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ORIGINAL ARTICLE

Risk factors for impaired pulmonary function and cardiorespiratory fitness in very long-term adult survivors of childhood acute lymphoblastic leukemia after treatment with chemotherapy only*

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ABSTRACT

Background: Survivors of childhood acute lymphoblastic leukemia (ALL) are at risk of late treatment-related side-effects. Data regarding prevalence and risk factors for impairments in pulmonary function and cardiorespiratory fitness are limited, and reported findings are inconsistent and inconclusive.

Material and methods: In a cross-sectional study, 116 ALL survivors (median 5 years at diagnosis, 29 years at follow-up, 53% females) were examined, median 23 years after treatment with chemotherapy only. Individual cumulative doses of cytostatic agents were calculated. Methods included blood tests, echocardiography, pulmonary function tests and cardiorespiratory exercise test.

Results: Females had lower % predicted gas diffusing capacity (DLCO) than males (mean [SD] 84 [13] versus 97 [14], $p < .001$). Impairment in DLCO was found in 34% females versus 7% males, $p < .001$. In a multiple linear regression model, female gender, body mass index (BMI) and smoking were risk factors for reduced % predicted DLCO, with a borderline significant effect of left ventricular ejection fraction (LVEF). Impaired cardiorespiratory fitness was found in 42% of the survivors, with a borderline increased risk in females, $p = .06$. Smoking and BMI were risk factors for reduced % predicted VO_2peak. Subjects exposed to anthracyclines had lower LVEF% and % predicted VO_2peak than those not exposed, (mean [SD] 56.2 [4.3] versus 59.2 [5.2], $p = .01$ and 86.9 [18.4] versus 92.8 [18.4], $p = .03$, respectively).

Conclusions: Impairments in pulmonary function and cardiorespiratory fitness are common in very long-term survivors of childhood ALL. Risk factors are female gender, BMI and smoking. In order to preserve pulmonary function and cardiorespiratory fitness, we suggest increased attention and targeted advice on modifiable lifestyle factors such as smoking, inactivity and overweight.

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Introduction

During the past decades, therapeutic improvements have dramatically increased the cure-rate and long-term survival of childhood malignancies [1]. However, the improved prognosis has allowed the occurrence of late, treatment-related side-effects [2,3].

The lungs are liable to suffer from adverse effects of chemotherapy. Numerous antineoplastic drugs have been linked to pulmonary toxicity, such as bleomycin, carmustine, lomustine, busulfan, methotrexate and cyclophosphamide [4,5]. Additionally, radiotherapy may affect pulmonary function [4,6]. In the Childhood Cancer Survivor Study, the risk of pulmonary complications was more than three times higher in childhood cancer survivors than in their siblings [7]. The study was based on self-reports from more than 12 000 survivors, but the information was not substantiated with objective data. In a systematic review of pulmonary outcomes in survivors of childhood cancer, restrictive and obstructive impairment, as well as gas diffusing capacity impairment, were described [3]. In a recent study of childhood cancer survivors with median 22 years follow-up, 45% were reported to have DLCO below 80% of predicted [8].

In studies on long-term pulmonary function in survivors of childhood onset acute lymphoblastic leukemia (ALL), both prevalence of impairment and degrees of severity vary widely [9–14]. However, those studies are now old [9–14], some had limited sample size [13,14] and the follow-up time rarely exceeded 10 years [9,13,14].

There is limited knowledge and inconsistent data regarding the clinical relevance of decreased pulmonary function in long-term ALL survivors; i.e., whether impairment is associated with reduced cardiorespiratory fitness. In a recent study

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of 91 survivors of ALL, exercise intolerance in activities of daily life was reported in 45% of the subjects [15].

In a single center cross-sectional study of a large and homogenous population of childhood ALL survivors who had all received treatment according to Nordic ALL protocols, we aimed (1) to assess very long-term effects of chemotherapy on pulmonary function and cardiorespiratory fitness in, and (2) to identify possible predictors of impairments in lung function and physical fitness.

Material and methods

Design and study population

The present study was part of a large, cross-sectional study covering a broad range of late treatment effects [16–19], including assessment of cardiac function [18]. All subjects included were survivors of childhood ALL, diagnosed in the period 1970–2002. The age at diagnosis was 16 years or less. All were treated at Oslo University Hospital, a tertiary center covering approximately half of the population in Norway (4.9 mill at the time of the study). The survivors were identified through the Cancer Registry of Norway. All adult survivors (>18 years old) and alive in 2009 were eligible for the study. In total, 210 survivors fulfilled the criteria, 160 agreed to participate and 140 completed the clinical examinations. Subjects who did not participate in the clinical study did not differ significantly from those included with respect to gender distribution, age at diagnosis and years of observation [19]. Pulmonary function tests and echocardiography were carried out in 138 subjects. Of these, five subjects did not perform the cardiopulmonary exercise test, (three were physically incapable and two declined). Since we wanted to study the effects of chemotherapy only, patients who had received craniospinal radiotherapy ($n = 20$) and/or bone marrow transplantation ($n = 3$) were excluded from the present study which hence comprised 116 subjects. All participants gave their written informed consent. The Regional Committee for Medical and Health Research Ethics approved the study (2009/926).

Treatment

At follow-up, medical records were reviewed for individual treatment data. The ALL treatment protocols have been reported earlier [20,21] and survival rates have been found to be among the highest in Europe and comparable to the United States [22,23]. Cumulative doses of intravenous chemotherapy (i.e., vincristine, methotrexate, cyclophosphamide and anthracyclines) were calculated, adjusted for body surface area. Anthracyclines doses were converted to doxorubicin isotoxic doses [24]. For the present study, oral or intraspinal administration of methotrexate were not analyzed.

Clinical assessment

The patients answered a questionnaire and underwent a clinical examination. Questions included history of smoking, physician diagnosed pulmonary or cardiac disease, other relevant current or previous diseases and use of current medication. The subjects were classified as current smokers or nonsmokers. Weight and height were measured and body mass index (BMI, kg/m^2) calculated. Overweight was defined as BMI $\geq$25 kg/m^2 and obesity was defined as BMI $\geq$30 kg/m^2, in line with the World Health Organization Classification [25]. Blood tests included hemoglobin (Hb) and N-terminal pro-brain natriuretic peptide (NT-Pro-BNP). The hospital's reference values for, respectively, males and females were: Hb 13.4–17.0 g/dL and 11.7–15.3 for subjects >12 years old, and NT-Pro-BNP <10 pmol/L and <20 pmol/L in the age group 18–48 years old.

Pulmonary function measurements

Pulmonary function tests included dynamic spirometry, determination of static lung volumes and single breath gas diffusing capacity (DLCO). Spirometric variables were forced vital capacity (FVC), forced expiratory volume in 1 s (FEV1) and the ratio FEV1/FVC. Lung volume variables were total lung volume (TLC) and residual volume (RV). Gas transfer variables were transfer factor for carbon monoxide, DLCO and DLCO divided by alveolar volume, VA. DLCO measurements were also corrected for Hb. All measurements were performed with the Vmax Pulmonary Function Unit (VIASYS Respiratory Care Inc, Yorba Linda, CA) and according to the guidelines recommended by the European Respiratory Society guidelines (ERS) [26–28]. The pulmonary function variables were expressed in absolute values and as a percentage of predicted normal values. Reference values were those recommended by ERS [29]. Obstructive impairment was defined as FEV1/FVC <0.7 according to The Global Initiative for Chronic Obstructive Lung Disease [30]. Restrictive impairment and impairment in DLCO were defined as <80% of predicted. These cutoff points correspond to the lower 5th percentiles in the reference material and in line with ERS recommendations [29].

Cardiopulmonary exercise test

Cardiopulmonary exercise testing was performed on a Sensormedics Vmax unit (VIASYS Respiratory Care Inc., Yorba Linda, CA) with an Ergoline 800 bicycle, (Bitz, Germany). The gas exchange units were calibrated daily. During exercise testing, 12-lead electrocardiography, oxygen saturation (SpO_2), gas exchange and ventilatory variables were monitored continuously. Testing was conducted until exhaustion, with respiratory exchange ratio (RER) > 1.10. The test consisted of three phases: a 2-min warm-up (20–50 Watt workload), an incremental exercise phase 8–12 min until exhaustion, and 2-min recovery phase [31]. VO_2peak was the primary outcome and was recorded together with max oxygen pulse, maximum minute ventilation, maximum workload, RER, SpO_2 and perceived exertion (Borg scale). The measured values were compared to reference values adjusted for gender and age [32]. Impaired cardiorespiratory fitness was defined as VO_2peak below 80% of predicted value [31,33].

Table 1. Demographics and clinical characteristics according to gender in 116 long-term survivors of childhood acute lymphoblastic leukemia treated with chemotherapy only.

		Total N = 116	Male N = 55 47%	Female N = 61 53%	p-value
Variables					
Age at diagnosis, median (range)		5.4 (0.3–16.0)	6.1 (0.6–16.0)	5.3 (0.3–15.5)	.69
Age at follow-up, median (range)		28.5 (18.6–46.5)	28.4 (19.2–45.8)	28.5 (18.6–46.5)	.66
Years of observation, median (range)		23.2 (7.4–40.0)	21.6 (7.9–37.5)	23.8 (7.4–40.0)	.33
Smoking, *n* (%)		22 (19%)	9 (16%)	13 (21%)	.41
Physican diagnosed asthma, *n* (%)		5 (4%)	1 (2%)	4 (7%)	.22
BMI, kg/m^2, mean (SD)		25.3 (5.2)	24.6 (3.8)	25.9 (6.1)	.21
Overweight, BMI ≥25, *n* (%)		44 (38%)	16 (29%)	28 (46%)	.047
Obese, BMI ≥30, *n* (%)		20 (17%)	6 (11%)	14 (23%)	.07
Hemoglobin, g/100 ml, mean (SD)		14.2 (1.3)	15.2 (0.9)	13.4 (0.9)	<.001
	N (%)	Median (range)			
Chemotherapy					
Vincristine, mg/m^2	116 (100)	22 (8–88)	22 (8–88)	22 (8–88)	.51
Methotrexate, g/m^2	110 (95)	21 (1–64)	21 (1–64)	8 (1–64)	.09
Antracyclines, mg/m^2	89 (77)	120 (40–510)	120 (40–510)	120 (40–510)	.20
Cyclophosphamide, g/m^2	38 (33)	3 (0.3–10)	3 (0.3–10)	3 (0.3–10)	.31

BMI: body mass index. Chemotherapy values are cumulative intravenous doses. Antracycline is doxorubicin equivalent dose. Data presented as mean (SD), median (range) or number (percent). Statistical comparison between male and female gender.

A significant desaturation in SpO_2 was defined as a drop of at least 4%-points during the test [31].

Echocardiography

The echocardiographic examination was carried out according to international recommendations [34], using Vivid 7/E9 scanners (GE, Horten, Norway). Left ventricular ejection fraction (LVEF) was assessed by Simpson's biplane rule [34]. Left ventricular systolic dysfunction was defined as a LVEF of <50% [35]. The results from the echocardiographic study have been reported in detail elsewhere [18].

Statistical analyses

Data are presented as mean (SD), median (range) or numbers (%). Group mean data were compared by Student's *t*-test or Mann–Whitney *U* test, as appropriate. Categorical data were compared by the Chi-square test. Multiple linear regression analyzes were used to detect associations between, respectively, pulmonary function and VO_2 peak, and relevant explanatory variables. The independent variables entered into the regression models were those that where hypothesized a priori for biological or clinical reasons, or found to be significant at the 20% level by previous univariate analyses. The covariate chemotherapy was entered into the models as continuous variables (i.e., the cumulative dose of each agent), and also dichotomized into above/below the median value of the cumulative dose. Additionally, the two drugs (anthracyclines and cyclophosphamide) that were administrated to only a portion of the subjects, were dichotomized into 'no exposure' = 0 versus 'exposure' = 1. All statistical tests were two sided, and *p*-values < .05 were considered statistically significant. All calculations were performed with IBM SPSS statistics version 23.

Results

Demographics and clinical characteristics of the study population according to gender are presented in Table 1. Males and females were comparable with respect to age at diagnosis, years of observation, smoking habits and physician-diagnosed asthma. In total, 44 (38%) of the subjects were overweight, of which 20 (17%) were obese. Mean values for Hb were within the normal range for both genders. Neither cumulative doses of chemotherapy nor exposure to, respectively, anthracyclines and cyclophosphamide, differed significantly between the genders.

Table 2 shows pulmonary and cardiac function by gender. Mean values for all lung function variables were above 80% of predicted for both genders. Three (3%) subjects had restrictive impairment, seven (6%) had obstructive impairment, and 25 (22%) had impaired gas diffusing capacity. Females had lower DLCO% predicted than males, $p < .001$. The difference persisted when DLCO was adjusted for Hb levels and also when smokers were excluded from the analysis (data not shown). Impaired DLCO was found in 4 (7%) males versus 21 (34%) females, $p < .001$. A weak, but significant correlation was found between DLCO% predicted and LVEF ($p = .047$). No significant correlations were found between DLCO% predicted and cumulative doses of any of the four chemotherapeutic agents. Subjects who had been exposed to, respectively, anthracyclines or cyclophosphamide had comparable DLCO% predicted to those who had not been exposed. In a multiple linear regression model, female gender, BMI and smoking were associated with reduced DLCO% predicted, with a borderline effect of LVEF (Table 4).

For the entire study group, mean LVEF was normal (def. > 50%) and there was no significant difference between the genders (Table 2). Three subjects had left ventricular systolic dysfunction (LVEF 46%, 44% and 43%, respectively). No significant correlation was found between LVEF% and cumulative doses of anthracyclines, but subjects who had been exposed to anthracyclines had lower LVEF% than those who had not been exposed (mean [SD] EF% 56.2 [4.3] versus 59.2 [5.2], $p = .01$). Two female subjects had NT-Pro-BNP levels slightly above the normal range (20 and 30 pmol/L, respectively).

Mean VO_2peak was above 80% of predicted in both genders (Table 3). Impaired cardiorespiratory fitness was found

Table 2. Pulmonary function and cardiac function in 116 long-term survivors of childhood acute lymphoblastic leukemia treated with chemotherapy only.

	Total $N = 116$	Male $N = 55$ 47%	Female $N = 61$ 53%	p value
Pulmonary function				
Total lung capactiy, % pred	102 (15)	101 (17)	102 (13)	.56
Forced vital capacity, % pred	103 (12)	103 (12)	104 (12)	.44
Forced expiratory volume, 1 s, % pred	98 (11)	98 (11)	98 (12)	.85
FEV1/FVC	0.81 (6)	0.80 (6)	0.82 (6)	.06
Gas diffusing capacity (DLCO),% pred	91 (15)	97 (14)	84 (13)	<.001
DLCO/alveolar volume, % pred	99 (16)	108 (16)	90 (12)	<.001
Restrictive impairment, *n* (%)	3 (3%)	1 (2%)	2 (3%)	.61
Obstructive impairment, *n* (%)	7 (6%)	5 (9%)	2 (3%)	.19
Gas diffusing impairment, *n* (%)	25 (22%)	4 (7%)	21 (34%)	<.001
Cardiac function				
Blood pressure, mmHg				
Systolic	125 (13)	131 (13)	120 (12)	<.001
Diastolic	72 (9)	72 (9)	71 (9)	.68
Heart rate, ECG	68 (11)	68 (12)	69 (10)	.69
NT-Pro-BNP, pmol/l	4.7 (4.5)	2.7 (2.1)	6.5 (5.3)	<.001
Echocardiography, LVEF %	57 (4.7)	56 (4.6)	57 (4.8)	.27

FEV1: forced expiratory volume 1 s; FVC: forced vital capacity; NT-Pro-BNP: N-terminal pro-brain natriuretic peptide; LVEF: Left ventricular ejection fraction. Data presented as mean (SD) or number (percent). Statistical comparison between male and female gender.

Table 3. Cardiopulmonary exercise test in 111 long-term survivors of childhood acute lymphoblastic leukemia treated with chemotherapy only.

	Total $N = 111$	Male $N = 53$ 48%	Female $N = 58$ 52%	p value
VO_2peak, L/min	2.6 (0.7)	3.2 (0.5)	2.1 (0.4)	<.001
VO_2peak/kg, ml/kg/min	35.0 (8.5)	39.6 (8.2)	30.8 (6.4)	<.001
VO_2peak, % predicted	85 (18)	89 (19)	83 (17)	.06
VO_2peak impairment	47 (42%)	18 (34%)	29 (50%)	.08
Peak heart rate	183 (12)	184 (13)	183 (12)	.51
Peak heart rate, % predicted	96 (6)	96 (7)	95 (6)	.40
SpO_2% before test	96 (1)	95 (1)	96 (1)	.09
SpO_2% at end of test	94 (2)	94 (2)	95 (2)	.11
Respiratory exchange ratio	1.20 (0.07)	1.22 (0.07)	1.18 (0.06)	.009

VO_2 peak: peak oxygen uptake; SpO_2: Oxygen saturation in blood. Data presented as mean (SD) or number (percent). Statistical comparison between male and female gender.

Table 4. Univariable and multivariable linear regression analysis with DLCO% predicted and VO_2peak% predicted as dependent variables

	Univariable analysis			Multivariable analysis		
Variable	β	95% CI	p value	β	95% CI	p value
DLCO % predicted						
Female gender	−13.2	−18.3, −8.1	<.001	−14.1	−19.1, −9.2	<.001
Age at diagnosis (years)	−0.2	−0.9, 0.5	.66		–	
Follow–up (years)	0.3	−0.1, 0.7	.14	0.3	−0.2, 0.7	.23
BMI (kg/m^2)	0.5	−0.0, 1.1	.06	0.6	0.2, 1.1	.01
Smoking	−11.3	−18.4, −4.3	.002	−9.8	−16.0, −3.6	.002
LVEF	0.6	0.0, 1.2	.047	0.5	−0.0, 1.1	.07
Anthracyclines	−4.7	−11.3, 1.9	.16	0.0	−7.4, 7.4	.99
VO_2peak % predicted						
Female gender	−6.5	−13.5, 0.4	.06	−4.3	−10.2, 1.7	.16
Age at diagnosis (years)	0.5	−0.4, 1.3	.31		–	
Follow-up (years)	0.5	0.0, 1.0	.06	0.6	−0.02, 1.0	.004
BMI (kg/m^2)	−1.6	−2.3, −1.0	<.001	−1.7	−2.3, −1.1	<.001
Smoking	−14.7	−23.6, −5.8	.001	−13.9	−21.4, −6.4	<.001
LVEF	1.0	0.3, 1.7	.01	0.3	−0.3, 1.0	.30
Anthracyclines	0.02	0.0, 0.1	.38		–	

BMI: body mass index; CI: confidence interval; DLCO: diffusing capacity for carbon monoxide; LVEF: left ventricular ejection fraction; VO_2 peak: peak oxygen uptake.

in 47 (42%) of the subjects; in 18 (34%) of the males and in 29 (50%) of the females, $p = .08$. No significant correlations were found between VO_2peak % predicted and cumulative doses of any of the four chemotherapeutic agents, but subjects who had been exposed to anthracyclines had lower VO_2peak than those who had not been exposed (VO_2peak % predicted mean [SD] 92.8 [18.4] versus 86.9 [18.4], $p = .03$). In a multiple linear regression model, BMI and smoking were associated with reduced VO_2peak % predicted (Table 4).

Discussion

The main findings of this study were that median 23 years after curative chemotherapy for childhood ALL, mean pulmonary function and cardiorespiratory fitness were within the lower predicted range for the survivors as a group. However, impairment in DLCO was found in 22% of the subjects and cardiorespiratory fitness was impaired in 42%. Risk factors for impairment in DLCO were female gender, BMI, smoking. Risk factors for impaired cardiorespiratory fitness were BMI and smoking. In sum, these findings underline the importance of long-term monitoring of survivors after ALL, and highlight a need for increased focus on smoking, physical activity and overweight. We encourage counseling on these modifiable lifestyle factors in the clinical oncology setting.

DLCO is known to be a sensitive test for detecting subclinical chemotherapy-induced lung injury [36]. We found a highly significant gender difference in gas diffusing capacity, as both a continuous (difference in means) and a dichotomous measure. Our findings confirm the results reported in a recent study of 121 survivors of childhood cancer by Armenian et al. [6]. They observed abnormalities in gas diffusion capacity in 35% of the subjects, with nearly four times higher risk in females than in males. Age at diagnosis and years of observation were similar in the two studies, but whereas our study was restricted to survivors of ALL treated with chemotherapy only, the study by Armenian et al. included a wide range of childhood cancer survivors with leukemias, lymphomas and solid tumors, some treated with radiotherapy and hematopoietic stem cell transplantation in addition to chemotherapy. Thus, our study underlines the fact that impaired pulmonary function and associated gender differences are multifactorial and present also in survivors not exposed to irradiation, bleomycin or hematopoietic stem cell transplantation. In accordance with Armenian et al, we found no association between cumulative chemotherapy doses and diffusion capacity abnormality.

Bleomycin is the model drug for studying cytotoxic lung injury. In studies of bleomycin-treated patients, where the different components of DLCO have been investigated separately, it appeared that pulmonary capillary blood volume was the component primarily affected [37]. Although mechanisms of bleomycin-induced toxicity are not necessarily transferable to other types of chemotherapy, it is conceivable that small vessel damage may be an important feature of cytotoxic lung injury in general. Why females should be more susceptible to microvascular lung injury than males is unclear and studies aimed to elucidate the underlying mechanisms are warranted.

In a review article, Armstrong *et al.* [38] reported that gender should be identified as a risk factor for numerous long-term adverse outcomes in cancer survivors, with female sex more commonly associated with higher risks. They found that the literature supported associations between female gender and obesity, cardiovascular outcomes, development of primary hypothyroidism and osteonecrosis. Due to limited data, they were not able to establish a link between female gender and pulmonary toxicity. They concluded that the results of the review suggest future investigations to further define gender as a risk factor for other treatment-specific outcomes. We think that our study offers a valuable contribution to the request by Armstrong *et al.* [38] by confirming that females have an increased risk of impairment in pulmonary function.

Smoking is known to be associated with a reduction in DLCO due to CO back pressure and carboxyhemoglobin (COHb) [39]. In DLCO measurements, adjustment for CO back pressure is not routinely done. Thus, the increased risk of impaired diffusing capacity seen in the currently smoking subjects, as compared to both never and former smokers, may partly have been mediated by an increase in COHb. However, since smoking habits were similar in males and females, smoking cannot explain the significant difference between the genders in DLCO% predicted.

Measurement of VO_2peak represents the gold standard assessment of cardiorespiratory fitness, and is useful to assess the global effect of pulmonary and cardiac impairments [40]. We found impaired cardiorespiratory fitness in 42% of the long-term ALL survivors, with no significant difference between the genders. Risk factors for reduced VO_2peak were BMI and smoking. Thirty-eight percent of the subjects were overweight, of whom 17% were obese, which is comparable to prevalence data reported from health surveys in Norway [41]. The proportion of smokers (19%) was high, being 4% points higher than the Norwegian population average (15%) [42]. Since preserving cardiorespiratory fitness by physical activity might be life-prolonging in cancer survivors, the clinical implication of our findings would be to focus on modifiable factors, i.e., smoking, overweight and exercise. Overweight and smoking are generally associated with physical inactivity, and young cancer survivors in these subgroups may in particular benefit from lifestyle counseling.

As survival after childhood cancer continues to improve, the role of effective countermeasures against treatment-related late effects is becoming increasingly important. In recent years, lifestyle change after cancer treatment has received attention, and physical activity and smoking cessation have been highlighted as modifiable factors that may improve the length and quality of life in long-term cancer survivors [43–45]. A report from the St. Jude Lifetime Cohort Study concluded that long-term adult survivors of childhood and adolescent malignancies who did not follow physical activity and diet guidelines set out by the World Cancer Research Fund and American Institute for Cancer were more likely to have metabolic syndrome with a more than two fold relative risk in both males and females [46].

The major strengths of the present study are the very long-term follow-up, the homogeneous patient population given uniform treatment according to Nordic protocols, and access to accurate and detailed treatment data for all subjects. An attendance of 66% is acceptable in very long-term childhood cancer survivors, and the participants did not differ from the non-participants with respect to gender, age at diagnosis and years of observation, which strengthen the external validity and the generalisability of our results.

We calculated the actually delivered cumulative doses of each drug, which is the recommended gold standard for ascertainment of treatment exposure [47]. Even so, it was a methodological challenge to analyze the impact of individual drugs on pulmonary function and cardiorespiratory fitness. Confounding due to concomitant use of multiple drugs would invariably be present, and clusters around the median doses made analyzing the drugs as continuous variables challenging. Also, whereas critical doses have been established for bleomycin [37] and for anthracyclines with respect to cardiotoxicity [48], there are no clear cutoffs recommended for vincristine, methotrexate, cyclophosphamide and anthracyclines with respect to pulmonary toxicity. All four drugs have been linked to pulmonary toxicity, but mostly through case reports or small observational studies [4,5]. Whereas nearly all subjects had received methotrexate (95%) and vincristine (100%), anthracyclines and cyclophosphamide had been given to, respectively, 77% and 33% of the subjects, and the latter two variables could therefore be dicotomized into 'exposure' vs 'no exposure'.

One limitation of the present study is lack of a control group for comparison of lung function. Theoretically, an ideal control group would have been established at the time of ALL treatment and followed since, an option that was neither possible nor realistic. Establishing a control group at follow-up would require recruiting a random sample of subjects from the general population. However, as pulmonary function in healthy subjects does not only depend on gender and age, but also on height (i.e., the size of the lungs), a random sample would lack possibilities for matching on height and accordingly be inappropriate to compare with. Thus, in our opinion, a large, healthy, nonsmoking reference population provides a more robust and reliable basis for comparison than a relatively small control group.

As in most studies of survivors of childhood cancer, pretreatment data on pulmonary function were not accessible. Median age at diagnosis was 5 years and reliable results of technically complicated tests like whole body phlethysmography and gas diffusing capacity are usually not obtained until after the age of approximately 6–7 years.

In summary, we found that median 23 years after curative chemotherapy for childhood ALL, 22% of the survivors had impaired gas diffusing capacity and cardiorespiratory fitness was impaired in 42%. Since the subjects were young (median age 29 years), longitudinal data are needed to determine if the impairments will progress or remain stable throughout their adulthood. We suggest increased attention and targeted advice on modifiable lifestyle factors such as overweight, smoking and inactivity in order to preserve pulmonary function and cardiorespiratory fitness after curative treatment with chemotherapy for childhood ALL. It may also seem prudent to bear in mind that female survivors of ALL appear to have an increased risk of pulmonary impairment as compared to males.

Disclosure statement

No potential conflict of interest was reported by the authors.

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