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Cardiorespiratory fitness in long-term lymphoma survivors after high-dose chemotherapy with autologous stem cell transplantation

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Background: Cardiorespiratory fitness as measured by peak oxygen consumption (VO_{2peak}) is a strong predictor of longevity and may be compromised by anticancer therapy, inactivity, and smoking. We compared VO_{2peak} among lymphoma survivors (LSs) with reference data from healthy sedentary subjects, after a 10.2-year (mean) follow-up post high-dose chemotherapy with autologous stem cell transplantation (HDT-ASCT). We further examined the association between VO_{2peak} and treatment, physical activity, smoking, pulmonary, and cardiac function.

Methods: Lymphoma survivors treated with HDT-ASCT in Norway 1987–2008 were eligible. VO_{2peak} was assessed by cardiopulmonary exercise testing. Pulmonary function testing and echocardiography were also conducted. Data on treatment, physical activity, and smoking were collected from hospital records and questionnaires. VO_{2peak} was compared with age–sex predicted reference data. Linear regression was used to associate clinical factors with VO_{2peak} cross-sectionally.

Results: A total of 194 LSs without heart failure were studied. Mean VO_{2peak} was 4.5% and 7.7% below norms in females and males, respectively. Twenty-two percent had impaired (<80% predicted) VO_{2peak} . Decreasing VO_{2peak} was associated with impaired diffusion capacity and current smoking, while physical activity level and VO_{2peak} were positively associated.

Conclusion: We suggest increased attention towards physical activity counseling and smoking cessation advice to preserve cardiorespiratory fitness in LSs after HDT-ASCT. Patients with impaired diffusion capacity may benefit from subsequent monitoring to detect pulmonary vascular diseases.

High-dose chemotherapy with autologous stem cell transplantation (HDT-ASCT) has been a treatment option for Hodgkin (HL) and non-Hodgkin lymphomas (NHL) since the mid-1980 (Linch *et al*, 1993; Schmitz *et al*, 2002). The number of lymphoma survivors (LSs) post HDT-ASCT has been steadily growing as treatment regimens and indications have evolved (Schmitz *et al*, 1996).

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In recent years, significant improvements in 5-year survival have been reported for patients receiving this therapy ranging 59–73% for HL and up to 62% for NHL (Vanderwalde *et al*, 2013; Smeland *et al*, 2013a, 2015).

As survival continues to improve, the proportion of LSs with treatment-related late effects increases (Bhatia *et al*, 2005), and the role of effective countermeasures is becoming increasingly important. The last decade, lifestyle change after cancer has received increased attention, and physical activity and smoking cessation have been highlighted as modifiable factors that may improve the length and quality of life among cancer survivors (Demark-Wahnefried *et al*, 2005). Recently, high cardiorespiratory fitness in male cancer survivors was associated with a one-third risk reduction of cancer mortality, compared with those with low cardiorespiratory fitness (Lakoski *et al*, 2015).

Cancer therapy may cause damage to organs involved in the transport or use of oxygen, and cardiac and pulmonary late effects related to pre HDT-ASCT therapies such as doxorubicin, bleomycin, and mediastinal irradiation are well known (Lund *et al*, 1996a, b; Murbraech *et al*, 2015). Such treatment-induced impairments, together with physical inactivity, might reduce cardiorespiratory fitness considerably in cancer survivors (Jones *et al*, 2009; Lakoski *et al*, 2012). Measurement of peak oxygen uptake (VO_{2peak}) by cardiopulmonary exercise testing represents the gold standard assessment of cardiorespiratory fitness, and is useful to assess the global effect of these impairments on cardiorespiratory fitness (Jones *et al*, 2008). Further, reduced cardiorespiratory fitness is a strong and inversely related predictor of adverse cardiovascular events in LSs (Adams *et al*, 2004; Jones *et al*, 2014). Therefore, preserving cardiorespiratory fitness by physical activity might be life-prolonging in intensively treated cancer survivors.

The present study is, to our knowledge, the first to systematically address cardiorespiratory fitness among long-term LSs after HDT-ASCT. Our primary aim was to compare VO_{2peak} with data from a healthy, sedentary reference population. Second, we examined VO_{2peak} according to treatment, physical activity, smoking, pulmonary impairment, cardiac function, and haemoglobin level among the LSs.

MATERIALS AND METHODS

Study population. The study population was recruited from all HL and NHL survivors treated with HDT-ASCT in Norway between 1987 and 2008 (Smeland *et al*, 2013b). A total of 399 LSs aged 18 years or older at HDT-ASCT, who were resident in Norway by March 2012, and not currently undergoing active treatment for relapsed disease, were eligible and invited to participate. After an average follow-up of 10.2 (range 3–25) years since HDT-ASCT, the participants were asked to attend an outpatient visit between March 2012 and March 2014, which included a symptom-limited cardiopulmonary exercise test, a pulmonary function test, echocardiography, blood sampling, and a questionnaire. The participants were recruited from Oslo University Hospital (OUH) ($n = 159$) and St Olavs University Hospital (Trondheim) ($n = 35$).

The study was approved by the South East Regional Committee for Medical and Health Research Ethics. Written informed consent was obtained from all participants.

Treatment. Treatment data were collected from medical records and databases at OUH and St Olavs University Hospital. The total number of treatment lines of chemotherapy given before HDT-ASCT was registered (1, 2, or ≥ 3). During 1987–1995, total body irradiation (TBI, 1.3 Gy twice daily for 5 consecutive days with lung shielding for two doses) followed by high-dose cyclophosphamide

(60 mg kg⁻¹ for 2 days) constituted the high-dose regimen. From 1995 onwards, the conditioning regimen was constrained to chemotherapy only, including carmustine, etoposide, cytarabine, and melphalan (BEAM). Cumulative doses of chest radiotherapy (RT) and chemotherapy were calculated and divided into categories: chest RT (unexposed, 1–13 Gy, >13–65 Gy), doxorubicin (<300 mg m⁻², 300–399 mg m⁻², 400–775 mg m⁻²), cyclophosphamide (0–3.49 g m⁻², 3.50–5.99 g m⁻², 6.00–12.30 g m⁻²), and bleomycin (unexposed, 1–12 international units (IU) · 10⁴/m², >12–21 IU · 10⁴/m²). Daunorubicin doses were converted to doxorubicin isotoxic doses using a conversion factor of 0.83 (Fullbright, 2011).

Symptom-limited cardiopulmonary exercise testing. Cardiopulmonary exercise testing and pulmonary function tests were performed on a SensorMedics Vmax unit (VIASYS Respiratory Care Inc., Yorba Linda, CA, USA) with an Ergoline 800 bicycle (Bitz, Germany). Patients recruited from Trondheim were exercise tested on a Jaeger Oxycon Pro unit (VIASYS Healthcare GmbH, Hochburg, Germany) coupled with a Monark Ergonomic 839E bicycle (Monark Exercise AB, Vansbro, Sweden). The gas exchange units were calibrated daily. During exercise testing, 12-lead electrocardiography, gas exchange, and ventilatory variables were monitored continuously, and testing was continued until exhaustion (respiratory exchange ratio (RER) >1.10). The test consisted of three phases: a 2-minute warm-up (20–50 Watt workload), an incremental exercise phase of 8–12 min until exhaustion, and 2-min recovery (American Thoracic Society; American College of Chest Physicians, 2003). VO_{2peak} was the primary outcome and was recorded together with peak oxygen pulse, maximum ventilation, maximum workload, RER, and perceived exertion (Borg scale). Following the procedure of Jones *et al* (2010), percent-predicted VO_{2peak} was calculated by dividing the measured values of our patients by those derived from age-sex dependent regression equations of VO_{2peak} from a healthy sedentary population (Fitzgerald *et al*, 1997; Wilson and Tanaka, 2000). Impaired VO_{2peak} was defined using the percent-predicted scale to account for sex-age difference, and set to <80% of predicted. Height and weight were measured, and body mass index (BMI) was calculated as kg m⁻².

Pulmonary function. Pulmonary function tests included dynamic spirometry, determination of static lung volumes, and gas diffusion capacity (Macintyre *et al*, 2005; Miller *et al*, 2005; Wanger *et al*, 2005). Recorded spirometric variables were forced vital capacity (FVC), forced expiratory volume in 1 s (FEV₁), and FEV₁/FVC. Static lung volume was recorded as total lung capacity (TLC). Gas diffusion was expressed by the transfer factor of the lungs for carbon monoxide (DLCO). Percentages of predicted normal lung function values were calculated based on the reference values recommended by the ERS (Quanjer *et al*, 1993). Pulmonary function was dichotomised according to obstructive impairment (FEV₁ <80% of predicted and FEV₁/FVC <0.7), restrictive impairment (TLC and FVC <80% of predicted, for 8 patients TLC data were missing and only FVC data were used to define restrictive impairment), and diffusion capacity impairment (DLCO <80% of predicted). These cutpoints correspond to the lower 5th percentiles in the reference material recommended by the ERS.

Echocardiography. Left ventricular ejection fraction (LVEF) was assessed by Simpson's biplane rule (Lang *et al*, 2005), and left ventricular systolic dysfunction (LVSD) was defined as a LVEF of <50% (Davies *et al*, 2001). Patients with heart failure ((HF), defined as current or prior symptoms according to Hunt *et al*, (2009)) were excluded to more clearly elucidate the influence of other factors than cardiac output on VO_{2peak} (Basset and Howley, 2000). The echocardiographic examination has been described in detail elsewhere (Murbraech *et al*, 2015).

Blood sampling. Blood samples were collected at 0800 h, and analysed for haemoglobin (Hb) level among other parameters. Anaemia was defined as Hb levels $<11.7 \text{ g dl}^{-1}$ (women) and $<13.4 \text{ g dl}^{-1}$ (men) (Rodgers *et al*, 2008).

Questionnaire. Self-reported physical activity was recorded as frequency (never, $<1/\text{week}$, $1/\text{week}$, $2\text{--}3/\text{week}$, almost daily), intensity (low, moderate, vigorous), and duration ($<15 \text{ min}$, $15\text{--}29 \text{ min}$, $30 \text{ min--}1 \text{ h}$, $>1 \text{ h}$), and has been validated previously (Kurtze *et al*, 2008). Minutes per week of physical activity ($0\text{--}100$, $101\text{--}180$, $181\text{--}375$) was calculated as a product of the frequency and duration variables. A summary score, reflecting overall physical activity level, was calculated by the following equation: $(\text{frequency}/5) + (\text{intensity}/3) + (\text{duration}/4)$, yielding an ordinal variable (range $1.18\text{--}3.00$) that was categorised into three equally sized thirds (low, medium, high), where inactive patients were placed in the low physical activity group (Nilsen *et al*, 2008). According to the World Health Organization (WHO) guidelines on physical activity, those who reported $\geq 150 \text{ min week}^{-1}$ of moderate intensity or $\geq 75 \text{ min week}^{-1}$ of vigorous intensity was categorised as 'meeting guidelines' and the rest as 'not meeting guidelines'. Smoking status was recorded as 'never', 'former', or 'current'.

Statistical analysis. Data are presented as mean \pm s.d., median (ranges), or numbers (%). Paired and independent samples *t*-tests were used for mean comparisons of normally distributed data, the Wilcoxon rank-sum test was used to compare ordinal data, and the Chi-square test was used to compare categorical data. Linear regression was used to estimate regression coefficients (RCs) with corresponding 95% confidence intervals (CIs) and *P*-values. $\text{VO}_{2\text{peak}}$, maximum ventilation, and maximum workload were examined in uni- and multivariable regression models according to relevant explanatory variables (specified in Table 3 and Supplementary Table S1, and Figure 3). After performing linear regression, the post-estimation command 'margins' of Stata 14 was used as described by Mitchell (2012) to derive adjusted means of $\text{VO}_{2\text{peak}}$ according to physical activity level across categories of cumulative doxorubicin, adjusted for gender, age at examination, BMI, smoking, and diffusion capacity.

Tests for significance were two-sided and *P*-values of ≤ 0.05 were considered as statistically significant. Variables with $P \leq 0.05$ in the univariable models or that were considered clinically relevant were included in the multivariable models. Tests for trend across categories were performed by entering categorical variables as continuous variables in the models. Data analyses were performed using Stata version 14 (StataCorp, College Station, TX, USA).

RESULTS

A total of 194 survivors of HL (21%) and NHL (79%), who completed exercise, pulmonary function, and echocardiographic testing, were included in the present analysis (Figure 1). Primary diagnosis, gender, age at survey, time from HDT-ASCT to survey, chest RT, and chemotherapy (cyclophosphamide and doxorubicin) did not differ between participants and non-participants (results not shown). Among the participants, mean age at examination was 55 years, two-thirds were men, 17% reported current smoking, and 47% met the WHO recommendation on physical activity. In women and men, $\text{VO}_{2\text{peak}}$ averaged 23.5 and $29.7 \text{ ml kg}^{-1} \text{ min}^{-1}$, respectively, and was impaired in 20% and 23% (Table 1).

$\text{VO}_{2\text{peak}}$ in LSs after HDT-ASCT compared with the reference population. Among female participants, the percent-predicted (PP) $\text{VO}_{2\text{peak}}$ averaged 95.5 (95% CI, 90.5–100.5), whereas that for

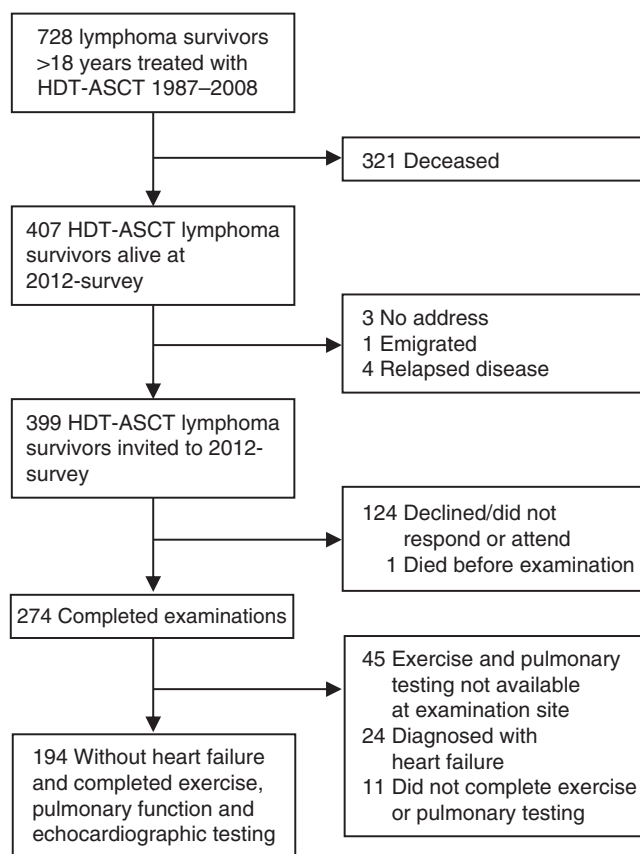


Figure 1. Overview of study design and exclusions.

males (PP 92.3, 95% CI 89.0–95.6) was significantly lower than the reference population (Figure 2).

When $\text{VO}_{2\text{peak}}$ was examined by level of physical activity, both the external comparison with the reference population (Figure 2) and the internal comparison (quartiles of $\text{VO}_{2\text{peak}}$, Table 2) were increasing in a dose-dependent manner. The low active LSs had significantly lower $\text{VO}_{2\text{peak}}$ (females: PP 87.5, 95% CI 78.8–96.3; males PP 85.8, 95% CI 82.0–89.7) than the reference population, while the $\text{VO}_{2\text{peak}}$ values of those who reported high activity did not differ significantly from the reference population (females: PP 105.6, 95% CI 94.8–116.5; males: PP 100.9, 95% CI 94.0–107.8) (Figure 2). For all physical activity measures, except intensity, there was a significant correlation with $\text{VO}_{2\text{peak}}$ expressed as impaired vs normal (Table 2).

Factors associated with $\text{VO}_{2\text{peak}}$, ventilation, and workload.

Table 3 shows uni- and multivariable models of factors associated with $\text{VO}_{2\text{peak}}$, maximum ventilation, and maximum workload. In the multivariable analysis, all outcomes were positively associated with an increase in physical activity level ($P_{\text{trend}} < 0.01$). Current smoking (RC -2.07 , $P = 0.05$) and impaired diffusion capacity (RC -2.33 , $P < 0.01$) were significantly associated with a decrease in $\text{VO}_{2\text{peak}}$. A reduction in maximum ventilation was associated with a cumulative bleomycin dose of $>12\text{--}21 \text{ IU} \cdot 10^4/\text{m}^2$ (RC -13.9 , $P = 0.05$, compared with the unexposed) and obstructive pulmonary impairment (RC -14.3 , $P < 0.01$). Maximum workload was positively associated with an increase in $\text{VO}_{2\text{peak}}$ (RC 58.5, $P < 0.01$) and inversely associated with impaired diffusion capacity (RC -7.2 , $P = 0.03$). No association with chest RT was found for any of the outcomes.

Physical activity level, doxorubicin exposure, and $\text{VO}_{2\text{peak}}$. Stratified on physical activity level, an increasing doxorubicin

Table 1. Participant characteristics at time of examination by gender

Variables	Gender		
	Total	Females	Males
Participants, N (%)	194 (100)	69 (36)	125 (64)
Age at primary lymphoma diagnosis, mean years (s.d.)	42 (13)	42 (14)	42 (13)
Age at examination, mean years (s.d.)	55 (12)	54 (14)	54 (11)
Time (years) since primary lymphoma diagnosis, mean (s.d.)	12.9 (6.6)	12.5 (6.1)	13.1 (6.8)
Time (years) since HDT-ASCT, mean (s.d.)	10.2 (5.8)	10.8 (5.9)	10.1 (5.9)
BMI, mean kg m ⁻² (s.d.)	26.3 (4.4)	25.8 (5.3)	26.6 (3.9)
Smoking, N (%)			
Never	77 (40)	28 (41)	49 (39)
Former	83 (43)	27 (39)	56 (45)
Current	34 (17)	14 (20)	29 (16)
Lymphoma subtypes, N (%)			
Hodgkin lymphoma (HL)	40 (21)	16 (23)	24 (19)
Non-Hodgkin lymphoma (NHL)	154 (79)	53 (77)	101 (81)
Cancer treatment			
Lines of chemotherapy pre HDT-ASCT, N (%)			
1	59 (30)	18 (26)	41 (33)
2	105 (54)	43 (62)	62 (49)
≥3	30 (16)	8 (12)	22 (18)
Type of HDT-ASCT, N (%)			
TBI + high-dose cyclophosphamide	33 (17)	11 (16)	22 (18)
BEAM treatment	161 (83)	58 (84)	103 (82)
Relapse post HDT-ASCT, N (%)	40 (21)	10 (14)	30 (24)
RIC allogeneic SCT post HDT-ASCT, N (%)	14 (7)	4 (6)	10 (8)
Chest-RT incl. TBI, mean Gy among exposed (s.d.)	25.2 (12.2)	25.3 (12.2)	25.1 (11.8)
Chest-RT excl. TBI, mean Gy among exposed (s.d.)	34.4 (7.9)	33.8 (10.4)	34.8 (6.0)
Doxorubicin, mean mg m ⁻² (s.d.)	320 (114)	326 (101)	317 (121)
Cyclophosphamide, mean g m ⁻² (s.d.)	4.6 (2.8)	4.3 (2.9)	4.7 (2.8)
Bleomycin, mean IU · 10 ⁴ /m ² among exposed (s.d.)	12.5 (4.8)	13.7 (4.2)	11.2 (5.3)
Peak exercise data			
VO ₂ peak, mean ml kg ⁻¹ min ⁻¹ (s.d.)	27.5 (7.5)	23.5 (6.5)	29.7 (7.1)
VO ₂ peak, mean l min ⁻¹ (s.d.)	2.23 (0.7)	1.69 (0.46)	2.57 (0.60)
Impaired VO ₂ peak, N (%)	43 (22)	14 (20)	29 (23)
O ₂ pulse (N = 191), mean ml beat ⁻¹ (s.d.)	14.0 (4.3)	10.0 (2.5)	16.0 (3.5)
VE (N = 193), mean l min ⁻¹ (s.d.)	94.8 (28.2)	71.4 (19.5)	107.8 (23.4)
RER, mean VCO ₂ /VO ₂ (s.d.)	1.18 (0.07)	1.19 (0.08)	1.17 (0.06)
Heart rate (N = 191), mean beats min ⁻¹ (s.d.)	167 (16)	167 (18)	168 (14)
Workload, mean Watts (s.d.)	171 (58)	126 (41)	196 (51)
Perceived exertion (N = 191), mean Borg (s.d.)	17.5 (1.0)	17.6 (1.0)	17.4 (0.9)
Exercise behaviour (N = 191)			
Minutes per week, N (%)			
0–100	53 (27)	18 (26)	35 (28)
101–180	72 (37)	29 (42)	43 (34)
181–375	66 (34)	22 (32)	44 (35)
Intensity, N (%)			
Low	85 (44)	31 (45)	54 (43)
Moderate	90 (46)	34 (49)	56 (45)
Vigorous	16 (8)	4 (6)	12 (10)
Summary score, N (%) ^a			
Low	81 (42)	25 (36)	56 (45)
Medium	53 (27)	27 (39)	26 (21)
High	57 (29)	17 (25)	40 (32)
WHO physical activity recommendation met, N (%) ^b	89 (47)	35 (51)	54 (44)
Pulmonary function			
FEV ₁ , mean L (s.d.)	3.03 (0.80)	2.37 (0.50)	3.40 (0.69)
FVC, mean L (s.d.)	3.98 (1.02)	3.06 (0.60)	4.49 (0.83)
FEV ₁ /FVC, mean ratio-value (s.d.)	0.76 (0.07)	0.77 (0.07)	0.76 (0.07)
TLC (N = 186), mean L (s.d.)	6.40 (1.59)	5.27 (1.00)	7.05 (1.50)
DLCO, mean mmol kPa ⁻¹ min ⁻¹ (s.d.)	7.88 (2.07)	6.32 (1.28)	8.74 (1.94)
Obstructive pulmonary function, N (%)	16 (8)	6 (9)	10 (8)
Restrictive pulmonary function, N (%)	12 (6)	3 (4)	9 (7)
Impaired gas diffusion capacity, N (%)	85 (44)	36 (52)	49 (39)

Table 1. (Continued)

Variables	Total	Gender	
		Females	Males
Cardiac function (N = 192)			
LVEF, mean percentage (s.d.)	56 (5)	56 (5)	55 (5)
LVSD, N (%)	13 (7)	3 (4)	10 (8)
Blood sample (N = 193)			
Haemoglobin, mean g dl ⁻¹ (s.d.)	14.0 (1.2)	13.2 (0.9)	14.5 (1.1)
Anaemia, N (%)	20 (10)	4 (6)	16 (13)

Abbreviations: BEAM = carmustine etoposide, cytarabine, and melphalan; BMI = body mass index; DLCO = carbon monoxide transfer factor; FEV₁ = forced expiratory volume in 1 s; FVC = forced vital capacity; HDT-ASCT = high-dose therapy with autologous stem cell transplantation; IU = international units; LVEF = left ventricular ejection fraction; LVSD = left ventricular systolic dysfunction; O₂pulse = oxygen pulse; RER = respiratory exchange ratio; RIC = reduced intensity conditioning; RT = radiotherapy; SCT = stem cell transplantation; s.d. = standard deviation; TBI = total body irradiation; TLC = total lung capacity; VE = ventilation; VO₂ = volume oxygen; WHO = World Health Organization.

^aCombining information on frequency, duration, and intensity.

^b≥150 min week⁻¹ of moderate intensity or ≥75 min week⁻¹ of vigorous intensity.

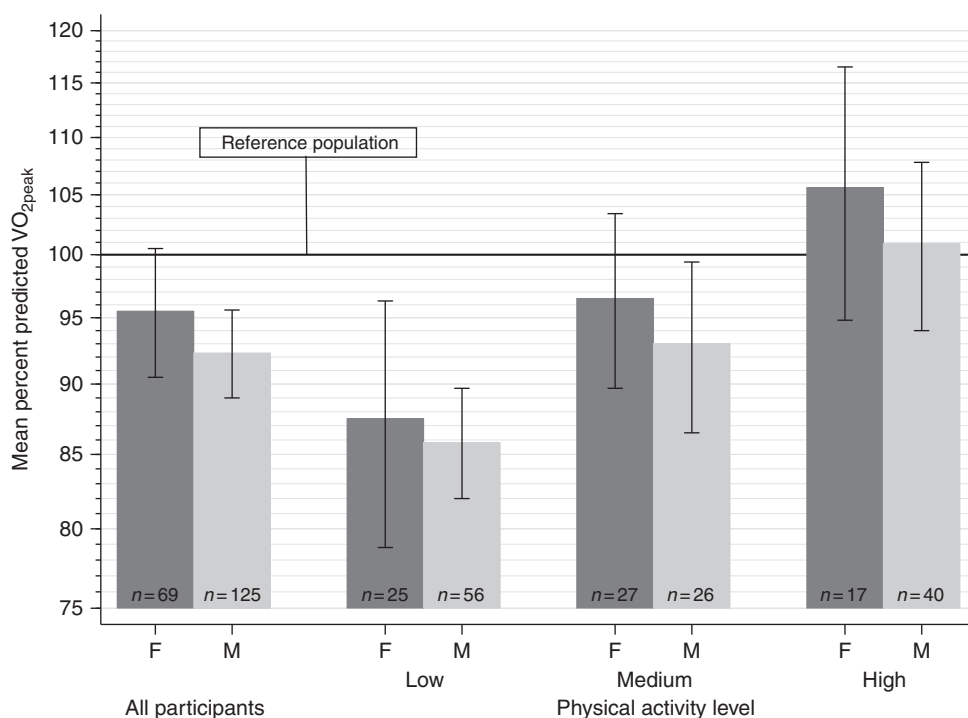


Figure 2. Mean peak oxygen uptake (VO_{2peak}) with 95% confidence intervals among 194 lymphoma survivors after HDT-ASCT compared with sex- and age-predicted reference values from a sedentary general population (Fitzgerald and Wilson/Tanaka equations). Abbreviations: F = female; M = male.

dose was associated with decreasing VO_{2peak} among the low active ($P_{\text{trend}} = 0.01$), while no such association was detected among the medium and highly active (Supplementary Table S1). Within the two highest doxorubicin dose groups (300–399 mg m⁻² and 400–775 mg m⁻²), significant differences in VO_{2peak} were found between the high and low activity groups (Figure 3).

DISCUSSION

VO_{2peak} among the LSs was on average 4.5% (women) and 7.7% (men) lower than age–sex predicted values from the healthy, sedentary reference population. Twenty percent of male and twenty-three percent of female LSs had impaired VO_{2peak}. Impaired diffusion capacity and current smoking were associated with a reduction in VO_{2peak}. LSs who reported high levels of

physical activity did, however, reach the VO_{2peak} level of the reference population. Further, a high physical activity level seemed to mitigate the inverse association between doxorubicin and VO_{2peak}. In sum, these findings underline the importance of long-term monitoring of LSs after HDT-ASCT, and highlight a need for increased focus on physical activity counseling and smoking cessation in the clinical oncology setting.

After a mean follow-up of 10.2 years since HDT-ASCT, 53% of the LSs were not meeting the physical activity recommendations and 17% were current smokers. As both are modifiable factors, they call upon oncology care providers to encourage lifestyle change. Although oncologists hold powerful roles as lifestyle promoters, and may benefit from the so-called ‘teachable moment’ provided by the diagnosis itself (Demark-Wahnefried *et al*, 2005), cancer survivors are often fatigued and it has proven difficult to change from an inactive to an active lifestyle. A study in Norwegian cancer survivors reported that only 12% changed from inactive

Table 2. Exercise behaviour by quartiles of peak oxygen uptake (VO_{2peak}) and by impaired vs normal VO_{2peak}

Self-reported physical activity at examination (N = 191)	Quartiles of VO_{2peak} ($ml\ kg^{-1}\ min^{-1}$) ^a				P-value	Impaired vs Normal VO_{2peak} ^b		P-value
	Quartile 1 (11.2–22.0)	Quartile 2 (22.1–26.9)	Quartile 3 (27.2–31.5)	Quartile 4 (31.7–47.5)		Impaired (<80% pred.)	Normal (≥80% pred.)	
Minutes per week, N (%)					0.02			0.02
0–100	17 (32.1)	15 (28.3)	17 (32.1)	4 (7.5)		18 (43)	35 (23)	
101–180	21 (29.2)	15 (20.8)	17 (23.6)	19 (26.4)		16 (38)	56 (38)	
181–375	11 (16.7)	16 (24.2)	15 (22.7)	24 (36.4)		8 (19)	58 (39)	
Intensity, N (%)					<0.01			0.27
Low	27 (31.7)	23 (27.1)	23 (27.1)	12 (14.1)		23 (55)	62 (42)	
Moderate	21 (23.3)	21 (23.3)	23 (25.6)	25 (27.8)		17 (40)	73 (49)	
Vigorous	1 (6.3)	2 (12.5)	3 (18.7)	10 (62.5)		2 (5)	14 (9)	
Summary score, N (%) ^c					<0.01			0.02
Low	26 (32.1)	22 (27.2)	23 (28.4)	10 (12.3)		26 (62)	55 (37)	
Medium	15 (28.3)	12 (22.6)	17 (32.1)	9 (17.0)		8 (19)	45 (30)	
High	8 (14.0)	12 (21.1)	9 (15.8)	28 (49.1)		8 (19)	49 (33)	
WHO recommendation, N (%) ^d					0.02			0.05
Not meeting	32 (31.4)	27 (26.5)	27 (26.5)	16 (15.7)		28 (67)	74 (50)	
Meeting	17 (19.1)	19 (21.4)	49 (25.7)	47 (24.6)		14 (33)	75 (50)	

Abbreviations: VO_2 = volume oxygen; WHO = World Health Organization.
^aPercentages tabulated row-wise.
^bPercentages tabulated column-wise.
^cCombining information on frequency, duration, and intensity.
^d150 min week⁻¹ of moderate intensity or 75 min week⁻¹ of vigorous intensity.

before diagnosis to active after treatment (Gjerset *et al*, 2011). Overweight, low educated, and smokers were associated with physical inactivity after treatment in the Gjerset *et al* (2011) study, and constitute subgroups that should receive more attention with respect to lifestyle counseling.

To our knowledge, only one other study has examined cardiorespiratory fitness in cancer survivors post HDT-ASCT (Tuchman *et al*, 2015). This study was, however, conducted in survivors of multiple myeloma, with a mean VO_{2peak} of 17.5 $ml\ kg^{-1}\ min^{-1}$ at the age of 60 years (Tuchman *et al*, 2015). Although both disease presentation and purpose/type of HDT-ASCT differ between multiple myeloma and lymphoma, we believe that the lower age and the exclusion of HF cases in the present study explain the 10 $ml\ kg^{-1}\ min^{-1}$ higher mean VO_{2peak} . There has been published a study protocol of a planned multicentre exercise-intervention trial in lymphoma and multiple myeloma survivors after HDT-ASCT in the Netherlands (Persoon *et al*, 2010), but to our knowledge no analysis of cardiorespiratory fitness in LSs after HDT-ASCT has been reported to date.

Although only a modest reduction in mean VO_{2peak} was observed between all patients and the reference population of healthy sedentary individuals, 43 in 194 patients had impaired VO_{2peak} . The larger proportion reporting low physical activity among the impaired vs the normal VO_{2peak} groups (62% vs 37%, respectively) could explain the relatively high number of patients with impaired VO_{2peak} . The increase in VO_{2peak} across levels of physical activity seen vs the reference population persisted in the internal comparison for all measures of exercise behaviour (i.e., minutes per week, intensity, summary score, and WHO recommendation). Further, in the multivariable prediction of VO_{2peak} a significant trend across levels of physical activity was observed. The significant difference in VO_{2peak} between high and low active LSs within the two highest doxorubicin dose groups suggests that a high physical activity level could mitigate the adverse effects of doxorubicin on VO_{2peak} . The inverse association between doxorubicin and VO_{2peak} among low active might be ascribed to doxorubicin-induced impairments in endothelial function and change in Ca^{2+} response in the skeletal muscle

(Chow *et al*, 2006; van Norren *et al*, 2009), while increased capillarisation and mitochondrial density could explain why VO_{2peak} was similar among highly active across doses of doxorubicin (Lakoski *et al*, 2012).

On the basis of the previously reported associations between chest RT and cardiopulmonary sequelae in LSs (Lund *et al*, 1996b; Adams *et al*, 2004; Murbraech *et al*, 2015), an inverse association between chest RT and VO_{2peak} would have been plausible but was, however, not seen in our data. This might be explained by the fact that we studied adult LSs, excluding RT-induced organ development impairments typically seen in childhood cancer survivors (Huang *et al*, 2011), and that only 10 (5%) patients received mantle field RT. The independent effect from current smoking on VO_{2peak} is in line with results from non-cancer populations (Hirsch *et al*, 1985; Suminski *et al*, 2009).

Cardiorespiratory fitness depends on the lung's diffusion capacity, the heart's stroke volume, the blood's Hb concentration, the endothelial function, and the skeletal muscle's capillary density and number of mitochondria (Hoppeler and Weibel, 1998). In addition to HDT-ASCT, the LSs might have been through intensive treatment regimens with high cumulative doses of doxorubicin, bleomycin and for some radiotherapy, all in which have been associated with deteriorative effects on organ systems involved in the oxygen transport (Lund *et al*, 1996b; Chow *et al*, 2006; van Norren *et al*, 2009; Murbraech *et al*, 2015). To assess more precisely which organ components might have been damaged by such anticancer therapy, single-organ exams are necessary in addition to the collective assessment of VO_{2peak} by cardiopulmonary exercise testing, and were recently highlighted as a need for future studies (Tuchman *et al*, 2015).

We performed echocardiography, pulmonary function testing, and blood sampling in order to dissect any single-organ impairments. As cardiac output is known to be the primary limiting factor for VO_{2peak} (Basset and Howley, 2000), patients with HF were excluded. We only detected left ventricular systolic dysfunction in 7% of the participants, and no association was found between LVEF and VO_{2peak} in the regression analysis. The pulmonary function tests revealed that 44% of our patients had impaired gas diffusion capacity, which accords with a recent study

Table 3. Peak oxygen uptake (VO_{2peak}), ventilation and workload associated with treatment exposures and other characteristics; presented as regression coefficients with P-values

	VO _{2peak} (ml kg ⁻¹ min ⁻¹)		Ventilation max (l min ⁻¹)		Workload max (Watt)	
	Univariable RC (P-value)	Multivariable RC (P-value)	Univariable RC (P-value)	Multivariable RC (P-value)	Univariable RC (P-value)	Multivariable RC (P-value)
Female gender	-6.27 (<0.01)	-5.47 (<0.01)	-36.5 (<0.01)	-33.3 (<0.01)	-70.8 (<0.01)	-12.0 (0.01)
Age at examination (years)	-0.29 (<0.01)	-0.28 (<0.01)	-0.8 (<0.01)	-0.7 (<0.01)	-2.1 (<0.01)	-0.6 (<0.01)
BMI (kg m ⁻²)	-0.37 (<0.01)	-0.53 (<0.01)	0.7 (0.11)	—	1.7 (0.07)	—
Smoking						
Never	0 (reference)	0 (reference)	0 (reference)	—	0 (reference)	0 (reference)
Former	-2.19 (0.06)	-0.41 (0.61)	2.3 (0.6)	—	-12.2 (0.18)	-1.2 (0.74)
Current	-2.91 (0.06)	-2.07 (0.05)	-8.2 (0.16)	—	-26.3 (0.03)	-4.6 (0.32)
Years since diagnosis	0.02 (0.78)	—	0.4 (0.19)	—	0.2 (0.79)	—
Years since HDT-ASCT	0.06 (0.49)	—	0.5 (0.14)	—	0.7 (0.33)	—
Trend across lines of chemotherapy pre HDT-ASCT (1, 2, ≥3)	0.49 (0.55)	—	1.5 (0.63)	—	-3.1 (0.62)	—
Type of HDT-ASCT regimen						
TBI + high-dose cyclophosphamide	-0.17 (0.91)	—	-3.8 (0.48)	—	-2.8 (0.80)	—
BEAM (ref.)	0 (reference)	—	0 (reference)	—	0 (reference)	—
Relapse post HDT-ASCT (ref. no relapse)	-0.13 (0.92)	—	-3.9 (0.44)	—	-12.5 (0.23)	—
Chest RT (N)						
Unexposed (120)	0 (reference)	—	0 (reference)	—	0 (reference)	—
1–13 Gy (32)	0.86 (0.57)	—	6.0 (0.29)	—	7.9 (0.5)	—
> 13–65 Gy (42)	1.75 (0.19)	—	3.4 (0.5)	—	15.1 (0.15)	—
P-trend	0.18	—	0.39	—	0.14	—
Doxorubicin (N)						
< 300 mg m ⁻² (69)	0 (reference)	0 (reference)	0 (reference)	0 (reference)	0 (reference)	0 (reference)
300–399 mg m ⁻² (51)	-2.32 (0.09)	-0.87 (0.35)	-8.2 (0.12)	0.4 (0.90)	-18.9 (0.08)	2.6 (0.51)
400–775 mg m ⁻² (74)	-1.58 (0.21)	-1.26 (0.16)	-5.9 (0.22)	0.7 (0.83)	-11.3 (0.25)	6.1 (0.1)
P-trend	0.22	0.15	0.23	0.83	0.26	0.1
Cyclophosphamide (N)						
0–3.49 g m ⁻² (56)	0 (reference)	—	0 (reference)	—	0 (reference)	—
3.50–5.99 g m ⁻² (68)	-0.48 (0.72)	—	-0.1 (0.98)	—	1.9 (0.86)	—
6.00–12.30 g m ⁻² (70)	-1.35 (0.32)	—	-2.5 (0.63)	—	-6.2 (0.55)	—
P-trend	0.31	—	0.61	—	0.53	—
Bleomycin ^a (N)						
Unexposed (18)	0 (reference)	0 (reference)	0 (reference)	0 (reference)	0 (reference)	0 (reference)
1–12 IU · 10 ⁴ /m ² (12)	-1.44 (0.61)	-0.91 (0.63)	-0.5 (0.96)	5.5 (0.43)	-14.6 (0.50)	-6.8 (0.41)
> 12–21 IU · 10 ⁴ /m ² (11)	-1.88 (0.51)	-2.16 (0.26)	-15.9 (0.14)	-13.9 (0.05)	-27.4 (0.22)	-13.7 (0.09)
P-trend	0.2	0.40	0.82	0.34	0.47	0.78
VO _{2peak} (l min ⁻¹)	—	—	—	—	75.4 (<0.01)	58.5 (<0.01)
Physical activity level						
Low	0 (reference)	0 (reference)	0 (reference)	0 (reference)	0 (reference)	0 (reference)
Medium	1.47 (0.23)	1.74 (0.05)	2.5 (0.6)	7.4 (0.03)	14.9 (0.12)	12.8 (0.01)
High	5.85 (<0.01)	4.43 (<0.01)	15.8 (<0.01)	12.5 (<0.01)	48.2 (<0.01)	17.6 (<0.01)
P-trend	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
Restrictive pulmonary function impairment (ref. no impairment)	0.01 (0.1)	—	1.5 (0.857)	—	0.4 (0.98)	—
Obstructive pulmonary function impairment (ref. no impairment)	-3.99 (0.04)	-1.80 (0.17)	-19.2 (0.01)	-14.3 (<0.01)	-23.3 (0.13)	—
Diffusion capacity impairment (ref. no impairment)	-3.90 (<0.01)	-2.33 (<0.01)	-14.1 (<0.01)	-4.6 (0.11)	-40.9 (<0.01)	-7.2 (0.03)
LVEF (%)	0.01 (0.92)	—	-0.4 (0.31)	—	-0.2 (0.80)	—
Haemoglobin (g dl ⁻¹)	2.08 (<0.01)	0.57 (0.14)	10.6 (<0.01)	1.9 (0.19)	24.8 (<0.01)	2.6 (0.12)

Abbreviations: BEAM = carmustine, etoposide, cytarabine, and melphalan; BMI = body mass index; HDT-ASCT = high-dose therapy with autologous stem cell transplantation; IU = international units; LVEF = left ventricular ejection fraction; RC = regression coefficient; RT = radiotherapy; TBI = total body irradiation; VO₂ = volume oxygen. Bold: RCs and P-values represent statistical significance at a 0.05 level.

^aUnexposed group split into NHL and HL patients, using unexposed HL patients as a reference (coefficient for unexposed NHL patients (n = 153) not shown).

by Armenian *et al* (2015) on long-term pulmonary function in childhood cancer survivors, where impaired diffusion capacity (defined as <75% predicted) was detected in 35% of the patients. Impaired gas diffusion capacity was independently associated with reduced VO_{2peak} and workload in the regression analysis. Although, the diffusive capacity of the lung is oversized in terms

of adequate oxygen saturation of the arterial blood in healthy individuals (Basset and Howley, 2000), our data showed that cardiorespiratory fitness among LSs without HF was indeed limited by impaired diffusion capacity. Although neither LVEF nor Hb concentration was independently associated with VO_{2peak}, we cannot rule out that these factors have contributed in conjunction

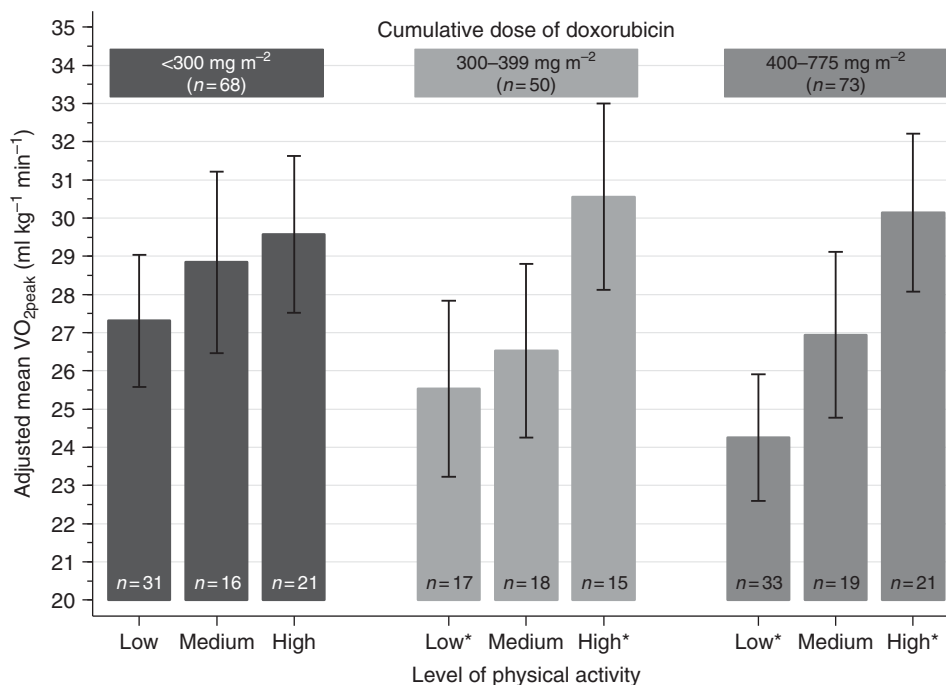


Figure 3. Mean peak oxygen uptake (VO_{2peak} , $ml\ kg^{-1}\ min^{-1}$) with 95% confidence intervals (CIs) by physical activity level (weighted sum of self-reported frequency, duration, and intensity) over groups of cumulative doxorubicin doses, adjusted for gender; age at survey (continuous); BMI (continuous); smoking (never, former, current); diffusion capacity (impaired, not impaired). Adjusted means were predicted by using Stata's post-estimation command 'margins' after linear regression. *Statistically significant difference between low and high physical activity level within doxorubicin group (i.e., non-overlapping CIs).

with impaired diffusion capacity and collectively reduced cardiorespiratory fitness in our patients as compared with the reference population.

Strengths of the present study include the large study population of only LSs after HDT-ASCT, in which cardiorespiratory fitness has not been reported on previously, and further the high-quality data from hospital records, from thorough medical exams, and from a validated questionnaire on physical activity. Further, the participants did not differ from non-participants, which strengthen the external validity and the generalisability of our results.

Our study was, however, limited to a cross-sectional analysis as we lacked pre-diagnostic data, and could not identify causal factors of cardiorespiratory fitness. Survival and risk of death analyses according to cardiorespiratory fitness were yet not possible due to the short period of time since testing and examination, but are warranted and will further elucidate whether preservation of cardiorespiratory fitness may prolong survival and reduce mortality in LSs after HDT-ASCT.

In summary, our data suggest that highly physically active LSs after HDT-ASCT could counteract the adverse effects from intensive anticancer treatment and reach the VO_{2peak} level of a sedentary, healthy reference population. Impaired diffusion capacity and current smoking were independent factors associated with decreasing VO_{2peak} . We therefore suggest increased attention towards physical activity counseling/interventions and smoking cessation advice in this patient group. Individuals with impaired diffusion capacity may benefit from subsequent monitoring to detect pulmonary vascular diseases.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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