European Journal of Preventive Cardiology
EUROPEAN SOCIETY OF CARDIOLOGY®

Original scientific paper

European Journal of Preventive Cardiology
2015, Vol. 22(6) 762–770

DOI: 10.1177/2047487314529348
ejpc.sagepub.com
SAGE

Prevalence of cardiovascular risk factors in long-term survivors of childhood cancer: 16 years follow up from a prospective registry

Francesco Felicetti[1,2], Fabrizio D'Ascenzo[3], Claudio Moretti[3], Andrea Corrias[4], Pierluigi Omedè[3], Walter Grosso Marra[3], Emanuela Arvat[2], Franca Fagioli[5], Enrico Brignardello[1] and Fiorenzo Gaita[3]

Abstract

Background: Childhood cancer survivors (CCSs) have an increased risk of overweight and dyslipidaemia, but the distribution and the potential relationships between anticancer therapies and cardiovascular risk factors have been heterogeneously and not prospectively described.

Methods: All consecutive CCSs with primary cancer diagnosed between 1973–2007 and subsequently referred to our outpatient clinic were enrolled. Hypercholesterolaemia (total cholesterol >200 and/or low density lipoprotein (LDL)>160 mg/dl) was the primary end point, hypertriglyceridaemia (triglycerides >200 mg/dl) and body mass index >30 kg/m^2 the secondary end points. Cox multivariate adjustments were performed to account for differences in cancer and treatments.

Results: A total of 340 patients were included (197 male, 143 female; mean age at last follow-up 24.1 ± 3.2). The most common diagnosis were haematological malignancies ($n = 227$) and brain tumours ($n = 51$). After a median follow-up of 16.1 years, hypercholesterolaemia was diagnosed in 67 CCSs (20%), hypertriglyceridaemia in 20 CCSs (6%) and obesity in 28 CCSs (8%). Total body irradiation and growth hormone deficiency increased the risk of both hypercholesterolaemia (hazard ratio (HR) = 2.7; confidence interval (CI) 1.2–4.4 and HR = 2.3; CI 1.1–4.9; all $p < 0.05$) and hypertriglyceridaemia (HR = 6.5; CI 1.4–31 and HR = 7.2; CI 1.1–43; all $p < 0.05$). The risk of hypercholesterolaemia was also higher in CCSs who underwent autologous haematopoietic stem cell transplantation (HR = 3.2; CI 1.7–5.9; $p < 0.001$) or platinum-based chemotherapy (HR = 2.7; CI 1.5–4.9; $p < 0.001$), whereas a previous diagnosis of brain tumour (HR = 10; CI 1.2–45; $p < 0.05$) and anthracyclines exposure (HR = 1.3; CI 1.2–26; $p < 0.05$) significantly predicted obesity.

Conclusion: CCSs show a high and variable risk for developing dyslipidaemia and obesity, depending on cancer diagnosis and treatments. Therefore, they need accurate and tailored control of their cardiovascular risk profile.

Keywords

Childhood cancer survivors, late-effects, dyslipidaemia, obesity, cardiovascular risk, long-term follow-up

Received 24 September 2013; accepted 5 March 2014

Introduction

Continuous improvements in treatment protocols over the last 40 years increased the probabilities of recovery up to 80% for children and adolescents affected by tumours.[1] As a consequence, the number of childhood cancer survivors (CCSs) among the general population is steadily increasing, with a potential burden of pathological alterations due to late toxicity of

[1]Transition Unit for Childhood Cancer Survivors, Città della Salute e della Scienza Hospital, Turin, Italy
[2]Division of Oncological Endocrinology, University of Torino, Turin, Italy
[3]Division of Cardiology, Città della Salute e della Scienza Hospital, Italy
[4]Division of Paediatric Endocrinology, Città della Salute e della Scienza Hospital, Turin, Italy
[5]Division of Paediatric Haematology/Oncology, Città della Salute e della Scienza Hospital, Turin, Italy

Corresponding author:
Fabrizio D'Ascenzo, Division of Cardiology, Department of Internal Medicine, Città della Salute e della Scienza Hospital, Turin, Italy.
Email: fabrizio.dascenzo@gmail.com

anticancer therapy. Thirty years after a diagnosis of paediatric tumour, chronic illnesses related to previous anticancer treatments affect two-thirds of survivors, potentially being so serious as to lead to disabling or life threatening diseases.[2]

The most common alterations involve the endocrine system, but several studies reported that, in CCSs, cardiovascular diseases are a leading cause of mortality and morbidity.[3,4] Radiation therapy involving the thorax and anthracycline-based chemotherapy may directly undermine the cardiovascular health of CCSs, leading to an increased risk of congestive heart failure, coronary artery and valvular diseases. Moreover, cranial or total body irradiation (TBI), as well as platinum-based chemotherapy, may induce the onset of cardiovascular risk factors (CVRFs) such as diabetes, obesity, dyslipidaemia and hypertension.[5,6] Finally, endocrine dysfunctions, mainly growth hormone deficiency (GHD) and hypogonadism (quite common in CCSs), may precipitate the development of CVRFs.[7,8]

Independently of the pathophysiological mechanisms, conflicting data are reported about the incidence and the predictors of CVRFs in adult survivors of childhood cancer.[6,7] The aim of this study was to investigate the distribution of CVRFs in a cohort of CCSs followed at a specialised adult-focused follow-up clinic, in order to evaluate the potential relationships between CVRFs and previous anti-cancer therapies.

Methods

The present study is reported according to the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) Group statement.[9]

Study design

Single centre high volume prospective work.

Setting and participants

All consecutive patients who were diagnosed with a paediatric cancer between 1973–2007, and subsequently referred to the Transition Unit for Childhood Cancer Survivors within the Città della Salute e della Scienza Hospital of Turin, Italy, were enrolled. This is a specialised adult-focused follow-up clinic headed by an endocrinologist and organised with a network of committed specialists. CCSs are usually 'transitioned' to the unit when they are aged over 18 years and off therapy for at least five years. The follow-up protocols applied to each patient are tailored on the basis of risk stratification, that is, to the cancer diagnosis and previous anti-cancer treatments, in agreement with the Children's Oncology Group guidelines.[10]

Variables and data source/measurement

For the study purpose CCSs were divided into seven groups, according to paediatric cancer diagnosis: acute lymphoblastic leukaemia (ALL), acute myeloblastic leukaemia (AML), Hodgkin's disease (HD), non-Hodgkin's lymphoma (NHL), brain tumours, sarcomas and others.

All the clinical information collected during follow-up was recorded in a specially designed prospective database including demographic information, all data relative to the cancer diagnosis, the treatments and medical history (relapses, second tumours, late toxicity at endocrine, cardiac, pulmonary levels etc.). In this setting, gonadal function was periodically evaluated and hormone replacement therapy was given in all hypogonadal patients. During childhood, in patients with auxological parameters indicating growth failure, GHD was diagnosed using standard provocative tests, after all other possible causes had been ruled out. About one-half of GHD patients had received GH (growth hormone) replacement therapy during childhood, but no one was treated in adulthood.

Body mass index (BMI), lipid profile (total cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL) and triglycerides), fasting blood glucose and blood pressure were recorded at each follow up visit. Moreover, information regarding the medications/drugs taken and the diet/lifestyle was also collected. Hypercholesterolaemia was defined as fasting total cholesterol >200 mg/dl, while hypertriglyceridaemia as fasting triglycerides >200 mg/dl.[11] Patients with BMI $>30\,kg/m^2$ were considered as being obese. Diabetes mellitus was defined according to the American Diabetes Association's criteria.[12] Patients with systolic blood pressure >140 mm Hg and/or diastolic blood pressure >90 mm Hg (or receiving drugs for hypertension) were considered as having hypertension.[13]

The Framingham risk score, the only derived and validated on patients younger than 40 years, was appraised for each patient.

The interval between the first visit in which a CVRF was identified and the last follow-up visit was considered for analysis.

End point

Hypercholesterolaemia was the primary end point, LDL levels, hypertriglyceridaemia and BMI $>30\,kg/m^2$ WERE the secondary ones.

Statistical analysis

Continuous variables are expressed as mean $\pm$ standard deviation (SD) or median and first and third quartiles

and were compared by analysis of variance (ANOVA) test and with student's *t*-test. Categorical variables are presented as counts and percentages, and were compared by chi-square test and with Fisher test. The *p* values unadjusted for multiplicity are reported throughout, with statistical significance set at the two-tailed 0.05 level.

Multivariable analysis was conducted performing Cox regression to identify independent predictors of end points.[14,15]

Statistical analyses were performed with SPSS version 12.0 (SPSS, Inc., Chicago, Illinois, USA).

Results

There were 340 patients who transitioned from the paediatric oncology centre to our unit and were enrolled. After transition, 10 of them were lost to follow-up. Primary tumours were distributed as follows: ALL ($n=115$; 33.8%), AML ($n=21$; 6.1%), HD ($n=62$; 18.2%), NHL ($n=29$; 8.5%), brain tumours ($n=51$; 15.0%), sarcoma ($n=39$; 11.5%) and other paediatric cancers ($n=23$; 6.7%) (Figure 1). Age at cancer diagnosis was lower for patients with ALL and AML (Table 1). The relationships between childhood cancer diagnosis and anticancer treatments are detailed in Table 1.

The 330 patients still followed had a median follow-up time of 16.1 years (range: 5.1–33.0 years). Hypertension and diabetes mellitus were uncommon (5.3% and 1.5%, respectively). Hypercholesterolaemia was found in 67 patients (20%), being more frequent in survivors of brain tumour ($n=19$; 37%), ALL ($n=24$; 21%) and sarcoma ($n=10$; 25%). Hypertriglyceridaemia was diagnosed in 20 CCSs (6%), especially in those treated for AML ($n=5$; 23%) and brain tumours ($n=5$; 9.8%). The cumulative incidence of each CVRF associated with cancer diagnosis is detailed in Table 2.

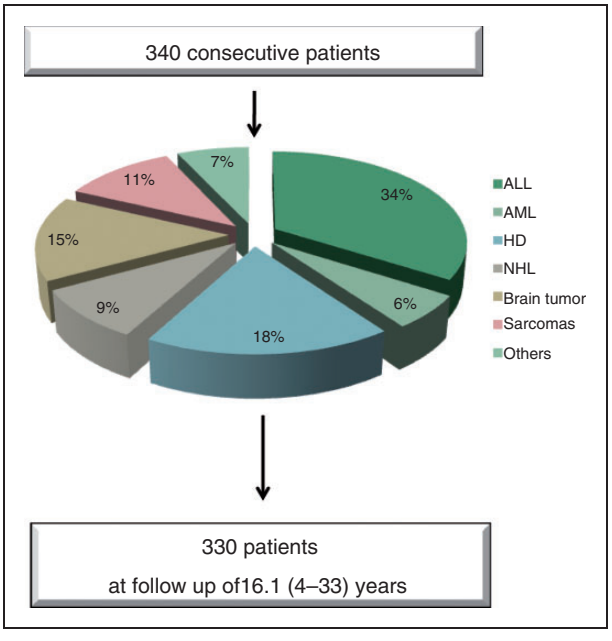

Figure 1. Study profile. ALL: acute lymphoblastic leukaemia; AML: acute myeloblastic leukaemia; HD: Hodgkin's disease; NHL: non-Hodgkin's lymphoma.

Compared to other cancer diagnoses, the onset of lipid profile alterations was earlier in AML (7.5 ± 2.9 years), brain tumour (14.7 ± 20.1 years) and sarcoma (15.1 ± 5.3 years) survivors ($p < 0.001$). Obesity was found in 28 CCSs (8%), mainly brain tumour ($n=9$; 21%) survivors (Table 2).

Dyslipidaemic patients were mostly treated with diet and lifestyle, with improvement of the lipid profile (Table 2, Figure 2), which was significant only for total cholesterol levels, (235 ± 20 vs 221 ± 20; $p < 0.001$). The Framingham risk score was low for all patients (Table 2).

At multivariate analysis (Figure 3 and Supplementary Material, Table A), age at diagnosis as continuous variable was a predictor of hypercholesterolaemia (hazard ratio (HR) = 1.1; confidence interval (CI) 1.0–1.2; $p < 0.001$) and obesity (HR = 1.12; CI 1.05–1.2; $p < 0.001$). TBI significantly increased the risk of hypercholesterolaemia (HR = 2.7; CI 1.2–4.4; $p < 0.05$) and hypertriglyceridaemia (HR = 6.5; CI 1.4–31; $p < 0.05$). The same was found for GHD (HR = 2.3; CI 1.1–4.9; $p < 0.05$ and HR = 7.2; CI 1.1–43; $p < 0.05$, respectively). The patients submitted to autologous haematopoietic stem cell transplantation (auto-HSCT) or treated with platinum-based chemotherapy showed the highest hazard to develop hypercholesterolaemia (HR = 3.2; CI 1.7–5.8; $p < 0.001$ and HR = 2.7; CI 1.5–4.9; $p < 0.001$, respectively). The risk of obesity was higher in brain tumour survivors (HR = 10.0; CI 1.2–45; $p < 0.05$) or in patients previously treated with anthracyclines (HR = 1.3; CI 1.2–26; $p < 0.05$). Age, auto-HSCT, TBI, platinum-based chemotherapy and GHD were also independent predictors of LDL levels higher than 160 mg/dl (HR = 1.2: CI 1.1–3.0; HR = 5.5: CI 3.4–10.0; HR = 3.4: CI 2.0–5.0; HR = 4.5: 3.0–7.0; HR = 4.1: CI 3.0–9.0, respectively)

Discussion

The most important results of this prospective study, representing one of the few ambulatory cohorts of CCSs followed for a long time, are (a) these patients are exposed to a high risk of developing dyslipidaemia and obesity despite young age; (b) brain tumour, TBI and deficit of growth hormone represent the 'red flags'

Table 1. Cancer diagnosis and treatments.

	ALL ($n=115$; 34%)	AML ($n=21$; 6%)	HD ($n=62$; 18%)	NHL ($n=29$; 12%)	Sarcomas ($n=39$; 12%)	Brain tumours ($n=51$; 15%)	Others ($n=23$; 6.7%)	p
Age at last follow up	26.2 ± 5.7	24.4 ± 5.4	28.2 ± 8.5	27.6 ± 5.4	28.1 ± 5.3	24.5 ± 4.6	25.2 ± 6.3	1.00
Age at diagnosis	8.73 ± 6.26	6.42 ± 0.36	15.26 ± 0.36	12.91 ± 2.62	13.39 ± 0.46	10.38 ± 0.18	11.93 ± 4.18	<0.001
Quintiles:								
0–5;	43 (37)	1 (5)	1 (2)	2 (7)	3 (8)	10 (20)	9 (40)	
5–10:	39 (34)	8 (38)	11 (18)	8 (27)	8 (21)	15 (29)	6 (26)	
10–15;	24 (21)	9 (43)	37 (60)	14 (48)	20 (51)	22 (43)	6 (26)	
15–20;	2 (9)	3 (14)	13 (21)	5 (17)	8 (21)	4 (8)	2 (9)	
Recurrence	26 (23)	–	7 (11)	–	4 (10)	8 (16)	2 (9)	0.01
Male gender	70 (61)	9 (43)	36 (58)	21 (73)	17 (44)	30 (59)	14 (61)	0.22
Chemotherapy	115 (100)	20 (95)	62 (100)	29 (100)	37 (95)	38 (74)	20 (87)	<0.001
Drugs:								<0.001
Alkylating agents	98 (85)	13 (62)	46 (74)	29 (100)	35 (89)	31 (61)	12 52)	
Anthracyclines	109 (94)	20 (95)	59 (95)	28 (97)	35 (89)	1 (2)	9 (40)	
Antimetabolites	114 (99)	20 (95)	6 (10)	29 (100)	13 (33)	17 (33)	5 (22)	
Platinum-based	1 (1)	1 (5)	–	–	17 (44)	25 (49)	7 (31)	
Plant alkaloids	107 (93)	1 (5)	60 (97)	27 (93)	23 (59)	26 (51)	9 (39)	
Bleomycin	2 (1.7)	–	52 (84)	1 (3.4)	22 (56)	1 (2)	6 (26)	
Asparaginase	106 (99)	1 (4.8)	2 (3.2)	12 (41)	1 (2.6)	–	–	
Epipodophyllotoxins	32 (28)	15 (71)	8 (13)	19 (66)	22 (57)	27 (53)	6 (26)	
Steroids	111 (97)	4 (19)	45 (73)	29 (100)	–	9 (17)	6 (26)	
Radiotherapy:	46 (40)	10 (47)	58 (94)	10 (34)	16 (41)	42 (83)	10 (44)	<0.001
Head	34 (29)	–	1 (2)	7 (24)	2 (5)	39 (77)	1 (4.3)	
Neck	–	–	53 (85)	2 (7)	2 (5)	26 (51)	1 (4.3)	
Chest	–	–	49 (70)	2 (7)	7 (18)	26 (51)	–	
Upper abdomen	–	–	17 (24)	1 (3.4)	3 (8)	25 (49)	5 (22)	
Lower abdomen	–	3 (2.6)	5 (8.1)	–	7 (18)	25 (49)	1 (4.3)	
Total body irradiation	17 (15)	10 (47)	–	–	–	–	2 (8.7)	<0.001
HSCT								<0.001
Allogenic	24 (21)	5 (24)	–	1 (3.4)	–	–	4 (17)	
Autologous	10 (8.7)	8 (38)	5 (8.1)	–		13 (33)	4 (18)	

HSCT: haematopoietic stem cell transplantation.

Table 2. Prevalence and treatment of cardiovascular risk factors.

	ALL ($n=115$; 34%)	AML ($n=21$; 6%)	HD ($n=62$; 18%)	NHL ($n=29$; 12%)	Sarcomas ($n=39$; 12%)	Brain tumours ($n=51$; 15%)	Others ($n=23$; 6.7%)	p
Hypogonadism	20 (17)	7 (33)	6 (10)	1 (3.4)	6 (15)	24 (47)	3 (813)	<0.001
GHD	10 (9)	6 (29)	1 (2)	0 (0)	1 (2.6)	32 (67)	2 (8.7)	<0.001
GH replacement therapy	6 (5.2)	2 (9.5)	–	.	.	19 (37)	–	<0.001
Diabetes mellitus	2 (1.7)	1 (4.8)	–	–	–	–	2 (8.7)	0.05
Hypertension	4 (3.4)	–	1 (1.5)	1 (3)	2 (5)	3 (6)	1 (4)	0.71
Body mass index (kg/m^2)	24.3 ± 2.7	23 ± 3.5	22.7 ± 5.8	26.7 ± 7.8	24.9 ± 4.8	27.7 ± 6.6	24 ± 4	0.003
– less than 18.4	5 (5.6)	–	4 (7)	–	1 (3.3)	–	3 (16)	0.091
– between 18.5–24.9	58 (64)	11 (52)	25 (40)	11 (38)	20 (67)	29 (66)	12 (63)	0.84
– between 25–29.9	19 (16)	1 (8)	4 (7)	6 (27)	6 (20)	6 (14)	4 (21)	0.34
– more than 30	8 (9)	1 (8)	5 (9)	2 (11)	3 (10)	9 (21)	–	0.31
Hypercholesterolaemia	24 (21)	2 (9,5)	5 (8)	4 (14)	10 (25)	19 (37)	3 (13)	<0.001
Hypertriglyceridaemia	7 (6)	5 (23)	1 (1.6)	–	–	5 (9.8)	2 (8.7)	0.01
Time from diagnosis to development of hypercholesterolaemia/hypertriglyceridaemia	20.8 ± 8.2	7.5 ± 2.9	24.1 ± 11.0	28.6 ± 6.2	15.1 ± 5.3	14.65 ± 20.12	23.9 ± 8.8	<0.001
Lipid levels before treatment (mg/dl):								
Total cholesterol	272 ± 62	201 ± 44	242 ± 33	230 ± 11	226 ± 7	243 ± 9	246 ± 28	<0.001
HDL	43 ± 7	67 ± 28	48 ± 67	57 ± 16	62 ± 7	80 ± 22	56 ± 3	<0.001
LDL	182 ± 27	104 ± 17	166 ± 21	155 ± 8	132 ± 22	163 ± 12	153 ± 24	<0.001
Triglycerides	175 ± 191	261 ± 49	154 ± 111	100 ± 22	91 ± 45	144 ± 77	191 ± 119	<0.001
Treatment:								0.05
Diet	25 (28)	5 (22)	4 (6)	5 (15)	9 (23)	19 (43)	4 (16)	
Statin	3 (3)	2 (8)	2 (4)	–	–	4 (8)	1 (4)	
Omega-3 fatty acid	2 (2)	–	–	–	–	1 (2.6)	–	
Fibrate	1 (0.9)	1 (4.8)	1 (2)	–	1 (2.5)	1 (2.6)	–	
Lipid levels after treatment (mg/dl):								
Total cholesterol	218 ± 26	201 ± 24	229 ± 39	211 ± 35	223 ± 26	216 ± 33	214 ± 9	<0.001
HDL	43 ± 15	51 ± 21	47 ± 15	53 ± 12	61 ± 13	51 ± 15	42 ± 20	0.001
LDL	150 ± 34	101 ± 16	166 ± 15	150 ± 8	113 ± 14	131 ± 27	141 ± 9	<0.001
Triglycerides	135 ± 151	191 ± 59	127 ± 30	89 ± 21	67 ± 25	145 ± 27	141 ± 69	<0.001
Framingham risk score	1% ± 0.2	1% ± 0.4	1% ± 0.3	1% ± 0.2	1% ± 0.4	1% ± 0.4	1% ± 0.3	0.85

ALL: acute lymphoblastic leukaemia; AML: acute myeloblastic leukaemia; GH: growth hormone; GHD: growth hormone deficiency; HD: Hodgkin's disease; HDL: high density lipoprotein; LDL: low density lipoprotein; NHL: non-Hodgkin's lymphoma.

depicting an high risk; (c) hypertension and diabetes mellitus are less frequent; (d) correct management of dyslipidaemia remains unclear.

Several studies showed that CCSs, when compared to general population, had a high prevalence of CVRF; nevertheless, in most cases these results are based on patient self-report questionnaires.[5,16] Our study, on the contrary, was based on clinical data collected by dedicated physicians during follow-up visits, demonstrating in a more accurate way the increased risk of long-term adult survivors for developing CVRFs. Compared with subjects of a similar age included in a cross-sectional study conducted in Spain on healthy subjects (ENRICA study; Table 3), our CCSs had higher levels of total cholesterol, LDL and triglycerides. Moreover, the prevalence of dyslipidaemia in the higher risk groups (AML, ALL, brain tumour) was greater than that reported in the Spanish study, investigating a population with a baseline cardiovascular risk equivalent to the Italian one.[17]

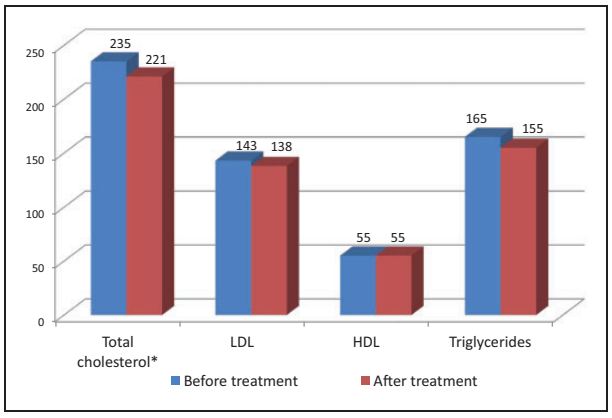

Figure 2. Lipid levels before and after treatment (all values are reported in mg/dl). HDL: high density lipoprotein; LDL: low density lipoprotein.*The only significant difference, <0.001.

Dyslipidaemia and obesity are more frequent in CCSs treated with TBI or who developed GHD, as demonstrated at multivariate analysis. Effects of the exposure of patients to specific anticancer therapies, rather than the different cancer diagnosis itself, probably explain these findings. The association between TBI and the development of hypertriglyceridaemia has been previously reported, while the influence of TBI on cholesterol levels is doubt.[6] The pathophysiological mechanisms have been not fully understood, but

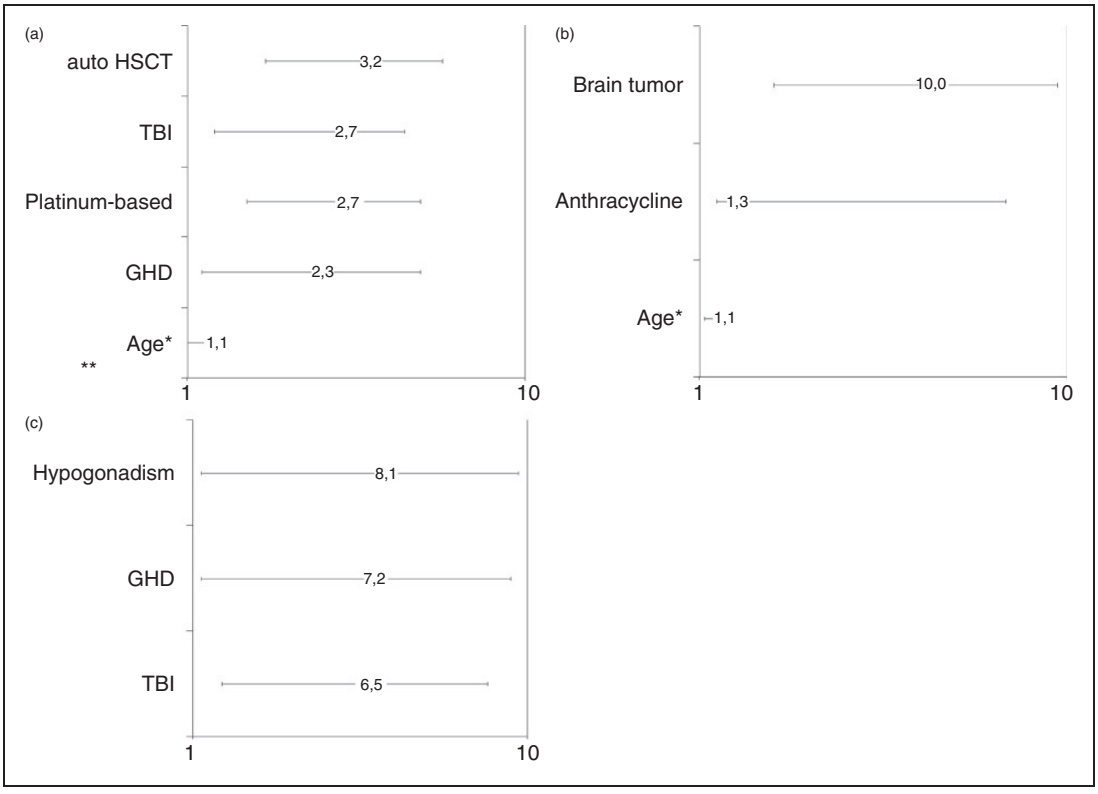

Figure 3. Multivariate predictors of (a) hypercholesterolaemia, (b) obesity and (c) hypertriglyceridaemia. GHD: growth hormone deficiency; TBI: total body irradiation. *Age at diagnosis as a continuous variable. **The same variables were also predictors for low density lipoprotein (LDL) values higher than 160 mg/dl.

Table 3. Lipid levels in our cohort of childhood cancer survivors (CCSs) compared to low cardiovascular risk country unselected population (the ENRICA Study – group aged 18–29 years).

	ALL ($n = 115$; 34%)	AML ($n = 21$; 6%)	HD ($n = 62$; 18%)	NHL ($n = 29$; 12%)	Sarcomas ($n = 39$; 12%)	Brain tumours ($n = 51$; 15%)	Others ($n = 23$; 6.7%)	Enrica study ($n = 1164$)
Lipid profile before treatment (mg/dl):								
Total cholesterol	272 ± 62	201 ± 44	242 ± 33	230 ± 11	226 ± 7	243 ± 9	246 ± 28	165.4 ± 13
HDL	43 ± 7	67 ± 28	48 ± 67	57 ± 16	62 ± 7	80 ± 22	56 ± 3	46.2 ± 20
LDL	182 ± 27	104 ± 17	166 ± 21	155 ± 8	132 ± 22	163 ± 12	153 ± 24	100 ± 1
Triglycerides	175 ± 191	261 ± 49	154 ± 111	100 ± 22	91 ± 45	144 ± 77	191 ± 119	95.5 ± 2.3

ALL: acute lymphoblastic leukaemia; AML: acute myeloblastic leukaemia; HD: Hodgkin's disease; HDL: high density lipoprotein; LDL: low density lipoprotein; NHL: non-Hodgkin's lymphoma.

the hypothalamic irradiation probably plays a central role.[16,18]

Previous studies have described the effects of GH on lipid metabolism.[19–21] Anyway, replacement therapy has no clear beneficial effect on the development of CVRFs.[22,23] For this reason, and also taking into account the (still debated) oncological risk related to GH, in adulthood the replacement therapy is not routinely prescribed to our GHD patients (as stated in the Methods section).

Chemotherapy, auto-HSCT and hypogonadism represented other aetiological factors, although less frequently reported. A relationship between platinum-based chemotherapy and hypercholesterolaemia has been shown in patients with bone/soft-tissue sarcomas or brain tumours.[24] On the contrary, the increased risk of hypercholesterolaemia in patients submitted to auto-HSCT has been reported less frequently.[25] Indeed, studies on metabolic status in HSCT patients usually emphasise the role of graft versus host disease (GVHD), TBI (and/or GHD, that is a common late effect of irradiation), but these conditions are usually associated to allogenic transplants.[6,25]

As far as hypogonadism is considered, it has been reported to increase the risk of metabolic syndrome even in patients on replacement therapy.[26]

The BMI-associated risk of cardiovascular mortality seems to be mediated through other CVRFs.[27] In our cohort, dyslipidaemia and obesity were related. The increase in BMI, that we found mainly in brain tumours survivors, likely results from the concurrence of several causes, including the hypothalamic/hypophyseal damage due to surgery or radiation therapy and the coexisting impairment of mobility due to a brain injury. Lifestyle habit modifications such as less physical activity and distorted nutrition, due to psychological distress and/or depressive disorders, may also play a role in the development of obesity and dyslipidaemia. Indeed, even if CCSs - on average - seem to have less psychological distress than a normal population, the proportion of survivors at risk for high psychological distress is very large.[28] Moreover CCSs, compared to subjects without cancer, may experience greater impairment from major depressive disorders.[29] Anyway, the psychological distress is related to the history of cancer itself rather than to cancer type or previous treatments. Thus, psychological distress is equally distributed among CCSs, so it cannot explain the differences between groups. Lastly, the presence of cognitive damage - not rare in CCSs cured for a brain tumour - could also have a negative impact on the lifestyle.[16,26]

Surprisingly, a previous treatment with anthracyclines was also a predictor of obesity. This result, although requiring confirmation, suggests that these

drugs may not only directly induce heart failure[3] but could also contribute to the development of risk factors.

In our cohort, due to absence of cardiovascular comorbidities and to the young age, almost all patients have been treated with diet and lifestyle changes alone.[30–32] However, in these patients it was difficult to control cholesterol levels this way. Nevertheless, only few randomised controlled trials (mainly in progress and without hard end points) have tried to test the effect of statin on these patients,[33] so that great variability in their medical management still exists.

The incidence of diabetes mellitus (1.5%) and hypertension (5%) was low. Diabetes mellitus was reported less frequently than in other studies: for example the work of Meacham et al.[34] showed an incidence of 2.5%, but our patients were younger than those included in other studies.[34–36]

Rates of hypertension were similar to those found in a study of 125 patients, showing – for a median age of 30 years – an incidence of about 5.4%.[37] Although infrequent, hypertension should be strictly monitored because of its deleterious effect on cerebrovascular events.

This work shows some limitations. First it derives from a single centre registry, although based on a large sample size with long follow-up. Moreover, given the low incidence, multivariate analysis was not performed for hypertension and diabetes mellitus. Finally, we appraised BMI and not waist circumference; however, in a recent study[38] the BMI was demonstrated to be the only parameter related to prognosis in the primary prevention of cardiovascular events.

In conclusion, for physicians managing CCSs, the increased risk of clinical or subclinical cardiovascular events should be taken into account clearly, especially in subjects treated with TBI and/or HSCT or those cured for brain tumours or haematologic malignancies. Actually, these patients should be closely monitored in order to manage their enhanced cardiovascular risk, despite their young age. Furthermore, it should be considered that all scores commonly used to stratify risk of cardiovascular events, as well as the therapies commonly used, are developed and validated on older patients,[39,40] likely resulting in an underestimated burden of comorbidities.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest

The authors declare that there is no conflict of interest.

References

1. Jemal A, Siegel R, Ward E, et al. Cancer statistics 2006. *CA Cancer J Clin* 2006; 56: 106–130.
2. Oeffinger KC, Mertens AC, Sklar CA, et al. Chronic health conditions in adult survivors of childhood cancer. *N Engl J Med* 2006; 355: 1572–1582.
3. De Ville de Goyet M, Moniotte S, et al. Cardiotoxicity of childhood cancer treatment: Update and current knowledge on long-term follow-up. *Pediatr Hematol Oncol* 2012; 29: 395–414.
4. Oeffinger KC. Are survivors of acute lymphoblastic leukemia (ALL) at increased risk of cardiovascular disease? *Pediatr Blood Cancer* 2008; 50: 462–467.
5. Van Waas M, Neggers SJ, Pieters R, et al. Components of the metabolic syndrome in 500 adult long-term survivors of childhood cancer. *Ann Oncol* 2010; 21: 1121–1126.
6. Oudin C, Simeoni MC, Sirvent N, et al. Prevalence and risk factors of the metabolic syndrome in adult survivors of childhood leukemia. *Blood* 2011; 117: 4442–4428.
7. Chemaitilly W and Sklar CA. Endocrine complications in long-term survivors of childhood cancers. *Endocr Relat Cancer* 2010; 17: R141–R159.
8. Felicetti F, Manicone R, Corrias A, et al. Endocrine late effects after total body irradiation in patients who received hematopoietic cell transplantation during childhood: A retrospective study from a single institution. *J Cancer Res Clin Oncol* 2011; 137: 1343–1348.
9. STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) Group. Strobe Statement. Strengthening the reporting of observational studies in epidemiology, www.strobe-statement.org/index.php?id=strobe-home (2009, accessed 20 January 2014).
10. The Children's Oncology Group. Long-term follow-up guidelines for survivors of childhood, adolescent, and young adult cancers. Version 3.0, www.survivorshipguidelines.org (2008, accessed 20 January 2014).
11. Reiner Z, Catapano AL, De Backer G, et al. ESC Committee for Practice Guidelines. ESC/EAS Guidelines for the management of dyslipidaemias: The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). *Eur Heart J* 2011; 32: 1769–1818.
12. American Diabetes Association. Executive summary: Standards of medical care in diabetes – 2013. *Diabetes Care* 2013; 36: S4–S10.
13. Mancia G, Fagard R, Narkiewicz K, et al. ESH/ESC Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens* 2013; 31: 1281–1357.
14. Biondi-Zoccai G, Romagnoli E, Agostoni P, et al. Are propensity scores really superior to standard multivariable analysis? *Contemp Clin Trials* 2011; 32: 731–740.
15. D'Ascenzo F, Cavallero E, Biondi-Zoccai G, et al. Use and misuse of multivariable approaches in interventional

cardiology studies on drug-eluting stents: A systematic review. *J Interv Cardio* 2012; 25: 611–612.
16. Pietilä S, Mäkipernaa A, Sievänen H, et al. Obesity and metabolic changes are common in young childhood brain tumor survivors. *Pediatr Blood Cancer* 2009; 52: 853–859.
17. Guallar-Castillón P, Gil-Montero M, León-Muñoz LM, et al. Magnitude and management of hypercholesterolemia in the adult population of Spain, 2008–2010: The ENRICA Study. *Rev Esp Cardiol (Engl Ed)* 2012; 65: 551–558.
18. Blijdorp K, van Waas M, van der Lely AJ, et al. Endocrine sequelae and metabolic syndrome in adult long-term survivors of childhood acute myeloid leukemia. *Leuk Res* 2013; 37: 367–371.
19. Verhelst J and Abs R. Cardiovascular risk factors in hypopituitary GH-deficient adults. *Eur J Endocrinol* 2009; 161: S41–S49.
20. Woodmansee WW, Zimmermann AG, Child CJ, et al. Incidence of second neoplasm in childhood cancer survivors treated with GH: An analysis of GeNeSIS and HypoCCS. *Eur J Endocrinol* 2013; 168: 565–573.
21. Gaillard RC, Mattsson AF, Akerblad AC, et al. Overall and cause-specific mortality in GH-deficient adults on GH replacement. *Eur J Endocrinol* 2012; 166: 1069–1077.
22. Lombardi G, Di Somma C, Grasso LF, et al. The cardiovascular system in growth hormone excess and growth hormone deficiency. *J Endocrinol Invest* 2012; 35: 1021–1029.
23. Palmeiro CR, Anand R, Dardi IK, et al. Growth hormone and the cardiovascular system. *Cardiol Rev* 2012; 20: 197–207.
24. Meinardi MT, Gietema JA, van der Graaf WT, et al. Cardiovascular morbidity in long-term survivors of metastatic testicular cancer. *J Clin Oncol* 2000; 18: 1725–1732.
25. Baker KS, Chow E and Steinberger J. Metabolic syndrome and cardiovascular risk in survivors after hematopoietic cell transplantation. *Bone Marrow Transplant* 2012; 47: 619–625.
26. Corona G, Mannucci E, Petrone L, et al. NCEP-ATPIII-defined metabolic syndrome, type 2 diabetes mellitus, and prevalence of hypogonadism in male patients with sexual dysfunction. *J Sex Med* 2007; 4: 1038–1045.
27. Dudina A, Cooney MT, Bacquer DD, et al. Relationships between body mass index, cardiovascular mortality, and risk factors: A report from the SCORE investigators. *Eur J Cardiovasc Prev Rehabil* 2011; 18: 731–742.
28. Michel G, Rebholz CE, von der Weid NX, et al. Psychological distress in adult survivors of childhood cancer: The Swiss Childhood Cancer Survivor study. *J Clin Oncol* 2010; 28: 1740–1748.
29. Pirl WF, Greer J, Temel JS, et al. Major depressive disorder in long-term cancer survivors: Analysis of the National Comorbidity Survey Replication. *J Clin Oncol* 2009; 27: 4130–4134.
30. Brouwer CA, Gietema JA, Vonk JM, et al. Body mass index and annual increase of body mass index in long-term childhood cancer survivors; relationship to treatment. *Support Care Cancer* 2012; 20: 311–318.
31. D'Ascenzo F, Agostoni P, Abbate A, et al. Atherosclerotic coronary plaque regression and the risk of adverse cardiovascular events: A meta-regression of randomized clinical trials. *Atherosclerosis* 2013; 226: 178–185.
32. Müller-Riemenschneider F, Meinhard C, Damm K, et al. Effectiveness of nonpharmacological secondary prevention of coronary heart disease. *Eur J Cardiovasc Prev Rehabil* 2010; 17: 688–700.
33. ClinicalTrials.gov. Statin therapy in young adult survivors of childhood cancer, http://clinicaltrials.gov/show/NCT01733953 (2014, accessed 20 January 2014).
34. Meacham LR, Sklar CA, Li S, et al. Diabetes mellitus in long-term survivors of childhood cancer. Increased risk associated with radiation therapy: A report for the childhood cancer survivor study. *Arch Intern Med* 2009; 169: 1381–1388.
35. Karakurt H, Sarper N, Kılıç SÇ, et al. Screening survivors of childhood acute lymphoblastic leukemia for obesity, metabolic syndrome, and insulin resistance. *Pediatr Hematol Oncol* 2012; 29: 551–561.
36. Surapolchai P, Hongeng S, Mahachoklertwattana P, et al. Impaired glucose tolerance and insulin resistance in survivors of childhood acute lymphoblastic leukemia: Prevalence and risk factors. *J Pediatr Hematol* 2010; 32: 383–389.
37. Cardous-Ubbink MC, Geenen MM, Schade KJ, et al. Hypertension in long-term survivors of childhood cancer: A nested case-control study. *Eur J Cancer* 2010; 46: 782–790.
38. Bombelli M, Facchetti R, Fodri D, et al. Impact of body mass index and waist circumference on the cardiovascular risk and all-cause death in a general population: Data from the PAMELA study. *Nutr Metab Cardiovasc Dis* 2013; 23: 650–656.
39. Mueller S, Fullerton HJ, Stratton K, et al. Radiation, atherosclerotic risk factors, and stroke risk in survivors of pediatric cancer: A report from the childhoodcancer survivor study. *Int J Radiat Oncol Biol Phys* 2013; 86: 649–655.
40. Van der Pal HJ, van Dalen EC, Kremer LC, et al. Risk of morbidity and mortality from cardiovascular disease following radiotherapy for childhood cancer: A systematic review. *Cancer Treat Rev* 2005; 31: 173–185.