

Discussion

The present study showed that lean body mass was strongly associated with maximal lower extremity muscle strength, which was further significantly associated with functional performance in HNSCC patients. These associations were similar to associations observed in healthy individuals. In HNSCC patients' lean body mass, maximal muscle strength and functional performance were significantly reduced at baseline compared to healthy individuals. These deficits were evened out following 12 weeks of progressive resistance training, where the HNSCC patients were no longer significantly different from healthy controls in lean body mass, muscle strength or functional performance. As proposed earlier [19], studies are warranted to further comprehend the specific needs of rehabilitation in specific cancer patients. The findings from the present study strongly underline and support the clinical relevance of lean body mass in HNSCC patients following radiotherapy and emphasize the importance of interventions to prevent or reverse the loss of lean body mass.

Table II. Associations between lean body mass, maximal muscle strength and functional performance.

	HNSCC patients				Healthy individuals			
	Crude model		*Adjusted model*		*Crude model*		*Adjusted model*	
Dependent and independent variable	R^2	Coefficient [95% CI]	R^2	Coefficient [95% CI]	R^2	Coefficient [95% CI]	R^2	Coefficient [95% CI]
Isometric KE								
Body weight	0.30	2.5	0.50	2.4	0.31	2.5	0.71	1.3
	p < 0.0001*	[0.5;3.4]	p < 0.0001*	[1.0;3.7]	p = 0.004	[0.9;4.2]	P < 0.0001*	[0.4;2.9]
Isokinetic KE								
Body weight	0.32	2.1	0.57	2.3	0.43	2.3	0.71	1.6
	p < 0.0001*	[1.3;2.9]	p < 0.0001*	[1.3;3.2]	p = 0.0005*	[1.1;3.4]	p = 0.0001*	[0.4;2.9]
Isometric KE								
Lean body mass	0.58	5.0	0.63	5.5	0.68	4.2	0.75	2.5
	p < 0.0001*	[3.9;6.1]	p < 0.0001*	[3.6;7.4]	p < 0.0001*	[2.9;5.5]	P < 0.0001*	[0.2;4.7]
Isokinetic KE								
Lean body mass	0.56	4.0	0.67	4.8	0.70	3.3	0.80	3.0
	p < 0.0001*	[3.1;4.9]	p < 0.0001*	[3.4;6.2]	p < 0.0001*	[2.4;4.3]	p < 0.0001*	[1.5;4.5]
Isometric KF								
Lean body mass	0.50	2.4	0.59	2.0	0.66	2.4	0.71	1.6
	p < 0.0001*	[1.8;3.1]	p < 0.0001*	[0.9;3.0]	p < 0.0001*	[1.7;3.2]	p = 0.0001*	[0.2;2.9]
Isokinetic KF								
Lean body mass	0.49	2.2	0.61	2.2	0.68	2.2	0.78	1.7
	p < 0.0001*	[1.6;2.8]	p < 0.0001*	[1.3;3.1]	p < 0.0001*	[1.5;2.8]	p < 0.0001*	[0.5;2.7]
10 m max gait speed								
Isometric KE/	0.27	0.26	0.31	0.2	0.38	0.3	0.43	0.2
bodyweight	p < 0.0001*	[0.1;0.4]	p = 0.0001*	[0.1;0.4]	p = 0.001	[0.1;2.0]	p = 0.03	[−0.1;0.5]
30 s arm curl								
Isometric KE	0.34	0.04	0.44	0.05	0.29	0.05	0.34	0.1
	p < 0.0001*	[0.03;0.06]	p < 0.0001*	[0.03;0.07]	p = 0.006	[0.01;0.08]	p = 0.08	[0.0;0.12]
30 s chair rise								
Isometric	0.26	3.6	0.34	3.8	0.28	3.8	0.33	2.4
KE/Bodyweight	p < 0.0001*	[2.0;5.2]	p < 0.0001*	[1.7;5.9]	p = 0.008	[1.1;6.6]	p = 0.09	[−2.6;7.5]
Stair climb								
Isometric KE/	0.13	0.3	0.21	0.2	0.30	0.4	0.32	0.4
Bodyweight	p = 0.004	[0.1;0.5]	p = 0.007	[0.1;0.5]	p = 0.005	[0.1;0.7]	p = 0.1	[−0.1;0.9]
Physical function								
10 m max gait speed	0.14	17			0.001	−0.5		
	p = 0.003	[6;28]			p = 0.88	[−7.8;6.7]		
Physical function								
30 s arm curl	0.06	0.9			0.29	0.2		
	p = 0.046	[0.02;1.7]			p = 0.006	[−0.1;0.6]		
Physical function								
30 s chair rise	0.16	1.2			0.22	0.4		
	p = 0.001	[0.5;2.0]			p = 0.03	[0.03;0.8]		
Physical function								
Stair climb	0.10	−2.5			0.13	−1.1		
	p = 0.015	[−4.0;−0.5]			p = 0.11	[−2.4;0.3]		

Results from the linear regression models on associations between body weight, lean body mass, maximal muscle strength - isokinetic knee extension (KE) and knee flexion (KF), functional performance and self-reported physical function in radiotherapy-treated HNSCC patients and healthy individuals. Results from the crude and adjusted models are presented. The dependent variable in the linear regression analyses are expressed in **bold letters** with the independent below**.** The results from the crude and adjusted linear regression models are presented as R^2 indicating how well the variation of the dependent variable can be explained by the variation of the independent variable. In addition, the regression coefficients describe the magnitude of change in the dependent variable when the independent variable changes. In both models asterisks indicate statistical significance of association. After Bonferroni correction a p-value $<$ 0.0006 was considered statistically significant (denoted *).

The R^2-values of the adjusted models indicate that as much as 59–67% of the variation in maximal muscle strength was explained by the variation in lean body mass in HNSCC patients, while 21–44% of the variation in functional performance was explained by the variation in muscle strength in HNSCC patients. In accordance with the present study, Jager-Wittenaar et al. [14] found an association between lean body mass decline and decline of hand grip strength. However, the cross-sectional

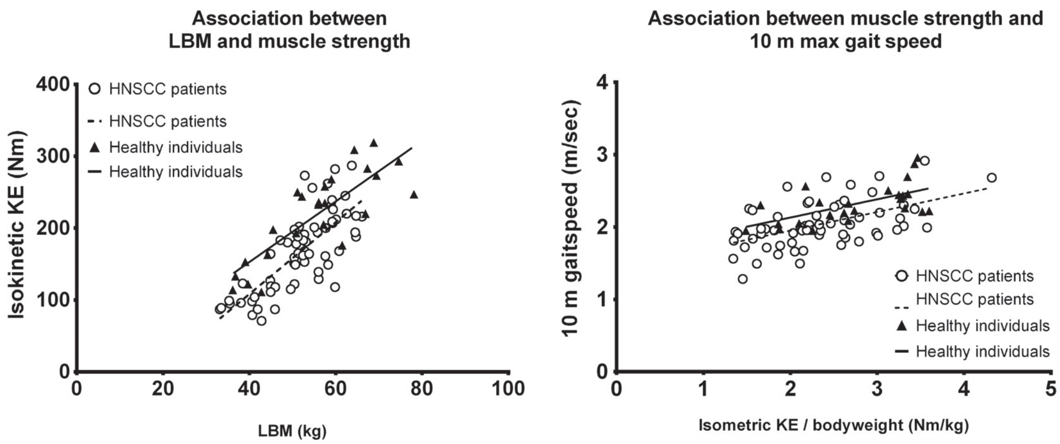

Figure 1. Associations between lean body mass, muscle strength and functional performance.

Left: Association between lean body mass, isometric knee extension (KE, Newton-meters) in HNSCC patients and healthy individuals. Right: Association between isometric KE adjusted for body weight (Newton-meters/kg) and 10 m max gait speed (m/s) in HNSCC patients and healthy individuals.

Table III. Body composition, maximal muscle strength and functional performance values in HNSCC patients and healthy individuals.

	HNSCC patients			HNSCC patients (baseline) versus healthy individuals		HNSCC patients (post-training) versus healthy individuals	
	Baseline	Post-training	Healthy individuals	Crude diff.	Gender adjusted diff. [95% CI]	Crude diff.	Gender adjusted diff. [95% CI]
Body weight, kg	71.2 ± 1.5	74.1 ± 1.8	79.5 ± 2.8	−8.3 ± 3.1	−9.7 ± 2.8* [−15.2;−4.3]	−5.4 ± 3.0	−6.8 ± 2.8 [−1.2;−12.4]
Body mass index	22.9 ± 0.4	23.7 ± 0.5	25.5 ± 0.7	−2.6 ± 0.8	−2.8 ± 0.8* [−4.4;−1.2]	−1.8 ± 0.8	−1.9 ± 0.8 [−0.3;−3.4]
Lean body mass, kg	52.0 ± 1.0	54.9 ± 2.5	55.5 ± 2.5	−3.7 ± 2.3	−5.6 ± 1.5* [−8.6;−2.7]	−0.6 ± 2.4	−2.1 ± 1.5 [−5.1;0.9]
Fat mass, kg	17.3 ± 1.0	16.5 ± 1.1	20.8 ± 1.6	−3.7 ± 1.9	−3.5 ± 1.9 [−7.2;0.3]	−4.3 ± 2.0	−4.1 ± 1.6 [−0.3;−8.0]
Maximal muscle strength							
Isometric KE, Nm	167 ± 7	214 ± 10	218 ± 13	−51 ± 15	−62 ± 12* [−86;−39]	−4 ± 16	−15 ± 12 [−9;40]
Isometric KF, Nm	97 ± 4	121 ± 4	119 ± 7	−22 ± 7	−28 ± 5* [−39;−17]	−1 ± 6	−5 ± 6 [−7;16]
Isokinetic KE, Nm	142 ± 6	171 ± 8	152 ± 10	−11 ± 12	−17 ± 9 [−35;0.4]	18 ± 13	10 ± 10 [−31;10]
Isokinetic KF, Nm	81 ± 3	106 ± 5	92 ± 7	−11 ± 7	−16 ± 6 [−27;−5]	13 ± 7	8 ± 6 [−19;3]
Functional performance							
10 m max gait speed, m/s	2.0 ± 0.0	2.3 ± 0.1	2.3 ± 0.1	−0.3 ± 0.1	−0.3 ± 0.1* [−0.5;−0.2]	0.0 ± 0.1	−0.1 ± 0.1 [−0.2;0.1]
30 s arm curls, repetitions	18 ± 1	24 ± 1	23 ± 1	−5 ± 1	−5 ± 1* [−8;−3]	1 ± 1	1 ± 1 [−2;3]
30 s chair rise, repetitions	18 ± 1	24 ± 1	23 ± 1	−5 ± 1	−5 ± 1* [−8;−3]	1 ± 1	0 ± 1 [−2;3]
Stair climb, steps/s	2.6 ± 0.1	3.0 ± 0.1	3.1 ± 0.1	−0.4 ± 0.1	−0.5 ± 0.1* [−0.7;−0.2]	0.0 ± 0.1	−0.1 ± 0.1 [−0.3;0.2]

Body composition, maximal muscle strength and functional performance values in HNSCC patients at baseline (n = 64) and following 12 weeks of progressive resistance training (n = 55) and healthy age-matched controls (n = 24). Data presented as mean ± SEM. Statistical group differences based upon multiple regression analyses adjusted for gender are denoted *(p < 0.0001) with 95% confidence intervals. After Bonferroni correction a p-value < 0.0006 was considered statistically significant. KE, knee extension; KF, knee flexion; Nm, Newton-meters.

design of the present study precludes direct comparison to the study of Jager-Wittenaar. Furthermore, in prostate patients receiving androgen suppression therapy Galvão et al. [20] found associations between appendicular skeletal muscle mass and maximal leg extension strength (assessed by the one repetition maximum test) and larger leg extension strength was associated with better functional performance (i.e. five-times chair rise performance and 6-min walk test) [20], indicating that the observed associations exist in other cancer patients. Differences in strengths of associations between lean body mass and strength between studies may be explained by the different patient characteristics (e.g. treatment status, age and gender) as well as different methods of evaluation of muscle strength and functional performance.

The present study clearly demonstrated that after radiotherapy HNSCC patients were significantly inferior to the healthy individuals regarding lean body mass, maximal muscle strength and functional performance. Thus, lean body mass, muscle strength and functional performance in HNSCC patients were 10%, 15% and 18% lower, respectively, than in the healthy individuals. Considering our data in conjunction with the extensive lean body mass loss reported in radiotherapy-treated HNSCC patients [1,14], it is strongly suggested that preservation and/or fast re-establishing of lean body mass should be a major rehabilitation goal, when trying to maintain and/or rebuild muscle strength and functional performance in these patients.

As shown previously [2,17], progressive resistance training is feasible and effective in rebuilding lean body mass and maximal muscle strength in HNSCC patients following radiotherapy. In fact, 12 weeks of training increased lean body mass by more than 4% and maximal muscle strength by approximately 20%. Thus, as shown by our analysis, the training of HNSCC patients effectively increased the levels of lean body mass, maximal muscle strength and functional performance to the levels of a group of matched healthy individuals. This strongly emphasize, that the inferior physical state of the patients following radiotherapy is reversible by means of training.

The coefficients of the regression analyses between lean body mass and maximal KE strength ranging from 4.0–5.4 Nm/kg lean body mass indicate theoretically, that if lean body mass is increased by 1 kg (approximately 2% of the mean lean body mass of the HNSCC patients) maximal muscle strength will increase by 4.0–5.4 Nm (approximately 3% of the mean maximal KE strength of the HNSCC patients). The training intervention induced larger increases in muscle strength than expected from the increases in lean body mass according to the regression model [2,17]. This discrepancy is likely explained by the additive effects of neural adaptations as well as possible changes in muscle quality following training [21].

We observed lower R^2-values of the associations between muscle strength and functional performance, indicating that other factors than muscle strength significantly influence functional performance. These factors may include task habituation, motor skills, balance and sensation of safety. In addition, a possible ceiling effect in the functional performance tests potentially inhibits better performance despite larger lean body mass.

Body weight is an easily obtainable outcome measure that has been associated with prognosis [7], QoL and patient reported physical function in HNSCC patients [22]. Moreover, a reduction in total body weight is often used as a clinical predictor of increased morbidity and mortality in HNSCC patients [7]. Interestingly, our findings imply that lean body mass is a stronger predictor of post-treatment maximal muscle strength than total body weight. We observed lower R^2-values between body weight and muscle strength in the HNSCC patients compared to the R^2-values between lean body mass and muscle strength, indicating that lean body mass predicts the level of muscle strength in these patients better than total body weight. It may be speculated that lean body mass could also be used as a superior predictor of morbidity and mortality in HNSCC patients compared to body weight. Importantly, in this respect, the potential presence of sarcopenic obesity (high adipose mass and low lean body mass) in a normal weight or even overweight HNSCC patients following treatment might conceal a negative prognosis of this subgroup of patients. Applying lean body mass as a predictor of clinical outcome instead of body weight would take sarcopenic obesity into account as proposed previously [9,23].

As a sub-analysis, the association between functional performance and patient reported physical function was investigated. We found no significant associations and low R^2-values indicate that only 6–16% of the variation in patient reported functional performance is explained by the variation in functional performance. These findings are interesting and strongly suggest that other factors in addition to objectively measured functional performance largely influence the patient's own perception of their level of physical function. This could be due to implicit individual conception of physical function, cognitive impairments or depression related to illness as proposed previously [24]. The findings are also in agreement with previous reports of low to moderate correlations between patient reported physical activity and actual functional performance in other groups of patients such as patients with low back pain [25].

The strengths of the present study are that lean body mass, muscle strength and functional performance are objectively measured using validated and reliable methods in a well-defined group of HNSCC patients and that the levels are compared to a group of healthy individuals. This enables a deeper understanding of the functional performance and health status of HNSCC patients, which is needed to optimize interventions, aimed at maintaining or improving functional performance and decreasing the risk of physical impairments.

The primary limitation of the present study is the cross-sectional design, which precludes conclusions on causal relationships between lean body mass and muscle strength. Nonetheless, the force generating capacity of muscle per unit of cross sectional area is well established in healthy people [26] providing the direction of the association. The direction of the association between muscle strength and functional performance is, however, arguable, since higher muscle strength could induce a better functional performance and vice versa.

Co-morbidity is common in HNSCC patients [27], however due to the physical demands in participating in a progressive resistance training protocol, patients with WHO performance status > 2, patients with co-morbidity and other malignancies including alcohol abuse hindering completion of exercise training protocol were not included in the DAHANCA 25 trials. Thus, the weakest patients were not likely to be enrolled in the studies. Nevertheless, the fact that the included HNSCC patients expressed significant lower levels of all investigated endpoints compared with healthy controls, only underline the relevance of the problem in these patients. Including the weakest patients would likely increase this difference.

Due to the risk of type I errors induced by multiple testing, Bonferroni corrections were employed. Being highly conservative, the Bonferroni correction may generate false negatives. Nevertheless, the consistent associations and group differences throughout the present study indicate a strong trend and fortify the conclusions from the analyses.

In conclusion, significant associations were observed between lean body mass, maximal muscle strength and functional performance in the present study. After radiotherapy HNSCC patients expressed significant lower levels of these variables than healthy individuals, however, following a period of resistance training, these deficits were reversed. These finding emphasize the clinical relevance of lean body mass in HNSCC patients following radiotherapy and suggest that preservation and/or reestablishing of lean body mass is important to maintain the highest possible muscle strength and best functional performance in HNSCC patients.

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