Risk and determinants of low and very low bone mineral density and fractures in a national cohort of Dutch adult childhood cancer survivors (DCCSS-LATER) a cross-sectional study

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Risk and determinants of low and very low bone mineral density and fractures in a national cohort of Dutch adult childhood cancer survivors (DCCSS-LATER): a cross-sectional study

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Summary

Background Childhood cancer survivors are at risk of developing skeletal comorbidities later in life. We aimed to assess risk factors for low and very low bone mineral density (BMD), and the risk of and risk factors for any fractures and vertebral fractures in a national cohort of Dutch adult childhood cancer survivors.

Methods In this cross-sectional study, we used data from the DCCSS LATER cohort, which comprised individuals who were alive for at least 5 years after diagnosis of childhood cancer (ie, histologically confirmed malignancies or Langerhans cell histiocytosis), were diagnosed before the age of 19 years, and who had been treated at one of seven Dutch paediatric oncology centres between 1963 and 2002 (hereafter referred to as survivors). For this study, we invited survivors aged 18–45 years, who were alive as of Oct 10, 2016, living in the Netherlands, and who were deemed eligible by their treating physician to participate. We assessed BMD using dual-energy x-ray absorptiometry (DXA). Self-reported fractures that occurred at least 5 years after cancer diagnosis were assessed using available medical history and compared with population-level data from the Swedish national registry. We assessed vertebral fractures in a subset of participants using a vertebral fracture assessment. We assessed associations between the occurrence of low (Z-score of ≤–1) or very low (Z-score of ≤–2) BMD, fractures, and vertebral fractures and demographic, treatment-related, endocrine, and lifestyle-related factors using logistic regression analysis.

Findings Between April 29, 2016, and Jan 22, 2020, 3996 (64·8%) of 6165 individuals from the DCCSS LATER cohort were invited to participate, of whom 2003 (50·1%) were enrolled (mean age at participation was 33·1 years [SD 7·2], 966 [48·2%] were female, and 1037 [51·8%] were male [data on ethnicity and race were not available due to national policies]). 1548 (77·3%) had evaluable DXA scans for assessment of BMD, 1892 (94·5%) provided medical history of fractures, and 249 (12·4%) were assessed for vertebral fractures. 559 (36·1%) of 1548 had low BMD at any site, and 149 (9·6%) had very low BMD at any site. The standardised incidence ratio of any first fracture was 3·53 (95% CI 3·06–4·06) for male participants and 5·35 (4·46–6·52) for female participants. 33 (13·3%) of 249 participants had vertebral fractures. Male sex, underweight, high carboplatin dose, any dose of cranial radiotherapy, hypogonadism, hyperthyroidism, low physical activity, and severe vitamin D deficiency were associated with low BMD at any site and male sex, underweight, cranial radiotherapy, growth hormone deficiency, and severe vitamin D deficiency were associated with very low BMD at any site. Additionally, male sex, former and current smoking, and very low lumbar spine BMD were associated with any fractures, whereas older age at follow-up, previous treatment with platinum compounds, growth hormone deficiency, and low physical activity were specifically associated with vertebral fractures.

Interpretation Survivors of childhood cancer are at increased risk of any first fracture. Very low lumbar spine BMD was associated with fractures, highlighting the importance of active BMD surveillance in high-risk survivors (ie, those treated with cranial, craniospinal, or total body irradiation). Moreover, our results indicate that intensive surveillance and timely interventions for endocrine disorders and vitamin deficiencies might improve bone health in childhood cancer survivors, but this needs to be assessed in future studies.

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Research in context

Evidence before this study

Childhood cancer survivors are at risk of developing skeletal adverse effects in later life , such as low bone mineral density (BMD) and fractures. The International Late Effects of Childhood Cancer Guideline Harmonization Group recently published internationally harmonised recommendations for BMD surveillance in childhood, adolescent, and young adult cancer survivors who are alive at least 2 years after discontinuation of treatment . Additionally, they identified gaps in knowledge on low and very low BMD and fractures in survivors of childhood cancer to guide future research. The International Late Effects of Childhood Cancer Guideline Harmonization Group searched PubMed and MEDLINE for publications in English between Jan 1, 1990, and May 12, 2021, using the search terms "childhood cancer" AND ("survivors" OR "late effects") AND "osteoporosis", and all relevant synonyms or examples, and we updated this search with publications up to July 1, 2022. According to their and our findings, there is a paucity of evidence on risk factors for very low BMD (Z-score of ≤–2), and on the risk of and risk factors for fractures and vertebral fractures. Particularly, although reduced BMD is associated with fractures in the general older population, this association is less well established in younger adults, including in childhood cancer survivors.

Added value of this study

In using a large national cohort of Dutch adult childhood cancer survivors (ie, aged 18–45 years at invitation and alive for at least 5 years after diagnosis), we assessed the previously established gaps in the available literature. We found that adult childhood cancer survivors are at increased risk of fractures and vertebral fractures. And we found that very low lumbar spine BMD was significantly associated with fractures. Moreover, we identified associations between low and very low BMD and vertebral fractures and several modifiable factors (eg, growth hormone deficiency, hypogonadism, hyperthyroidism, low physical activity, low dietary calcium intake, severe vitamin D deficiency, vitamin B12 deficiency, and folic acid deficiency). High-dose carboplatin was identified as a treatment-related risk factor for low BMD (Z-score of ≤–1).

Implications of all the available evidence

Our findings highlight the importance of BMD surveillance in high-risk survivors (ie, treated with cranial, craniospinal, or total body irradiation) as previously recommended by the International Late Effects of Childhood Cancer Guideline Harmonization Group. Moreover, our findings suggest that more intensive surveillance and timely interventions for the assessed endocrine disorders and vitamin deficiencies could improve bone health in survivors of childhood cancer. However, this needs to be assessed in future prospective or interventional studies.

Introduction

The number of individuals who survive childhood cancer continues to increase as a result of improved treatment regimens and supportive care strategies.[1] However, most individuals who survive childhood cancer have late adverse effects as a result of the malignancy itself, cancer treatment, comorbidities, or the effect of the cancer experience on lifestyle habits. These adverse effects include skeletal sequelae such as low bone mineral density (BMD) and fractures.[2–4] These fractures are of concern because they might not only lead to temporary pain and immobilisation, but also to chronic morbidity and mortality.[5]

In the general older population (ie, aged ≥50 years), low BMD increases fracture risk,[6] but in younger individuals this association is less well established.[7] Therefore, the occurrence of fragility fractures (especially vertebral fractures) is important with regard to the diagnosis of osteoporosis and considerations regarding treatment for younger individuals.[7] Previous studies have shown that vertebral fractures are common during and shortly after treatment for childhood acute lymphoblastic leukaemia.[8,9] However, the prevalence of and risk factors for vertebral fractures after other childhood cancer types are unknown, and there is little evidence regarding risk factors associated with non-vertebral fractures in this population.[10,11]

The International Late Effects of Childhood Cancer Guideline Harmonization Group recently identified low-quality evidence for the association between low BMD and fractures in childhood, adolescent, and young adult survivors of cancer (with survivor defined as an individual who is alive at least 2 years after completing treatment).[12] Nevertheless, supported by evidence from the global general adult population, the International Late Effects of Childhood Cancer Guideline Harmonization Group recommended BMD surveillance for high-risk survivors (ie, those treated with cranial, craniospinal, or total body irradiation). Additionally, directions for future research in this field were delineated, including identification of risk factors for very low BMD (Z-score of ≤–2) and for vertebral and non-vertebral low-trauma fractures. Filling these knowledge gaps could improve surveillance strategies and provide insights into underlying mechanisms and potential interventions to prevent bone fragility in adult childhood cancer survivors.

The aims of this study were as follows: to assess the risk of and potential risk factors for low (Z-score of ≤–1) and very low (Z-score of ≤–2) BMD and different types of fractures in a national cohort of adult childhood cancer survivors; to investigate the association between low and very low BMD and fractures in this cohort; and

to determine the prevalence of and potential risk factors for vertebral fractures (detected by vertebral fracture assessment) in a subset of these survivors.

Methods

Study design and population

In this cross-sectional study, we included data from the Dutch Childhood Cancer Survivor Study (DCCSS) LATER cohort.[13] The DCCSS LATER cohort consists of individuals who were alive for at least 5 years after diagnosis of childhood cancer (ie, histologically confirmed malignancies or Langerhans cell histiocytosis), diagnosed before the age of 19 years, and treated in one of the seven Dutch paediatric oncology centres between Jan 1, 1963, and Dec 31, 2001 (hereafter referred to as survivors). For the present analysis, we invited participants aged 18–45 years, who were alive as of Oct 10, 2016, living in the Netherlands, and who were deemed to be eligible according to their treating physician.

This study was approved by the Institutional Review Board of the Amsterdam University Medical Center, Netherlands (number 2011/116). Informed consent was obtained from all participating survivors.

Data collection and definitions

Demographic, disease-related, and therapy-related data for primary tumours, recurrences, and subsequent malignancies were derived from medical records. All additional data were collected during a single late-effects outpatient clinic visit between June 28, 2016, and Feb 28, 2020.

At this clinic visit, we used dual-energy x-ray absorptiometry (DXA; Hologic Discovery A and Horizon A, Marlborough, MA, USA) to measure lumbar spine BMD (L1–L4) and total body BMD in six of seven Dutch paediatric oncology centres, and total hip BMD in three of these clinics. Because all survivors were aged 18–50 years at follow-up, BMD values were expressed as Z-scores, which represent the number of SDs that BMD differs from age-matched and sex-matched reference data provided by the DXA manufacturer. We assessed total body BMD and not total body less head BMD because reference data were only available for total body BMD in this age group. We defined low BMD as a Z-score of –1 or lower and very low BMD as a Z-score of –2 or lower using BMD thresholds and terminology to describe low bone mass as recommended by the International Society for Clinical Densitometry.[14] We assessed the risk of and risk factors for low BMD alone and very low BMD alone because more participants had low BMD than did have very low BMD, which increased the number of potential confounders that could be adjusted for in multivariable analysis. Additionally, we considered this threshold relevant in the context of childhood, adolescent, and young survivors because Z-scores equal to or less than –1 but higher than –2 might predispose them to developing very low BMD as they age. Finally, studies in older populations have shown that every 1 SD reduction in BMD increases fracture risk.[6,15] Because this finding cannot be simply extrapolated to younger adults, we assessed multiple BMD thresholds. If osteosynthesis or foreign materials were present, BMD results for that particular site were excluded.

We collected participants' medical history to characterise self-reported fractures that occurred at least 5 years after cancer diagnosis. Fracture history included information on the number of fractures, fracture site or sites, year of fracture or fractures, and whether the fracture was radiologically confirmed according to the participant. We categorised fractures into any fracture experienced, long bone fracture (ie, lower and upper limbs), resulting from unidentified or unknown trauma, and clinically significant fragility fracture (hereafter referred to as fragility fractures, including vertebral, lower and upper limb, or hip fracture).[11,16] We assessed vertebral fractures in a subset of participants who were enrolled at the University Medical Center Groningen (Groningen, Netherlands) for whom vertebral fracture assessments by DXA were available. We chose to use the term vertebral fracture, although a vertebral deformity assessed by vertebral fracture assessment might not always be a vertebral fracture.[17] We assessed the presence, severity, and morphology of vertebral fractures of the thoracolumbar spine (T2–L4) using the Genant semiquantitative method.[18] A grade 1 fracture was considered to be a mild vertebral fracture (20–25% reduction of anterior, middle, or posterior vertebral height), grade 2 a moderate vertebral fracture (>25 to 40% reduction), and grade 3 was a severe vertebral fracture (>40% reduction).

Potential risk factors

We collected therapy-related data from medical records, including chemotherapy regimens and total cumulative doses, radiotherapy fields and fractionated dose, and hematopoietic stem cell transplantation. We determined cumulative glucocorticoid doses on the basis of previous treatment protocols and calculated the prednisone-equivalent dose.[19] If the treatment protocol was missing, we estimated this dose on the basis of disease type and decade of treatment. We chose chemotherapy and radiotherapy dose thresholds on the basis of clinical relevance or previous reports in the literature. We derived BMI from height and bodyweight measurements (kg/m²), and categorised BMI into underweight (<18·5 kg/m²), normal weight (≥18·5 to <25 kg/m²), overweight (≥25 to <30 kg/m²), and obesity (≥30 kg/m²). We also noted whether participants had ever been diagnosed with endocrine disorders (ie, growth hormone deficiency, hypogonadism, or hyperthyroidism). We defined hypothyroidism on the basis of current free thyroxine (FT4) and thyroid-stimulating hormone (TSH) concentrations because participants with hypothyroidism might have had a period of hyperthyroidism—eg, as a result of their medication. Additionally, participants completed various questionnaires, including items on

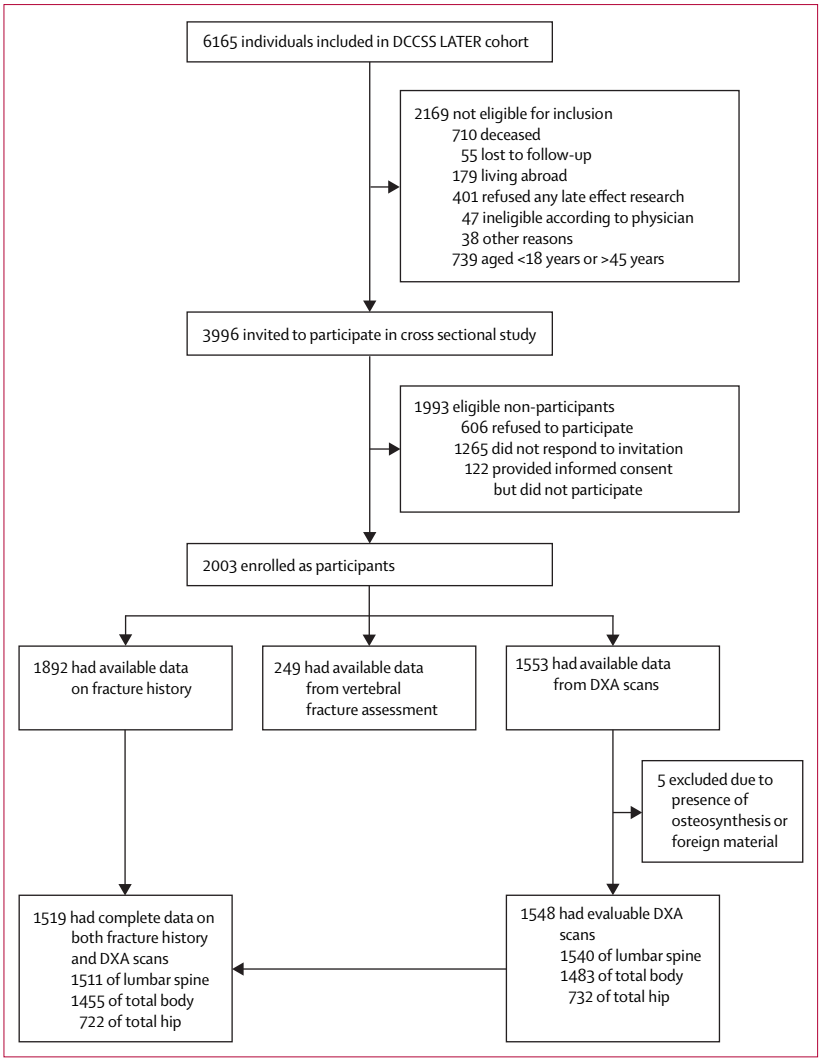

Figure 1: **Study participants**
Participants could be included in multiple assessments. DCCSS LATER=Dutch Childhood Cancer Survivor LATER Study. DXA=dual-energy x-ray absorptiometry.

individual lifestyle behaviours. Peripheral blood samples were taken after an overnight fast, and stored at –80°C in the DCCSS LATER study biobank (Princess Máxima Center for Pediatric Oncology, Utrecht, Netherlands). We assessed serum TSH, FT4, insulin-like growth factor 1 (IGF-1), 25-hydroxyvitamin D (25OHD), folic acid, vitamin B12, and homocysteine levels (Erasmus Medical Center, Rotterdam, Netherlands). Current sex hormone concentrations were not available, and neither were complete data on the number of participants with an endocrine disorder that had been treated. Definitions of the potential risk factors are shown in the appendix (pp 3–4).

See Online for appendix

Statistical analysis

We summarised patient demographic, disease-related, and therapy-related characteristics using descriptive statistics. We compared the characteristics of study participants with those of eligible non-participants (ie, individuals in the DCCSS LATER cohort who were eligible for inclusion in this cross-sectional analysis, but who did not participate for any reason) and the total DCCSS LATER cohort using the χ^2 test. Additionally, characteristics of participants with a DXA scan or vertebral fracture assessment were compared with the characteristics of eligible non-participants plus participants without a DXA scan or vertebral fracture assessment and the total DCCSS LATER cohort. The incidence of any first fracture that occurred between 1987 and 2014 was compared with sex-adjusted and age-adjusted population-level fracture incidence data from the Swedish national registry because Dutch population-level data were not available. We calculated the standardised incidence ratio of any first fracture by sex and age group using the statistical package popEpi.[20] The standardised incidence ratio reflects the proportion of observed fractures and expected fractures corrected for person-years at risk. The fractures of which the year of fracture was missing or seemed to have occurred less than 5 years after diagnosis were excluded from the standardised incidence ratio calculations. We first assessed risk factors for low and very low BMD and different types of fractures (yes *vs* no) using univariable logistic regression analysis. We did a Fisher's exact test for determinants with less than five observations in a group. We included potential risk factors for low and very low BMD and fractures in multivariable models on the basis of the univariable analysis results (ie, if the univariable analysis generated a p value of <0·2) and results of previously reported studies (ie, sex, age at follow-up, and BMI).[12] We adjusted for BMI and not for both fat mass and lean mass because these two variables were collinear with each other and therefore could not both be included in the multivariable models. We estimated separate multivariable models for demographic and treatment-related risk factors and for endocrine and lifestyle-related risk factors to avoid mediation by endocrine deficiencies. Additionally, an interaction term between sex and hypogonadism was added to our models to assess sex differences in the effect of hypogonadism. We also did a sensitivity analysis in which we only included fractures that were confirmed to have taken place more than 5 years after cancer diagnosis. For prevalent vertebral fractures (yes *vs* no), we only assessed the effect of risk factors using univariable models because of the small sample size.

We considered p values of less than 0·05 to be significant. We did all analyses using in R (version 4.0.3).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, writing of the report, or the decision to submit for publication.

	Participants (n=2003)	Participants with DXA scan (n=1553)	Eligible non-participants (n=1993)	Eligible non-participants and participants without DXA scan (n=2443)	Total DCCSS LATER cohort (n=6165)	p value (participants *vs* eligible non-participants)*	p value (participants *vs* total DCCSS LATER cohort)*
Sex	..	..	..	..	..	<0·0001; 0·00019	0·0036; 0·070
Male	1037 (51·8%)	819 (52·7%)	1217 (61·1%)	1435 (58·7%)	3433 (55·7%)	..	..
Female	966 (48·2%)	734 (47·3%)	776 (38·9%)	1008 (41·3%)	2731 (44·3%)	..	..
Transgender	0	0	0	0	1 (<1%)	..	..
Primary childhood cancer (ICCC)	..	..	..	..	..	<0·0001; <0·0001	<0·0001; <0·0001
Leukaemias, myeloproliferative diseases and myelodysplastic diseases	748 (37·3%)	609 (39·2%)	696 (34·9%)	835 (34·2%)	2094 (34·0%)	..	..
Lymphomas and reticuloendothelial neoplasms	373 (18·6%)	282 (18·2%)	349 (17·5%)	440 (18·0%)	1062 (17·2%)	..	..
CNS and miscellaneous intracranial and intraspinal neoplasms	192 (9·6%)	139 (9·0%)	298 (15·0%)	351 (14·4%)	844 (13·7%)	..	..
Neuroblastoma and other peripheral nervous cell tumours	119 (5·9%)	97 (6·2%)	94 (4·7%)	116 (4·7%)	324 (5·3%)	..	..
Retinoblastoma	10 (0·5%)	6 (0·4%)	13 (0·7%)	17 (0·7%)	33 (0·5%)	..	..
Renal tumours	237 (11·8%)	175 (11·3%)	200 (10·0%)	262 (10·7%)	596 (9·7%)	..	..
Hepatic tumours	18 (0·9%)	14 (0·9%)	28 (1·4%)	32 (1·3%)	52 (0·8%)	..	..
Bone tumours	90 (4·5%)	71 (4·6%)	84 (4·2%)	103 (4·2%)	370 (6·0%)	..	..
Soft tissue and other extraosseous sarcomas	134 (6·7%)	107 (6·9%)	129 (6·5%)	156 (6·4%)	450 (7·3%)	..	..
Germ cell tumours, trophoblastic tumours, and neoplasms of gonads	60 (3·0%)	37 (2·4%)	78 (3·9%)	101 (4·1%)	232 (3·8%)	..	..
Other malignant epithelial neoplasms and melanomas	20 (1·0%)	15 (1·0%)	23 (1·2%)	28 (1·1%)	102 (1·7%)	..	..
Other and unspecified malignant neoplasms	2 (0·1%)	1 (0·1%)	1 (0·1%)	2 (0·1%)	6 (0·1%)	..	..
Age at diagnosis, years†	..	..	..	..	..	0·99; 0·52	<0·0001; <0·0001
0–4	998 (49·8%)	786 (50·6%)	994/1989 (50·0%)	1206/2439 (49·4%)	2727/6016 (45·3%)	..	..
5–9	553 (27·6%)	435 (28·0%)	551/1989 (27·7%)	669/2439 (27·4%)	1628/6016 (27·1%)	..	..
10–14	366 (18·3%)	273 (17·6%)	359/1989 (18·0%)	452/2439 (18·5%)	1285/6016 (21·4%)	..	..
15–17	86 (4·3%)	59 (3·8%)	85/1989 (4·3%)	112/2439 (4·6%)	376/6016 (6·3%)	..	..
Age at invitation to cross-sectional study, years‡	..	..	..	..	..	0·53; 0·19	<0·0001; <0·0001
<18	NA	NA	NA	NA	49/3991 (1·2%)	..	..
18–29	771 (38·5%)	616 (39·7%)	522/1387 (37·6%)	677/1837 (36·9%)	1313/3991 (32·9%)	..	..
30–39	871 (43·5%)	663 (42·7%)	629/1387 (45·3%)	837/1837 (45·6%)	1511/3991 (37·9%)	..	..
≥40	361 (18·0%)	274 (17·6%)	236/1387 (17·0%)	323/1837 (17·6%)	1118/3991 (28·0%)	..	..
Follow-up time since cancer diagnosis, years§	..	..	..	..	..	0·21; 0·74	<0·0001; <0·0001
10–20	466 (23·3%)	362 (23·3%)	432 (21·7%)	536 (21·9%)	981/4811 (20·4%)	..	..
20–30	916 (45·7%)	719 (46·3%)	956 (48·0%)	1153 (47·2%)	1931/4811 (40·1%)	..	..
30–40	544 (27·2%)	417 (26·9%)	546 (27·4%)	673 (27·5%)	1393/4811 (29·0%)	..	..
40–50	77 (3·8%)	55 (3·5%)	59 (3·0%)	81 (3·3%)	460/4811 (9·6%)	..	..
50–60	0	0	0	0	46/4811 (1·0%)	..	..
Radiotherapy¶‖							
Any radiotherapy	676/2002 (33·8%)	493/1552 (31·8%)	566/1989 (28·4%)	749/2439 (30·7%)	2527/6135 (41·2%)	0·00029; 0·48	<0·0001; <0·0001
Cranial**	320/1995 (16·0%)	227/1546 (14·7%)	180/1382 (13·0%)	273/1831 (14·9%)	..	0·015; 0·85	..
Abdomen or pelvis	148/1992 (7·4%)	107/1543 (6·9%)	63/1382 (4·6%)	104/1831 (5·7%)	..	0·00071; 0·13	..
Total body	83/1992 (4·2%)	59/1543 (3·8%)	28/1382 (2·0%)	52/1831 (2·8%)	..	0·00061; 0·11	..

(Table 1 continues on next page)

	Participants (n=2003)	Participants with DXA scan (n=1553)	Eligible non-participants (n=1993)	Eligible non-participants and participants without DXA scan (n=2443)	Total DCCSS LATER cohort (n=6165)	p value (participants *vs* eligible non-participants)*	p value (participants *vs* total DCCSS LATER cohort)*
(Continued from previous page)							
Chemotherapy¶||							
Any chemotherapy	1784 (89·1%)	1385 (89·2%)	1603/1990 (80·6%)	2002/2440 (82·0%)	5005/6128 (81·7%)	<0·0001; <0·0001	<0·0001; <0·0001
Alkylating agents	1015/1904 (53·3%)	798/1483 (53·8%)	581/1323 (43·9%)	798/1744 (45·8%)	..	<0·0001; <0·0001	..
Anthracyclines	1067/1984 (53·8%)	830/1537 (54·0%)	628/1373 (45·7%)	865/1820 (47·5%)	..	<0·0001; 0·00019	..
Platinum compounds	297/2001 (14·8%)	221/1551 (14·2%)	168/1386 (12·1%)	244/1836 (13·3%)	..	0·024; 0·42	..
Vinca alkaloids	1589/2001 (79·4%)	1244/1551 (80·2%)	1015/1386 (73·2%)	1360/1836 (74·1%)	..	<0·0001; <0·0001	..
Methotrexate	939/2001 (46·9%)	756/1551 (48·7%)	588/1386 (42·4%)	771/1836 (42·0%)	..	0·0096; <0·0001	..
Glucocorticoids	1165 (58·2%)	917/1553 (59·0%)	738/1387 (53·2%)	986/1837 (53·7%)	..	0·0043; 0·0017	..
Haematopoietic stem cell transplantation¶	..	..	..	..	..	0·00020; 0·086	0·23; 0·67
Autologous	54/1989 (2·7%)	40/1545 (2·6%)	33/1978 (1·7%)	47/2422 (1·9%)	155/5918 (2·6%)	..	..
Allogenic	95/1989 (4·8%)	68/1545 (4·4%)	54/1978 (2·7%)	81/2422 (3·3%)	231/5918 (3·9%)	..	..
Surgery¶||							
Any surgery	965/1988 (48·3%)	733/1549 (47·3%)	1003/1981 (50·6%)	1235/2430 (50·8%)	3185/6067 (52·2%)	0·14; 0·031	0·0022; 0·00054
Amputation	42 (2·1%)	29 (1·9%)	29/1387 (2·1%)	42/1837 (2·3%)	..	0·99; 0·40	..

Data are n (%) or n/N (%), unless otherwise stated. ICCC=International Classification for childhood cancer. NA=not applicable (excluding survivors aged <18 or >45 years). *First p value for participants *vs* eligible non-participants or total DCCSS LATER cohort, and second p value is for participants with a DXA scan *vs* eligible non-participants plus participants without a DXA scan or the total DCCSS LATER cohort. †Not reported for survivors refusing registration research. ‡Not reported for eligible non-participants who refused to participate in this cross-sectional study. §Not reported for survivors refusing any late effect research, and those who were ineligible due to reasons such as death, loss to follow-up, or living abroad. ¶For primary cancer and recurrences. ||Subgroup data not reported for survivors who refused to participate in this cross-sectional study. **Including cranial radiotherapy for brain tumours and craniospinal radiotherapy.

Table 1: **Baseline characteristics DCCSS LATER cohort**

Results

Between April 29, 2016, and Jan 22, 2020, all 6165 individuals in the DCCSS LATER cohort were screened for eligibility for this cross-sectional study and 3996 were found to be eligible and invited to participate, of whom 2003 chose to participate and enrolled (figure 1). The 1993 potentially eligible participants who did not participate due to non-response, choosing not to participate (refusal), or survivors who provided informed consent but did not participate were used as the eligible non-participant comparative cohort. Mean age at participation was 33·1 years (SD 7·2), 966 (48·2%) participants were female, and 1037 (51·8%) were male, and median time since cancer diagnosis was 25·3 years (IQR 20·3–31·3). Data on race and ethnicity were not available as per national policies. Compared with eligible non-participants, a greater proportion of participants were female, the distribution of primary cancer diagnoses was more varied, and a greater proportion received radiotherapy and chemotherapy as well as haematopoietic stem cell transplantation; however, the absolute differences that we observed were small (table 1). Additionally, participants were less likely to have had CNS tumours than were eligible non-participants. The participating cohort and eligible non-participant population were similar in terms of age at cancer diagnosis, age at study invitation, follow-up time, and surgery frequency (table 1).

We obtained DXA scans from 1553 (77·5%) of 2003 participants. Participants with a DXA scan were similar to those of eligible non-participants plus participants without a DXA scan regarding age at cancer diagnosis, age at study invitation, follow-up time, and frequency of previous treatment with radiotherapy, platinum compounds, and haematopoietic stem cell transplantation (table 1). Five participants had osteosynthesis or foreign material at all measured skeletal sites, such that none of their BMD results were interpretable. Therefore, 1548 (77·3%) participants had DXA scan measurements that were evaluable. Medical history of self-reported fractures was available for 1892 (94·5%) participants, and we did vertebral fracture assessment in 249 (12·4%) participants. The participants with a vertebral fracture assessment were similar to those of eligible non-participants plus participants without a vertebral fracture assessment regarding almost all characteristics; however, a higher proportion of participants who had a vertebral fracture assessment had received methotrexate and a lower proportion had received platinum compounds than among the eligible non-participants and participants without a vertebral fracture assessment (appendix pp 5–7). A higher proportion of participants who had a vertebral fracture assessment had received methotrexate, but a lower proportion had received platinum compounds than among the eligible non-participants (appendix pp 5–7). 952 fractures occurred

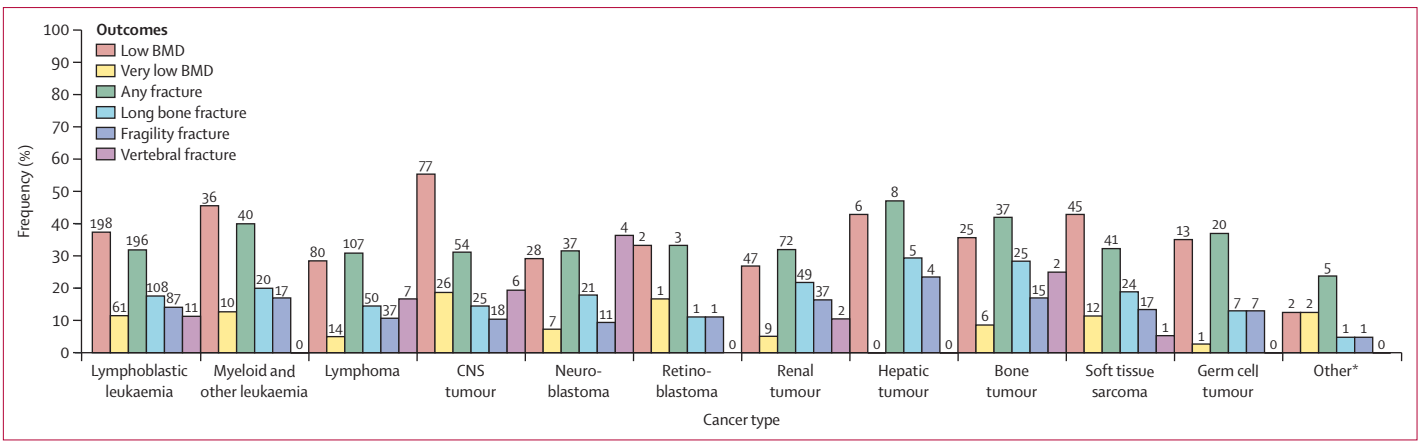

Figure 2: **Frequency of low and very low BMD and fractures, per cancer diagnosis**
BMD was assessed in 1548 survivors with evaluable DXA scans. Data on fracture history (ie, any fracture, long bone fracture, and fragility fracture) was available in 1892 survivors. Vertebral fracture assessment were done in a subset of 249 survivors. Absolute numbers are shown above the bars. BMD=bone mineral density. DXA=dual-energy x-ray absorptiometry. *Other and unspecified malignant neoplasms.

among the 1892 participants with available data, of which 620 were first fractures. The year of fracture was missing for 170 (17·9%) fractures and 164 (17·2%) fractures seemed to have occurred less than 5 years after diagnosis according to the year of fracture (appendix p 8). These fractures were retained in most analyses, but excluded from the standardised incidence ratio calculations. 26 (1·3%) participants received medication such as vitamin D supplementation, bisphosphonates, or other bone-targeted therapy; these individuals were retained in the analyses because this proportion was low and we could not differentiate between participants who received vitamin D versus bisphosphonates or other bone-targeted therapy.

Low BMD at any site occurred in 559 (36·1% [95% CI 33·7–38·6]) of 1548 participants, and very low BMD in 149 (9·6% [8·2–11·2]) participants. Low lumbar spine BMD occurred in 430 (27·9% [25·7–30·2]) of 1540 participants with evaluable lumbar spine DXA scans, low total body BMD occurred in 314 (21·2% [19·1–23·3]) of 1483 participants with evaluable scans, and low total hip BMD occurred in 126 (17·2% [14·6–20·2] of 732 participants with evaluable scans, whereas very low lumbar spine BMD occurred in 111 (7·2% [6·0–8·6]) of 1540 participants, very low total body BMD occurred in 67 (4·5% [3·5–5·7]) of 1483 participants, and very low total hip BMD occurred in 13 (1·8% [0·9–3·0]) of 732 participants. Low BMD was most often present among participants who had previously had myeloid and other leukaemias and CNS tumours, and very low BMD was most often present among those who had previously had CNS tumours (figure 2).

620 (32·8% [95% CI 30·7–34·9]) of 1892 participants had experienced any fracture, 336 (17·8% [16·1–19·6]) had a long bone fracture, and 252 (13·3% [11·8–14·9]) had a fragility fracture after diagnosis (appendix p 9). Fractures were most often localised in the lower arm (270 [28·4%] of all 952 fractures). The standardised incidence ratio of any first fracture was 3·53 (95% CI 3·06–4·06) for male participants and 5·35 (4·46–6·52) for female participants compared with the Swedish population-level data. We found substantial increase in risk across both sexes and all assessed age groups. The standardised incidence ratio per age group was relatively stable for male participants, whereas for female participants the standardised incidence ratio was highest for those who were had their first fracture when aged 5–10 years (standardised incidence ratio 7·11 [95% CI 4·21–11·23]) and when aged 30–40 years (7·47 [4·27–12·11]; appendix p 10). Long bone and fragility fractures were most frequently seen in participants who had previously had hepatic tumours, bone tumours, renal tumours, and myeloid and other leukaemias (figure 2). 63 fractures (6·6% of all fractures) occurred in participants who had previously had bone tumours, of which 23 (36·5%) occurred at the primary tumour site.

43 prevalent vertebral fractures were observed in 33 (13·3% [95% CI 9·3–18·1]) of 249 participants who had a vertebral fracture assessment. In 31 (93·9%) of 33 participants, a vertebral fracture had not been mentioned by the participant during fracture history. Most vertebral fractures were grade 1 fractures (29 [67·4%] of 43) and had a wedge morphology (31 [72·1%]; appendix p 2). Vertebral fractures were most prevalent in participants who had previously had neuroblastomas, bone tumours, and CNS tumours (figure 2).

Risk factors for low and very low BMD using univariable logistic regression analysis are shown in the appendix (pp 11–18).

In multivariable analysis including demographic and treatment-related risk factors, male sex (odds ratio [OR] 2·15 [95% CI 1·71–2·72]), underweight (4·01 [2·06–7·80]), and high carboplatin dose (≥2000 mg/m²; 2·07 [1·18–3·64]) were associated with low BMD at any site (appendix p 19). Moreover, a dose effect association

	Very low BMD at any site (n=149)	Very low lumbar spine BMD (n=111)	Very low total body BMD (n=67)
Demographic factors			
Sex (male)	2·68 (1·81–3·98; p<0·0001)	3·77 (2·31–6·14; p<0·0001)	1·81 (1·04–3·14; p=0·034)
Age at follow-up (per year)	1·00 (0·97–1·03; p=0·99)	1·02 (0·97–1·07; p=0·36)	0·97 (0·93–1·01; p=0·14)
BMI*	..	..	0·96 (0·90–1·02; p=0·18)
Underweight	6·71 (3·63–12·43; p<0·0001)	7·77 (4·04–14·97; p<0·0001)	..
Normal	1 (ref)	1 (ref)	..
Overweight or obesity	0·47 (0·31–0·71; p=0·00042)	0·36 (0·22–0·60; p<0·0001)	..
Treatment-related factors			
Follow-up time (per year)	..	0·97 (0·92–1·02; p=0·23)	..
Total body irradiation (yes *vs* no)	1·76 (0·82–3·75; p=0·15)	0·78 (0·32–1·95; p=0·60)	3·83 (1·41–10·45; p=0·0087)
Cranial radiotherapy (yes *vs* no)†	2·92 (1·87–4·59; p<0·0001)	2·03 (1·18–3·50; p=0·011)	5·34 (2·96–9·63; p<0·0001)
Carboplatin (yes *vs* no)	1·57 (0·84–2·95; p=0·16)	1·46 (0·70–3·04; p=0·31)	1·96 (0·88–4·36; p=0·10)
Glucocorticoid (prednisone-equivalent) dose, mg/m²			
0	1 (ref)	1 (ref)	1 (ref)
>0 to <10 000	0·95 (0·64–1·43; p=0·82)	1·04 (0·65–1·66; p=0·87)	0·93 (0·51–1·71; p=0·82)
≥10 000	1·48 (0·66–3·31; p=0·34)	2·22 (0·90–5·47; p=0·082)	1·33 (0·45–3·92; p=0·61)

Data are odds ratios with 95% CIs and p values in parentheses. Models were adjusted for all variables included in the model. BMD=bone mineral density. *Adjusted for amputation; and for very low total body BMD, BMI was analysed as continuous variable due to limited power. †Including cranial radiotherapy for brain tumours and craniospinal radiotherapy.

Table 2: **Demographic and treatment-related risk factors for very low BMD, using multivariable logistic regression analysis**

for cranial radiotherapy was found (>0 to <20 Gy: OR 2·40 [95% CI 1·27–4·55]; ≥20 to <40 Gy: 2·54 [1·50–4·30]; and ≥40 Gy: 3·91 [2·41–6·34]). A shorter follow-up time was associated with low lumbar spine BMD (0·96 [0·92–0·99]) and previous exposure to total body irradiation was associated with low total body BMD (>0 to <10 Gy: 2·82 [1·16–6·83], and ≥10 Gy: 3·51 [1·25–9·90]) and with low total hip BMD (≥10 Gy: 4·61 [1·18–17·93]). We also found an association between high dose alkylating agents (≥8000 g/m²) and low total hip BMD (2·31 [1·29–4·13]; appendix p 19).

Male sex, underweight, and cranial radiotherapy increased the risk of very low BMD at any site (table 2). Additionally, an association was found between previous exposure to total body irradiation and very low total body BMD. Participants who received glucocorticoids with a prednisone-equivalent dose of 10 000 mg/m² or higher had an OR for very low BMD at any site of 1·48 (95% CI 0·66–3·31), very low lumbar spine BMD of 2·22 (0·90–5·47), and very low total body BMD of 1·33 (0·45–3·92).

In the multivariable model with endocrine and lifestyle-related risk factors, hypogonadism (OR 2·82 [95% CI 1·50–5·28]), hyperthyroidism (2·30 [1·03–5·16]), low physical activity (1·67 [1·21–2·31]), and severe vitamin D deficiency (1·81 [1·25–2·61]) were associated with low BMD at any site (appendix p 20). The interaction term between sex and hypogonadism was added to our models to assess sex differences in the effect of hypogonadism on low BMD, but the number of participants with relevant data were too low to establish robust models. Additionally, participants with growth hormone deficiency (OR 2·75 [95% CI 1·51–5·01]) or folic acid deficiency (1·44 [1·02–2·05]) had an increased risk of low lumbar spine BMD. Nine (8%) participants with growth hormone deficiency had a height below –2 SD.

Growth hormone deficiency and severe vitamin D deficiency were associated with very low BMD at any site and low physical activity and vitamin B12 deficiency were associated with very low total body BMD (table 3). 89 (17·8%) of 501 individuals with at least one of the assessed vitamin deficiencies (ie, severe vitamin D deficiency, vitamin B12 deficiency, or folic acid deficiency) had multiple deficiencies. The number of participants who had very low total hip BMD was too low to do a multivariable analysis.

Risk factors for any fracture, long bone fracture, and fragility fracture using univariable logistic regression models are shown in the appendix (pp 21–24).

In multivariable analysis, male sex, former and current smoking, and very low lumbar spine BMD were associated with fractures at any site (table 4). Male sex, obesity, former smoking, low dietary calcium intake, and very low lumbar spine BMD were associated with long bone fractures. Obesity and very low lumbar spine BMD were also associated with the occurrence of fragility fractures. A sensitivity analysis in which we only included fractures that were confirmed to have occurred more than 5 years after cancer diagnosis according to year of fracture showed similar results as the main analysis (appendix p 25). In these models for long bone and fragility fractures, the effect of very low lumbar spine BMD increased (OR 2·22 [95% CI 1·26–3·93] for long bone and 2·63 [1·43–4·81] for fragility fracture) compared with the main analysis.

Older age at follow-up (OR 1·06 per year [95% CI 1·01–1·12]), previous treatment with platinum compounds

(2·78 [1·00–7·71]), growth hormone deficiency (3·33 [1·08–10·29]), and low physical activity (2·44 [1·03–5·78]) were associated with vertebral fractures in univariable analyses (appendix pp 26–28). Additionally, we observed a higher prevalence of vertebral fractures in participants who had been treated with spinal radiotherapy (four [40·0%] of ten who had spinal radiotherapy *vs* 29 [12·1%] of 239 who did not have spinal radiotherapy; p=0·030); however, all of these participants also had growth hormone deficiency. The OR for prevalent vertebral fracture was 1·74 (95% CI 0·69–4·36)with cranial radiotherapy, 1·79 (0·86–3·77) with low BMD, 1·86 (0·70–4·99) with very low BMD, and 1·88 (0·77–4·54) with severe vitamin D deficiency (appendix pp 26–28).

	Very low BMD at any site (n=149)	Very low lumbar spine BMD (n=111)	Very low total body BMD (n=67)
Endocrine-related factors			
Hypogonadism	1·48 (0·68–3·21; p=0·32)	0·69 (0·23–2·04; p=0·50)	2·33 (0·95–5·71; p=0·063)
Growth hormone deficiency	4·42 (2·13–8·33; p<0·0001)	2·41 (1·02–5·72; p=0·045)	4·68 (2·11–10·40; p=0·0001)
Hyperthyroidism	1·42 (0·50–4·06; p=0·51)	..	..
Lifestyle-related factors			
Smoking	..	..	..
Never	..	1 (ref)	..
Former	..	1·50 (0·79–2·88; p=0·22)	..
Current	..	1·66 (0·93–2·94; p=0·084)	..
Low physical activity	1·47 (0·91–2·39; p=0·12)	1·72 (0·95–3·09; p=0·071)	1·93 (1·05–3·53; p=0·033)
Severe vitamin D deficiency	1·86 (1·12–3·08; p=0·017)	1·79 (1·00–3·21; p=0·051)	1·99 (1·03–3·85; p=0·041)
Vitamin B12 deficiency	1·84 (0·78–4·34; p=0·16)	..	3·84 (1·52–9·69; p=0·0044)
Folic acid deficiency	..	..	1·24 (0·63–2·44; p=0·54)

Data are odds ratios with 95% CIs and p values in parentheses. Models were adjusted for sex, age at follow-up, BMI (adjusted for amputation; continuous), and all other variables included in the model. BMD=bone mineral density.

Table 3: **Endocrine and lifestyle-related risk factors for very low BMD, using multivariable logistic regression analysis**

Discussion

In a Dutch national cohort of adult childhood cancer survivors (ie, alive for at least 5 years after diagnosis), we found a substantial increase in fracture risk for individuals of all sexes and of all ages compared with Swedish population-level data. To our knowledge, this is the first study to compare fracture incidence in long-term survivors of childhood cancer with population-level data using sex-adjusted and age-adjusted person-years at risk. One previous questionnaire-based study that compared fracture frequencies between adult childhood cancer survivors (ie, aged ≥18 years and alive 5 years after the date of diagnosis) and their siblings during their lifetime found no increased risk for survivors,[10] whereas two other studies found an increased hazard of admission to hospital due to fractures for 5-year childhood cancer survivors compared with children and adolescents from selected birth cohorts[3] and compared with their healthy sibling.[21] We found that 13·3% of adult childhood cancer survivors (mean age 33 years) had a prevalent vertebral fracture, which might indicate osteoporosis.[22] This frequency substantially exceeds the prevalence of approximately 3% observed in adults younger than 60 years from the general population (in Norway and China).[23,24] A Canadian study including 5-year survivors of childhood acute lymphoblastic leukaemia showed a higher prevalence of vertebral fractures (in 57 [23·3%] of 245) than we found in our cohort.[8] Moreover, the fact that the standardised incidence ratio for any first fracture was highest in female survivors when they were aged 30–40 years, and that older age at follow-up was a risk factor for vertebral fracture in this study, suggests that skeletal morbidity could become even more prominent as survivors of childhood cancer age.

We found that very low lumbar spine BMD was associated with any type of fracture, and with long bone and fragility fractures in adult childhood cancer survivors. Although we anticipated this association on the basis of scientific literature in older populations, it had been less clearly established in young adult populations, including survivors of childhood cancer. To date, only one study in survivors of haematological malignancies has found an association between low BMD and fractures, estimated with a univariable model.[11] The association we identified between very low lumbar spine BMD and fractures is a pivotal finding, and it might support the hypothesis that BMD surveillance for high-risk survivors (ie, those treated with cranial, craniospinal, or total body irradiation as recently presented by the International Late Effects of Childhood Cancer Guideline Harmonization Group[12]) can prevent fractures when adequate interventions are initiated in case of low or very low BMD. However, we acknowledge that in this study we included fractures that occurred before BMD assessment. Vertebral fractures were found to mostly be serious, although were often unknown injuries, highlighting the relevance of spine imaging. Notably, a 1 SD reduction in BMD was associated with vertebral fracture, which is similar to observations in the general older population.[22]

Our results support BMD surveillance for adult childhood cancer survivors treated with cranial or craniospinal radiotherapy or total body irradiation, as recently presented by the International Late Effects of Childhood Cancer Guideline Harmonization Group.[12] Additionally, we found that low BMD was associated with a higher dose of cranial radiotherapy, although we did not observe a safe cranial radiotherapy dose (ie, a dose that was not significantly associated with low BMD). The observed effects of cranial radiotherapy, and to a lesser extent of total body irradiation, are

	Any fracture (n=620)	Long bone fracture (n=336)	Fragility fracture (n=252)
Demographic			
Sex (male)	1·48 (1·15–1·92; p=0·0027)	1·45 (1·06–1·99; p=0·022)	1·08 (0·77–1·52; p=0·67)
Age at follow-up (per year)	0·99 (0·97–1·01; p=0·25)	0·98 (0·96–1·01; p=0·20)	0·99 (0·96–1·01; p=0·26)
BMI*			
Underweight	0·84 (0·40–1·77; p=0·65)	0·95 (0·39–2·33; p=0·91)	1·13 (0·46–2·79; p=0·79)
Normal weight	1 (ref)	1 (ref)	1 (ref)
Overweight	1·07 (0·81–1·42; p=0·64)	1·29 (0·91–1·83; p=0·15)	1·39 (0·95–2·02; p=0·089)
Obesity	1·06 (0·71–1·60; p=0·76)	1·75 (1·10–2·78; p=0·018)	1·66 (1·01–2·73; p=0·046)
Age at diagnosis (per year)	0·98 (0·95–1·01; p=0·27)	0·98 (0·94–1·02; p=0·26)	0·98 (0·94–1·02; p=0·31)
Haematopoietic stem cell transplantation†	..	1·53 (0·86–2·71; p=0·14)	1·59 (0·86–2·94; p=0·14)
Lifefstyle-related factors			
Smoking			
Never	1 (ref)	1 (ref)	1 (ref)
Former	1·92 (1·36–2·70; p=0·00022)	1·55 (1·03–2·33; p=0·036)	1·51 (0·98–2·33; p=0·063)
Current	1·69 (1·22–2·35; p=0·0016)	0·99 (0·65–1·51;p=0·95)	0·84 (0·53–1·33; p=0·45)
Heavy drinking	..	..	1·75 (0·77–3·96; p=0·18)
Low dietary calcium intake	..	1·40 (1·02–1·93; p=0·039)	..
Low physical activity	0·89 (0·63–1·26; p=0·51)	..	..
Severe vitamin D deficiency	..	..	1·31 (0·82–2·09; p=0·27)
Increased homocysteine levels	0·96 (0·54–1·69; p=0·87)	..	..
Very low lumbar spine BMD	1·85 (1·15–2·97; p=0·011)	1·85 (1·09–3·15; p=0·022)	2·08 (1·19–3·64; p=0·010)

Data are odds ratio with 95% CIs and p values in parentheses. Models were adjusted for all variables included in the model. BMD=bone mineral density. *Adjusted for amputation. †With myeloablative conditioning.

Table 4: **Risk factors for fractures, using multivariable logistic regression analysis**

conceivably related to the presence of hypothalamic–pituitary deficiencies, including central hypogonadism and growth hormone deficiency, which we also identified as risk factors for low and very low BMD. However, total body irradiation might also damage other endocrine glands and bones directly. Due to small sample size, we were not able to assess whether associations between cranial radiotherapy or total body irradiation and BMD were different for survivors with and without endocrine disorders. We identified an association between high dose alkylating agents (≥8000 g/m²) and low total hip BMD, which might be due to the fact that alkylating agents are known to induce primary hypogonadism, especially at higher doses.[25] Unfortunately, gonadal hormone status was not available at the time of our analysis. Furthermore, high-dose carboplatin (≥2000 g/m²) increased the risk of low BMD in this study, which is consistent with carboplatin-induced trabecular bone loss, as observed in healthy mice.[26]

Our findings suggest that more intensive surveillance and adequate interventions for the assessed endocrine disorders (as recently proposed by the International Late Effects of Childhood Cancer Guideline Harmonization Group[27]) and vitamin deficiencies might be needed to reduce the risk of low and very low BMD and fractures for adult survivors of childhood cancer. In addition to hypogonadism and growth hormone deficiency, we found that hyperthyroidism was a risk factor for low BMD at any site and low lumbar spine BMD, although not for very low BMD. The contribution of hyperthyroidism to an increased risk of low or very low BMD had not been previously assessed in adult childhood cancer survivors, but is a known risk factor in the general adult population because excess thyroid hormones stimulate bone resorption and consequently decrease BMD.[28] Only one study had previously assessed the effect of vitamin deficiencies on BMD deficits in childhood cancer survivors who were in remission and at least 2 years after therapy, and found that survivors with vitamin D deficiency (concentrations of <20 nmol/L) had a more than three-times increased risk of reduced BMD compared with those without vitamin D deficiency.[29] Our results suggest that the effects of vitamin deficiencies on BMD are not limited to vitamin D deficiency because deficiencies in vitamin B12 and folic acid were also associated with reduced BMD, which is consistent with observations in the general middle-aged and older population (ie, approximately ≥40 years).[30,31] The exact underlying mechanisms for the association between vitamin B12 and folic acid deficiencies and low BMD are not fully understood.[31]

We also identified several modifiable risk factors for vertebral fractures (ie, growth hormone deficiency, low physical activity, and possibly severe vitamin D deficiency). Larger studies are needed to validate these results. The fact that most of the vertebral fractures were asymptomatic and not all survivors with a prevalent vertebral fracture had low or very low BMD underscores the importance of vertebral imaging to adequately assess bone health.[7]

Our study has several limitations that should be considered when interpreting our results. The observed differences between the characteristics of participants and eligible non-participants could indicate selection bias, although for some characteristics we only had data from non-responders, and not from refusers, and absolute differences were small. Furthermore, because we combined survivors of all cancer types in our analyses, generalisation of our results should be done carefully. For example, because very low BMD was more prevalent in survivors of CNS tumours, who were less likely to participate in this study, the prevalence of very low BMD might actually be higher than reported.

Additionally, the method we used to characterise fractures (ie, by medical history) could be subject to recall bias, and although most of the reported fractures had been radiographically confirmed according to the participant, we did not have access to these radiographs. The exact year that fractures occurred was missing or the fracture seemed to have occurred less than 5 years after cancer diagnosis (according to the year of fracture) for a substantial number of fractures. These first fractures, and all subsequent fractures, could not be compared with the Swedish population-level data because they could not be taken into account in the standardised incidence ratio calculation. This, and the fact that we used Swedish population-level data (a country that is known to have a higher fracture incidence than the Netherlands),[32,33] might have led to an underestimation of the standardised incidence ratio of any first fracture in our cohort. Because this was a cross-sectional study, we could only assess associations between current risk factors and a history of fractures, and not their effect on future incident fractures. Also, we had no information available regarding the level of trauma that preceded the fractures, and therefore could not distinguish low-trauma fractures from other fractures. However, we attempted to approximate this type of fracture by separately analysing long bone fractures and fractures in skeletal sites commonly associated with osteoporosis (ie, clinically significant fragility fractures). We only did vertebral fracture assessments for a subgroup of our cohort, which restricted our ability to detect independent risk factors for vertebral fractures. Finally, although only a small subgroup of our cohort with growth hormone deficiency had a height of less than −2 SD and our endocrine model was adjusted for BMI, the fact that BMD Z-scores were not height-adjusted could have falsely increased the effect of growth hormone deficiency on low and very low BMD.

In summary, long-term adult childhood cancer survivors are at increased risk of clinical vertebral and non-vertebral fractures compared with the general population. Moreover, because most vertebral fractures identified by vertebral fracture assessment were asymptomatic, our calculations probably underestimate the true magnitude of skeletal morbidity among adult childhood cancer survivors. Reduced BMD (especially very low lumbar spine BMD) was found to be a strong indicator for increased fracture risk, which underscores the importance of active BMD surveillance for high-risk survivors. We identified high-dose carboplatin as a new treatment-related risk factor for low BMD, whereas glucocorticoids (prednisone-equivalent dose) was not associated with low or very low BMD or fractures. Our data suggest that more intensive surveillance for endocrine disorders might be advised, as recommended by the International Late Effects of Childhood Cancer Guideline Harmonization Group,[27] because timely interventions for survivors of cancer with endocrine disorders (including hyperthyroidism), and supplementation of calcium, vitamin D, vitamin B12, and folic acid deficiencies could improve bone health.

Contributors

JEvA, DTCdW, SMFP, SJCMMN, and MMvdH-E contributed to the study funding, concept, and design. JEvA, DTCdW, VGP, RAJN, MGGH, ACHdV, JJL, EvD-dB, HJvdP, LCMK, CMR, MvdH-vdL, ABV, ML, DB, DSO, IH, SAAvdB, WJET, SJCMMN, and MMvdH-E contributed to data acquisition. JEvA, DTCdW, MF, SJCMMN, and MMvdH-E contributed to data analysis and interpretation. JEvA, DTCdW, SJCMMN, and MMvdH-E drafted the manuscript. JEvA, DTCdW, VGP, MF, RAJN, MGGH, ACHdV, JJL, EvD-dB, HJvdP, SMFP, LCMK, CMR, MvdH-vdL, ABV, ML, DB, HMvS, DSO, IH, SAAvdB, JdH, WJET, SJCMMN, and MMvdH-E contributed to manuscript revision and approval. JEvA, DTCdW, MF, MvdH-vdL, SJCMMN, and MMvdH-E had full access to all data in the study and take responsibility for data integrity, verification, and analysis. All authors had access to all the data reported in the study and accept responsibility to submit for publication.

Declaration of interests

IH declares institutional contracts from Abbott, Siemens Healthineers, and Beckman Coulter. CMR declares a non-commercial charity grant funding, and a personal grant for Jr Group Leaders 2013–2018 (Dutch Cancer Society). All other authors declare no competing interests.

Data sharing

The data underlying this Article were provided by the DCCSS-LATER consortium under license. Data will be shared on reasonable request to the corresponding author with permission of the DCCSS-LATER consortium. These data are not publicly available due to privacy and ethical restrictions; information is available online.

For more on **data access policies** see https://english.ccmo.nl/investigators/data-retention-periods-for-medical-research

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