

ORIGINAL ARTICLE



Compulsory military service as a measure of later physical and cognitive performance in male survivors of childhood cancer

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ABSTRACT

Background: Compromised physical fitness and cognitive difficulties have been reported as late effects of cancer treatment during childhood. To assess this issue, the military rankings of cancer survivors in medical checkups at call-up, and conscripts' physical and cognitive performance during the first weeks of compulsory military education were compared to those of matched population controls without a history of cancer.

Material and methods: A total of 1680 male patients born between 1960 and 1992 with a malignancy diagnosed before the age of 16 who were alive at the call-up age (18 years) were identified using the Finnish Cancer Registry, and five age, sex and place of residence matched controls for each patient using the Population Register Centre. Data on military service were gathered from Finnish Defense Forces. A conditional logistic regression analysis, the GEE-method with the cumulative logit link function, the chi-square test, the chi-square test for trend and a one-way analysis of variance were used in different analyses.

Results: Cancer survivors were exempted from military service more often than the controls ($p < .001$). The fit-for-service frequency was highest for survivors of kidney tumors (68%) and lowest after irradiated brain tumors (19%). In service, the results of the 12-min running test were poorer than those of controls for leukemia/non-Hodgkin lymphoma ($p = .03$) and brain tumor ($p = .01$) survivors. Interestingly, the standing long-jump test was the only muscle test for which survivor groups performed worse than controls. Performance on cognitive tests only differed from controls in brain tumor survivors.

Conclusions: Exemption from service is still common under the current guidelines, but fit-for-service survivors do well in military education. These results can be used for reassuring survivors that completion of military service is possible for those fulfilling the national general guidelines for military fitness.

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Introduction

During military service, good physical performance is tested under extreme conditions, and good cognitive and social capacities are required to complete training. The physical, neurocognitive and social functions of childhood cancer survivors could be limited due to cancer and treatment. The potential physical sequelae include cardiovascular dysfunction, structural musculoskeletal changes and changes in body composition as well as neuropathy. Chest irradiation or treatment with anthracyclines may lead to reduced exercise capacity due to cardiomyopathy, endothelial damage and/or pulmonary dysfunction [1]. A recent study showed a higher hazard ratio for cardiovascular late morbidities in survivors of childhood lymphomas, brain tumors, leukemia and testicular malignancies compared with siblings [2]. Limb surgery or amputations may cause significant physical or functional limitations for bone tumor survivors [3]. In Wilms' tumor patients, radiotherapy may cause disruption of tissue growth. Therefore, patients may suffer from poor development of

both muscle and bone within the radiation field [4]. Musculoskeletal, pulmonary and hearing problems have been described after treatment of neuroblastoma [5]. Some chemotherapeutic agents used to treat childhood cancer have been shown to reduce muscle strength and decrease motor performance [6].

Becoming overweight and balance problems are common, especially after brain tumors [7]. In the Childhood Cancer Survivor Study group's (CCSS) report, it was shown that especially survivors of brain tumors, and bone/soft tissue sarcoma have lower muscular strength of the lower-extremities and that their cardio-respiratory performance and mobility are impaired [8].

The cognitive performance of children treated for cancer depends on various factors (e.g., age, gender, brain development and treatment) that interact with each other [9]. Numerous studies have documented that children treated with cranial radiation therapy may suffer from neurocognitive dysfunction, defined as problems with thinking, learning and memory function [9,10]. Deficits in working memory and

processing speed have been shown to be correlated with the intensity of chemotherapy or radiation therapy as well as with the degree of white matter damage [9], and a brain tumor itself may damage healthy brain tissue. Among brain tumor (BT) survivors, neurocognitive impairment has been shown to progress over time, and dysfunctions seem to appear earlier if treatment has included both cranial irradiation and chemotherapy [11]. The reported adverse late effects of chemotherapy alone are contradictory, but many earlier studies found at least minor cognitive impairment [12]; however, children with similar diagnoses and treatments often have different outcomes, as tolerance of side effects varies among individuals [13].

In Finland, obligatory national military service is generally considered a natural stage in a young man's life, and good military fitness is viewed as an indicator of general well-being [14]. Performing well in the service has a positive effect on one's self-esteem. Disqualification or early discharge, on the other hand, can be a traumatic experience and can cause emotional harm. All young Finnish men participate in the recruitment process the year they become 18. Before entering the military, the applicants must have medical examinations performed by a civilian physician. A call-up board determines the suitability, military fitness class and placement of recruits. Exemption from military service has previously been a recommendation (before 1991) for young men with a history of cancer [15]. However, already at that time the attitudes of the call-up doctors had started to change towards more permissive statements. The current conditions (since 1991) for entering the service are as follows: disease remission for the past five years, good functional capacity and agreement from the conscript's personal oncologist. Those qualified for military service undergo both cognitive and physical testing during their period of service. The results of these tests are available in a national register, supplying unique material for the study of the late

effects of treatment in a large group of male cancer survivors.

The aims of this study were (1) to examine the current acceptance rate of cancer survivors to the compulsory military service in Finland and to compare it with the era before current health standards (valid since 1991); (2) to examine how the conscript survivors perform in physical and cognitive tests during the first weeks of the military education, and (3) to examine how the conscript survivors perform in the service. Comparisons were made with matched population controls without a history of cancer.

Subjects and methods

All males diagnosed with cancer before the age of 16 who were born between 1960 and 1992 and were alive on their 18th birthday were identified using the Finnish Cancer Registry (FCR). Information about diagnosis and primary treatment details (surgery, radiation) was obtained from the FCR. The FCR does not include information about the dose and field of irradiation or the chemotherapy protocol used. Five controls for each patient were retrieved from the Population Register Centre of Finland (PRC), matched by sex, age (same month and year of birth) and municipality at the time of cancer diagnosis. The inclusion criteria were met by 1680 cancer patients and 8399 controls (Figure 1).

Call-up evaluation

All Finnish male citizens have a call-up to compulsory military service during the year they become 18 years of age. Since 1991, the official guidelines for medical examinations have changed, and males cannot be exempted from service only based on a cancer diagnosis. Based on a physical examination and a specific questionnaire, men are divided into four military fitness categories (A, B, C and E). Category A includes

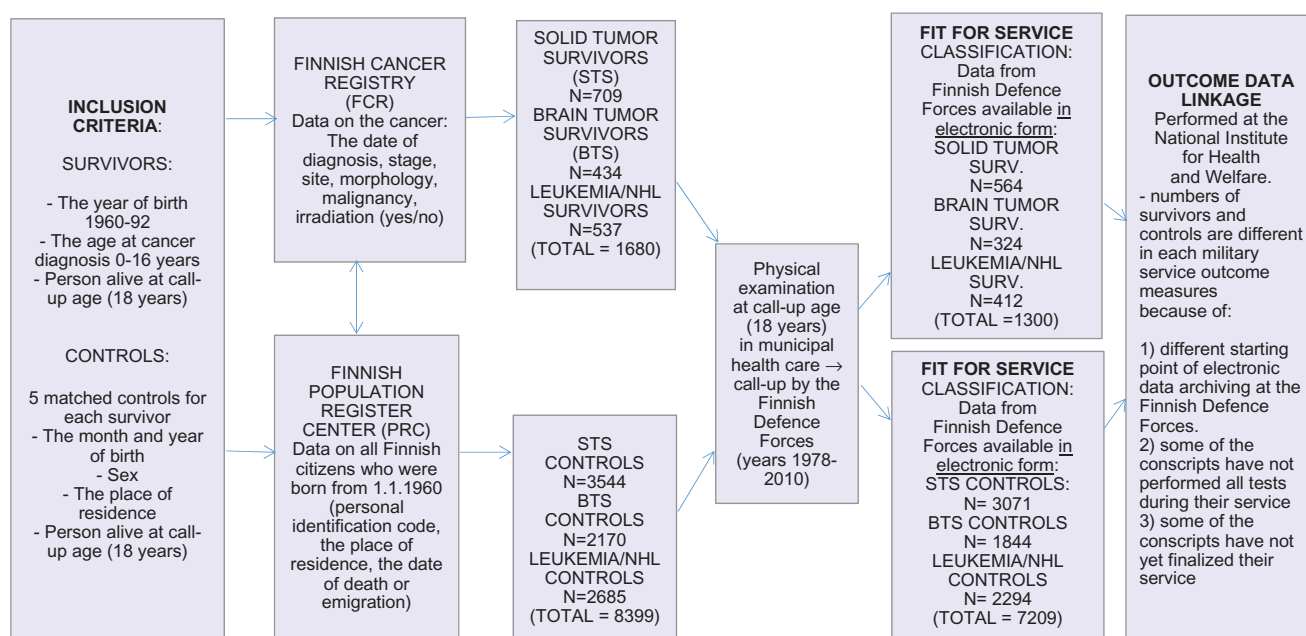


Figure 1. Flow chart describing the inclusion criteria, data sources, and information of data linkages at different steps of data collection.

those who are regarded as healthy and have been in remission for at least five years. Category B includes survivors in remission for at least five years and having an otherwise acceptable ability to function. A cancer survivor is excluded from military service if he has a severe disability or illness (category C). Survivors in remission for less than five years, or otherwise not yet evaluable, are included in category E which means that a new evaluation must be performed after two years [16].

Physical fitness tests in military service

Conscripts complete tests that measure physical capacity during the first weeks of service. For example, maximal aerobic endurance is evaluated by a twelve-minute running test (Cooper test), and musculoskeletal capacity is measured by a standing long jump (maximal muscular strength), sit-ups (evaluation of body's flexor muscles, dynamic endurance) and pushups (dynamic muscle strength of upper extremities, static endurance of body muscles) as well as by a back muscle test. For each test, there are normative age- and gender-dependent tables of test measures (points from 0.25 to 5 with 0.25 steps) by which ones performance is categorized into a certain class (weak, moderate, good, excellent). A fitness index is calculated from the results of the Cooper and muscular fitness tests (produced by a MILFIT program). The fitness index thus measures both aerobic and muscular fitness.

Cognitive evaluation in military service

During the first weeks of military service, conscripts also perform tests for cognitive and leadership skills (basic ability tests 1 and 2). Basic ability test P1 includes measurements of visuospatial, verbal and arithmetic skills as well as conscripts' general learning capacity. Each test area is evaluated through 40 tasks, and the test result is a summary of the performance for each task. The test results range from 1 to 9 ("standard nine") with an average of 5. A result lower than 5 indicates lower-than-average cognitive ability, and a result higher than 5 indicates higher-than-average cognitive ability. Test P2 includes an evaluation of tolerance to psychological stress and leadership tendency. Test profiles from P1 can be used for research purposes, but P2 results are completely confidential.

Military education of the enlisted survivors

The conscripts perform at first a six-week basic training which categorizes them for the following educational training. The duration of military service varies from 180 to 270 days for rank-and-file service members, and to 362 days for reserve officers and some rank-and-file positions that require special technical skills.

The data linkage was performed at the National Institute for Health and Welfare. Permits for registry linkage were obtained from the Finnish Ministry of Social Affairs and Health, Finnish Defense Forces (FDF), and the PRC. The study

was approved by the clinical research review office of the South-West Finland Hospital District.

Statistical analysis

Cancer survivors were grouped into three categories: leukemia/NHL (based on similarities in central nervous system directed therapies), solid tumors (ST) and brain tumors (BT). Time of call-up was divided to two categories (<1991 and 1991-) based on the changed medical checkup guidelines. Time of diagnosis was divided based on time points of changing national treatment protocols (before 1992, 1992–2001, after 2001) for the leukemia/NHL group (diminishing cranial irradiation), and by decades (before 1990, 1990–1999, after 1999) for the other groups where treatment protocols were not that uniform in each center. Irradiation (directed to CNS) was analyzed as an explanatory variable for leukemia/NHL and BT groups (groups combined). Age at diagnosis was analyzed in three groups based on the age at Finnish school entries (pre-school age <7 years, lower grades of comprehensive school 7–12 years, upper grades of comprehensive school >12 years).

Because the data were matched, comparisons between the survivors and controls were made using a conditional logistic regression analysis for dichotomous response variables, the GEE-method with the cumulative logit link function for ordinal response variables and mixed models, with the matching group as a random effect for continuous variables. Among the survivors, associations between two nominal variables were investigated using the chi-square test, between ordinal and nominal variables using the chi-square test for trend and between nominal and continuous variables using a one-way analysis of variance. The statistical analyses were performed using SAS for Windows, version 9.3 (Turku, Finland). *p*-values below .05 were considered statistically significant.

Results

Information on the enlistment data of 1300 cancer survivors and their 7209 controls (Table 1) was collected. Data on 380 cancer survivors and 1190 controls were not available from the electronic archives of FDF. Cancer was diagnosed before the age of seven in 39.7% of the patients, at 7–12 years in 27.8% and after 12 years in 32.5%.

Call-up evaluation

Cancer survivors were exempted from military service more often than their matched controls (45.6% and 7.8%, respectively, $p < .001$, Table 1). The reasons for exemption and delay are shown in Table 2. The main cause was a history of cancer (52.8%) in the survivor cohort and mental disorders (47.6%) in the control group. Exemptions based on a past cancer diagnosis were more frequent among the survivors evaluated before 1991 (62%) than those evaluated after 1991 (42%) ($p < .001$). Classification to military fitness categories differed based on cancer diagnoses (Table 1). The exemption (class C) frequency was highest for bone (81.2%) and brain tumor survivors (63.3%) and lowest for kidney tumor survivors (30.3%).

Table 1. Male childhood cancer survivors categorized by the results of military fitness classification at call-up.

Cancer type	Military fitness classification group				Total	p-value
	A N (%)	B N (%)	C N (%)	E N (%)		
Brain tumors						
Total	80 (24.7%)	32 (9.9%)	205 (63.3%)	7 (2.1%)	324	
Irradiated	10 (10.0%)	9 (9.0%)	80 (80.0%)	1 (1.0%)	100	
Leukemia						
Total	155 (52.2%)	25 (8.4%)	101 (34.0%)	16 (5.4%)	297	
Irradiated	46 (39.0%)	14 (11.9%)	49 (41.5%)	9 (7.6%)	118	
Non-Hodgkin lymphomas	54 (47.0%)	11 (9.6%)	44 (38.3%)	6 (5.2%)	115	
Hodgkin lymphomas	44 (44.0%)	8 (8.0%)	43 (43.0%)	5 (5.0%)	100	
Soft tissue sarcomas	47 (48.5%)	7 (7.2%)	43 (44.3%)	0 (0.0%)	97	
Kidney tumors	36 (47.4%)	16 (21.0%)	23 (30.3%)	1 (1.3%)	76	
Malignant bone tumors	8 (12.5%)	3 (4.7%)	52 (81.2%)	1 (1.6%)	64	
Neuroblastomas	21 (50.0%)	2 (4.8%)	18 (42.8%)	1 (2.4%)	42	
Other malignancies	91 (49.2%)	24 (13.0%)	64 (34.6%)	6 (3.2%)	185	
Total	536 (41.2%)	128 (9.8%)	593 (45.6%)	43 (3.3%)	1300	
Controls	5900 (81.8%)	509 (7.1%)	562 (7.8%)	238 (3.3%)	7209	<.001

A: five or more years in remission, healthy; B: five or more years in remission, mild limitations in health; C: not eligible for service; E: not yet evaluable.

Table 2. The reasons (sometimes multiple) for being exempted (45.6% vs. 7.8%) at military call-ups (at the age of 18 years).

Reason for exemption/delay	Survivors		Controls	
	N	%	N	%
Cancer	342	53.8 ^a	1 ^b	0.2
Neurologic disease	42	6.6	33	5.9
Psychiatric disorder	44	6.9	264	47.6 ^a
Infectious disease	2	0.3	1	0.2
Endocrinologic disease	35	5.5	39	7.0
Respiratory disease	4	0.6	30	5.4
Circulatory disease	7	1.1	7	1.3
Gastrointestinal disease	5	0.8	17	3.1
Dermal disease	3	0.5	14	2.5
Musculoskeletal/connective tissue disease	20	3.1	25	4.5
Urogenital disease	4	0.6	7	1.3
Ocular disease	11	1.7	7	1.3
Ear disease	4	0.6	8	1.4
Congenital malformation/chromosomal abnormality	15	2.3	25	4.5
Injury/Intoxication/hemato-logical disease	16	2.5	26	4.7
Unknown/not reported	39	6.1	58	10.4

The total number of evaluable survivors was 1300 and their matched controls 7209. The number of persons who received exemption was 593 and 562, respectively.

^aGroup's most common reason for exemption.

^bCancer diagnosis between the age of 16 and 18 years.

Leukemia (52.2%) and neuroblastoma (50.0%) survivors were most often classified under class A.

During the most recent treatment era (after 1999/2001), survivors were more often enlisted to category A (75%/71%) than before ($p=.001$) as the corresponding figures for category A during previous era were 49%/51% and 32%/54%. Treatment with cranial irradiation (leukemia/NHL, BT) had a significant ($p<.001$) effect on the fitness category, as 72.4% of patients in category A (60.5% in B, 53.4% in C) had not been treated with irradiation. Age at diagnosis had a significant ($p<.001$) effect on the fitness category only for leukemia/NHL survivors, as the ranking was A for 63% of those under 7 years at diagnosis, 62% for 7–12 year olds and 28% for those above 12 years at diagnosis.

Assessment of physical fitness during service

Data on physical and cognitive tests for the enlisted men were not available in electronic form over the whole study period, which explains the varying numbers in the tables.

Data on survivors and controls were gathered similarly from the database which should diminish bias in information. The results of physical fitness test categories performed during the first weeks of service are presented in Table 3. The total fitness index was significantly worse than the controls only for BT survivors. The results of the Cooper running test and muscular fitness were worse than those of controls for both leukemia/NHL and BT survivors. Cranial irradiation influenced the results, as among both leukemia and BT survivors, only those with irradiation had significantly poorer results than the controls (Table 4). Regarding the separate muscle strength tests, the results for the pull-ups, pushups, sit-ups and back muscle tests did not differ significantly from those of controls in any of the three survivor groups (data not shown); however, for the standing long jump, leukemia/NHL ($p<.001$), solid tumor ($p=.005$) and BT ($p=.001$) survivors had significantly worse results than their controls. The results were similar in both irradiated and non-irradiated survivors.

Assessment of cognitive performance during service

The results of the cognitive test during the first weeks of service are presented in Table 5. Enlisted leukemia/NHL survivors did not show significantly worse results than their controls for the cognitive tests. The mean value for the whole test was 4.7 for non-irradiated leukemia survivors, 4.2 for irradiated leukemia survivors and 5.1 for NHL survivors. The corresponding values for the controls were 4.7, 4.9 and 4.8, respectively. Conscript solid tumor survivors performed as well as their controls on the cognitive tests; however, for brain tumor survivors, there was a decline in all tested cognitive skills. Non-irradiated survivors performed significantly worse than controls in all test categories. It was surprising that irradiated survivors had lower scores than controls only in visuospatial tests, but the small number of enlisted survivors may explain this.

Military education of the enlisted survivors

Interrupting service was as common among survivors (6.2%) as controls (6.6%). Of all survivors, 76% were trained as rank-and-file service members, 19% as noncommissioned officers

Table 3. Results of physical tests performed during compulsory military service for survivors who had already begun service.

	Solid tumor survivors and their controls			Brain tumor survivors and their controls			Leukemia/NHL survivors and their controls		
	N (%)	N (%)	p-value	N (%)	N (%)	p-value	N (%)	N (%)	p-value
Fitness index			.24			<.05			.14
Excellent	20 (8%)	242 (10%)		6 (8%)	92 (10%)		13 (8%)	112 (9%)	
Good	87 (33%)	851 (34%)		18 (24%)	310 (32%)		49 (30%)	443 (34%)	
Moderate	97 (37%)	952 (38%)		30 (40%)	378 (39%)		68 (41%)	510 (39%)	
Poor	57 (22%)	478 (18%)		21 (28%)	186 (19%)		35 (21%)	276 (18%)	
Cooper test			.18			.01			.03
Excellent (>3000m)	19 (7%)	229 (9%)		5 (7%)	85 (9%)		8 (5%)	111 (9%)	
Good (>2600m)	81 (32%)	811 (32%)		19 (25%)	307 (32%)		45 (27%)	417 (32%)	
Fair (>2200m)	101 (39%)	1029 (41%)		25 (33%)	394 (40%)		84 (50%)	561 (43%)	
Poor (<2000m)	57 (22%)	459 (18%)		26 (35%)	183 (19%)		30 (18%)	206 (16%)	
Muscle fitness			.19			.02			.05
Excellent	36 (13%)	350 (14%)		7 (9%)	142 (15%)		22 (13%)	175 (13%)	
Good	70 (26%)	763 (30%)		15 (20%)	273 (28%)		35 (21%)	394 (30%)	
Moderate	84 (32%)	777 (31%)		27 (36%)	289 (30%)		63 (38%)	420 (33%)	
Poor	76 (29%)	635 (25%)		26 (35%)	265 (27%)		46 (28%)	305 (24%)	

Table 4. Performance for physical tests during compulsory military service for brain tumor and leukemia survivors presented by their irradiation treatment status.

	Brain tumors non-irradiated		p-value	Brain tumors irradiated		p-value	Leukemia non-irradiated		p-value	Leukemia irradiated		p-value
	N (%)	N (%)		N (%)	N (%)		N (%)	N (%)		N (%)	N (%)	
Fitness index			.24			.02			.31			<.01
Excellent	4 (7%)	59 (10%)		2 (15%)	28 (9%)		11 (12%)	47 (8%)		1 (3%)	34 (9%)	
Good	15 (26%)	184 (30%)		0 (0%)	105 (35%)		29 (33%)	191 (32%)		6 (17%)	137 (37%)	
Moderate	23 (41%)	245 (40%)		5 (39%)	119 (39%)		33 (37%)	243 (41%)		15 (43%)	143 (39%)	
Poor	15 (26%)	127 (20%)		6 (46%)	52 (17%)		16 (18%)	114 (19%)		13 (37%)	53 (15%)	
Cooper test			.10			<.01			.62			<.01
Excellent	3 (5%)	49 (8%)		1 (7%)	33 (11%)		7 (8%)	44 (7%)		0 (0%)	37 (10%)	
Good	17 (30%)	192 (31%)		1 (7%)	92 (30%)		24 (26%)	181 (30%)		7 (19%)	132 (36%)	
Moderate	17 (30%)	256 (41%)		5 (36%)	123 (40%)		43 (47%)	262 (44%)		22 (61%)	149(41%)	
Poor	19 (35%)	120 (20%)		7 (50%)	57 (19%)		17 (19%)	108 (18%)		7 (19%)	50 (14%)	
Muscle fitness			.10			.08			.61			<.01
Excellent	6 (11%)	87 (14%)		1 (7%)	45 (15%)		17 (19%)	83 (14%)		1 (3%)	46 (12%)	
Good	11 (19%)	172 (28%)		2 (14%)	90 (30%)		20 (23%)	174 (29%)		6 (17%)	114 (31%)	
Moderate	20 (36%)	190 (31%)		5 (36%)	83 (27%)		29 (33%)	180 (30%)		14 (40%)	127 (35%)	
Poor	19 (34%)	168 (27%)		6 (43%)	85 (28%)		22 (25%)	162 (27%)		14 (40%)	80 (22%)	

Table 5. Results for cognitive tests during compulsory military service for survivors who had begun service.

	Solid tumor survivors and their controls			Brain tumor survivors and their controls			Leukemia/NHL survivors and their controls		
	Survivors N = 115 mean (SD)	Controls N = 959 mean (SD)	p-value	Survivors N = 45 mean (SD)	Controls N = 592 mean (SD)	p-value	Survivors N = 88 mean (SD)	Controls N = 757 mean (SD)	p-value
Cognitive tests									
General talent	4.71 (1.85)	4.88 (1.88)	.26	3.82 (1.59)	4.80 (1.89)	<.01	4.76 (1.88)	4.80 (1.85)	.88
Mathematical	4.64 (1.85)	4.80 (1.90)	.31	3.96 (1.61)	4.71 (1.90)	<.01	4.95 (2.09)	5.04 (1.98)	.72
Verbal	4.41 (1.87)	4.70 (1.94)	.06	3.67 (1.72)	4.62 (1.94)	<.01	4.72 (1.92)	4.62 (1.83)	.64
Visual	5.03 (1.96)	5.12 (2.01)	.62	4.20 (1.88)	5.05 (2.03)	<.01	4.67 (1.97)	4.72 (1.95)	.82
	Non-irradiated brain tumors			Irradiated brain tumors ^a			Irradiated leukemias ^{a,b}		
	Survivors N = 34 mean (SD)	Controls N = 366 mean (SD)	p-value	Survivors N = 7 mean (SD)	Controls N = 192 mean (SD)	p-value	Survivors N = 12 mean (SD)	Controls N = 194 mean (SD)	p-value
General talent	3.76 (1.63)	4.80 (1.88)	<.01	3.43 (1.27)	4.79 (1.90)	.06	4.17 (2.55)	4.97 (1.89)	.15
Mathematical	3.44 (1.65)	4.61 (1.92)	<.01	3.71 (1.60)	4.61 (2.04)	.25	4.00 (2.49)	4.72 (1.84)	.20
Verbal	3.85 (1.62)	4.72 (1.93)	.01	3.86 (1.68)	4.68 (1.88)	.25	4.33 (1.87)	4.86 (1.93)	.36
Visual	4.24 (1.94)	5.07 (2.07)	.03	3.43 (1.62)	5.07 (1.97)	.03	4.50 (3.00)	5.30 (1.97)	.13

^aDetails on possible irradiation were not available for each survivor.^bResults for non-irradiated leukemias compared with their controls were as follows: general talent 4.73 vs. 4.71 $p = .94$, Mathematical 4.79 vs. 4.66 $p = .67$, Verbal 4.73 vs. 4.56 $p = .52$, and Visual 4.77 vs. 4.94 $p = .56$.

and 5% as reserve officers. The corresponding values for the controls were 72%, 22% and 5%, respectively. The figures did not differ significantly ($p = .83$). Interestingly, the figures for brain tumor survivors versus their matched controls ($p = .48$) were 74.7% (70.6%), 21.3% (24.1%) and 4.0% (5.3%), respectively.

Discussion

Few studies have been conducted on childhood cancer survivors and their performance in military service. It was found that survivors were exempted from military service more often than controls, though the proportion of exempted

survivors declined after 1991 when guidelines were revised. During the most recent treatment era (from 1999 to 2001), survivors were also more often enlisted to the best category A than before. For those accepted for service, the results of the aerobic performance test were significantly poorer than those of controls after treatment for leukemia/NHL and brain tumors but not after treatment for solid tumors. Irradiation treatment seemed to explain the poorer running test results. Regarding muscle fitness, the BT survivors scored significantly poorer than controls, and a poorer trend was also identified for leukemia/NHL survivors. Interestingly, the standing long jump (leg muscle test) was the only test for which all three survivor groups performed worse than their controls. Performance on cognitive tests did not significantly differ from controls other than for brain tumor survivors. Despite the limitations of physical test results during service, the enlisted survivors' performance was comparable to their controls during their military education. Conscript survivors did not discontinue service more often than controls, and were trained (military rank) similarly as controls.

Historically, disqualification from military service was based solely on a past cancer diagnosis, regardless of the outcome [16]. In the late 1980s [18] and also 10 years later [15], the exemption rate for Finnish cancer survivors was near 40%. Since 1991, the official requirements for entering the service have still liberalized [16]. However, it was found that as many as 45% of the survivors were still exempted. Similar exemption rates have been reported in other countries [17]; however, the frequency of interrupting service has declined to the same level as the controls, which may indicate that the evaluation of fitness is more precise with the current guidelines.

The Cooper test was originally designed to assess aerobic capacity, which correlates with cardiorespiratory fitness. Cardiorespiratory fitness can be compromised by several chemotherapeutic agents used in the treatment of childhood malignancies. Anthracyclines have known adverse effects on the heart [1], while alkylating agents and bleomycin have been associated with pulmonary toxicity [18]. It was found that only solid tumor survivors fared as well as their matched controls for the Cooper test. In the other two survivor groups, treatment with irradiation seemed to impair the results, which is in accordance with previous findings [4,15].

The quite low fit-for-service proportions as well as problems encountered during physical tests (impaired standing long jump) can be explained by previous findings presented in the literature. In a recent CCSS study, osteosarcoma survivors were compared with other survivors, and their general health, mental health and anxiety levels were not different; however, their functional status, activity limitations and pain were more likely to be an issue [3]. Bone tumor survivors have also been reported to have an increased risk of persistent peripheral neuropathy induced by chemotherapeutic agents [3]. In a study on survivors of Ewing sarcoma, almost two-thirds of survivors had chronic conditions, which is not surprising given the routine use of moderate- to high-dose anthracyclines, alkylating agents, musculoskeletal surgeries and radiation during treatment [19]. The treatment protocols of childhood HL usually include anthracyclines with or

without irradiation, and, therefore, HL treatments are often associated with cardiovascular late-effects and even pulmonary dysfunctions [20]. Survivors of HL unexposed to cardiotoxic treatments may also have adverse cardiovascular effects [20].

Survivors of kidney tumors were most often fit-for-service (69%), but a large proportion was classified as exhibiting a fair but not excellent performance (category B). This might be due to the musculoskeletal deformities caused by irradiation [4]. Wilms' tumor survivors have also had reduced ankle and wrist dorsiflexor strength, which are mainly caused by chemotherapy agents [6]. For the neuroblastoma survivors, their fit-for-service frequency was 57%, and the highest proportion of survivors (50%) qualified for the best fitness category was among them. Neuroblastoma survivors may have motor or sensory deficits, and spinal cord compression may complicate neurological functions and thereby decrease physical capacity [21]. It could be assumed that most neuroblastoma survivors fit-for-service were those treated for stage I and II diseases or even stage IVS and were thus not exposed to long chemotherapies or irradiation treatment.

Chemotherapeutic agents used in the treatment of childhood cancer have catabolic effects and can cause muscular weakness and decreased motor performance [6]. The muscular fitness index was lower than controls for BT and leukemia/NHL survivors, which is clearly influenced by irradiation. An earlier study showed that cranial irradiation increases the risk for testicular damage and causes growth hormone (GH) deficiency in male survivors of childhood ALL [22]. Therefore, decreased levels of testosterone and GH might explain the impaired muscular fitness of cranially irradiated leukemia patients; however, the scores for leg muscle strength, measured by the standing long jump test, were significantly poorer than those of controls in all three survivor groups. This finding might indicate that even low doses of chemotherapeutic agents or the effects of cancer on living habits can cause significant muscular weakness, and individual sensitivity may vary.

More than one-third of all brain tumor survivors and one-fifth of those treated with irradiation were qualified for military service. Physical limitations seem to continue to occur after treating patients with modern protocols [23]. In addition, the exercise capacity of BT survivors may decline due to the increased risk for adults to become overweight or obese [7]. This is consistent with the finding that even brain tumor survivors who were fit-for-service had problems with physical and cognitive performance. Irradiated survivors appeared to have the poorest muscular and endurance test results.

The findings of the cognitive performance of solid tumor survivors who were fit-for-service were comparable with the controls. This is quite straightforward, as most solid tumor patients do not receive therapy for the central nervous system. Surprisingly, HL survivors have recently been reported to be a risk group for impaired CNS integrity [24]. In this study, solid tumor survivors who were fit-for-service as a group had no significant decline in cognitive performance; however, the results suggest that brain tumor survivors experience declines in verbal, visuospatial and mathematical

performance. This is supported by previous findings regarding general cognitive skills, the ability to use memory functions and visuospatial abilities [25]. In the future, whether fractionated cranial irradiation reduces the occurrence of cognitive deficits should be investigated. Surprisingly, in this study, non-irradiated brain tumor survivors had the most severe decline in cognitive tests; however, this result may have been influenced by the small number of survivors with irradiation who were fit-for-service. Irradiated leukemia survivors had lower scores on the cognitive test than their controls, but the difference was not statistically significant, likely due to the small number of individuals tested.

This nationwide register-based study offers new information regarding the physical and cognitive performance of cancer survivors in military service. The results support positive outcomes for enlisted conscripts, which may also have a positive influence on survivors' quality of life. The limitations of the study include the lack of data on the cognitive and physical performance of survivors who were exempted from service as well as the lack of exact data on the dose levels of cancer treatments. Some service data were also missed because of the lack of electronic data files in the beginning of our study period.

Conclusions

More than half of the male childhood cancer survivors are fit for military service, and the enlisted survivors cope well with service, as discontinuations are not common. Regarding the changes in fit-for-service figures, it was shown that those evaluated before 1991 were less likely to be fit-for-service. Thus, it seems that alterations in health qualification directions along with changes in cancer treatments had an effect on the military classifications of childhood cancer survivors.

The possibility of being fit-for-service was affected by the irradiation used for treatment. Interestingly, during the most recent treatment era (from 1999 to 2001), more patients were classified as category A, which may reflect the reduction of prophylactic cranial irradiation. As expected, cranially irradiated survivors had lower test results during service than their healthy peers for both aerobic and muscular fitness. All survivor groups showed some impairment in leg muscle strength. This impairment could be a consequence of cancer itself, the chemotherapeutic agents (e.g., vincristine) used or the survivors' low general physical activity. The results showed that the level of military training was comparable to that of the general population, which is in line with earlier findings [15]. The possibility to perform the compulsory military training may support social adjustment and coping after cancer, and according to these results, more than half of male childhood cancer survivors are able to achieve this goal.

Disclosure statement

Authors Ritva Ahomäki, Kai Parkkola, Jaakko Matomäki, Arja Harila-Saari and Päivi M. Lähteenmäki have no conflicts of interest to declare. The authors alone are responsible for the content and writing of this article.

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References

- [1] Miller AM, Lopez-Mitnik G, Somarriba G, et al. Exercise capacity in long-term survivors of pediatric cancer: an analysis from the cardiac risk factors in Childhood Cancer Survivors Study. *Pediatr Blood Cancer*. 2013;60:663–668.
- [2] Kero AE, Järvelä LS, Arola M, et al. Cardiovascular morbidity in long-term survivors of early-onset cancer: a population-based study. *Int J Cancer*. 2014;134:664–673.
- [3] Fernandez-Pineda I, Hudson MM, Pappo AS, et al. Long-term functional outcomes and quality of life in adult survivors of childhood extremity sarcomas: a report from the St. Jude Lifetime Cohort Study. *J Cancer Surviv*. 2017;11:1–12.
- [4] Mäkipernäa A, Heikkilä JT, Merikanto J, et al. Spinal deformity induced by radiotherapy for solid tumours in childhood: a long-term follow up study. *Eur J Pediatr*. 1993;152:197–200.
- [5] Laverdiere C, Cheung NK, Kushner BH, et al. Long-term complications in survivors of advanced stage neuroblastoma. *Pediatr Blood Cancer*. 2005;45:324–332.
- [6] Hartman A, van den Bos C, Stijnen T, et al. Decrease in peripheral muscle strength and ankle dorsiflexion as long-term side effects of treatment for childhood cancer. *Pediatr Blood Cancer*. 2008;50:833–837.
- [7] Ness KK, Morris EB, Nolan VG, et al. Physical performance limitations among adult survivors of childhood brain tumors. *Cancer*. 2010;116:3034–3044.
- [8] Hoffman MC, Mulrooney DA, Steinberger J, et al. Deficits in physical function among young childhood cancer survivors. *J Clin Oncol*. 2013;31:2799–2805.
- [9] Askins MA, Moore BD. 3rd Preventing neurocognitive late effects in childhood cancer survivors. *J Child Neurol*. 2008;23:1160–1171.
- [10] Mulhern RK, Palmer SL. Neurocognitive late effects in pediatric cancer. *Curr Probl Cancer*. 2003;27:177–197.
- [11] Reimers TS, Mortensen EL, Schmiegelow K. Memory deficits in long-term survivors of childhood brain tumors may primarily reflect general cognitive dysfunctions. *Pediatr Blood Cancer*. 2007;48:205–212.
- [12] Conklin HM, Krull KR, Reddick WE, et al. Cognitive outcomes following contemporary treatment without cranial irradiation for childhood acute lymphoblastic leukemia. *J Natl Cancer Inst*. 2012;104:1386–1395.
- [13] D'agostino NM, Edelstein K. Psychosocial challenges and resource needs of young adult cancer survivors: implications for program development. *J Psychosoc Oncol*. 2013;31:585–600.
- [14] Multimäki P, Sourander A, Nikolakaras G, et al. Childhood predictors of military fitness: a prospective, community-based, follow-up study from age 8 to age 18. *Mil Med*. 2008;173:146–154.
- [15] Lähteenmäki PM, Salmi HA, Salmi TT, et al. Military service of male survivors of childhood malignancies. *Cancer*. 1999;85:732–740.
- [16] Rannikko J, Siitonen S. Health standards for military fitness 2012. The Finnish Defence Forces [serial online]. Tampere: Juvenes Print; 2012. p. 42–50. Available from: <http://puolustusvoimat.fi/asiointi/aineistot/ohjesaannot-ja-oppaat>
- [17] Monaco GP. Socioeconomic considerations in childhood cancer survival. Society's obligations. *Am J Pediatr Hematol Oncol*. 1987;9:92–98.
- [18] Mäkipernäa A. Long-term quality of life and psychosocial coping after treatment of solid tumours in childhood. A population-based study of 94 patients 11–28 years after their diagnosis. *Acta Paediatr Scand*. 1989;78:728–735.
- [19] Ginsberg JP, Goodman P, Leisenring W, et al. Long-term survivors of childhood Ewing sarcoma: report from the childhood cancer survivor study. *J Natl Cancer Inst*. 2010;102:1272–1283.

- [20] Lipshultz SE, Landy DC, Lopez-Mitnik G, et al. Cardiovascular status of childhood cancer survivors exposed and unexposed to cardiotoxic therapy. *JCO*. 2012;30:1050–1057.
- [21] Gunes D, Uysal KM, Cetinkaya H, et al. Paravertebral malignant tumors of childhood: Analysis of 28 pediatric patients. *Childs Nerv Syst*. 2009;25:63–69.
- [22] Siimes MA, Lie SO, Andersen O, et al. Prophylactic cranial irradiation increases the risk of testicular damage in adult males surviving ALL in childhood. *Med Pediatr Oncol*. 1993;21:117–121.
- [23] Rueegg CS, Michel G, Wengenroth L, et al. Physical performance limitations in adolescent and adult survivors of childhood cancer and their siblings. *PLoS One*. 2012;7:e47944.
- [24] Krull KR, Sabin ND, Reddick WE, et al. Neurocognitive function and CNS integrity in adult survivors of childhood hodgkin lymphoma. *J Clin Oncol*. 2012;30:3618–3624.
- [25] Ullrich NJ, Embry L. Neurocognitive dysfunction in survivors of childhood brain tumors. *Semin Pediatr Neurol*. 2012;19:35–42.