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COMMENTARY

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Can supervised group-based multimodal exercise improve health-related quality of life in women with ovarian cancer undergoing chemotherapy?

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1 | INTRODUCTION

For women with ovarian cancer, 70% are diagnosed in an advanced stage of disease and carry a poor prognosis with a 5-year survival rate of 41% in stage III and 23% in stage IV (NORDCAN, 2019). The majority are offered combination chemotherapy and may face impaired health-related quality of life (HRQoL) due to the burden of symptoms and multiple chemotherapy-induced side effects such as fatigue, gastrointestinal disorders, pain, nausea/vomiting, sexual discomfort and peripheral neuropathy (Lockwood-Rayermann, 2006; Mishra et al., 2012). Supportive efforts to ameliorate the negative effects on HRQoL are therefore needed.

Non-pharmacological interventions such as nurse-led telephone interventions, pain-reducing or psycho-educational programmes to address reductions in HRQoL have shown no convincing effect in women with ovarian cancer (Cook et al., 2015; Davis & Carpenter, 2015; Kalter et al., 2018). Likewise and despite the increased attention given to exercise oncology (McTiernan et al., 2019), only a few small-scaled intervention studies ($n = 17–30$), are available examining HRQoL in women with ovarian cancer undergoing chemotherapy, which is why the results must be applied with caution (Mizrahi et al., 2015; Moonsammy et al., 2013; Newton et al., 2011; von Gruenigen et al., 2011). A Danish randomised controlled trial called Body & Cancer was conducted in Denmark involving a supervised, hospital-based, high-to-low intensity exercise intervention with physical, psychological and social components that showed significant effects on fatigue and improved physical function in patients ($n = 269$) with 21 different cancer diagnoses (Adamsen et al., 2009). The intervention has been implemented nationwide as a standard 6-week rehabilitation programme for Danish cancer patients. Based on data from the Body & Cancer programme, the primary aim of the present study was to investigate the potential benefits of the multimodal exercise programme on HRQoL in women with ovarian cancer undergoing chemotherapy, which is an underreported subpopulation in exercise literature.

2 | METHOD

This study employs a retrospective pre-post quasi-experimental design conducted at the Body & Cancer setting at Copenhagen University Hospital, Rigshospitalet in Denmark. The primary criterion for participation was performance status 0–1 (WHO) and undergoing chemotherapy simultaneously with the Body & Cancer programme. More detailed inclusion and exclusion criteria are published in *British Medical Journal* 2009 (Adamsen et al., 2009). Eligibility for the present study was women with ovarian cancer who had completed the Body & Cancer programme between 2007 and 2019 and completed the cancer-specific questionnaire, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC QLQ-C30) at baseline and after 6 weeks of intervention.

The Body & Cancer programme comprises 9 h of weekly group-based supervised training, four times a week for 6 weeks, corresponding to a total of 43 metabolic equivalent of tasks per week. On Mondays, Wednesdays and Fridays, training consisted of strength training (60 min/day), aerobic capacity (30 min/day) and relaxation training (30 min/day). On Tuesdays, body awareness 90-min training was performed. Massage (30 min) was provided on Tuesdays and Fridays (Adamsen et al., 2006, 2009). Participant adherence was assessed as attendance on every training day of in total 24 days.

Demographic and clinical data were obtained from patient medical record. In order to differentiate effects within various stages of cancer diagnosis, an algorithm (see legend Table 1) was used to dichotomise stages of disease into evidence of disease (ED) or no evidence of disease (NED) (Adamsen et al., 2009). Aerobic capacity (VO_2max [L/min]), strength (1-repetion maximum [1RM] [kg]) and patient-reported outcomes on HRQoL were measured at baseline and after 6 weeks of intervention. The EORTC QLQ-C30 was used to measure HRQoL and comprises 30 items, divided into 15 scales with three categories, resulting in an overall score of global health status (GHS)/quality of life, functional scores and symptom scores (Fayers et al., 2001). Clinically important changes in EORTC QLQ-C30 scores of 5–10 are defined as minor, while scores >10 are defined as moderate (ibid). Statistical analyses were conducted using IBM SPSS version 27 to measure one-group differences in paired *t*-test analyses with 95% confidence intervals and a significance level set to $p < 0.05$. EORTC QLQ-C30 scores were controlled for normal distribution of standardised residuals. Since a quasi-experimental retrospective design is prone to bias, explorative analysis was performed to detect confounding effects from explanatory demographic and clinical covariates on EORTC QLQ-C30 change score. EORTC QLQ-C30 subscales with clinically important changes and important symptoms or side effects described in the literature in participants (Lockwood-Rayermann, 2006) were included in an adjusted exploratory analysis with a description of coefficient of determination, 95% confidence intervals and a significance level, set to either $p < 0.05$ or $0.05 \leq p < 0.1$.

The study was approved by the Danish Data Protection Agency (file no. p-2020-1079). In accordance with the Helsinki Declaration, participants provided oral and written consent.

3 | RESULTS

One hundred thirty-five women with ovarian cancer participated in the Body & Cancer programme. Demographics on the 100 included participants who fulfilled pre-post EORTC QLQ-C30 questionnaires are provided in Table 1. The majority (82%) received treatment with taxanes and carboplatin with or without immunotherapy every 3 weeks. The participant adherence to the exercise programme was 78.1% (SD 15.1), corresponding to 18 out of 24 training sessions.

The percentage of participants who did regular physical exercise >3 h per week decreased from 65% before diagnoses to 41% after diagnoses and at study baseline. Likewise, the percentage of participants with a sedentary activity level grew from 4% to 18%.

The findings showed clinically important differences in 11 out of 15 EORTC QLQ-C30 subscales (delta >5) after participating in the six-week Body & Cancer programme (Table 2), with superior effects (≥7.5 points) for insomnia, role functioning, appetite loss and GHS. Average physiological improvements for the participants were seen in aerobic

TABLE 1 Demographic and clinical characteristics at baseline

	Total *n*	Mean ± SD/median (range)
Age in years		55.4 ± 10.9
Educational level		
Lower level of education	24	
Secondary school or university graduate	74	
Unknown	2	
Married or cohabiting	75	
Occupational activity		
Half time	20	
Full time	43	
Not working (pensioner, unemployed, student)	34	
Unknown	3	
Body mass index (BMI)		24.5 ± 4.3
Physical activity level[a]		
Sedentary (mostly reading, watching television, etc.)	18	
Walking/cycling for pleasure < 3 h per week	38	
Regular physical exercise > 3 h per week	38	
Intense physical activity > 4 h per week	3	
Unknown	3	
Disease status		
Evidence of disease (ED)[b]	64	
No evidence of disease (NED)[c]	36	
Treatment		
Adjuvant chemotherapy	27	
Chemotherapy for advanced disease	73	
Received cycles of chemotherapy		4 (0–10)

Note: $n = 100$.
[a]The self-reported level of physical activity was determined using the Saltin–Grimby Physical Activity Level Scale (Grimby et al., 2015).
[b]ED: Non-optimally debulked stage II (microscopic) or stage III; stage III and IV receiving neoadjuvant or palliative chemotherapy; relapse of disease.
[c]NED: Optimally debulked stage Ic, IIa, IIb receiving adjuvant chemotherapy and stage III (following second surgery receiving adjuvant chemotherapy).

TABLE 2 Health-related quality of life measured in EORTC QLQ-C30 outcomes and estimated differences

EORTC QLQ-C30 subscale	Mean SD		Mean diff. [95% CI]	*p* value
	Pre	Post (6 weeks)		
GHS/quality of life	58.5 (22.3)	66.0 (19.6)	7.5 [3.6; 11.4][a]	<0.000**
Physical functioning	80.4 (16.7)	87.5 (11.1)	7.1 [4.3; 9.9][a]	<0.000**
Role functioning	63.8 (29.9)	74.3 (26.4)	10.5 [4.8; 16.2][b]	<0.000**
Emotional functioning	74.6 (19.7)	78.9 (16.6)	4.3 [0.8; 7.9]	0.016**
Cognitive functioning	75.7 (22.8)	78.7 (18.9)	3.0 [−1.3; 7.3]	0.169
Social functioning	74.5 (28.2)	81.5 (20.2)	7.0 [2.7; 11.3][a]	0.002**
Fatigue	45.0 (24.6)	39.3 (23.0)	−5.7 [−10.3; −1.1][a]	0.017**
Nausea and vomiting	12.7 (16.7)	8.3 (14.3)	−4.3 [−8.2; −0.4]	0.031**
Pain	22.7 (23.9)	17.3 (21.4)	−5.3 [−10.2; −0.5][a]	0.032**
Dyspnoea	24.7 (27.9)	18.0 (25.7)	−6.7 [−12.4; −0.9][a]	0.023**
Insomnia	38.3 (34.3)	26.0 (31.9)	−12.3 [−18.8; −5.8][b]	<0.000**
Appetite loss	16.3 (24.8)	8.7 (16.8)	−7.7 [−12.7; −2.6][a]	0.003**
Constipation	28.3 (32.9)	21.0 (30.6)	−7.3 [−13.7; −0.9][a]	0.026**
Diarrhoea	15.7 (25.7)	8.3 (17.3)	−7.3 [−11.9; −2.7][a]	0.002**
Financial difficulties	10.7 (24.1)	7.0 (20.3)	−3.7 [−7.4; 0.1]	0.055

Note: $n = 100$.
Abbreviations: CI, confidence interval; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30; GHS, Global Health Status; Mean diff., mean difference; Pre, at baseline of the study; SD, standard deviation.
[a]Clinically relevant value defined as delta 5–10 points.
[b]Clinically relevant value defined as delta >10 points.
**The significance level $p < 0.05$.

TABLE 3 Pre-post physiological outcomes

	Mean		Mean diff (%)	95% CI
	Pre	Post (6 weeks)		
VO_2max (L/min)	1.73	1.86	0.12 (7%)	[0.08; 0.17]
Leg press (kg)	72.57	91.32	18.75 (25.8%)	[14.40; 23.10]
Leg extension (kg)	37.46	45.52	8.05 (21.5%)	[5.94; 10.17]
Chest press (kg)	21.87	27.21	5.34 (24.4%)	[4.18; 6.50]

Pre, at baseline of the study; CI, confidence interval. $n = 68$;

capacity (VO_2max +7%), leg press (+25.8%), leg extension (+21.5%) and in chest press (+24.4%) (Table 3).

The adjusted exploratory analysis showed few significant associations between selected EORTC QLQ-C30 subscales and identified demographic and/or clinical covariates, though the general impact was modest ($R^2 \sim 5$–6%) (Table 4). There was a markedly positive change in GHS for participants with ED (delta +10.9) compared to participants with no ED (delta −10.5) ($p = 0.010$).

The EORTC QLQ-C30 functional subscale, role function, had a clinically important moderate change for participants with a sedentary activity level (+19.0) or low activity level (physical exercise <3 h per week) (+16.4) compared to participants with a high physical activity level (>3 h per week) (+3.6). The fatigue symptom score for participants with a sedentary activity level decreased with 15.2 points, compared to participants with a low (−5.9) or a high physical activity level at baseline (−3.9) (Table 4).

4 | DISCUSSION AND CONCLUSION

Our study presents the potential benefits of a multimodal exercise programme on HRQoL in 100 women diagnosed with ovarian cancer undergoing chemotherapy participating in the Body & Cancer programme. The findings demonstrate several minor clinical improvements in HRQoL domains (Fayers et al., 2001). These may just border minimal important differences as recently suggested for ovarian cancer patients (Musoro et al., 2020). Although the women had a marginally worse baseline level of functional and symptom scores using EORTC QLQ-C30, they still had the greatest improvements in HRQoL, compared to previously published Body & Cancer studies (Adamsen et al., 2006; Adamsen et al., 2009). Notably, the findings indicate that those with ED, high symptom burden and lowest physical activity level have most to gain from exercise training. This may have clinical importance since a study by Andersen et al. suggested that various

TABLE 4 Exploratory analysis of selected EORTC QLQ-C30 scales adjusted for important clinical variables

EORTC QLQ-C30 subscale	Clinical variable	R^2	Subscale	*B*	95% CI	*p* value
Δ GHS	Disease status	0.06	NED	−10.5	[−18.4; −2.5]	0.010**
			ED (ref./intercept)	10.9	-	-
Δ role functioning	Physical activity level at baseline	0.06	Sedentary	19.0	[0.1; 37.9]	0.049**
			PA < 3 h/w	16.4	[0.3; 32.5]	0.046**
			PA > 3 h/w (ref./intercept)	3.6	-	-
	Disease status		NED	−2.7	[−20.2; 14.9]	0.761
			ED (ref./intercept)	3.6	-	-
Δ fatigue	Physical activity level at baseline	0.05	Sedentary	−15.2	[−30.4; 0.1]	0.051*
			PA < 3 h/w	−5.9	[−18.9; 7.1]	0.368
			PA > 3 h/w (ref./intercept)	−3.9	-	-
	Disease status		NED	7,0	[−7.2; 21.1]	0.332
			ED (ref./intercept)	−3.9	-	-
Δ insomnia	Physical activity level at baseline	0.06	Sedentary	−15.6	[−41,8; 10.7]	0.242
			PA < 3 h/w	−2.2	[−26,6; 22.1]	0.857
			PA > 3 h/w (ref./intercept)	2.2	-	-
	Body mass index		<20	−30.8	[−60.2; −1.4]	0.04**
			20.1–25	−5.7	[−27.9; 16.5]	0.609
			>25.1 (ref./intercept)	2.2	-	-

Note: Adjusted general linear model. $n = 97–100$.
Abbreviations: Δ (delta), difference between pre and posttest; B, coefficient; CI, confidence interval; EORTC QLQ-C30, ED, evidence of disease; European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30; GHS, global health status; NED, no evidence of disease; PA, physical activity level hours/week; R^2, the coefficient of determination; Ref./intercept: reference group.
*The significance level $0.05 \leq p < 0.1$. **$p < 0.05$.

cancer patients with ED had a significantly higher level of symptoms and/or treatment-induced side effects (Andersen et al., 2006). Furthermore, a recent large-scaled randomised controlled trial in physically inactive breast cancer patients during adjuvant chemotherapy found no significant improvement in HRQoL when participating in a 12-week exercise intervention (Møller et al., 2020). Evidence are generally lacking in sedentary or physically inactive cancer populations (Turner et al., 2018). Accordingly, the specific improvements in fatigue, insomnia and role function for participants with a low physical activity level at baseline in this study are encouraging.

The positive results of the study must be taken with caution. First, this quasi-experimental study does not have a randomised control group. However, since Body & Cancer is a programme that is available to Danish cancer patients, requiring a control group may have been unethical. Second, data were collected over a long period of time with obvious selection bias. Several clinical variables with a significant association to the change in HRQoL have been investigated, but due to a limited power, there may be clinical variables that were not covered by the exploratory analysis.

To our knowledge, there are only few exercise intervention studies examining HRQoL in women with ovarian cancer during chemotherapy, which is why this underreported subpopulation requires additional attention in future exercise-based randomised controlled studies (Mishra et al., 2012). In accordance with our findings, we recommend that supervised exercise interventions should include high-to-moderate activity training for at least 6-week duration.

In conclusion, our findings demonstrate that a supervised, group-based, multimodal exercise intervention may have potential benefit on HRQoL and physiological improvements in women diagnosed with ovarian cancer undergoing chemotherapy. In accordance with the American College of Sports Medicine (Schmitz et al., 2019), we highly recommend clinicians to implement outreach strategies in order to engage patients with ovarian cancer irrespective of their stage of disease to be physically active during chemotherapy. We emphasise that there is a potential role for exercise in subgroups in women with ovarian cancer with high symptom burden.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study area available from the corresponding author upon reasonable request.

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