Included studies bone mineral density surveillance

Evidence in CAYA cancer survivors

Year	Bibliography
2021	Bhandari et al. Prevalence and risk factors for vitamin D deficiency in long-term childhood cancer survivors. *Pediatr Blood Cancer*. 2021 Apr 6;e29048.
2021	Fiscaletti et al. Predictors of Vertebral Deformity in Long-Term Survivors of Childhood Acute Lymphoblastic Leukemia: The PETALE Study. *J Clin Endocrinol Metab*. 2021 Jan 23;106(2):512-525.
2021	Im et al. Genome-wide Association Studies Reveal Novel Locus With Sex-/Therapy-Specific Fracture Risk Effects in Childhood Cancer Survivors. *J Bone Miner Res*. 2021 Apr;36(4):685-695.
2021	Latoch et al. A long-term trajectory of bone mineral density in childhood cancer survivors after discontinuation of treatment: retrospective cohort study. *Arch Osteoporos*. 2021 Feb 26;16(1):45.
2021	Tabone et al. Bone Mineral Density Evolution and Its Determinants in Long-term Survivors of Childhood Acute Leukemia. *Hemasphere*. 2021 Jan 12;5(2):e518.
2020	Bloomhardt et al. Severity of reduced bone mineral density and risk of fractures in long-term survivors of childhood leukemia and lymphoma undergoing guideline-recommended surveillance for bone health. *Cancer*. 2020;126(1):202-210.
2020	Isaksson et al. Low bone mineral density is associated with hypogonadism and cranial irradiation in male childhood cancer survivors. *Osteoporos Int*. 2020;31(7):1261-1272.
2020	Liuhto et al. Diseases of renal function and bone metabolism after treatment for early onset cancer: A registry-based study. *Int J Cancer*. 2020;146(5):1324-1332.
2020	Van Iersel et al. Clinical impact of hypothalamic-pituitary disorders after conformal radiation therapy for pediatric low-grade glioma or ependymoma. *Pediatr Blood Cancer*. 2020 Dec;67(12):e28723.
2020	Van Santen et al. Fractures, Bone mineral density, and final height in craniopharyngioma patients with a follow-up of 16 years. *J Clin Endocrinol Metab*. 2020;105(4):E1397-E1407.
2020	Zürcher et al. High impact physical activity and bone health of lower extremities in childhood cancer survivors: A cross-sectional study of SURfit. *Int J Cancer*. 2020;147(7):1845-1854.
2019	De Matteo et al. Quantitative Ultrasound of Proximal Phalanxes in Childhood Acute Lymphoblastic Leukemia Survivors. *J Pediatr Hematol Oncol*. 2019;41(2):140-144.
2019	Lemay et al. Prevention of Long-term Adverse Health Outcomes With Cardiorespiratory Fitness and Physical Activity in Childhood Acute Lymphoblastic Leukemia Survivors. *J Pediatr Hematol Oncol*. 2019;41(7):E450-E458.
2019	Sloof et al. The Impact of Physical Activity on the Health of Young Adult Survivors of Childhood Cancer: An Exploratory Analysis. *J Adolesc Young Adult Oncol*. 2019 Oct;8(5):602-609.
2019	Van Atteveld et al. Prediction of low and very low bone mineral density among adult survivors of childhood cancer. *J Clin Oncol*. 2019;37(25):2217-2225.
2019	Van Iersel et al. Hypothalamic-Pituitary Disorders in Childhood Cancer Survivors: Prevalence, Risk Factors and Long-Term Health Outcomes. *J Clin Endocrinol Metab*. 2019;104(12):6101-6115.

2018	Im et al. Genome-wide search for higher order epistasis as modifiers of treatment effects on bone mineral density in childhood cancer survivors. *Eur J Hum Genet*. 2018;26(2):275-286.
2018	Remes et al. Bone mineral density is compromised in very long-term survivors of irradiated childhood brain tumor. *Acta Oncol*. 2018 May;57(5):665-674.
2018	Wei et al. Bone Mineral Density Corrected for Size in Childhood Leukaemia Survivors Treated with Haematopoietic Stem Cell Transplantation and Total Body Irradiation. *Horm Res Paediatr*. 2018;89(4):1-9.
2018	Mueller et al. Hospitalization and mortality among pediatric cancer survivors: a population-based study. *Cancer Causes Control*. 2018;29(11):1047-1057.
2017	Chemaitilly et al. Premature Ovarian Insufficiency in Childhood Cancer Survivors: A Report From the St. Jude Lifetime Cohort. *J Clin Endocrinol Metab*. 2017;102(7):2242-2250.
2017	Molinari et al. Assessment of the late effects on bones and on body composition of children and adolescents treated for acute lymphocytic leukemia according to brazilian protocols. *Rev Paul Pediatr*. 2017;35(1):78-85.
2017	Siegel et al. Risk factors and surveillance for reduced bone mineral density in pediatric cancer survivors. *Pediatr Blood Cancer*. 2017;64(9).
2017	Siviero-Miachon et al. Visfatin is a positive predictor of bone mineral density in young survivors of acute lymphocytic leukemia. *J Bone Min Metab*. 2017;35(1):73-82.
2016	Den Hoed et al. Genetic variation and bone mineral density in long-term adult survivors of childhood cancer. *Pediatr Blood Cancer*. 2016;63(12):2212-2220.
2016	Mogil et al. Effect of Low-Magnitude, High-Frequency Mechanical Stimulation on BMD Among Young Childhood Cancer Survivors: A Randomized Clinical Trial. *JAMA Oncol*. 2016;2(7):908-914.
2016	Wilson et al. Modifiable Factors Associated with Aging Phenotypes among Adult Survivors of Childhood Acute Lymphoblastic Leukemia. *J Clin Oncol*. 2016;34(21):2509-2515.
2015	Chemaitilly et al. Anterior hypopituitarism in adult survivors of childhood cancers treated with cranial radiotherapy: a report from the St Jude Lifetime Cohort study. *J Clin Oncol*. 2015;33(5):492-500.
2015	Den Hoed et al. Bone mineral density after childhood cancer in 346 long-term adult survivors of childhood cancer. *Osteoporos Int*. 2015;26(2):521-529.
2015	Dubnov-Raz et al. Changes in fitness are associated with changes in body composition and bone health in children after cancer. *Acta Paediatr*. 2015;104(10):1055-1061.
2015	Han et al. Poor bone health at the end of puberty in childhood cancer survivors. *Pediatr Blood Cancer*. 2015;62(10):1838-1843.
2015	Pluijm et al. Catch-up of bone mineral density among long-term survivors of childhood cancer? Letter to the editor: Response to the article of Gurney et al. 2014. *Pediatr Blood Cancer*. 2015 Feb;62(2):369-370.
2014	Esbenshade et al. Screening for vitamin D insufficiency in pediatric cancer survivors. *Pediatr Blood Cancer*. 2014;61(4):723-728.
2014	Gurney et al. Bone mineral density among long-term survivors of childhood acute lymphoblastic leukemia: Results from the St. Jude Lifetime Cohort Study. *Pediatr Blood Cancer*. 2014;61(7):1270-1276.
2014	Hobusch et al. Do long term survivors of ewing family of tumors experience low bone mineral density and increased fracture risk? *Clin Orthop Relat Res*. 2014;472(11):3471-3479.

2014	Kaste et al. Calcium and cholecalciferol supplementation provides no added benefit to nutritional counseling to improve bone mineral density in survivors of childhood acute lymphoblastic leukemia (ALL). *Pediatr Blood Cancer*. 2014;61(5):885-893.
2014	Watsky et al. Bone turnover in long-term survivors of childhood acute lymphoblastic leukemia. *Pediatr Blood Cancer*. 2014;61(8):1451-1456.
2013	Choi et al. Factors related to decreased bone mineral density in childhood cancer survivors. *J Korean Med Sci*. 2013;28(11):1632-1638.
2013	Hudson et al. Clinical ascertainment of health outcomes among adults treated for childhood cancer. *JAMA - J Am Med Assoc*. 2013;309(22):2371-2381.
2013	Sawicka-Żukowska et al. Does Q223R Polymorphism of Leptin Receptor Influence on Anthropometric Parameters and Bone Density in Childhood Cancer Survivors? *Int J Endocrinol*. 2013;2013:1-9.
2013	Staba Hogan et al. New health conditions identified at a regional childhood cancer survivor clinic visit. *Pediatr Blood Cancer*. 2013;60(4):682-687.
2012	Cohen et al. Bone density in post-pubertal adolescent survivors of childhood brain tumors. *Pediatr Blood Cancer*. 2012;58(6):959-963.
2012	Gawade et al. Association of bone mineral density with incidental renal stone in long-term survivors of childhood acute lymphoblastic leukemia. *J Cancer Surviv*. 2012;6(4):388-397.
2012	Mostoufi-Moab et al. Bone density and structure in long-term survivors of pediatric allogeneic hematopoietic stem cell transplantation. *J Bone Min Res*. 2012;27(4):760-769.
2012	Polgreen et al. Modifiable risk factors associated with bone deficits in childhood cancer survivors. *BMC Pediatr*. 2012;12:40.
2012	Wilson et al. Fractures among long-term survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. *Cancer*. 2012;118(23):5920-5928.
2011	Demirkaya et al. Time-dependent alterations in growth and bone health parameters evaluated at different posttreatment periods in pediatric oncology patients. *Pediatr Hematol Oncol*. 2011;28(7):588-599.
2011	Follin et al. Bone loss after childhood acute lymphoblastic leukaemia: an observational study with and without GH therapy. *Eur J Endocrinol*. 2011;164(5):695-703.
2011	Joyce et al. Association of muscle strength and bone mineral density in adult survivors of childhood acute lymphoblastic leukemia. *Arch Phys Med Rehabil*. 2011;92(6):873-879.
2011	Le Meignen et al. Bone mineral density in adult survivors of childhood acute leukemia: impact of hematopoietic stem cell transplantation and other treatment modalities. *Blood*. 2011;118(6):1481-1489.
2011	Van Den Heijkant et al. Effects of growth hormone therapy on bone mass, metabolic balance, and well-being in young adult survivors of childhood acute lymphoblastic leukemia. *J Pediatr Hematol Oncol*. 2011;33(6):231-238.
2010	Benmiloud et al. Long-term effects on bone mineral density of different therapeutic schemes for acute lymphoblastic leukemia or non-Hodgkin lymphoma during childhood. *Horm Res Paediatr*. 2010;74(4):241-250.
2009	Kaste et al. Pediatric Hodgkin lymphoma survivors at negligible risk for significant bone mineral density deficits. *Pediatr Blood Cancer*. 2009;52(4):516-521.
2009	Muszynska-Roslan et al. Is the treatment for childhood solid tumors associated with lower bone mass than that for leukemia and Hodgkin disease? *Pediatr Hematol Oncol*. 2009;26(1):36-47.

2008	Jones et al. CRHR1 polymorphisms predict bone density in survivors of acute lymphoblastic leukemia. *J Clin Oncol*. 2008;26(18):3031-3037.
2008	Miyoshi et al. Endocrinological analysis of 122 Japanese childhood cancer survivors in a single hospital. *Endocr J*. 2008;55(6):1055-1063.
2007	Leung et al. A prospective cohort study of late sequelae of pediatric allogeneic hematopoietic stem cell transplantation. *Med*. 2007;86(4):215-224.
2007	Muszynska-Roslan et al. Body composition and bone mass in survivors of childhood cancer. *Pediatr Blood Cancer*. 2007;48(2):200-204.
2006	Kaste et al. Changes in bone mineral density in survivors of childhood acute lymphoblastic leukemia. *Pediatr Blood Cancer*. 2006;46(1):77-87.
2006	Kaste et al. QCT versus DXA in 320 survivors of childhood cancer: association of BMD with fracture history. *Pediatr Blood Cancer*. 2006;47(7):936-943.
2006	Pietilä et al. Bone mineral density is reduced in brain tumour patients treated in childhood. *Acta Paediatr*. 2006;95(10):1291-1297.
2006	Ruza et al. Bone mineral density and bone metabolism in children treated for bone sarcomas. *Pediatr Res*. 2006;59(6):866-871.
2006	van Beek et al. No difference between prednisolone and dexamethasone treatment in bone mineral density and growth in long term survivors of childhood acute lymphoblastic leukemia. *Pediatr Blood Cancer*. 2006;46(1):88-93.
2005	Alikasifoglu et al. Bone mineral density and serum bone turnover markers in survivors of childhood acute lymphoblastic leukemia: Comparison of megadose methylprednisolone and conventional-dose prednisolone treatments. *Am J Hematol*. 2005;80(2):113-118.
2005	Marinovic et al. Improvement in bone mineral density and body composition in survivors of childhood acute lymphoblastic leukemia: A 1-year prospective study. *Pediatrics*. 2005;116(1).
2004	Mandel et al. Skeletal morbidity in childhood acute lymphoblastic leukemia. *J Clin Oncol*. 2004;22(7):1215-1221.
2004	Pluskiewicz et al. Skeletal status in survivors of acute lymphoblastic leukemia assessed by quantitative ultrasound at the hand phalanges: A longitudinal study. *Ultrasound Med Biol*. 2004;30(7):893-898.
2003	Azcona et al. Reduced bone mineralization in adolescent survivors of malignant bone tumors: Comparison of quantitative ultrasound and dual-energy x-ray absorptiometry. *J Pediatr Hematol Oncol*. 2003;25(4):297-302.
2003	Holzer et al. Bone mineral density in long-term survivors of highly malignant osteosarcoma. *J Bone Joint Surg Br*. 2003;85(2):231-237.
2002	Pluskiewicz et al. Skeletal status in survivors of childhood acute lymphoblastic leukemia assessed by quantitative ultrasound: A pilot cross-sectional study. *Ultrasound Med Biol*. 2002;28(10):1279-1284.
1999	Brennan et al. Reduced bone mineral density in young adults following cure of acute lymphblastic leukaemia in childhood. *Br J Cancer*. 1999;79(11-12):1859-1863.
1998	Hesseling et al. Bone mineral density in long-term survivors of childhood cancer. *Int J Cancer Suppl*. 1998;11:44-47.
1998	Nysom et al. Bone mass after treatment for acute lymphoblastic leukemia in childhood. *J Clin Oncol*. 1998;16(12):3752-3760.
1996	Henderson et al. Bone density in survivors of childhood malignancies. *J Pediatr Hematol Oncol*. 1996;18(4):367-371.

Evidence from evidence-based guidelines in other populations

Year	Bibliography
2020	Kuhlen et al. Guidance to Bone Morbidity in Children and Adolescents Undergoing Allogeneic Hematopoietic Stem Cell Transplantation. *Biol Blood Marrow Transplant*. 2020 Feb;26(2):e27-e37.
2019	Marcucci et al. Bone Health in Childhood Cancer: Review of the Literature and Recommendations for the Management of Bone Health in Childhood Cancer Survivors. *Ann Oncol*. 2019 Jun 1;30(6):908-920.
2014	Gordon et al. 2013 Pediatric Position Development Conference: Executive Summary and Reflections. *J Clin Densitom*. 2014 Apr-Jun;17(2):219-24.

Evidence tables bone mineral density surveillance

Who needs bone mineral density surveillance?

Who needs BMD surveillance?				
Aaron et al. Identification of a Single-Nucleotide Polymorphism Within CDH2 Gene Associated With Bone Morbidity in Childhood Acute Lymphoblastic Leukemia Survivors. Pharmacogenomics. 2019 Apr;20(6):409-420.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Retrospective cohort study Treatment era: 1987-2010 Follow-up: At least 5 years >CR; Median time since stop therapy is 13.1 years (range 4-29 years)	Type and number of non-participants: NR Type and number of participants: 242 childhood US ALL survivors, Dx age <19 years, attained age <40 years, European origin, DFCI protocol 87-01, 91-01,95-01,2000-01 and 2005-01 Diagnoses: ALL (refractory, relapsed, and transplanted, as well as ALL patients with syndromes and hereditary bone disease excluded) Age at diagnosis: Median 4 years (range 0-18 years) Age at follow-up: Median 21.9 years (range 9-41) Controls: NA	Chemotherapy: GCs 100% Cumulative dose GCs (prednisone equivalents): median 9,025 (range 4,078-30,210) MTX 100% Cumulative dose MTX: median 6,723 (range 1,004-12,999) Radiotherapy: CRT 143 (59%) <18 Gy 30 (12.4%) ≥18 Gy 113 (46.7%) SCT: None Limb amputation: None Other: NR	Outcome definitions: Low BMD: BMD Z-score ≤-1 BMD Z-score ≤-2 Vertebral fractures (VF) using the Genant semiquantitative method Low cross-sectional area (CSA) CSA Z-score ≤-1 CSA Z-score ≤-2 BMD measurement modality: DXA (Lunar) of the LS (L2-4) and TB, and pQCT (XCT 2000) at 4% and 65% of the radial bone length. Spinal radiographies for VF from T4 to L4 vertebrae. Results: LS BMD Z-score ≤-1: 25.2% LS BMD Z-score ≤-2: 5.8% Mean LS BMD Z-score: -0.2 (range -2.9-3.1) TB BMD Z-score ≤-1: 25.2% TB BMD Z-score ≤-2: 5.8% Mean TB BMD Z-score: -0.2 (range -3.3-3.5) At least 1 VF: 22.3% CSA Z-score ≤-1 at 4%: 34%	Strengths: -One of the scarce genome wide studies Limitations: -No data on representability of the cohort -No replication cohort -No functional validation -Time of VF assessment is unclear **Risk of bias** A. Selection bias: Unclear Reason: number of eligible patients (original cohort) not described. B. Attrition bias: Low risk Reason: almost all included participants underwent a DXA and pQCT scan. C. Detection bias: Low risk Reason: low BMD by DXA is a hard end-point, not susceptible to

			CSA Z-score ≤-2 at 4%: 8% CSA Z-score ≤-1 at 65%: 25% CSA Z-score ≤-2 at 65%: 8% SNP rs1944294 (A>T) in the CDH2 gene is associated with CSA Z-score ≤-1 at 4% of the radial bone length, p=1.4x10^{-4}. Allelic OR 2.6 (95%CI 1.58–4.28). No SNPs were associated with low BMD. Multivariable model: CDH2 beta 1, OR 2.7 (95%CI 1.5-4.9), P=0.001	subjectivity of the assessor and reasonable cut-points were used. <u>D. Confounding:</u> Low risk Reason: all important prognostic factors were taken adequately into account.

Abbreviations: ALL=acute lymphoblastic leukemia; BMD=bone mineral density; CI=confidence interval; CRT=cranial radiotherapy; CSA=cross-sectional area; DXA=dual-energy X-ray absorptiometry; GCs=glucocorticoids; LS=lumbar spine; MTX=methotrexate; NR=not reported; OR=odds ratio; QCT=quantitative computed tomography; SCT=stem cell transplantation; SNP=single nucleotide polymorphism; TB=total body; VF=vertebral fractures.

Who needs BMD surveillance?				
Alikasifoglu et al. Bone mineral density and serum bone turnover markers in survivors of childhood acute lymphoblastic leukemia: Comparison of megadose methylprednisolone and conventional-dose prednisolone treatments. Am J Hematol 2005;80:113-118.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Cross sectional single center cohort study. Treatment era: Diagnosed January 1995 – December 2000 Follow-up: 3.4 (1.8) years after cessation of therapy	Type and number of non-participants: 49 of 108 (45.4%) ALL patients were not enrolled in order to get two comparable groups with respect to time interval since OT Type and number of participants: 59 ALL children (36 boys) - modified St. Jude ALL Total Therapy Study XI protocol. Diagnoses: ALL (100%) Age at diagnosis: Mean (SD) 5.5 (3.5) years Age at follow-up: Mean (SD) 11.7(3.5) years, range 6-19 years Prepubertal/Pubertal: 28/31 Group 1 (see Treatment section): 14/16 Group 2: 14/15 Controls: Normative values from the manufacturer were used.	Chemotherapy: Modified St. Jude ALL Total Therapy Study XI protocol GC dose: Group 1 (n=30): Prednisolone 60 mg/m^2 29 days Group 2: (n=29): Methylprednisolone 900 mg/m^2 7 days (1-7 days), followed with 600 mg/m^2 8 days (8-15 days) daily and then every other day up to day 29 (days 17, 19, 21, 23, 25, 29) Cumulative doses: Vincristine 1.5 mg/m^2 (tot. 4 days), Daunorubicin 30 mg/m^2(2 or 3 days) L-Asparaginase 200 U/kg (6 or 9 days) Cytosine arabinoside 300 mg/m^2 (3 days) Cyclophosphamide 300 mg/m^2(2 days) Etoposide 3-6 mg/kg (2 days) Methotrexate (intrathecal) 12 ore 10 or 8 mg based on age (3 days) Prednisone (intrathecal) 24 or 20 or 16 mg based on age (3 days) Cytosine arabinoside (intrathecal) 36 or 30 or 24 mg (3 days) High-dose methotrexate 50 mg/m^2 (2 days) Radiotherapy: 45/59 (76%) Group 1: 19/30 (63.3%)	Outcome definitions: BMD Z-scores BMD measurement modality: DXA (Hologic, QDR-4500A) of the lumbar spine (L_1- L_4) Results: Mean (Z-score) (L_1- L_4) BMD Z-score Total cohort: -1.73 (0.84); Group 1 vs. Group 2: -1.75 (0.83) vs. -1.66 (1.21), p=0.74. Prepubertal vs. Pubertal Total cohort NS Group 1: NS Group 2: NS Group 1: CRT vs. No CRT: NS Group 1 with CRT vs. Group 2 with CRT: NS **Stepwise regression analysis** (L_1- L_4) BMD Z-score was predicted by height Z- score (t=4.58, P=0.0001) and years since OT (t=2.80 P=0.006) after testing for age at diagnosis (t=0.461, NS), BMI Z-score (t=0.457, NS),CRT (t=- 0.613, NS), and puberty (t=0.129, NS),	Strengths: -Comparison of two clinically comparable groups of ALL patients who had been treated with very different doses of GCs. Limitations: -Selection criteria for the enrolled -patients not described in detail. A rather small sample size. **Risk of bias** A. Selection bias: High risk Reason: only 55.6% of the cohort was enrolled in respect to time interval since OT; no information is provided about patients who were not enrolled. However, low risk of bias between Group 1 and 2 as derived from a previous randomized trial. (ref 17.) B. Attrition bias: High risk Reason: Only 54.6% of the eligible ALL patients enrolled in the study. C. Detection bias: Low risk Reason: L1-L4 BMD DXA Z-scores were used as an endpoint. D. Confounding: Low risk

		Group 2: 26/29 (89.7%) SCT: 0% Limb_amputation:0%		Reason: Effect of clinical parameters (age at diagnosis, sex, pubertal status, BMI, duration after cessation of therapy, cranial radiotherapy) on BMD were taken into account in a multiple regression analysis. In the BMD Z-score, age and sex were taken into account.

Abbreviations: ALL=acute lymphoblastic leukemia; BMD=bone mineral density; BMI=body mass index; CRT=cranial radiotherapy; DXA=dual-energy X-ray absorptiometry; GCs: glucocorticoids; NS=not significant; OT=off-therapy; SCT=stem cell transplantation; SD=standard deviation.

Who needs BMD surveillance?				
Benmiloud et al. Long-term effects on bone mineral density of different therapeutic schemes for acute lymphoblastic leukemia or non-Hodgkin lymphoma during childhood. Horm Res Paediatr. 2010;74:241-250.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Cross-sectional single center cohort study Treatment era: NR Follow-up: Mean time since treatment (±SD) 15.0 ± 4.5 years.	Type and number of non-participants: 52 non-participants out of 150 who were invited (n=127 ALL and n=23 NHL). No further information of them reported. Of those 98 (65%) who completed evaluation 9 were excluded: 4 non-completed growth 1 because of acromegaly 1 lacking DXA data 3 treated with BMT without TBI Total non- participants: n=53 ALL and n=8 NHL) Type and number of participants: 89 survivors of ALL or NHL in remission and surviving ≥ 5 yrs after cancer diagnosis Diagnoses: ALL 74 (83%) NHL 15 (17%) Age at diagnosis: Median 4.8 years (P5-P95 2.2 – 13.8) Age at follow-up: Median 24.7 years (P5-P95 16.5 – 30.0) Adults: n=79 (range 18-30 years) Adolescents n=10 (range 16.0 -17.9)	FRALLE protocols used for ALL, B-NHL or ALCL protocols used for NHL. Corticosteroids Prednisolone 89/89 (100%): 40-60 mg/m^2 for 4-6 weeks, then at variable doses every month for 6-36 months; Cumulative dose, range: 1,200 – 5,400 mg/m^2 Additional Dex 47/88 (52.8%): – 26/47 during CRT (2 mg/m^2/day, cumulative dose 30 mg/m^2); – 21/47 as part of high-dose chemotherapy (initial dose 10-20 mg/m^2, cumulative dose 150-350 mg/m^2). Radiotherapy RT at any site: 48/89 (53.9%) CNS RT 32/89 (36%); -CRT 29/89 (32.6%); 18-24 Gy -CSRT 3/89 (3.4%); 10 Gy TBI 16/89 (18.0%); 8-13 Gy over 1 or 2 days SCT 16/89 (18.0%) Allogenic n=9 Autologous n=7 Final Groups considered based on treatment: Group I: only chemotherapy	Outcome definitions: Low BMD: Z-score ≤-1.0 but > 2.0 Very low BMD: Z-score ≤-2 BMD measurement modality: DXA (Hologic, 2000 Plus) -Lumbar spine (LS, L1-L4) BM(A)D -femoral neck (FN) BMD g/cm^2 -non-dominant total hip (Hip) BMD g/cm^2 **Results**: Low BMD: At any site: 44/89 (49%) At the LS: 36/89 (40.4%) At the FN: 21/89 (23.6%) At the Hip: 26/89 (29.2%) Very low BMD: At any site: 9/89 (10.1 %) At the LS: 9/89 (10.1%) At the FN: 2/89 (2.2%) At the Hip: 2/89 (2.2%) **Risk factors for low BMD** (BMD Z-score values are shown if significant differences): -Male gender vs. female At any site: 29/44 (66%) vs. 15/45 (33%), **p < 0.001** At the LS: 27/44 vs. 9/45, **p<0.01** LS BMD z-score (SD): -1.00 ± 1.10 vs. -0.20 ± 1.05, **p<0.01** At the FN: 13/44 vs. 8/45, NS At the Hip: 13/44 vs. 13/45, NS	Strengths: -Long follow-up period -Only patients who had completed growth were included -Very clear statistical analyses taking many risk factors into account -Well-written paper -BMAD analyzed Limitations: -Only risk factors for low BMD were assessed (not for very low BMD) -Results of multivariable regression analyses not in depth showed/displayed **Risk of bias** A. Selection bias: Low risk Reason: all patients fulfilling the criteria invited B. Attrition bias: High risk Reason: 59% of the invited patients included into analyses C. Detection bias: Low risk Reason: low BMD by DXA is a hard end-point, not susceptible to subjectivity of the assessor D. Confounding:

	Controls: None. Reference values for BMD scores used to calculate z-scores.	Group II: chemotherapy + CRT Group III: chemotherapy + TBI/SCT Chronic GVHD n=4 Fractures: n=2 during therapy Endocrine defects already diagnosed prior to study GHD: n=2 Hypogonadism -Males on HRT n=8/44 -Females on HRT n=6/45 -Females on Contraceptives 29/45 Endocrine defects diagnosed at study Total GHD: n=20/87 Male hypogonadism: n=12/44	- Age at diagnosis >9 years vs. <9 years: At any site: 12/23 (52%) vs. 32/66 (48%), NS At the LS: 10/23 vs.26/66, NS At the FN: 7/23 vs.14/66, NS FN BMD z-score (SD): -0.62 ± 0.85 vs. -0.09 ± 1.06, **p<0.05** At the Hip: 7/23 vs.19/66, NS - Group II vs. Group I: At any site NR At the LS: 15/32 vs.14/41, NS LS BMD Z-score (SD): -0.96 ± 0.87 vs. -0.28 ± 1.25, **p<0.05** At the FN: 11/32 vs.4/41, **p<0.05** FN BMD Z-score (SD): -0.48 ± 0.85 vs. 0.21 ± 1.03, **p<0.01** At the Hip: 13/32 vs. 6/41, **p<0.05** Hip BMD Z-score (SD): -0.64 ± 0.73 vs. 0.20 ± 0.91, **p<0.01** - Group III vs. Group I: At any site NR At the LS: 7/16 vs.14/41, NS At the FN: 6/16 vs.4/41, **p<0.05** FN BMD z-score (SD): -0.85 (0.96) vs. 0.21 (1.03), **p<0.001** At the Hip: 7/16 vs. 6/41, **p<0.05** Hip BMD z-score (SD): -0.70 ± 1.12 vs. 0.20 ± 0.91, **p<0.01** Addictional Dex (n=47) vs. no addictional Dex (n=41): At any site NR At the LS: 22/47 vs.8/41, **p<0.05** LS BMD z-score (SD): -0.89 ± 0.93 vs. -0.23 ± 1.27, **p<0.05** At the FN: 15/47 vs.5/41, **p<0.05** FN BMD z-score (SD): -0.45 (0.95) vs. 0.06 (1.06), **p<0.05** At the Hip: 38/47 vs.17/41, **p<0.01**	Low risk Reason: All important prognostic factors were taken adequately into account.

			Hip BMD Z-score (SD): -0.56 ± (0.83) vs. 0.10 (1.03), **p<0.01** NS difference at any site between - ALL vs. NHL - GHD (n=20, 23%) vs. non GHD (n=67, 73%) -GHD Group II 7/32 (22%) -GHD Group III 8/16 (50%) - male HH (n=12) vs. no HH -male HH in Group III 8/10 (80%) - female HH (n=8) vs no HH (39) - females HH in Group III 6/6 (100%) - Cumulative Dex dose 30 mg/m^2 Vs. >150 mg/m^2 - in Group III: autologous vs. allogenic BMT - in Group III: chronic GvHD yes vs. no **Risk factor for very low BMD** (BMD Z-score values are shown if significant differences) - Age at diagnosis >9 years vs. <9 years: At the LS: 5/23 vs.4/66, NS At the FN: 2/23 vs. 0/66, **p<0.05** FN BMD z-score (SD): -0.62 ± 0.85 vs. -0.09 ± 1.06, **p<0.05** At the Hip: 2/23 vs.0/66, **p<0.05** Hip BMD Z-score (SD): -0.50 ± 1.01 vs. -0.18 ± 0.96, NS - Group III vs. Group II: At the LS: 1/16 vs.4/32, NS At the FN: 2/16 vs.0/41, **p<0.05** FN BMD z-score (SD): -0.85 (0.96) vs. -0.48 (0.85), p NS At the Hip: 2/16 vs. 0/41, **p<0.05** Hip BMD z-score (SD): -0.70 ± 1.12 vs. -0.64 ± 0.73, NS	

			In synthesis: Low and very low BMD more common at any site in Group II and Group III compared with Group I: 19/32 (59%) vs. 9/16 (56%) vs. 16/41 (39%), respectively, $p < 0.01$. **Correlations** No correlation between BMD and age at diagnosis or time elapsed since cancer therapy (r and p NR). **Multivariable logistic regression analysis for the prediction of low BMD at the LS, FN and Hip** (β and R^2 NR) *after adjusting for: age, gender, treatment group, Dex dose range, GHD yes/no or HH yes/no) LS BMD: male gender ($p < 0.001$) FN BMD and Hip BMD: treatment group ($p=0.010$), Dex dose range ($p=0.014$) LS BMAD males vs. females: 0.324 ± 0.043 vs. 0.374 ± 0.048, $p<0.001$ BMAD NS in - ALL vs. NHL - Age at diagnosis <9 vs. >9 years - GHD vs. no GHD -male hypogonadism vs. no hypogonadism - Additional Dex vs. no additional Dex - Group I vs Group II vs Group III.	

Abbreviations: ALL=acute lymphoblastic leukemia; BMAD= bone mineral apparent density; BMD=bone mineral density; CRT=cranial radiotherapy; CSRT=craniospinal radiotherapy; Dex=dexamethasone; DXA=dual-energy X-ray absorptiometry; FN=femoral neck; GCs=glucocorticoids; GHD=growth hormone deficiency; GvHD = graft versus host disease; HH=hypogonadism; LS=lumbar spine; NHL=non-Hodgkin lymphoma; NR=not reported; NS=not significant; SCT=stem cell transplantation; β=regression coefficient.

Who needs BMD surveillance?				
Bhandari et al. Prevalence and risk factors for vitamin D deficiency in long-term childhood cancer survivors. Pediatr Blood Cancer. 2021 Apr 6;e29048.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Cross-sectional single center cohort study Treatment era: NR, approximately between 1955 and 2018 Follow-up: Median 14.2 years (range 2–65 years) since completing therapy	Type and number of non-participants: 5 survivors (1.2%) without 25OHD levels Type and number of participants: 446 (98.8%) consecutive childhood cancer survivors seen from March 2018 to September 2020 at the City of Hope long-term follow-up clinic 120 (26.9%) underwent DXA examination Diagnoses: Leukemia/lymphoma: 313 (70.2%) Solid tumor: 111 (24.9%) Nonmalignant hematologic disease: 22 (4.9%) Age at diagnosis: NR Age at follow-up: Mean (SD) 27.5 (11.4) years Controls: NR	Chemotherapy: Prednisone: None: 153 (42.5%) Cumulative dose 1-4275 mg/m2: 104 (28.9%) Cumulative dose >4275 mg/m2: 103 (28.6%) Methotrexate: None: 207 (59.7%) Cumulative dose 1-3690 mg/m2: 70 (20.2%) Cumulative dose >3690 mg/m2: 70 (20.2%) Radiotherapy: NR Correspondence with the authors learned that 68% of survivors treated with allogeneic HSCT received TBI, and that 32% of survivors treated with autologous HSCT received TBI (i.e. 24% of all participants) SCT: No: 264 (59.2%) Autologous: 44 (9.9%) Allogeneic: 138 (30.9%) Limb amputation: NR Other: VDD (≤20 ng/ml): 24% VDI (21-29 ng/ml): 38.6%	Outcome definitions: Reduced BMD: LS BMD Z-score ≤-1 BMD measurement modality: DXA (GE Lunar iDXA; GE Healthcare, Madison, WI) of the lumbar spine Results: **Prevalence** LS BMD Z-score ≤-1: 40/118 (33.9%) **Multivariable model** LS BMD Z-score ≤-1: VDD: OR 3.58, 95%CI 1.33-9.59, p=0.01 HCT (no or autologous vs. allogeneic): OR 2.63, 95%CI 1.17-5.91, p=0.02 Sex: NS Race/ethnicity: NS	Strengths: -Long follow-up period -Relationship between 25OHD levels and BMD Z-scores adequately analyzed, using a clinically relevant threshold (<20 ng/ml) Limitations: -Only BMD Z-score ≤-1 analyzed, not BMD Z-score ≤-2 -DXA scans were only performed in a subset of patients -26.9%- (at risk per COG LTFU guidelines) -The subset of patients that underwent DXA were not comparable to patients that did not (for treatment exposures) -No lateral spine X-ray were performed in order to detect asymptomatic vertebral fractures (over-estimation of BMD if present) -No information on HCT conditioning regimen (i.e. TBI) **Risk of bias** A. Selection bias: Low risk Reason: 98.8% of eligible survivors participated in this study B. Attrition bias: High risk Reason: only 118 of the 446 included survivors (27%) had DXA examination. There were no

				statistically significant differences in age, race/ethnicity, sex, or income status between those who did and did not have a DXA scan. However, DXA was performed per COG LTFU guidelines, so there were differences in treatment exposure <u>C. Detection bias:</u> Low risk Reason: low BMD by DXA is a hard end-point, not susceptible to subjectivity of the assessor <u>D. Confounding:</u> Low risk Reason: age and BMI were not included in the multivariable model. However, in the univariable model, they showed no significant association with reduced BMD

Abbreviations: BMD=bone mineral density; BMI=body mass index; COG=Children's Oncology Group; DXA=dual-energy X-ray absorptiometry; HCT=hematopoietic stem cell transplantation; LTFU=long-term follow-up; LS=lumbar spine; NR=not reported; NS=not significant; OR=odds ratio; SD=standard deviation; TBI=total body irradiation; VDD=vitamin D deficiency; VDI=vitamin D insufficiency

Who needs BMD surveillance?				
Bloomhardt et al. Severity of Reduced Bone Mineral Density and Risk of Fractures in Long-Term Survivors of Childhood Leukemia and Lymphoma Undergoing Guideline-Recommended Surveillance for Bone Health. Cancer. 2020 Jan 1;126(1):202-210.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Retrospective cohort study Treatment era: NR (DXA evaluation took place between 2004 and 2016, so treatment era was approximately between 1981 [or earlier] and ~2014 based on follow-up range) Follow-up: Mean (SD) 6.0±5.0 years (range 2.0-35.1) after treatment	Type and number of non-participants: 671 survivors of childhood leukemia or lymphoma attending the childhood survivor clinic of Yale New Haven Hospital or Seattle's children hospital for follow-up care were potentially eligible. 129 survivors did not receive BMD evaluation by DXA based on guideline recommendations. The 129 survivors without DXA scans were similar in sex and race to those with DXA scans but were less likely to be diagnosed with ALL and more likely to be diagnosed with another acute leukemia or Hodgkin lymphoma ($P < .01$) Type and number of participants: 542 survivors of childhood leukemia or lymphoma, diagnosed <20 years of age, completed BMD evaluation by DXA >2 years after completion of cancer therapy, and who had no precancer condition affecting BMD. Diagnoses: ALL: n= 353 (65.1%) Other acute leukemia: n=35 (6.5%) Hodgkin lymphoma: n=79 (14.6%)	Chemotherapy: Dexamethasone: n=323 (59.6%) Prednisone: n=192 (35.4%) Any glucocorticoid: n=515 (95%) Cyclophosphamide equivalent dose, mg/m2 0: n=81 (14.9%) 1-8000: n=409 (75.5%) >8000: n=52 (9.6%) High-dose methotrexate Yes: n=136 (25.8%) No: n=391 (74.2%) Radiotherapy: Cranial radiation: Yes: n=112 (20.7%) No: n= 430 (79.3%) Total body irradiation: Yes: n=44 (8.1%) No: n=497 (91.9%) SCT: NR Limb amputation: NR Other: NA	Outcome definitions: Low BMD: Z-score <-1 Very low BMD: Z-score <-2 (Z-score was adjusted for height in patients aged 4-20 years) Fractures: post-therapy nondigit fractures (yes/no) were according to patient report on clinician review of systems. Long-bone fractures included leg, arm, ankle, or wrist. BMD measurement modality: Lumbar spine BMD by DXA (Hologic) Results: Low LS BMD: n=93 (17.2%) Very low LS BMD: n=19 (3.5%) Frequency of fractures: Non-digit (1 or more posttreatment) fracture: n=116 (21.4%) Upper extremity long bone (includes wrist): n=66 (12.2%) Lower extremity long bone (includes ankle): n=29 (5.4%) Hand/foot: n=22 (4.1%) Vertebra: n=4 (0.7%) Other (clavicle, rib, jaw, pelvis, nose): n=21 (3.9%) Multiple fractures: 2 fractures: n=16 (3.0%) ≥3 fractures: n=9 (1.7%)	Strengths: -Large sample size -Non-response analysis -Fracture data Limitations: -Retrospective study design -Selective cohort -Fracture assessment not described in method section and sentences in the results and discussion section indicate that the fracture assessment was based on self-report and not confirmed by radiographs -assessment between BMD and fractures was not multivariable **Risk of bias** A. Selection bias: High risk Reason: BMD assessment by DXA was based on guideline recommendations, so only 'high risk' patients included. Non-response analysis showed that those with and without a DXA had different cancer diagnoses, indicating selection bias B. Attrition bias: Low risk Reason: all included survivors completed BMD evaluation C. Detection bias:

	Non-Hodgkin lymphoma: n=75 (13.8%) <u>Age at diagnosis:</u> 0-4 years: n=250 (46.1%) 5-9 years: n=106 (19.6%) 10-14 years: n=66 (12.2%) 15-19 years: n=120 (22.1%) <u>Age at follow-up:</u> Mean (SD) 15.5±6.5 years (range 4.4-52.2) <u>Controls:</u> NA		Multivariable model treatment factors: Age at diagnosis (years) 0-4: reference, 5-9: OR 1.6, 95%CI 0.8-3.1, 10-14: OR 2.6, 95%CI 1.4-5.1, 15-19 OR 3.9, 95%CI 1.8-8.3,p<.01 Sex (male) OR 1.4, 95%CI 0.9-2.4, p=.12 Race (white) OR 2.5, 95%CI 1.1-5.4, p=.02 Dexamethasone (y/n) OR 1.4, 95%CI 0.8-2.5, p=.22 Cyclophosphamide equivalent dose, mg/m2 0 Reference 1-8000 OR 0.8, 95%CI 0.4-1.6, >8000 OR 1.1, 95%CI 0.4-2.9, p=.67 High-dose methotrexate (y/n) OR 0.9, 95%CI 0.5-1.6, p=.79 Cranial radiation (y/n) OR 1.1, 95%CI 0.6-1.9, p=.86 Multivariable model chronic conditions: Age at diagnosis (years) 0-4: reference, 5-9: OR 1.6, 95%CI 0.8-3.1, 10-14: OR 2.6, 95%CI 1.4-5.1, 15-19: OR 3.9, 95%CI 1.8-8.3, p<.01 Sex (male) OR 1.4, 95%CI 0.9-2.4, p=.06 Race (white) OR 2.5, 95%CI 1.1-5.4, p=.02 Growth hormone deficiency (y/n) OR 2.1, 95%CI 0.8-5.1, p=.12 Thyroid hormone deficiency (y/n) OR 0.8, 95%CI 0.4-1.7, p=.50 Hypogonadism (y/n) OR 0.9, 95%CI 0.3-2.4, p=.83 Body mass index: underweight OR 3.5, 95%CI 1.1-11.5,	Low risk Reason: low BMD by DXA is a hard end-point, not susceptible to subjectivity of the assessor <u>D. Confounding:</u> High risk: Reason: Z-scores in participants 4-20 years were height-for-age adjusted and separate models for treatment factors and chronic conditions were employed. However, the model for treatment factors was not adjusted for attained age and BMI, and the model for chronic conditions was not adjusted for attained age. The association between low BMD and fractures was only analyzed with a univariable model.

			normal reference, overweight OR 0.3, 95%CI 0.1-0.6, obese OR 0.3, 95%CI 0.2-0.6, p<.01 Association low BMD and fractures: The risk of any nondigit post-therapy fracture was significantly increased for patients who had low BMD compared with those without low BMD (OR, 2.2; 95% CI, 1.3-3.7), as was the risk specifically in long bones (OR, 2.7; 95% CI, 1.5-4.7)	

Abbreviations: ALL=acute lymphoblastic leukemia; BMD=bone mineral density; CI=confidence interval; DXA=dual-energy X-ray absorptiometry; LS=lumbar spine; NA=not applicable; NR=not reported; OR=odds ratio; SCT=stem cell transplantation; SD=standard deviation.

Who needs BMD surveillance?				
Chemaitilly et al. Anterior Hypopituitarism in adult survivors of childhood cancer treated with cranial radiotherapy: a report from the St Jude Lifetime Cohort Study. J Clin Oncol 2015. 33:492-500.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Retrospective cohort study Treatment era: NR Follow-up: Mean age since primary cancer diagnosis 27.3 years (range 10.8 to 47.7).	Type and number of non-participants: Eligible cohort: 1175 (427 non-participants) Participants more likely to be white. Type and number of participants: 748 CCS exposed to cranial radiotherapy, >10 years post diagnosis of childhood cancer, treatment at SJCRH, age >18 years. Diagnoses: Leukaemia: 543 (72.6%) Lymphoma: 33 (4.4%) CNS tumour: 90 (12%) Embryonal: 30 (4%) Bone and soft tissue sarcoma: 38 (5.1%) Carcinoma: 11 (1.5%) Other: 3 (0.4%) Age at diagnosis: Age at cranial radiotherapy: Mean: 7.6 years (range 0.1 to 26 years) Age at follow-up: Mean age 34.2 years (range 19.4 to 59.6 years) Controls: n/a	Chemotherapy: NR Radiotherapy: Cranial radiotherapy dose: 1-14.9 Gy n=40 (5.3%) 15-21.9 Gy n=208 (27.8%) 22-29.9 Gy n=316 (4.1%) >40 Gy n=153 (20.5%) SCT: NR Limb amputation: NR Other:	Outcome definitions: Low BMD defined as Z-score <-2 BMD measurement modality: Quantitative CT with GE VCT lightSpeed 64-detector (GE healthcare). Volumetric trabecular BMD for lumbar vertebrae L1 and L2. Age and sex specific Z-scores. Results: Risk factors Untreated GHD (OR 1.78, 95% CI 0.99 to 3.18, p=0.05) Untreated LH/FSH deficiency (OR 2.42, 95% CI 1.10 to 5.30, **p=0.03**).	Strengths: -Large study -Long follow up Limitations: -Only assessed growth hormone deficiency and LH/FSH deficiency as risk factors for low BMD. -Did not discuss chemotherapy regimens for patients. **Risk of bias** A. Selection bias: High risk Reason: the study group consisted of less than 75% of the original cohort, with significant differences in ethnicity between participants and non-participants B. Attrition bias: Low risk Reason: the outcome was assessed for more than 75% of the study group C. Detection bias: Low risk Reason: low BMD by QCT is a hard end-point, not susceptible to subjectivity of the assessor D. Confounding: High risk Reason: not adjusted for age, sex and weight. Height adjustment

				not needed (volumetric BMD measured).

Abbreviations: BMD=bone mineral density; CCS=childhood cancer survivor; CI=confidence interval; CNS=central nervous system; GHD=growth hormone deficiency; NR=not reported; OR=odds ratio; QCT=quantitative computed tomography; SCT=stem cell transplantation; SJCRH=St. Jude Children's Research Hospital.

Who needs BMD surveillance?				
Chemaitilly et al. Premature ovarian insufficiency in Childhood Cancer survivors: A report from the St Jude Lifetime Cohort. J Clin Endocrinol Metab. 102(7):2242-2250.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Cross-sectional study Treatment era: NR Follow-up: Median 24 years after cancer diagnosis (range 10.2 to 48.1)	Type and number of non-participants: Eligible cohort: 1644 female survivors. Available for study: 988 (60.1%). Participants more likely to have received cranial radiation (p=0.03) and alkylating agents (p=<0.001). No significant differences in patient demographics, age at cancer diagnosis or age at study. Type and number of participants: CSS: 921. >10 years post diagnosis of childhood cancer, treatment at SJCRH, age >18 years. Diagnoses: Leukaemia: 398 (43.2%) Lymphoma: 165 (17.9%) CNS tumour: 52 (5.7%) Embryonal tumours: 178 (19.3%) Bone and soft tissue sarcoma: 105 (11.4%) Carcinomas: 12 (1.3%) Other: 11 (1.19%) Age at diagnosis: 0-4 years: 370 (40.2%) 5-9 years: 206 (22.4%) 10-14 years: 208 (22.6%) >15 years: 137 (14.9%) Age at follow-up:	Chemotherapy: Alkylating agents n=542 (58.8%) Radiotherapy: Pelvic radiotherapy n=153 (13.3%) Ovarian radiotherapy n=200 (21.7%) <100 cGy 53 (5.8%) 100–999 cGy 53 (5.8%) 1000–1999 cGy 32 (3.5%) ≥2000 cGy 27 (2.9%) Unknown 35 (3.8%) Hypothalamic/pituitary radiation n=291 (31.6%) <1000 cGy 0 (0%) 1000–1499 cGy 16 (1.7%) 1500–2999 cGy 219 (23.8%) ≥3000 cGy 56 (6.1%) SCT: Not specified Limb amputation: NR Other: NA	Outcome definitions: Low BMD defined as Z-score <-2.0 Primary ovarian insufficiency: persistent amenorrhea with evidence of a primary ovarian origin before the age of 40 years. Oestradiol <17pg/mL, FSH >30IU/l BMD measurement modality: Quantitative CT with GE VCT lightSpeed 64-detector (GE healthcare). Volumetric trabecular BMD for lumbar vertebrae L1 and L2. Age and sex specific Z-scores. Results: Risk factors Primary ovarian insufficiency (y/n): OR 5.07, 95% CI 1.97 to 13.05	Strengths: -Large study, robust data analysis -Long follow-up period Limitations: -Only looked at single risk factor (primary ovarian insufficiency) **Risk of bias** A. Selection bias: High risk Reason: study group less than 75% of original cohort and significant differences in cancer treatment. B. Attrition bias: Low risk Reason: outcome was assessed for >75% of study group (cross-sectional study) C. Detection bias: Low risk Reason: BMD by QCT is hard end point, not susceptible to subjectivity of assessor. D. Confounding: Low risk Reason: BMI and TBI taken into account; not adjusted for age. However, Z-scores were used as endpoint. Sex not applicable.

	Median age 31.7 years (range 19.0-60.6) Controls: not applicable			

Abbreviations: BMD=bone mineral density; BMI=body mass index; CCS=childhood cancer survivor; CNS=central nervous system; NR=not reported; NA=not applicable; OR=odds ratio; QCT=quantitative computed tomography; SCT=stem cell transplantation; SJCRH=St. Jude Children's Research Hospital; TBI=total body irradiation.

Who needs BMD surveillance?				
Choi et al. Factors related to decreased bone mineral density in childhood cancer survivors. J Korean Med Sci 2013:28:1632-1638.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Cross-sectional study Treatment era: NR Follow-up: Time from initial diagnosis to measurement of BMD (SD): 4.4±2.5 in males, 5.4±3.2 years in females.	Type and number of non-participants: NR Type and number of participants: CCS: n=78. Patients with growth hormone deficiency or adrenal insufficiency were excluded. Diagnoses: ALL: 38 (49%) AML: 35 (45%) CML: 5 (6%) Age at diagnosis: Mean 7.2±3.8 years (males) Mean 7.7±3.9 years (females) Age at follow-up: Mean 11.6±3.4 years (males) Mean 13.0±3.3 year (females) Mean 12.4±3.4 (total) Controls: No control group. Reference data of pediatric BMD was obtained from the manufacturer.	Chemotherapy: Glucocorticoids for chemotherapy: 33/78 (42%) Radiotherapy: 48/78 (62%) SCT: 50/78 (64%) Limb amputation: NR Other: Glucocorticoids for GVHD: 41/78 (53%) Hypogonadism: 20 (26%) Hypothyroidism: 1 (1%)	Outcome definitions: Not defined. BMD measurement modality: DXA (Delphi, Hologic) lumbar spine (L1-L4) and femoral neck Z-scores. Results: Lumbar spine BMD Z-score: mean (SD): -0.91±1.41 Femoral neck BMD Z-score (SD): mean -1.13±1.79 Lumbar spine BMD Z-score <-2: 20/78 (25.7%) Femoral neck BMD Z-score <-2: 19/78 (24.4%) Risk factors for lumbar spine BMD Z-score <-2: Older age at diagnosis **p=0.023** Older age at HSCT **p=0.026** Longer duration of glucocorticoids for GvHD **p=0.007** Current age, follow-up time, radiation dose, BMI SDS, serum calcium, P, ALP and IGF-1: NS HSCT OR 4.29 (95%CI 1.13-16.28), **p=0.02** cGVDH OR 6.99 (95%CI 2.18-20.55), **p<0.001** GC for GVDH OR 3.7, **p=0.02** Sex, radiation, relapse and hypogonadism: NS.	Strengths: - Limitations: -No baseline DXA assessment -No discussion of chemotherapy used/ type of glucocorticoids, or duration of glucocorticoids before HSCT **Risk of bias** A. Selection bias: Unclear Reason: No discussion of size of total cohort of CCS B. Attrition bias: Low risk Reason: Outcome was assessed for all patients (cross-sectional study). C. Detection bias: Low risk Reason: BMD by DXA is a hard end point, not susceptible to subjectivity of assessor. Z-score <-2 reasonable cut-point. D. Confounding: Low risk Reason: Sex was not included as possible confounder in the multivariable model, however, Z-score was used as endpoint, and sex was NS in univariable model.

			<u>Risk factors for lumbar spine Z-score <-2 with multivariable logistic regression model:</u> Longer duration of glucocorticoids for GvHD OR 1.124, CI 1.052-1.2, **p=0.001** Lower BMI SDS OR -.586, CI 0.362-0.948, **p=0.03** Disease (AML vs. ALL) and age at diagnosis: NS. <u>Risk factors for lower lumber spine Z-score:</u> HSCT **p=0.03** Chronic GvHD **p=0.006** Steroid use **p=0.04**	

Abbreviations: ALL=acute lymphoblastic leukemia; AML=acute myeloid leukemia; CI=confidence interval; CML=chronic myeloid leukemia; BMD=bone mineral density; BMI=body mass index; CCS=childhood cancer survivor; DXA=dual-energy X-ray absorptiometry; GCs=glucocorticoids; GvHD=graft versus host disease; NR=not reported; NS=not significant; OR=odds ratio; SCT=stem cell transplantation; SD=standard deviation.

Who needs BMD surveillance?				
De Matteo et al. Quantitative Ultrasound of Proximal Phalanxes in Childhood Acute Lymphoblastic Leukemia Survivors. J Pediatr Hematol Oncol. 2019;41(2):140-144.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Cross-sectional study Treatment era: NR Follow-up: Mean 41.2 ±37.8 months (95% CI: 49.9, 32.5)	Type and number of non-participants: 343 CCS (ALL, 172 males) followed-up at the Santobono-Pausilipon clinic. All childhood ALL survivors who were treated according to a AIEOP protocol, at least 6 months from therapy and visited the clinic between Nov 2012 and Dec 2013 were included. Type and number of participants: 72 survivors (32 males) Diagnoses: ALL (100%) Age at diagnosis: Mean 61 ± 45 months (95% CI: 71, 51) Age at follow-up: Mean 318 ± 130 months (95% CI: 348, 288) Controls: Large control group of Italian subjects aged 3 to 21 years provided by Baroncelli et al	Chemotherapy: AIEOP ALL-2000 study protocol, 17 a BFM back-bone treatment.. Cumulative dose (±SD): MTX (mg): males 9088±6706, females 8427±4563 L-ASP (mg): males 73,538±46,717, females 70,393±33,238 DNM (mg): males 113±104, females 102±44 VCR (mg): males 11±5, females 11±6 PDN (mg): males 660±791, females 739±904 DXM (mg): males 399±211, females 354±173 CPM (mg):males 2680±1305, females 2557±1201 ARA-C (mg): males 4254±4859, females 2421±2543 6-MP (mg): males 18,233±8542, females 21,039±8525 ADM (mg): males 110±51, females 151±249 6-TG (mg): males 798±401, females 777±434 Radiotherapy: 3 males (4.2%, dose NR) SCT: No Limb amputation: No Other: -	Outcome definitions: Low BMD: AD-SoS Z-score ≤ -2 BMD measurement modality: QUS measurement using the DBM Sonic 1200 Bone Profiler (IGEA, Carpi, Modena, Italy) of the first phalanx in the nondominant hand (fingers II to V). The amplitude-dependent speed of sound (AD-SoS) was measured in m/s and expressed as Z-score. Results: Ten subjects (13.8%) presented a Z-score below −2. Mean AD-SoS Z-score was −1.22 ± 1.19 (95% CI: −1.5,−0.94) in all survivors; mean AD-SoS z-score in male survivors was −1.18 ± 1.18 (95% CI: −1.58, −0.78), whereas in female survivors it was −1.24 ± 1.21 (95% CI: −1.61, −0.87); the difference between sex was not significant. BMD was significantly lower when compared with the reference population in the entire sample and in both sexes. Correlations: A negative correlation was found between AD-SoS z-score and age at diagnosis (P=0.01, R2=0.0351)	Strengths: -Large control group Limitations: -Sample size -No comparison with DXA data **Risk of bias** A. Selection bias: Unclear Reason: It is unclear how many survivors of the n=343 were eventually eligible (after applying the inclusion criteria) and how many survivors did not give informed consent for example. Furthermore, five subjects with bone toxicity during treatment were treated with bisphosphonates and 9 with vitamin D supplementation and included in the study. B. Attrition bias: Low risk Reason: all included survivors underwent QUS. C. Detection bias: Unclear Reason: QUS is an operator dependent measurement, although measurements were performed by the same skilled operator. It is unclear whether this operator was blinded for important prognostic factors.

			Negative correlation with BMI (P=0.0001). Positive correlation was instead observed between AD-SoS z-score and duration of follow-up (P=0.01, R2=0.0371) No significant correlation was detected between Z-score and cumulative cytotoxic and steroid doses. **Multiple linear regression models:** Age at ALL diagnosis (R^2=0.04, p=0.01) Duration of off-therapy period (R^2=0.04, P=0.01) adjusted for sex, age at QUS, and BMI. (cumulative cytotoxic and steroid doses: NS).	<u>D. Confounding:</u> Low risk Reason: analyses were adjusted for age, sex and BMI.

Abbreviations: 6-MP=6-mercaptopurine; 6-TG=6-thioguanine; ADM=adriamycin; AD-SoS=amplitude-dependent speed of sound; ALL=acute lymphoblastic leukemia; ARA-C=aracytin; BMD=bone mineral density; BMI=body mass index; CI=confidence interval; CPM=cyclophosphamide; DNM=daunomycin; DXM=dexamethasone; L-ASP=L-asparaginase; MTX=methotrexate; NR=not reported; NS=not significant; PDN=prednisone; QUS=quantitative ultrasound; RT=radiotherapy; SCT=stem cell transplantation; SD=standard deviation; VCR=vincristine.

Who needs BMD surveillance?				
Den Hoed et al. Bone mineral density after childhood cancer in 346 long-term adult survivors of childhood cancer. Osteoporos Int. 2015 Feb;26(2):521-9.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: retrospective single-center cohort study with cross-sectional data Treatment era: 1965-2003 Follow-up: Median time after cessation of treatment 16.7 years (IQR 12.4–23.0)	Type and number of non-participants: The survivors in whom a DXA scan was performed (n=346) were not different with respect to gender and smoking behaviour as compared to patients without a DXA scan. In contrast, survivors with DXA scans had more often: leukaemia or lymphoma, more often treated with prednisone, older age at diagnosis and at follow-up. Type and number of participants: 346 adult CCS ≥5 y after cessation Diagnoses: ALL: 166 (50.0 %) AML: 17 (4.9 %) HL: 44 (12.7 %) NHL: 46 (13.3 %) Brain tumour: 21 (6.1 %) Renal tumour: 21 (6.1 %) Sarcoma: 18 (5.2 %) Neuroblastoma: 13 (3.7 %) Age at diagnosis: Median 7.0 years (IQR 3.5–12.0) Age at follow-up: Median 24.5 years (IQR 20.1–29.5) Controls: NA	Chemotherapy: **Prednisone** 217 (63.6 %) cumulative dose (mg/m2) 1,870 [1,840–9,615] (median/interquartile) **Dexamethasone** 127 (37.0 %) cumulative dose (mg/m2))236 [236–1,360] (median/interquartile) **Cyclophosphamide** 171 (49.7 %) cumulative dose (mg/m2) 3,000 [2,000–5,000] (median/interquartile) **Methotrexate**) 222 (64.9 %) cumulative dose (mg/m2) 8,250 [5,490–20,960] (median/interquartile) **Ifosfamide**) 37 (10.8 %) cumulative dose (mg/m2)10,000 [6,000–30,000] (median/interquartile) Radiotherapy: **No** 253 (73.1 %) **Cranial-spinal** 57 (16.5 %) 25 [15–54] **Total body** 13 (3.8 %) 35 [24–35] **Brain tumour** 15 (4.3 %) 8 [8–12] **Abdomina**l 8 (2.3 %) 20 [15–45] SCT: 17 (4.9%) Limb amputation: NR Other: Smoking 61/299 available data ; 20.4 % at time of DXA	Outcome definitions: Osteoporosis: LS or TB BMD Z-score ≤−2 (prevalence) Osteopenia: LS or TB BMD Z-score ≤−1 (prevalence and risk models) Adjusted for body height BMD measurement modality: DXA of the lumbar spine (mainly reflecting trabecular Bone mass) and total body (approximately 80 % of the cortical bone) Results: **Prevalence:** osteopenia in all subtypes of paediatric cancer: 45% of the CCS. 38% osteopenia of the total body, 27% osteopenia of the lumbar spine, 20% both osteopenia. Osteoporosis: 9% (total body), 3% (lumbar spine) Compared to healthy peers, the mean BMDTB Z-score was significantly lower in survivors of ALL, AML, NHL, brain tumour, sarcoma and neuroblastoma The mean BMDLS Z-score was significantly lower in survivors of ALL and sarcomas. **Multivariable analysis** **BMD total body**: prednisone (OR=1.8; (1.0–3.1)) / Age at DXA (>30 years vs. ≤30) (OR=2.0 (1.1–3.5)) / BMI at DXA (kg/m2) <18.5 vs. 18.5–25 (OR= 4.0 (1.4–11.1)) /	Strengths: - Large study sample - Long follow-up period Limitations: -Only treatment-related risk factors for low BMD were assessed; no information about fractures, physical exercise, diet, etc. **Risk of bias** A. Selection bias: High risk Reason: survivors with DXA scans had more often leukaemia or lymphoma, were more often treated with prednisone and had an older age at diagnosis and at follow-up too. B. Attrition bias: Low risk Reason: outcome for all the study group C. Detection bias: Low risk Reason: low BMD by DXA is a hard end-point, not susceptible to subjectivity of the assessor D. Confounding: Low risk Reason: All important prognostic factors were taken adequately

	But values of the CCS were then compared with reference values of a previously reported cohort of healthy Dutch peers, and these BMD values were expressed as age- and gender-matched standardized deviation scores. Reference values of these healthy peers were measured on the same Lunar Prodigy from the same decade and in the same institute as the survivors.	Hormone replacement therapy (women only) 9 (115; 7.8 %) at time of DXA AMH <1 ng/ mL at DXA (women only) 48 (168, 28.6%)	BMI >25 vs. 18.5–25 (OR= 0.5 (0.3–0.9)) / Cranial/cranial-spinal (vs. no)(OR= 2.5 (1.2–5.2)) chemotherapeutic agents, smoking not associated with BMDTOTAL BODY osteopenia. **Multivariable analysis** **BMD lumbar spine**: Age at diagnosis (<12 y vs. ≥12) (OR= 2.3 (1.1–4.8)) (this parameter was no more significant in linear regression)/ gender (men vs women) OR= 2.3 (1.2–4.2)/ BMI at DXA (kg/m2) <18.5 vs. 18.5–25 (OR= 3.7 (1.3–10.5)) / BMI >25 vs. 18.5–25 (OR= 0.5 (0.3–1.1)) / Cranial/cranial-spinal (vs. no)(OR= 2.5 (1.2–5.2)) Chemotherapeutic agents and prednisone, smoking not associated with BMD Lumbar spine osteopenia. RT could not be included (patient number <5)	into account, and BMD adjusted for height Z-score

Abbreviations: ALL=acute lymphoblastic leukemia; AML=acute myeloid leukemia; BMD=bone mineral density; BMI=body mass index; CCS=childhood cancer survivor; DXA=dual-energy X-ray absorptiometry; HL=Hodgkin's lymphoma; LS=lumbar spine; NHL=non-Hodgkin lymphoma; NR=not reported; NS=not significant; OR=odds ratio; SCT=stem cell transplantation; SD=standard deviation; TB= total body.

Who needs BMD surveillance?				
Den Hoed et al. Genetic variation and bone mineral density in long-term adult survivor of childhood cancer. Pediatr Blood Cancer 2016: 63: 2212-2220.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Retrospective study Treatment era: Patients treated 1965-2003 Follow-up: Recruited in clinic between 2003-2008 Median follow up time 18 yrs (5-40 yrs)	Type and number of non-participants: 752 pts (2003-2008) CCS 400/752 with DXA 366/400 Caucasian ethnicity 334/366 DNA available Excluded patients had a shorter FU time (13vs18 yrs; p=0.02) and were younger (22vs27, P=0.01) Type and number of participants: **334 CCS** with DNA available who had completed treatment for at least 5 yrs Diagnoses: ALL 147 (44%) AML 13 (4%) HL 38 (11%) NHL 37 (11%) Brain Tumor 17 (5%) Renal Tumor 42 (13%) Sarcomas 14 (4%) Neuroblastomas 12 (4%) Other 14 (4%) Age at diagnosis: Median age 6.3 yrs (range 0-16.8) Age at follow-up: Median age at FU 26.1 yrs (18.1-49.3 yrs) Controls: NR	Chemotherapy: Cyclophosphamide 152/327 (46%) cumulative dose 3,000 mg/m2 Ifosfamide 6/208 (3%) cumulative dose 6,000 mg/m2 Methotrexate 124/130 (95%) cumulative dose 20,780 mg/m2 Radiotherapy: Cranial-spinal 56/334 (17%) (25 Gy) Total body 14/334 (4%) (33.6 Gy) Brain Tumor 12/334 (4%) (8 Gy) Abdominal 9/334 (3%) (20 Gy) SCT: 14/319 (4.2%) Limb amputation: NR Other: NR	Outcome definitions: **Possible correlation of risk of low BMD in CCS and single-nucleotide polymorphism(SNPs)**: COLA1; TNFSF11; TNFRSF11A; TNS-FRSF11B; VDR; ESR1; WLS; LRP5; MTHFR; MTRR; IL6 BMD measurement modality: BMD of lumbar spine (BMDLS) and Total body BMD (BMDTB) measured by DXA scan (Lunar Prodigy or Lunar DPX-L adjusted for Body Height SDS (because BMAD were not available in the records) Results: **Mean BMDTB** -0.47 (SD: 1.10, p<0.01). **Univariate analysis**: -lower BMDTB associated with axial radiotherapy, bone marrow transplantation, lower BMI, age above 30 yrs at FU, previous administration of prednisone, cyclophosphamide or methotrexate. Lower BMDTB in CCS with: - two minor alleles of **ESR1** (p=0.04) - two minor alleles of **LPR5** (p=0.01) **Multivariable model low BMDTB**:	Strengths: This is the first study that correlate the genetic variation in long term bone loss in adult CCS, demonstrating a standardized difference between the genotypes of more than 30% Limitations: -Retrospective design of the study -Fracture risk or presence of fracture were not considered in FU -Different treatment and diagnosis included and not stratified genetic for therapy or diagnosis **Risk of bias** A. Selection bias: High risk Reason: patients selected were less than 75% of the original court (334/752) B. Attrition bias: Low risk Reason: all patients included were analyzed (100%) C. Detection bias: Low risk Reason: low BMD by DXA is a hard end-point, not susceptible to subjectivity of the assessor Genetic analysis also does not need blinded assessor

			-lower height, weight at follow up (p<0.01; p=0.04) -previous applied radiotherapy (p=0.01) -**ESR1** (p=0.01) -**LPR5** (p=0.02) **Mean BMDLS** -0.27 (SD: 1.03, P<0.01). **Univariate analysis**: Lower BMDLS was associated with age above 12 years at diagnosis, lower BMI at follow up, lower age at FU, prednisone or glucocorticoid use, cyclophosphamide, MTX. Three SNPs were associated with impaired BMDLS: **- two minor alleles of ESR1** (p=0.03) -**LPR5** (p=0.03) **-VDR haplotype 3** (p=0.02) **Multivariable model lower BMDLS**: -male gender (p<0.01) -lower body weight at follow up (p<0.01) -radiotherapy (p=0.03) - **LPR5** (p=0.01)	<u>D. Confounding:</u> Low risk Reason: data were adjusted for height, weight, radiotherapy and potential confounders associated with BMD in univariable analysis

Abbreviations: ALL=acute lymphoblastic leukemia; AML=acute myeloid leukemia; BMD=bone mineral density; BMI=body mass index; CCS=childhood cancer survivor; DXA=dual-energy X-ray absorptiometry; FU= follow-up; HL=Hodgkin's lymphoma; LS=lumbar spine; NHL=non-Hodgkin lymphoma; NR=not reported; NS=not significant; OR=odds ratio; SCT=stem cell transplantation; SD=standard deviation; TB= total body.

Who needs BMD surveillance?				
Esbenshade et al. Screening for vitamin D insufficiency in pediatric cancer survivors. Pediatr Blood Cancer. 2014 Apr;61(4):723-8.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Retrospective single-centre cohort study with cross-sectional data Treatment era: 1998-2011 (not really precise but patients presented to Survivorship Clinic between February 2008 and September 2011 And 2.68 years (range 0.03–10.83) off therapy Follow-up: 2.68 years (range 0.03–10.83) off therapy	Type and number of non-participants: Cohort 233 - Of these patients, 171 (73.4%) screening with a total 25-hydroxy (OH) vitamin D level Type and number of participants: Cohort of all patients with a hematologic malignancy (70.8% leukemia) or LCH, who were <23 years at diagnosis, treated with at least 28 days of total corticosteroids as part of their chemotherapy regimen Diagnoses: ALL 121 (70.8 %) AML 1 (0.6 %) Lymphoma 36 (21.1%) LCH 13 (7.6%) Age at diagnosis: NR Age at follow-up: Age at time of DXA 12.05 [4.23-22.4]](median/interquartile) Controls: 97 healthy individuals between the ages of 1–21 years from the roster of children in the Vanderbilt pediatric endocrinology clinic or Vanderbilt general pediatrics clinic between June 2010 and January 2013 who had	Chemotherapy: Cumulative steroid: prednisone equivalent dosing in mg/m2: prednisone dosing in mg/m2 +(6.67 * dexamethasone dosing mg/m2) Radiotherapy: NR SCT: NR Limb amputation: NR Other: Ethnicity	Outcome definitions: total 25-hydroxyvitamin D concentrations = 25OHD2+ 25OHD3. 25-OHD VDI = 20–30 ng/ml; VDD = <20 ng/ml season during which vitamin D levels were measured was taken into account In a subset of the cohort, total Z-scores for total body BMD and lumbar BMD, which account for age and gender, were assessed. Osteopenia on DXA scan was defined as Z-score <-1.0 and osteoporosis as a Z-score <-2 BMD measurement modality: BMD and anterior posterior lumbar spine (L1–L4) BMD : DXA Whole body (N=91) and lumbar spine (N=88) DXA scans were included for analysis in cancer survivors who met COG guidelines for DXA screening due to corticosteroid exposure and had a VDL measured within two weeks of the DXA scan. Results: **Prevalence** Vitamin D abnormalities were present in 50.3% of the cancer survivor cohort; 34.5% had VDI (59/171) and 15.8% had VDD (27/171, whom 2 were supplemented during therapy)	Strengths: -Large study sample for vit D Limitations: -Small follow-up period -Only corticosteroid taken into account **Risk of bias** A. Selection bias: Low risk Reason: 73.4% of all eligible participant were included. B. Attrition bias: High risk Reason: outcome for all the study group for vit OH, however only in 50% for BMD (n=91) C. Detection bias: Low risk Reason: low BMD by DXA or 25OHvitD is a hard end-point, not susceptible to subjectivity of the assessor D. Confounding: High risk Reason: treatment not really described

	blood work obtained for other reasons and VDL were obtained from that blood sample. Patients were excluded from the control group if they had known osteopenia,osteoporosis, osteogenesis imperfecta, previously diagnosed VDI/ VDD, more than two bone fractures during the past year, chronic or current glucocorticoid use, thyrotoxicosis, gastrointestinal disease such as celiac disease causing possible malabsorption, diabetes mellitus, history of or current malignancy, or were of non-weight bearing status.		No significant difference in the prevalence of VDI (P=0.309) or VDD (P=0.365) between the survivorship and control groups **Multivariate analysis VDI or VDD**: BMI >85th percentile 5.44 (2.53, 11.67), Non-Caucasian or Hispanic 4.45 (1.49, 13.35), Age in years at survivorship visit (15 vs. 8) 2.17 (1.18, 3.96), Vitamin D level drawn summer versus winter 0.12 (0.04, 0.36), Vitamin D level drawn fall versus winter 0.35 (0.12, 1.00) **No SF for VDD only** Cumulative steroid not significant Same risk factors in control group **BMD**: Median whole body DXA scan Z-score (n=91) : 0.1 (-4.2, 3.6) and not significantly correlated with 25-OHvit D levels lumbar spine DXA scan Z-score (n=89) 0.0 (-4.2, 3.3) not correlated with 25OH vitD level	

Abbreviations: ALL=acute lymphoblastic leukemia; AML=acute myeloid leukemia; BMD=bone mineral density; BMI=body mass index; DXA=dual-energy X-ray absorptiometry; LCH=Langerhans cell histiocytosis; NR=not reported; NS=not significant; SCT=stem cell transplantation; VDD=vitamin D deficiency; VDI=vitamin D insufficiency.

Who needs BMD surveillance?				
Fiscaletti et al. Predictors of Vertebral Deformity in Long-Term Survivors of Childhood Acute Lymphoblastic Leukemia: The PETALE Study. J Clin Endocrinol Metab. 2021 Jan 23;106(2):512-525.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Cross-sectional single center cohort study Treatment era: 1987 to 2010 Follow-up: Median 15.1 years (range 5.4 to 28.2 years) since cancer diagnosis	Type and number of non-participants: 342 eligible survivors: -31 eligible survivors declined -60 eligible survivors were lost to follow-up or living abroad The survivors who were included in the study (n = 245) were not statistically different in age at diagnosis, sex, relapse risk profile, radiotherapy exposure, and age at the time of participation in the study than those who declined entry in the study (n = 31) Type and number of participants: 251 survivors agreed to participated, 245 childhood ALL survivors included in the study Diagnoses: ALL (100%) Age at diagnosis: Median (IQR) 4.8 (3.0 to 9.8) years Age at follow-up: Median (IQR) 21.7 (16.8 to 26.1) years Controls: NA	Chemotherapy: Steroids: 100% Mean prednisone equivalent dose (SD): 11 777 (5023) Methotrexate: 100% Mean MTX cumulative dose (SD): 6297 (1528) Radiotherapy: CRT: 145 (59%) SCT: 0% (exclusion criterion) Limb amputation: NA Other: NA	Outcome definitions: Vertebral fractures (Genant semiquantitative method) Age- and sex- specific LS BMD Z-scores (predictor) BMD measurement modality: DXA of the lumbar spine (L2-L4) using a GE Lunar Prodigy (GE Lunar Corporation, Madison, WI) scan. Vertebral deformities were assessed from anterior and lateral thoracolumbar spine radiographs. Two pediatric radiologists with extensive experience in pediatric musculoskeletal radiology separately scored the spine radiographs from T1 to L4 vertebrae using the modified Genant semiquantitative method. Results: **Prevalence of fractures** 106 vertebral fractures (VF) in 57 survivors (23%; 19F, 38M) 75 survivors (37F, 38M) with non-VF (31%) **Mean (SD) LS BMD Z-score** in pts with and without VF: -0.5 (1.0) *vs* -0.1 (1.1), **p=0.015** **Multivariable model** Vertebral fractures:	Strengths: -Systematic assessment of vertebral fractures -Relatively large, well-characterized cohort Limitations: -Only surivors of childhood ALL included, not other types of cancer **Risk of bias** A. Selection bias: Low risk Reason: 72% of the eligible survivors were included in the study, and these were not statistically different in age at diagnosis, sex, relapse risk profile, radiotherapy exposure, and age at the time of participation in the study than those who declined entry in the study (n = 31) B. Attrition bias: Low risk Reason: all 245 survivors had vertebral fracture assessment, and for 240 survivors (98%), information on all prognostic factors were available C. Detection bias: Low risk Reason: vertebral fracture assessment is reader dependent,

			LS BMD Z-score: RR 0.91, 95%CI 0.75-1.11, p=0.350 Age at diagnosis (yr): RR 1.01, 95%CI 0.96-1.06, p=0.784 Male sex: RR 1.94, 95%CI 1.16-3.24, p=0.01 Prednisone equivalent dose (per 1000 mg/m2): RR 1.05, 95%CI 1.00-1.10, p=0.03 Back pain: RR 2.45, 95%CI 1.56-3.84, p<0.001 CRT: NS MTX: NS **Multivariable model (males)** Vertebral fractures: LS BMD Z-score: RR 0.73, 95%CI 0.58-0.93, p=0.0095 Age at diagnosis (yr): RR 0.99, 95%CI 0.93-1.05, p=0.75 Time since diagnosis: RR 0.98, 95%CI 0.91-1.04, p=0.45 Prednisone equivalent dose (per 1000 mg/m2): RR 1.04, 95%CI 0.99-1.10, p=0.11 Back pain: RR 2.76, 95%CI 1.66-4.60, p<0.001 **Multivariable model (females)** Vertebral fractures: LS BMD Z-score: NS Age at diagnosis (yr): NS Time since diagnosis: NS Prednisone equivalent dose (per 1000 mg/m2): NS Back pain: NS	but two pediatric radiologists with extensive experience in pediatric musculoskeletal radiology separately scored the spine radiographs. Discordant findings regarding vertebral deformity grading occurred in only 10% of images and were jointly reanalyzed for consensus. <u>D. Confounding:</u> Low risk Reason: BMI and current age were not included in the multivariable model. However, these parameters were not associated with vertebral deformities in univariable analysis

Abbreviations: ALL=acute lymphoblastic leukemia; BMD=bone mineral density; BMI=body mass index; CI=confidence interval; CRT=cranial irradiation; DXA=dual-energy X-ray absorptiometry; IQR=interquartile range; LS=lumbar spine; MTX=methotrexate; NA=not applicable; NS=not significant; RR=relative risk; SCT=stem cell transplantation; SD=standard deviation; VF=vertebral fracture

Who needs BMD surveillance?				
Gawade et al. Association of bone mineral density with incidental renal stone in long-term survivors of childhood acute lymphoblastic leukemia. J Cancer Surviv. 2012 Dec;6(4):388-97.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Retrospective single-center cohort study with cross-sectional data Treatment era: 1962-1999 (not really precise but patients members of the St. Jude Lifetime Cohort enrolled between December 2007 and march 2011 And 10 years from initial diagnosis) Follow-up: 26.1 (21.5, 31.6) years from diagnosis	Type and number of non-participants: Among survivors eligible for this study (1,159), participants (662) were more likely to be female (337 (50.9 %) vs. 222 (44.7 %), P=0.04) and white (614 (92.7 %) vs. 442 (88.9 %), P=0.02) than nonparticipants (n=497) Type and number of participants: 662 of 1,180 potentially eligible cohort of all patients with ALL, >18 years + ≥ 10 years from their original cancer diagnosis Diagnoses: ALL Age at diagnosis: 4.5 (3, 8) Age at follow-up: 31 (26, 37) Controls: None	Chemotherapy: All received glucocorticoids: 9,560 (1,120, 10,160) mg/m² and methotrexate 5,268.6 (2,596, 14,193) mg/m² Cyclophosphamide 228 received none (34%); [1-8.119] mg/m² 144 (21.7%); [8.120-10.234] 147 (22.2%); [10,235–51,367] 143 (21.6%) Anthracycline: 212 (32%) received none; [1-100] mg/m² 305 (46.1%); [101-400] 135 (20.4%); ≥ 400 10 (1.5%) Radiotherapy: Out of the 20 participants that received renal radiation, 16 TBI (10 for relapse, 5 initially, 1 for secondary AML), 1 renal radiation as a result of direct renal irradiation for renal infiltrates, 3 mantle radiation for secondary Hodgkin's disease 18 cranial RT < 18 Gy, 185 received18-24 Gy, 237 received ≥ 24 Gy SCT: 16 Limb amputation: NR Other: ethnicity	Outcome definitions: BMD and its Z-score Incidental renal stone BMD measurement modality: BMD from the direct axial images quantitative computed tomography of the midvertebral bodies L1 and L2. In the case of fracture or deformity identified in either L1 or L2, the affected vertebral body was excluded, and one of the images of a vertebral body from T11 to L4 was reviewed. BMD was defined as the average of values obtained from L1 and L2 and Z-score was calculated 2 radiologists searched for presence of renal stones in either kidney or both kidneys. Renal stones were defined as incidental if ≥ 1 stone was identified in 1 kidney. Review of the medical records with incidental renal stones to find if they were symptomatic. Results: **Prevalence** BMD Z-score −0.36 (−1.14, 0.36) in a predominantly Caucasian (92.7 %) cohort of 662 ALL survivors out of which 337 (50.9 %) were female. The BMD Z-score was ≤−2 SD in 34	Strengths: -Large study sample Limitations: -It concerns the risk of incidental renal stone -Cumulative dose of anthracycline and glucocorticoid : how was it calculated? **Risk of bias** A. Selection bias: High risk Reason: only 662/1180 eligible participants (56%) were included B. Attrition bias: Low risk Reason: outcome same for all of the study group C. Detection bias: Low risk Reason: BMD by QCT is not subjective D. Confounding: Low risk Reason: multivariable analysis in which all appropriate confounders are included

			(5.2 %), and incidental renal stones were detected in 73 (11 %) of the ALL survivors. **Multivariate analysis** NA	

Abbreviations: ALL=acute lymphoblastic leukemia; AML=acute myeloid leukemia; BMD=bone mineral density; NA=not available; NR=not reported; QCT=quantitative computed tomography; RT=radiotherapy; SCT=stem cell transplantation; SD=standard deviation; TBI= total body irradiation.

Who needs BMD surveillance?				
Gurney et al. Bone Mineral Density Among Long-Term Survivors of Childhood Acute Lymphoblastic Leukemia: Results From the St. Jude Lifetime Cohort Study. Pediatr Blood Cancer. 2014 Jul;61(7):1270-6.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Retrospective single-center cohort study with cross-sectional data, St Jude Life Cohort Treatment era: NR Follow-up: Not specified, had to be at least 10 years post-diagnosis to be included	Type and number of non-participants: NR Type and number of participants: Group 1: Patients with ALL, >18 years + ≥ 10 years from their original cancer diagnosis Group 2=ACT clinic: Patients > 2 years after treatment + > 5 years from diagnosis until they are age 18 years or older and at least 10 years post-diagnosis. Of the 883 active participants, 845 had BMD test (61% of the 1,383 eligible cohort) - Of those, 400 had a prior BMD test conducted in the ACT clinic for analysis of BMD change over time Diagnoses: ALL Age at diagnosis: Median 5.02 yrs (IQR 3.07–9.33) Age at follow-up: Median 31.3 yrs (IQR 25.6–37.4) Controls:	Chemotherapy: Glucocorticoids (1 mg prednisone=0.15 mg dexamethasone) prednisone : 9,520 (1,120–10,400) mg/m² Etoposide 0.0 (0.0–9,208) Teniposide 0.0 (0.0–3,241) Methotrexate 5,426 (2,596–18,332) mg/m² Cyclophosphamide 3,490 (0.0–9,556) Anthracycline 46 (0.0–88) mg/m² Vincristine 41 (6.3–57) Radiotherapy: Spinal radiation: 15 Gy and almost every patient who received spinal radiation also received at least 24 Gy cranial radiation. 18 cranial RT < 18 Gy, 185 [18-24[Gy, 237 ≥ 24 Gy SCT: 21 (20 allogeneic HSCT for high risk or relapsed ALL or secondary AML + 1 autologous HSCT for a 2nd brain tumor) Limb amputation: NR Other: ethnicity	Outcome definitions: BMD and its Z-score via QCT BMD measurement modality: BMD from the direct axial images quantitative computed tomography of the midvertebral bodies L1 and L2. BMD was defined as the average of values obtained from L1 and L2 and Z-score was calculated Results: **Prevalence** BMD Z-score of -2 : 5.7% Z-score -1 to -2 : 23.8%. 70.5% BMD Z-score in the normal range (>-1). cumulative prevalence BMD Z-score of <-1 at age 40 years was 37.9% (95% CI 33.3–42.5%) overall, 46.2% (95%CI 39.9–52.4%) for males and 28.3% (95% CI 21.9–34.9%) for females. **Multivariate analysis** The presence of endocrine dysfunction was not significantly associated with BMD category. *Nota bene* low proportion of participants receiving hormonal therapy precluded assessment of the impact of replacement therapy on BMD (4/326 with GH deficiency, 10/47 with premature	Strengths: -Large study sample -Use of QCT Limitations: -Age at time of treatment was not included in multivariable analysis -Craniospinal RT is significant, particularly for women – but we don't know if there is a difference of cranio-spinal RT between men and women (for example age at this time) -Cumulative dose of anthracycline and glucocorticoid : how was it calculated? **Risk of bias** A. Selection bias: Unclear Reason: no data about non-participant B. Attrition bias: Low risk Reason: outcome for all the study group C. Detection bias: low risk Reason: low BMD by DXA is a hard end-point, not susceptible to subjectivity of the assessor D. Confounding: High risk

			ovarian insufficiency, and 35/102 with testosterone insufficiency) BMD Z-score <-1 or >-1: neither methotrexate dose nor glucocorticoid dose was statistically associated with BMD category attained age decreased risk (OR=0.97 [0.94–0.99] and sex = male increased 2.38 [1.74–3.27] cranial radiation dose of ≥24 Gy [OR] 2.05, 95% CI 1.21–3.46), as Craniospinal irradiation (OR 1.88, 95% CI 1.05–3.37) compared to those with no cranial or spinal radiation exposure – more of an effect for females When analyzed by sex: cumulative etoposide dose per 100 mg/m2 units OR=1.01 [1.00–1.01], p= 0.015	Reason: Attained age seems to be protective but for 367 they were screened before and counseled for VITD calcium and lifestyle Age at diagnosis was not taken into account in multivariable analysis Sex has different impact but we don't know if there was difference in treatment between sex

Abbreviations: ACT=after completion of therapy; ALL=acute lymphoblastic leukemia; AML=acute myeloid leukemia; BMD=bone mineral density; CI=confidence interval; IQR=interquartile range; NR=not reported; QCT=quantitative computed tomography; RT=radiotherapy; SCT=stem cell transplantation.

Who needs BMD surveillance?				
Henderson et al. Bone Density in survivors of Childhood Malignancies 1996 Journal of Paediatric Haematology and Oncology18(4): 367-371.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Cross sectional Observational Treatment era: Children' Cancer Group protocols Authors state this varied over 15yr period of study Follow-up: At least 12 months post chemotherapy Mean time since treatment: 4.3 yrs range 12mths-14.5yrs	Type and number of non-participants: Not described Type and number of participants: N=60 Received chemotherapy prior to skeletal maturity At least 1 yr post chemotherapy Most treated according to Childrens Cancer Group protocols (undefined) Diagnoses: **Solid Tumours 15/60:** Wilms 5 PNET 3 Teratoma 2 Ewing 1 Hepatoblastoma 1 **Haematological 45/60:** ALL 30 ANLL 3 HL 5 NHL 7 Age at diagnosis: Age at starting chemotherapy given: Mean 6.3 yrs range 0.3-16.7 yrs Age at follow-up: Mean 12.4 yrs range 5.5 to 20.1 yrs Controls:	Chemotherapy: **Solid Tumours:** n=2 had ifofosfamide **Haem. tumours:** ALL+NHL – glucocorticoids and methotrexate ANLL +HL – glucocorticoids Radiotherapy: 15 patients (14 ALL/1 NHL) received cranial irradiation (no dose given) SCT: NR Limb amputation: none Other: NR	Outcome definitions: Not defined for BMD in methods In the results table BMD divided into Z-scores: <-2.0 -2.0 to -1.0 -1.0 to 0 0 to 1.0 1.0 to 2.0 BMD measurement modality: DXA (Hologic model 1000W) Lumbar spine only Z-scores using own paediatric reference range up to age 17 *(ref 25)* (Z-scores matched those provided by manufacturer) Results: Mean LS BMD Z-score for all patients = -0.28 ± 0.14 (SE) Range -3.3 to 1.89 Prevalence of low LS BMD Z-scores <-2 5/60 Z-score -2.0 to -1.0 9/60 Z-score -1.0 to 0 21/60 Z-score > 0 25/60 **Univariate regression analyses**: LS BMD was related to: Weight Z-score, p=0.0001 Heght Z-score, P=0.0015 BMI percentile, **p=0.005** Older age at evaluation, **p=0.04**	Strengths: -Weight and Height Z-scores accounted for -Own reference range for DXA – cross referenced to manufacturer with nearly identical results in patients up to 17 years. Limitations: -Full population not described. -Treatment risk factors not well defined; -Relatively short time from treatment; -Only LS BMD analyzed. **Risk of bias** A. Selection bias: Unclear Reason: full population not described. B. Attrition bias: Unclear Reason: recruitment and consent process not described. C. Detection bias: Low risk Reason: DXA is an objective measure. D. Confounding: Unclear Reason: adjustment for Height/Weight/BMI/age/Tanner staging performed, however

	No control group/ For DXA Lumbar BMD referred own paediatric reference range up to age 17 *(ref 25)* *(*45/60 patients were younger than 17yrs)		Longer interval since chemotherapy, **p=0.04** Radiotherapy**,** p=0.08 Lower calcium intake, **p=0.003** Not related to: diagnosis, puberty at chemotherapy, RT other than CRT, skinfolds, use of glucocorticoids, methotrexate, ifosfamide RT (n=14) vs no RT (n=16): -0.62 ± 0.33 (SE?) vs. -0.05 ± 0.24 (SE?), p=0.16 **Multiple Regression Analysis: Predictors of low BMD Z-score:** Weight Z-score best predictor (R^2= 0.33, **p=0.0001)** Low Calcium intake (cumulative $R^2$0.42, **p=0.004)** Height Z-score (cumulative $R^2$0.49, **p=0.01)** Weakly predictive Cranial Irradiation (cum $R^2$0.51, p=0.15) Not predictive: age at evaluation, BMI percentile, time since chemotherapy, low calcium intake.	models tested are not well defined (all the variables together? Different models?)

Abbreviations: ALL=acute lymphoblastic leukemia; ANLL=acute nonlymphocytic leukemia; BMD=bone mineral density; DXA=dual-energy X-ray absorptiometry; HL=Hodgkin's lymphoma; LS=lumbar spine; NHL=non-Hodgkin lymphoma; NR=not reported; RT=radiotherapy; SCT=stem cell transplantation; SE=standard error.

Who needs BMD surveillance?				
Hesseling et al. Bone Mineral Density in Long-Term Survivors of Childhood Cancer. 1998 Int. J. Cancer 11 44-47.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Cross sectional Treatment era: Patients treated between 1974 and 1992 Follow-up: Median length of FU 112 months	Type and number of non-participants: Total of 163 long term survivors treated between 1974 and 1992 at Stellenburg Hospital, South Africa **66 non participants** (23 had been lost to FU, 25 declined, 18 DXA was not possible) Type and number of participants: Total of 163 long term survivors treated between 1974 and 1992 at Stellenburg Hospital, SA **97 participants** Diagnoses: ALL 22 AML 2 CNS tumors (total 16) Astrocytoma 6 Medulloblastoma 5 Craniopharyngioma 3 Optic glioma 1 Other 1 Wilms' tumor 10 Lymphoma (total 16) HL 8 NHL 5 Burkitt's 3 Neuroblastoma 7 Retinoblastoma 3 Germ cell tumors 3 Langerhan's disease 4	Chemotherapy: 41/97 children had corticosteroids Cumulative dose 1,200 -9,300 mg Radiotherapy: 34/97 had CRT (18-54 Gy) SCT: NR Limb amputation: NR Other:	Outcome definitions: BMD Z-score <-2 = significant osteopenia >-2 but <-1 osteopenia >-1 normal History of Fracture BMD measurement modality: Hologic L1-L4 spinal BMD by DXA Used manufacturer references. Age and gender matched. No local data available. Results: 13/97 children had Z-scores <-2.0 31/97 children had Z-scores >-2.0 <-1 14/97 had history of fractures. All fractures associated with trauma (no significant difference in BMD between those who fractured and those who did not). **Univariate analyses** According to LS BMD Z-score: Weight for height (p=0.016) and height for age (p=0.011) Z-scores at diagnosis were different; Height for age (p<0.001) and weight for age (p=0.006) Z-scores at follow-up were different. CRT >18 Gy (n=16) vs dose =16 Gy lower BMD (p=0.001) **Simple linear regression**	Strengths: -Described whole survivor population and treatment period Limitations: -Only spinal BMD measured -Height only significant associated factor to BMD but was not accounted for in DXA – so small bone size likely explanation for (?most) of the low BMD – added to this authors comment on local SA population is already short compared to global reference data. -No documentation of surgery/chemotherapy/SCT regimens -No assessment of hormonal/pubertal status **Risk of bias** A. Selection bias: High risk Reason: only half of study population was assessed but no details of the "non-participant" cohort described B. Attrition bias: Low risk Reason: cross-sectional study. All participants had DXA/end-point data C. Detection bias: Low risk

	Osteosarcoma 2 Rhabdomyosarcoma 2 Kaposi's sarcoma 2 Fibrosarcoma 1 Hepatic sarcoma 1 Hepatoblastoma 1 Ovarian carcinoma 1 Nasopharyngeal carcinoma 1 PNET 1 Teratoma 1 Thyroid carcinoma 1 <u>Age at diagnosis:</u> Median age at diagnosis 54 months <u>Age at follow-up:</u> Median age at follow up 179 months <u>Controls:</u> None		-Height for age and weight for age at follow-up (p< 0.001, R2 =0.04) Rank correlation data: -Increasing CRT dose and lower BMD (r=NR, p<0.001 -in ALL patients receiving 18–24 Gy (n=NR): increasing dose correlated with BMD (r= NR, p=0.04). <u>No significant correlations</u>: Cumulative prednisone dose and BMD Z-scores **Multiple Regression analysis** (stepwise regression) "Height for age at follow-up" Z-score was only significant factor associated with BMD	Reason: blinding not mentioned in the protocol but low BMD by DXA is not subjective. <u>D. Confounding:</u> High risk Reason: population South African children. Likely height SDS already lower than global references – but no local data available; also likely to have nutritional and hormonal deficiencies (not assessed); No pubertal/Tanner stage assessment; Multiple regression analyses seem to test only the impact of anthropometrics on spinal BMD (no other risk factor, as CRT)

Abbreviations: ALL=acute lymphoblastic leukemia; AML=acute myeloid leukemia; BMD=bone mineral density; CNS=central nervous system; CRT=cranial radiotherapy; DXA=dual-energy X-ray absorptiometry; FU=follow-up; HL=Hodgkin's lymphoma; LS=lumbar spine; NHL=non-Hodgkin lymphoma; NR=not reported; PNET=primitive neuroectodermal tumor; SCT=stem cell transplantation.

Who needs BMD surveillance?				
Hobusch et al. Do long Term Survivors of Ewing Family of Tumors experience low bone mineral density and increased fracture risk? Clin Orthop Reklat Res 2014; 472: 2471-3479.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Cross-sectional Treatment era: Patients treated between 1963 to 2005 Follow-up: Minimum FU 5 years after treatment; Mean FU 15 years (5-48 years)	Type and number of non-participants: 183 CCS treated in the same institution. 83/183 died of disease 67/100 responded 11/67 excluded 56 participants Type and number of participants: 56/100 (29 males, 27 females) CCS at minimum FU of 5 years. Diagnoses: 50 Ewing sarcoma 6 primitive neuroectodermal tumor Age at surgery: Mean age at surgery 16 yrs (2-52 years) Age at follow-up: Mean age at FU 32 years (16-61 years) Controls: NR	Chemotherapy: **56/56 (100%) received polychemotherapy and BMD evaluation:** - **9 VACA** (vincristine, Actynomycin D, cyclophosphamide, doxorubicin) - **32 VAIA** (vincristine, actinomycin D, ifosfamide, doxorubicin)/ **EVAIA** (etoposide+VAIA) - **13 VIDE** (vincristine, ifosfamide, doxorubicin, etoposide)/ **VAI** (vincristine, actinomycin D, ifosfamide)/ **VAC** (vincristine, actinomycin D, cyclophosphamide) - **2 Other** Radiotherapy: **36/56 local radiation** **-**radiation field between 45 and 54 Gy (1.8 and 2 Gy for 5 times/ week) SCT: NR Limb amputation: **0/56** Other: -27 resection only -11 proximal femur megareplacement - 6 fibula for tibia transfer - 4 pelvic megaphrostesis	Outcome definitions: **Adults (according to WHO criteria):** - normal BMD:T score >-1 SD -osteopenia: T score between -1 and -2.5 SD -osteoporosis: T score <-2.5 SD **Adolescents (15-19 years)** - low BMD: lumbar spine Z-score <-2 SD (T-score , Z-score and bone mass in g/cm2 were mentioned as BMD [given the high correlation among the three parameters ; r=0.935; p<0.0001]) BMD measurement modality: **DXA scan of lumbar spine (L1-L4) and proximal femur of the controlateral side** : - 48 pts Hologic Discovery A S/N 45313 - 2 pts with Hologic QDR4500W - 2 pts with Lunar Prodigy -3 pts Lunar iDXA -1 pt Lunar DPX Corrected for different scans according to Genant et al. Results: 7/56 pts (13%; 6 males) osteoporosis 24/56 pts (43%; 12 males) osteopenia 25/56 pts (44%; 11 male) Normal BMD	Strengths: -Cross sectional in single center -Long follow up Limitations: -Small sample of patients -Pediatric and adults -No control group -Both high and low impact fractures analyzed **Risk of bias** A. Selection bias: High risk Reason: only 56% of total CCS (56/100) were included B. Attrition bias: Low risk Reason: >75% of participants were studied for BMD and fractures C. Detection bias: Low risk Reason: DXA scan was used and no blinded assessor is needed D. Confounding: Low risk Reason: multivariable analysis and Bonferroni were used to adjust for age at surgery, age at follow up, sex, chemotherapy protocol and BMI

		- 2 distal femur megareplacement - 2 proximal tibia megareplacement - 1 ulna transposition -1 fibula-prohumeral transfer	**BMD**: - Higher Z-score BMD LS for longer follow up (estimate 0.06; 95%CI 0.03-0.10 ; p=0.013) - Low BMI-Low femoral Z-score (estimate 0.09; 95%CI 0.04-0.14, p=0.002) - Patients younger at time of surgery had Higher T score of femoral neck in **multivariable** model but not after Bonferroni correction With the numbers available, gender, tumor-specific parameters and surgical features, radiation therapy, different chemotherapeutic protocols, and the duration of secondary amenorrhea had no influence on BMD in the multivariate model. **Fractures**: - 21 pts (41%) reported 29 fractures - 6 (11%) low impact fracture - 15 pts high impact fracture -3 pts >3 fractures -Radiation vs no radiation=NS **Fractures in 21/56 (38%) (p=0.332 for different BMD categories)**: - 38% of pts with normal BMD - 34% of pts with osteopenia - 50% of pts with osteoporosis **20% of fractures in radiation field**	

Abbreviations: BMD=bone mineral density; BMI=body mass index; CCS=childhood cancer survivor; DXA=dual-energy X-ray absorptiometry; FU= follow-up; LS=lumbar spine; NR=not reported; NS=not significant; SCT=stem cell transplantation; SD=standard deviation.

Who needs BMD surveillance?				
Holzer et al. Bone mineral density in long term survivors of high malignant osteosarcoma. J Bone Joint Surg 2003; 85-B: 231-7.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Cross-sectional Treatment era: 1970-1990 Follow-up: Mean 16±2.2 years	Type and number of non-participants: - 262 pts diagnosed of osteosarcoma - 172 received adjuvant or neoadjuvant chemotherapy - 82 candidates eligible: free from disease for at least 10 yrs after completion of treatment -16 could not be traced -Remaining 66 pts contacted -58 returned questionnaires -48 agreed to perform DXA scan Type and number of participants: - **58/82** CCS, of whom 48 (22 males; 26 females) agreed to have a DXA, after >10 yrs from therapy Diagnoses: Malignant Osteosarcoma: 31 femur, 13 tibia, 45 solitary lesion, 3 multiple lesions, 5 metastases at time of diagnosis Age at surgery: 6.07-19.84 yrs Age at follow-up: Mean 31±4.24 yrs (18-41 yrs) Controls: NR	Chemotherapy: 48 pts Chemotherapy with protocol COSS (incl. doxorubicin, high dose methotrexate, cyclophosphamide, bleomycin, dactinomycin, vincristine, cisplatin, and ifosfamide) Radiotherapy: N=1 SCT: NA Limb amputation: 3 patients have amputation 9 rotationplasty 36 limb preserving surgery Other: NR	Outcome definitions: -normal: BMD T-score <-1 SD -osteopenia: BMD T-score between -1.0 and -2.5 SD -osteoporosis: BMD T score <-2.5 SD BMD measurement modality: BMD T score of lumbar spine and femur of non-operated side measured by DXA scan (Hologic QDR 4500 or Lunar DPXL). Lunar values were standardized according to Genant et al. T-scores (ref population: Genant et al) and Z-scores (ref population: NHANES) were calculated. Results: - n=17 (35%) normal BMD - n=21 (44%) osteopenia - n=10 (21%) osteoporosis **BMD correlated**: - positively with Body weight (p=0.03) - negatively with type of endoprostesis (p=0.03) -positively with C-telopeptide (p=0.04) - negatively with menarchal age in women (p=0.01) - no differences or correlation with COSS protocols	Strengths: -First study on osteosarcoma and BMD -Long follow-up Limitations: -Small sample for subgroups (osteoporosis, osteopenia, normal) -All adults and only T-score considered -No multivariable analysis **Risk of bias** A. Selection bias: High risk Reason: less than 75% pf patients recruited in the study (58/82) B. Attrition bias: Low risk Reason: >75% of patients were studied by DXA (48/58) C. Detection bias: Low risk Reason: DXA scan was used and no blinded assessor is needed D. Confounding: High risk Reason: data were not adjusted for weight, BMI or age or sex

Abbreviations: BMD=bone mineral density; BMI=body mass index; DXA=dual-energy X-ray absorptiometry; LS=lumbar spine; NA=not applicable; NR=not reported; SCT=stem cell transplantation; SD=standard deviation.

Who needs BMD surveillance?				
Hudson et al. Clinical Ascertainment of Health Outcomes Among Adults Treated for Childhood Cancer. JAMA 2013; 309 (22): 2371-2381.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Cross sectional study assessing prevalence of conditions in survivors of childhood cancer enrolled in the St Jude Lifetime Cohort Study (SJLIFE) Treatment era: 1962-2001 SJLIFE Follow-up: Inclusion criteria: At least 10 years post treatment	Type and number of non-participants: N= 1130 enrolled on SJLIFE and eligible to participate (age > 18yrs, survival > 10yrs since diagnosis, within first 59 consecutive recruitment blocks of study) 680 declined to participate 277 expressed interest but not completed visit 124 completed questionnaires but not completed visit 49 lost to follow up Type and number of participants: STJLIFE study participants Age > 18 years At least 10 years post-treatment For whole study n=1713 N= 1142/1713 considered at risk of developing osteoporosis based on "at risk by treatment exposure defined in COG guidelines" Diagnoses: For all 1713 participants: n (%) **Leukemia** Acute lymphoblastic 765 (44.7) Acute myeloid 38 (2.2) Other Leukemia 6 (0.4) **Lymphoma** Hodgkin 218 (12.7) Non-Hodgkin 78 (4.6)	SJLIFE study overall had patients treated with numerous treatments: But only those treated with methotrexate/glucocorticoids or HPA irradiation were investigated for osteoporosis. Further breakdown provided in the online supplementary tables. Chemotherapy: Methotrexate 941/1713 Glucocorticoids 965/1713 Radiotherapy: HPA radiation 714/1713 SCT: NR Limb amputation: NR Other: NR	**Outcome definitions:** "Osteoporosis" Not defined further in paper "Osteopenia" given in supplementary table BMD measurement modality: DXA – not further defined in this paper or supplementary papers. Results: Patients at risk of osteoporosis: 1142/1173 Prevalence of osteoporosis N = 110/1142 (9.6%), 95% CI 8.0-11.5 Before SJLIFE diagnosis N=23/1142 (2%), 95% CI 1.3-3.0 Related SJLIFE diagnosis N=87/1142 (7,6%), 95% CI 6.1-9.3 23/110 had known osteoporosis 33/110 picked up on assessment Data from supplementary tables: 1432 patients had DXA 1142 had risk for skeletal effects defined by treatment with Methotrexate 941/1142 Glucocorticoids 911/1142 HP axis radiation 658/1142 Osteoporosis prevalence 80/941 for Methotrextae	Strengths: -Large, well characterized cohort Limitations: -Minimal information given about definition/diagnosis/type of DXA used. -Only assessed patients pre-determined to be at risk from treatment given using COG guidance (although this was a fairly large proportion of study population – 67%) -No control population **Risk of bias** A. Selection bias: High risk Reason: 60% participation for on-site evaluation. However authors comment that there was minimal difference between studied and source population in terms of demographics/disease/neighbourhood characteristics B. Attrition bias: Low risk Reason: cross sectional study C. Detection bias: Low risk Reason: blinding not mentioned in the protocol but low BMD by DXA not subjective

	CNS tumors Astrocytoma or glioma 67 (3.9) Medulloblastoma and PNET 38 (2.2) Ependymoma 15 (0.9) Other CNS tumors 21 (1.2) **Sarcoma** Ewing sarcoma family of tumors 58 (3.4) Osteosarcoma 71 (4.1) Rhabdomyosarcoma 47 (2.7) Non rhabdomyosarcoma 17 (1.0) **Embryonal tumors:** Germ cell tumor 20 (1.2) Neuroblastoma 64 (3.7) Wilms tumor 94 (5.5) **Other** Hepatoblastoma 4 (0.2) Melanoma 4 (0.2) Retinoblastoma 66 (3.9) Carcinomas 16 (0.9) Other neoplasms 6 (0.4) <u>Age at diagnosis:</u> For all 1713 participants: Mean (SD) 7.5 (5.5) yrs Median (range) 6.0 (0-24 yrs <u>Age at follow-up:</u> Mean (SD) 33.1 (8.1) yrs Median (range) 32 (18-60) yrs <u>Controls:</u> None		81/911 for GC's 91/658 for HP axis radiation Osteopenia prevalence 372/941 for Methotrexate 353/911 for GC's 296/658 for HP axis radiation **Multivariablee analysis:** None done	<u>D. Confounding:</u> High risk Reason: prevalence rates are likely an underestimate of incidence. Multivariable analyses not performed.

Abbreviations: BMD=bone mineral density; CI=confidence interval; CNS=central nervous system; COG=children's oncology group; DXA=dual-energy X-ray absorptiometry; GCs=glucocorticoids; HPA=hypothalamic-pituitary axis; NA=not applicable; NR=not reported; SCT=stem cell transplantation; SD=standard deviation.

Who needs BMD surveillance?				
Im et al. Genome-wide search for higher order epistasis as modifiers of treatment effects on bone mineral density in childhood cancer survivors. European Journal of Human Genetics 2018. 26:275–286.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Comparative study in St Jude cohort Treatment era: NR Follow-up: NR	Type and number of non-participants: NR Type and number of participants: A discovery cohort of 856 adult survivors of pediatric ALL Diagnoses: Pediatric ALL Age at diagnosis: 5.0 (0.2–19.5) Age at follow-up: 31.3 (18.4–59.7) Controls: Replication cohort consisting of 1428 adult survivors of any non-ALL pediatric cancer Age at diagnosis: 9.2 (0–24.8) Age at BMD measurement: 31.6 (18.5–65.9)	Chemotherapy: methotrexate (<5100, ≥5100 to <20000, ≥20000 mg/m2), and glucocorticoid (<2000, ≥2000 to <11000, ≥11000 mg/m2) Radiotherapy: Cumulative doses of cranial radiation (none, >0 to <2400, ≥2400 cGy), SCT: NR Limb amputation: NR Other: NR	Outcome definitions: SNPs influencing BMD BMD measurement modality: Quantitative computed tomography (L1-L2). A BMD Z-score was computed. Results: BMD Z-score (expressed in SD) Median (range) −0.4 (−3.5, 5.4) Controls: −0.2 (−5.5, 6.0) ≤−1 256 (29.9) Controls: 349 (24.4) ≥1 104 (12.1) Controls: 249 (17.4) 220 3-SNP interactions (10 interactions per chromosome) associated with BMD Z-score. Consistent with previous observations of regulatory complexes involving enhancer–promoter, enhancer–enhancer, or promoter–promoter interactions. Of the six regulatory 3-SNP interactions identified as candidate interactions (P < 3.5 x 10−11) among cancer survivors exposed to treatments, five were replicated in an independent cohort of survivors (N = 1428) as modifiers of treatment effects on BMD (P < 0.05). Analyses with publicly available bioinformatics data revealed that SNPs contributing	Strengths: -Large sample size -Replicated findings Limitations: -No second independent ALL survivor cohort available for replication **Risk of bias** A. Selection bias: High risk Reason: we do not know the original cohort. Age at diagnosis is different in patient and controls (5 vs 9 yrs) B. Attrition bias: Low risk Reason: SNP and BMD analyses were performed in all included participants. C. Detection bias: Low risk Reason: low BMD by QCT is a hard end-point, not susceptible to subjectivity of the assessor D. Confounding: High risk Reason: several confounding factors have not been considered (BMI, Tannner)

			to replicated interactions were enriched for gene expressions (P = 3.6 x 10−4) and enhancer states (P < 0.05) in cells relevant for bone biology. For each replicated interaction, implicated SNPs were within or directly adjacent to 100-kb windows of genomic regions that plausibly physically interact in lymphoblastoid cells.	

Abbreviations: ALL=acute lymphoblastic leukemia; BMD=bone mineral density; BMI=body mass index; NR=not reported; QCT=quantitative computed tomography; SCT=stem cell transplantation; SD=standard deviation; SNPs=single nucleotide polymorphisms.

Who needs BMD surveillance?				
Im et al. Genome-wide Association Studies Reveal Novel Locus With Sex-/Therapy-Specific Fracture Risk Effects in Childhood Cancer Survivors. J Bone Miner Res. 2021 Apr;36(4):685-695.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Genome-wide association study in two independent cohorts Treatment era: Discovery: 1970 to 1986 Replication: NR Follow-up: At least 5 years Discovery: Approximately 37 years Replication: Approximately 25 years	Type and number of non-participants: Discovery: 4713 eligible survivors. 62.7% (n = 2955) provided detailed lifetime fracture histories as a part of a larger follow-up questionnaire. After exclusion of survivors with a history of HSCT and/or missing covariate data, 2453 survivors were included Replication: 1867 eligible survivors. 84% (n=1569) provided detailed lifetime fracture histories. 1417 survivors were included in the analysis Type and number of participants: -2453 participants of European ancestry from the Childhood Cancer Survivor Study (discovery cohort) -1417 survivors of European ancestry from the St. Jude Lifetime Cohort Study (replication cohort) Diagnoses: Any type of childhood cancer (excluding bone tumor) Discovery: Leukemia 35.6% (874) Hodgkin lymphoma 15.0% (367) Kidney tumors 12.6% (309)	Chemotherapy: Corticosteroids: 47.2% discovery cohort, 48.3% replication cohort IV MTX: 18.5% discovery cohort, 29.2% replication cohort IT MTX: 38.4% discovery cohort, 38.3% replication cohort Radiotherapy: CRT: 45.9% discovery cohort, 38.5% replication cohort SCT: 0% (exclusion criterion) Limb amputation: NR Other: NA	Outcome definitions: History of clinical fractures (mainly self-report) BMD measurement modality: NA Results: Fracture frequency (post diagnosis) Discovery: 37.9% Replication: 46.0% **Multivariable models** Sex-combined model (adjusted for sex, attained height and weight, and premature menopause status) Corticosteroids (any vs. none): HR=1.13, 95%CI 0.96-1.32, p=0.14 IV methotrexate dose (100 g/m2): HR 1.20, 95%CI 1.00-1.45, p=0.05 IT methotrexate dose (100 mg/m2): HR=1.07, 95%CI 0.99-1.15, p=0.08 Radiation dosimetry dose (10 Gy): HR=0.99, 95%CI 0.95-1.03, p=0.58 Female-specific model (adjusted for attained height and weight, and premature menopause status, N=1,289) Corticosteroids (any vs. none): HR=1.08, 95%CI 0.86-1.38, p=0.50 IV methotrexate dose (100 g/m2): HR=1.02, 95%CI 0.76-1.37, p=0.90	Strengths: -Relatively large cohorts (although small in the context of GWAS) -Replicated finding -Biological underpinning of the finding Limitations: -Mainly questionnaire data -No BMD data -No adjustment for covariates at the time of fracture (e.g. height, weight, hormonal status) **Risk of bias** A. Selection bias: High risk Reason: less than 75% of eligible survivors were included in the discovery cohort B. Attrition bias: Low risk Reason: all included participants had data on fracture history C. Detection bias: High risk Reason: fractures were assessed by self-report. Vertebral fractures (frequently asymptomatic) are likely missed D. Confounding: Unclear

	Soft tissue sarcoma 9.7% (237) Central nervous system tumors 9.2% (226) Neuroblastoma 9.1% (224) Non-Hodgkin lymphoma 8.8% (216) Other – Replication: Leukemia 35.1% (497) Hodgkin lymphoma 12.5% (177) Kidney tumors 7.3% (104) Soft tissue sarcoma 7.5% (106) Central nervous system tumors 14.3% (203) Neuroblastoma 4.7% (66) Non-Hodgkin lymphoma 7.5% (106) Other 11.2% (158) <u>Age at diagnosis:</u> Discovery: Median (IQR) 5 (2-12) years Replication: Median (IQR) 6 (3-12) years <u>Age at follow-up:</u> Discovery: Median (IQR) 42 (36-48) years Replication: Median (IQR) 31 (26-39) years <u>Controls:</u> The replication cohort (SJLIFE)		IT methotrexate dose (100 mg/m2): HR=0.99, 95%CI 0.88-1.12, p=0.89 Radiation dosimetry dose (10 Gy): HR=0.98, 95%CI 0.92-1.05, p=0.58 Male-specific model (adjusted for attained height and weight, N=1,164) Corticosteroids (any vs. none): HR=1.15, 95%CI 0.93-1.42, p=0.19 IV methotrexate dose (100 g/m2): HR=1.46, 95%CI 1.15-1.85, p=1.8x10-3 IT methotrexate dose (100 mg/m2): HR=1.11, 95%CI 1.02-1.22, p=0.02 Radiation dosimetry dose (10 Gy): HR=0.99, 95%CI 0.94-1.04, p=0.68 **GWAS results** SNP replicated (only in females): rs1406815 (HAGHL gene), HR=1.43, p 8.2 × 10−9 (n = 1935 women) Treatment-stratified analysis of this SNP in females: No head/neck RT: HR=1.22, 95%CI 0.95–1.57, p=0.11 Any RT: HR=1.88, 95%CI 1.54-2.28, p=2.4 × 10−10 >36 Gray only: HR=3.79, 95%CI 1.95–7.34, p = 8.2 × 10−5	Reason: the analyses are adjusted for sex, age, premature menopause status and attained height and weight, but not for height and weight and other important covariates at time of fracture (mean time between first fracture and evaluation was approximatey 20 years)

Abbreviations: BMD=bone mineral density; CI=confidence interval; CRT=cranial irradiation; GWAS=genome-wide association study; HR=hazard ratio; IT=intrathecal; IQR=interquartile range; IV=intravenous; MTX=methotrexate; NA=not applicable; NR=not reported; RT=radiotherapy; SCT=stem cell transplantation; SD=standard deviation; SNP=single nucleotide polymorphism

Who needs BMD surveillance?				
Isaksson et al. Low bone mineral density is associated with hypogonadism and cranial irradiation in male childhood cancer survivors. Osteoporos Int. 2020 Jul;31(7):1261-1272.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Retrospective cross-sectional study Treatment era: 1970 and 2002 Follow-up: Mean (SD) 24.3 years (7.1)	Eligible cohort: 427 male CCS (Swedish Cancer Registry) affected with malignant disease or benign tumor in the CNS < 18 years of age, being alive as of December 2009 and >3 years since off-therapy Type and number of non-participants: 11 deceased, 10 not located 1 transferred to a testicular cancer survival cohort Of 405 men contacted by letter: 146 accepted - 6 dropped out Exclusion: - 1 due to management with surveillance for optic glioma - 6 due non-malignant disease - 8 due to a second malignancy or relapse within 3 years of inclusion Type and number of participants: 125 (29.3% of the original cohort) CCS surviving ≥ 3 yrs after cancer diagnosis	Chemotherapy: GCs 19 (15%) Alkylating agents 16 (13%) Median cyclophosphamide equivalent dose 4854 mg/m^2 MTX 17 (14%) Median methotrexate dose 11 g/m^2 Radiotherapy: Cranial irradiation 33 (26%) RT other than brain and/or testes 27 (22%) SCT: 2 (2%) Surgery Brain surgery 14 Surgery other than brain surgery 19 Additional Therapies: 13 testosterone replacement therapy (TRT) 17 GH therapy 8 GCs replacement therapy due to pituitary failure 3 immunosuppressive oral GCs due to kidney transplant or Crohn's disease 2 were on calcium and vitamin D	Outcome definitions: Low BMD: Z-score ≤-1 BMD measurement modality: FN: femoral neck BMD (g/cm2) TH: total hip (mean of right+left side) LS: lumbar spine L1–L4 by DXA (Lunar Prodigy; GE Healthcare Lunar, Madison,WI, USA); software versions 2.15–7.70 for the majority of participants; in 3 CCS and 41 controls, instrument failure obliged to use the Lunar iDXA (GE Healthcare Lunar, Madison, Wisconsin, USA). BMD data were adjusted to the Prodigy. **Low BMD:** **Childhood cancer survivors vs. controls** Total CCS: TH 26 (21%) LS 27 (22%) Controls TH 27 (22%) LS 35 (28%) **Therapeutic subgroups** EG CCS TH 15 (16%) LS 18 (20%) HyG CCS	Strengths: -Well analyzed cohort -Long follow-up period -Many multivariable regression analyses for low BMD were performed Limitations: -Use of 2 different DXA technique during study (DXA and iDXA) -Small numbers after break-down (i.e. therapeutic subgroups, diagnostic subgroups) -low BMD was defined as a BMD Z-score value <-1; there was no information about patients with a Z-score below -2 -Comparison between participants and non-participants were not reported. **Risk of bias** A. Selection bias: High risk Reason: the group analyzed for BMD consisted of 29.3% of the original cohort; moreover, differences between participants and no participants are not reported. B. Attrition bias: Low risk

	Comparison between participants and non-participants: NR CCS were categorized into subgroups according to gonadal status, diagnostic subgroups and therapeutic subgroups <u>Hypogonadism definition:</u> S-testosterone <10 nmol/L and/or S-LH >10 IU/L, or ongoing TRT **Diagnosis** leukaemia (n=27) intracranial tumour (n=28) lymphoma (n=21) testicular cancer (n=6) Wilms' tumour (n=8) bone tumour (n=6) other tumours (n=29) <u>Age at diagnosis:</u> Median 9.6 years (IQR 5.4–15.0) <u>Age at follow-up:</u> Median 33.7 years (IQR 30.2–40.1) GH trp 17 (14%) L-Tyroxin trp 17 (14%) GCs trp 8 (6.4%) Calcium+Vitamin D 2 (1.6%) EG 93 (74.4%) HyG 18 (14.4%) TRT 13 (10.4%) <u>Controls:</u> 125 age-matched controls from the general population Height CCS vs controls: 180 cm vs 182.0 cm (p NS)		TH 7 (39%) LS 5 (28%) <u>CCS on TRT</u> TH 4 (31%) LS 4 (31%) **<u>Therapeutic subgroups</u>** TH Brain Surgery 2 (14%) TH Surgery other than brain surgery 6 (32%) TH CT 4 (14%) TH Cranial irradiation 10 (30%) TH RT other than brain and/or testes 4 (15%) LS Brain Surgery 3 (21%) LS Surgery other than brain surgery 6 (32%) LS CT 2 (7.1%) LS Cranial irradiation 13 (39%) LS RT other than brain and/or testes 3 (11%) **<u>Diagnostic subgroups</u>** TH leukaemia 6 (22%) intracranial tumour 6 (22%) lymphoma 2 (10%) testicular cancer 3 (50%) Wilms' tumour 1 (13%) bone tumour - other tumours 8 (29%) LS Leukaemia 7 (27%) intracranial tumour 9 (33%) lymphoma 1 (5%) testicular cancer 1 (17%) Wilms' tumour 2 (25%) bone tumour 1 (17%) other tumours 6 (21%)	Reason: the outcome was assessed for all the study group except for 3 CCS and 2 controls. <u>C. Detection bias:</u> Low risk Reason: low BMD by DXA is a hard end-point, not susceptible to subjectivity of the assessor. <u>D. Confounding:</u> Low risk for BMD Z-score <-1 as outcome Reason: 1. correction for BMI was always undertaken; 2. Presence of a control group; 3. many different risk factors were taken into consideration in 5 different scenarios (type of treatment, diagnosis, type of hypogonadism always vs control group as ref.). High risk for continuous BMD values as outcome Reason: BMD was not adjusted for sex.

			<u>Mean BMD Z-score (SD)</u> **<u>Childhood cancer survivors vs. controls</u>** TH BMD Z-score (SD) Total CCS −0.17 (1.06) Controls −0.13 (1.09) EG CCS −0.05 (1.0) HyG CCS −0.85 (1.2) CCS on TRT −0.25 (0.92) FN BMD Z-score (SD) Total CCS − 0.14 (0.99) Controls − 0.16 (1.06) EG CCS − 0.16 (0.90) HyG CCS − 0.84 (1.2) CCS on TRT − 0.18 (1.0) LS BMD Z-score (SD) Total CCS − 0.25 (1.11) Controls − 0.36 (1.10) EG CCS − 0.16 (0.98) HyG CCS − 0.84 (1.5) CCS on TRT − 0.26 (1.1) **<u>Multivariable regression analyses:</u>** *<u>see Online Resource</u>* ***(a)*** *all CCS vs. controls;* ***(b)*** *untreated hypogonadal CCS and CCS receiving TRT, respectively, vs. eugonadal CCS;* ***(c)*** *therapeutic subgroups of CCS vs. controls;* ***(d)*** *CCS receiving chemotherapy excluding radiotherapy, and treated with alkylating agents, CCS receiving chemotherapy, excluding radiotherapy, and treated with methotrexate, and CCS receiving chemotherapy, excluding radiotherapy, and also treated with glucocorticoids separately, vs. controls;*	

			(e) *diagnostic subgroups of CCS vs. controls* ***(a)*** **Childhood cancer survivors vs. controls** **Mean BMD difference between CCS and controls (IQR):** **MODEL1** After adjustment for age, body mass index and current smoking TH BMD mean (IQR) − 0.014 (− 0.052; 0.023), p=0.44 LS BMD mean (IQR): 0.006 (− 0.030; 0.041), p=0.76 **MODEL 2** As MODEL1 after exclusion of 23 CCS on TRT and/or GH replacement and/or calcium + vitamin D treatment, and 3 CCS on immunosuppressive oral GCs TH BMD mean (IQR): − 0.008 (− 0.046; 0.031) p=0.69 LS BMD mean (IQR): 0.016 (− 0.020; 0.052) p=0.39 **Low bone mass: OR (95% CI)** **MODEL3** After adjustment for body mass index and current smoking TH BMD OR (95% CI): 0.94 (0.51; 1.7) p=0.84 LS BMD OR (95% CI): 0.67 (0.37; 1.2) p=0.19 **MODEL4**	

			As MODEL3 after exclusion of 23 CCS on TRT and/or GH replacement and/or calcium + vitamin D treatment, and 3 CCS on immunosuppressive oral GCs TH BMD OR (95% CI): 0.89 (0.46; 1.7) p=0.72 LS BMD OR (95% CI): 0.54 (0.28; 1.0) p=0.06 ***(b)* Therapeutic subgroups** **Mean BMD difference between HyG CCS and CCS on TRT *vs* EG CCS (IQR):** **MODEL1** After adjustment for age, body mass index and current smoking TH BMD mean (IQR): EG CCS Ref. HyG CCS TH BMD mean (IQR): − 0.139 (− 0.210; − 0.067) **p < 0.001** CCS on TRT TH BMD mean (IQR): − 0.063 (− 0.145; 0.019) p=0.13 LS BMD mean (IQR): EG CCS Ref. HyG CCS LS BMD mean (IQR): − 0.102 (− 0.174; − 0.030), **p= 0.006** CCS on TRT LS BMD mean (IQR): − 0.032 (− 0.115; 0.051) p=0.44 **MODEL2** As MODEL1 after exclusion of 23 CCS on TRT and/or GH replacement and/or calcium + vitamin D treatment, and 3 CCS on immunosuppressive oral GCs	

			TH BMD mean (IQR): EG CCS Ref. HyG CCS TH BMD mean (IQR): − 0.145 (− 0.241; − 0.075) **p< 0.001** CCS on TRT TH BMD mean (IQR): − 0.023 (− 0.111; 0.066) p= 0.61 LS BMD mean (IQR): EG CCS Ref. HyG CCS LS BMD mean (IQR): − 0.107 (− 0.179; − 0.035) **p= 0.004** CCS on TRT LS BMD mean (IQR): 0.017 (− 0.074; 0.108) 0.71 **MODEL3** After adjustment for body mass index and current smoking TH BMD OR (95% CI): EG CCS Ref HyG CCS TH BMD OR (95% CI): 4.1 (1.3;14) **p=0.02** CCS on TRT TH BMD OR (95% CI): 3.1 (0.77;13) p=0.11 LS BMD OR (95% CI): EG CCS Ref HyG CCS LS BMD OR (95% CI): 1.5 (0.46;5.1)p= 0.48 CCS on TRT LS BMD OR (95% CI): 1.9 (0.50;7.7)p= 0.33 **MODEL4** As MODEL3 after exclusion of 23 CCS on TRT and/or GH replacement and/or calcium + vitamin D treatment, and 3 CCS on immunosuppressive oral GCs TH BMD OR (95% CI): EG CCS Ref	

			HyG CCS <u>TH BMD OR (95% CI):</u> 4.3 (1.3;14) **p=0.02** CCS on TRT <u>TH BMD OR (95% CI):</u> 2.9 (0.60;14)p= 0.19 <u>LS BMD OR (95% CI):</u> EG CCS Ref HyG CCS <u>LS BMD OR (95% CI):</u> 1.9 (0.56;6.6) p=0.31 CCS on TRT <u>LS BMD OR (95% CI):</u> 1.3 (0.26;6.2) p=0.77 ***(c)* <u>Therapeutic subgroups</u>** **MODEL 1** After adjustment for age, body mass index and current smoking <u>TH BMD mean (IQR):</u> Brain surgery: 0.025 (− 0.056; 0.106) p=0.54 Surgery other than brain surgery − 0.022 (− 0.093; 0.048) p=0.53 CT 0.011 (− 0.049; 0.072) p=0.72 Cranial irradiation¤ − 0.076 (− 0.133; − 0.019) **p=0.009** RT other than brain and/or testes† 0.015 (− 0.046; 0.077) p=0.62 <u>LS BMD mean (IQR):</u> Brain Surgery 0.004(−0.071;0.079)p=0.92 Surgery other than brain surgery 0.028(−0.038;0.095) p=0.40 CT 0.017(−0.041;0.074)0.57 Cranial irradiation −0.071(−0.124;−0.018) **p=0.009** RT other than brain and/or testes 0.068(0.010;0.125)**p=0.02** **MODEL 2** As adjustment Model 1 and exclusion of 3 CCS on	

			immunosuppressive oral GCS and 2 CCS on calcium+vitaminD, with adjustment for hypogonadism and GH replacement <u>TH BMD mean (IQR):</u> Brain Surgery 0.025 (− 0.056; 0.105) p=0.55 Surgery other than brain surgery − 0.025 (− 0.093; 0.043) p=0.47 CT 0.005 (− 0.054; 0.063) p=0.87 Cranial irradiation − 0.071 (− 0.140; − 0.003) **p=0.040** RT other than brain and/or testes 0.003 (− 0.060; 0.067) p=0.92 <u>LS BMD mean (IQR):</u> Brain Surgery0.005(−0.072;0.081)p=0.90 Surgery other than brain surgery 0.027 (−0.037;0.092) p= 0.40 CT 0.010(−0.046;0.066) p=0.72 Cranial irradiation −0.075(−0.139;−0.010) **p=0.02** RT other than brain and/or testes 0.058(−0.002;0.117) p=0.06 **MODEL 3** After adjustment for body mass index and current smoking <u>TH BMD OR (95% CI):</u> Brain Surgery 0.63 (0.13; 3.0) 0.56 Surgery other than brain surgery − 1.7 (0.56; 4.8) p=0.36 CT 0.53 (0.17; 1.7) p=0.28 Cranial irradiation 1.5 (0.65; 3.7) p=0.33 RT other than brain and/or testes† 0.59 (0.19; 1.9) p=0.37 <u>LS BMD OR (95% CI):</u>	

			Brain Surgery 0.67(0.17;2.6) p=0.55 Surgery other than brain surgery 1.1(0.37;3.0) p=0.92 CT 0.17(0.04;0.78) **p=0.02** Cranial irradiation 1.5(0.69;3.5) p=0.29 RT other than brain and/or testes 0.30(0.08;1.1) p=0.06 **MODEL 4** As adjustment Model 3 and exclusion of 3 CCS on immunosuppressive oral GCS and 2 CCS on calcium+vitaminD, with adjustment for hypogonadism and GH replacement <u>TH BMD OR (95% CI):</u> Brain Surgery: 0.74 (0.14; 3.8) p=0.72 Surgery other than brain surgery: 1.8 (0.59; 5.5) p=0.30 CT 0.54 (0.17; 1.7) p=0.30 Cranial irradiation: 1.5 (0.50; 4.4) p=0.47 RT other than brain and/or testes† 0.49 (0.14; 1.7) p=0.26 <u>LS BMD OR (95% CI):</u> Brain Surgery 0.44 (0.09;2.2) p=0.32 Surgery other than brain surgery 1.1(0.37;3.1) p=0.89 CT 0.18(0.04;0.80) **p=0.02** Cranial irradiation 1.2(0.43;3.5) p=0.71 RT other than brain and/or testes 0.31(0.08;1.2) p=0.08 ***(d) alkylating agents, methotrexate vs controls***: NO ***significant diff n between categories***)	

			(e) diagnostic groups vs controls <u>Only significant Models are reported (online materials)</u> **Model 3** After adjustment for body mass index and current smoking <u>Lymphoma: LS BMD OR (95% CI):</u> 0.12 (0.02; 0.4), **p=0.04** **Model 4** as adjustment Model 3 with adjustment for hypogonadism and growth hormone replacement <u>Lymphoma: LS BMD OR (95% CI):</u> 0.13 (0.02; 1.0), **p=0.05**	

Abbreviations: BMD=bone mineral density; CCS=childhood cancer survivor; CI=confidence interval; CNS=central nervous system; DXA=dual-energy X-ray absorptiometry; EG=eugonadal; FN= femoral neck; GCs=glucocorticoids; GHD=growth hormone deficiency; HyG=hypogonadal untreated; IQR=interquartile range; LH/FSHD central hypogonadism; LS=lumbar spine; NA=not applicable; NR=not reported; OR=odds ratio; SCT=stem cell transplantation.

Who needs BMD surveillance?				
Jones et al. CRHR1 Polymorphisms Predict Bone Density in Survivors of Acute Lymphoblastic Leukemia. Journal of clinical oncology 2008. 26 (18), 3031-7.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Cross-sectional Treatment era: ALL (Total XI-XIII) between 1984 and 1997 Follow-up: At least 4 years of continuous remission	Type and number of non-participants: NA Type and number of participants: 309 long-term survivors of ALL Diagnoses: ALL Age at diagnosis: NA Age at follow-up: (not stated whether this is ag at dx or at FU, presumably at FU) Patients were grouped by age as follows: age group 1 (n=119) included patients younger than 14 years; group 2 (n=107) included patients aged 14 to 18 years; and group 3 (n=83) included adult patients older than 18 years. Controls: NA	Chemotherapy: **Total XI arms 2 and 3** 196 pts With XIII between 1984-1988/ posind: Cycl + VP16, AraC + VM26, MP +MTX, Pred + VCR/ postind MP/MTX 25% of 120 weeks/ Glucocorticoid induction: Pred 40 mg/m2 x 28 days/postind 25% of 120 weeks **Total XIII high-risk arm** between: 1991-1997 postind: VP16 + Cycl, MP + MTX, MTX + AraC, VP16 + AraC, Dex + VCR/ postind MP/MTX 25% of 120 weeks/ Glucocorticoid induction: Pred 40 mg/m2 x 28 days/postind 25% of 120 weeks **Total XI arm 1** 48 pts with LR between 1984-1988 posind: MP + MTX, Pred + VCR/ postind MP/MTX 75% of 120 weeks/ Glucocorticoid induction: Pred 40 mg/m2 x 28 days/postind 25% of 120 weeks **Total XIII low-risk arm** 1 between: 1991-1997 postind: MP + MTX, Dex or Pred + VCR/ postind MP/MTX 75% of 120 weeks Glucocorticoid induction: Pred 40 mg/m2 x 28 days/postind 25% of 120 weeks **Total XII 65** 1988-1991 poostind: MP + MTX, AraC + VM26/ postind MP/MTX 92% of 120 weeks/ Glucocorticoid induction: Pred 40 mg/m2 x 28 days/postind none	Outcome definitions: Association between CRHR1 polymorphisms and bone mineral deficits. BMD measurement modality: The bone mineral density (expressed as the mean of the L1-L2 trabecular bone) was by quantitative computed tomography (QCT) with a Siemens Somatom-Plus spiral CT scanner (Siemens, Iselin, NY) and with Mindwaves QCT Calibration Phantoms and software (Mindwaves Software, South San Francisco, CA), as previously described. Results: Bone density was lower in males (P=.005), in those who were not overweight (P<.0003), and in those who received intensive antimetabolites and glucocorticoids (P<.001). The G allele at the rs1876828 SNP was associated with lower Z-scores (P=.02) in males but tended to have the opposite association in females (P=.09).	Strengths: -Relatively large sample size -A priori hypothesis (candidate gene) Limitations: -No replication **Risk of bias** A. Selection bias: High risk Reason: original cohort number is unknown (also not stated in ref 1). B. Attrition bias: Low risk Reason: reason: SNP and BMD Analyses were performed in all included participants. C. Detection bias: Low risk Reason: low BMD by QCT is a hard end-point, not susceptible to subjectivity of the assessor. D. Confounding: Low risk Reason: all possible confounding factors (age, sex, ethnicity, BMI and protocol group) were tested and if necessary adjusted for.

		Radiotherapy: NR SCT: NR Limb amputation: NR Other: NR		

Abbreviations: ALL=acute lymphoblastic leukemia; BMD=bone mineral density; BMI=body mass index; FU=follow-up; NA=not applicable; NR=not reported; QCT=quantitative computed tomography; SCT=stem cell transplantation; SNP=single nucleotide polymorphism.

Who needs BMD surveillance?				
Joyce et al. Association of Muscle Strength and Bone Mineral Density in Adult Survivors of Childhood Acute Lymphoblastic Leukemia. Arch Phys Med Rehabil 2011;92:873-9.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Cross-sectional Treatment era: 1962 and 1999 Follow-up: 12.7 to 46.5 years from diagnosis of childhood ALL (median, 27.2y)	Type and number of non-participants: 1122 eligible: not contacted 181,declined ST JUDE life: 202, pending 212, missing functional assessment 12, DXA 22 Type and number of participants: 493 (261 women and 232 men) Diagnoses: ALL Age at diagnosis: Mean ± SD 6.3±4.3 Median (range) 5.0 (0.2 to 18.8) Age at follow-up: Mean ± SD 33.3_7.1 Median (range) 32.6 (20.4 to 54.4) Controls:	Chemotherapy: Glucocorticoids (mg/m2) Mean ± SD 6,183±5169 Median (range) 7610 (1120 to 23,632) Methotrexate (mg/m2) Mean _±SD 7842±7719 Median (range) 4944 (219.6 to 32,014) Cyclophosphamide (mg/m2) Mean ± SD 10,614±6645 Median (range) 9498.4 (300.0 to 38,487) Radiotherapy: Cranial radiation n(%) 347 (70) median dose, 1800cGy; range, 0–4670cGy SCT: NR Limb amputation: Limb Surgery Lower extremity n(%) 30 (6) Upper extremity n(%) 11 (2) *Including amputation, arthroplasty, arthroscopy, chondroplasty, decompression, hemiarthroplasty, fasciotomy, fixation, fusion, reconstruction, and repair.* Other:	Outcome definitions: Association between bone mineral density (BMD) and muscle strength BMD measurement modality: Whole body, anterior, lateral lumbar DXA (Hologic 4500 QDR-A fan beam system). All acquired BMD values were generated using the QDR software for Windows, version 12.1. BMD and lean body mass by anatomic sites were abstracted from DXA determined values. BMD determined in our cohort was compared with the normative database provided by the manufacturer. Muscle strength of upper extremities was measured using a Jamar hand-held dynamometer, and of lower extremities using a Biodex III isokinetic dynamometer. Results: Associations between BMD and muscle strength in lower extremities (R2 range, 0.33–0.40, P-value range <0.001 to 0.11) and strong, significant associations in upper extremities (left-side R2=0.558; rightside R2=0.560, P<0.001).	Strengths: -Large sample size Limitations: -Only muscle strength assessed, not other physical performance parameters **Risk of bias** A. Selection bias: High risk Reason: the study group consisted of only 44% of the eligible cohort B. Attrition bias: Low risk Reason: BMD and muscle strength measurements were performed in all included participants. C. Detection bias: Low risk Reason: low BMD by DXA is a hard end-point, not susceptible to subjectivity of the assessor D. Confounding: Low risk Reason: correlations were adjusted for age at diagnosis, sex, time since diagnosis, height, weight, osteoporosis medication use, cranial radiation, and scheduled glucocorticoid dose.

Abbreviations: ALL=acute lymphoblastic leukemia; BMD=bone mineral density; DXA=dual-energy X-ray absorptiometry; NR=not reported; SCT=stem cell transplantation; SD=standard deviation.

Who needs BMD surveillance?				
Kaste et al. QCT Versus DXA in 320 Survivors of Childhood Cancer: Association of BMD With Fracture History. Pediatric Blood and Cancer 2006a;47:936-943.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Retrospective, electronic record search, single center Treatment era: treatment era is not mentioned, the QCT and DXA were performed beweeen Dec 2000 and Aug 2003. Follow-up: There is no follow up. The aim of this study was to compare the two methodologies for BMD examinations in former pediatric cancer patients. 1. Correlation between BMD measurement by QCT and DXA 2. Relationship between absolute BMD values and patient characteristics 3. relationship between demographic characteristics and QCT- and DXA derived Z-Scores 4. Relationship between BMD and fracture history	320 former pediatric cancer patients were identified in the electronic research, who had both examinations in the same 24-hr period for different clinical or research indications Type and number of non-participants: 0 Type and number of participants: all 320 patients are included, for 160 patients fracture history was available Diagnoses: all types of pediatric cancer: 45,6% had leukemia/lymphoma 44,4% brain tumor 10,0% solid tumor Age at diagnosis: not mentioned Age at examinations: at least 5 years old at the time of examination median 16.43, range 5.05-35.98 Other characteristics: male 55.6%, female 44.4% white 86.6%, black 10.3%, hispanic 3.1% 160 Patients with fracture history available: traumatic fracture 26.3%	No treatment data in the whole paper.	Outcome definitions: Aim of the study in column 1 BMD measurement modality: **QCT:** Siemens Somatom-Plus spiral CT-Scanner, lumbar spine – L1 and L2 BMD was recorded for the individual vertebral body, and the mean value was calculated, normative values in the manufacturer´s reference database were used for calculating Z-score, generated by the QCT software program. **DXA:** Hologic 4500 QDR-A lumbar spine anterior projections L1-L4, lateral projections L2-L4. Calculation with the QDR software for windows (version 12.1). In this study the calculation of the BMAD was limited to L1 and L2 for direct comparison with the results of the QRT measurements. Normative values in the manufacturer´s reference database ere used for calculating Z-score, generated by the DXA software program. Results: Ad 1: assessed with Pearson correlation coefficients. Only moderate correlation between these two methods	Strengths: -Overall the study group is representative, but group with patients with fractures is small Limitations: -The big age range, because age is such an important factor for the development of BMD **Risk of bias** A. Selection bias: Low risk Reason: all patients included who were evaluated for a variety of research and clinical studies B. Attrition bias: Low risk Reason: retrospective study evaluating exams performed within 24 hours of each other; no attrition C. Detection bias: Low risk Reason: BMD by DXA and QCT is a hard end-point, not susceptible to subjectivity of the assessor D. Confounding: Unclear Reason: I suspect that the wide age range could lead to different

	atraumatic fracture 1.6% no fracture 64.4% Age at follow-up: no follow up Controls: no controls		concerning the Z-score (Pearson coefficient =0.52), especially for non-white patients. Ad2: multiple linear regression model: DXA: Significant association of areal BMD by DXA with age and race. Increasing age and non-white race were associated with higher BMD in L1 (P< 0.0001, P=0.0221) and in L2(P<0.0001 and P=0.0370). QCT: There was no association between age and gender for QCT-determined BMD; non-white patients had higher QCT BMD values than white patients (P<0.0001). Ad3: No relationship between age, gender, and low BMD (Z-score <-2) measured by QCT or DXA. However, white patients were 2.97 times as likely as non-white patients to have diminished BMD by QCT; by DXA, non-white patients were 2.t6 times as likely as white patients to have diminished BMD. But the reason could be that for QCT the reference values of white patients were used for all patients. For DXA there are race-specific reference data. Ad4: There was no association between positive history of traumatic fracture and diminished bone density (z<-2) determined by QCT or DXA.	outcomes at different ages, as the effect of puberty could potentially result in variable readings between QCT and DXA. the age range is from 5.05 until 35.98, this means all ages during growth period and also during adulthood. It could have been interesting to look if the difference between QCT and DXA results becomes less during growth and compare the results of patients before puberty, during puberty, and post-puberty

Abbreviations: BMD=bone mineral density; DXA=dual-energy X-ray absorptiometry; NR=not reported; QCT=quantitative computed tomography; SCT=stem cell transplantation.

Who needs BMD surveillance?				
Kaste et al. Changes in Bone Mineral Density in Survivors of Childhood Acute Lymphoblastic Leukemia. Pediatr Blood Cancer 2006b;46:77-78.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Retrospective, observational study, single institution Study I: n=141 Study II: n=57 Treatment era: Feb 1984-Sept1988 Follow-up: Study I: at least 4 years after completed therapy (mean time between diagnosis and study enrollment 11.7 years) Study II : 2-5 years after study I (mean time between diagnosis and study enrollment 16.1years) Physical examination in study I and II Height, weight, BMI, pubertal stage Questionnaire in study I and II: Nutritional supplements: calcium, vit D, C, multivitamins, exercise frequency and intensity, tobacco and alcohol Endocrine dysfunction Review of medical records to identify diagnoses of and therapeutic interventions for GH deficiency, hypothyroidism, and hypogonadism	Type and number of non-participants: Total XI n=268 patients non-participants 127 There were no significant differences in important variables between participants and non-participants, although the study group was slightly younger at diagnosis (median 3.4 years (0.9-17.4) than the total treatment cohort (4.6 years (0.2-18.7, p=0.003) Type and number of participants: Study I: n=141, female 51.1%, male 48.9%, white 89.4%, black 10.6% Study II: n=57, female 54%, male 45.6 Diagnoses: ALL Study I: risk group better 34.8, worse 65.2 study II: risk group better 39.7 worse 65.2 Exclusion criteria: Spinal RT, allogenic SCT, second malignancies, current pregnancy and lactation Age at diagnosis: Study I: median age 4 years (0.9-17.4)	Chemotherapy: St. Jude total XI prednisone, vincristine, asparaginase,teniposide, cytarabine, daunorubicine, triple ith, high-dose MTX. Radiotherapy: CRT 37% of 57; percentage of 141 NR SCT: No Limb amputation: No Other:	Outcome definitions: Evaluation of BMD of pediatric patients treated for ALL BMD measurement modality: QCT L1 and L2, mean BMD was the mean of L1- L2. Compared to age and sex-matched population, data provided by the manufacturer of the QCT software for calculation of BMD Z-Score. Cortical BMD was estimated by analyzing the raw data from study I and II. The interest was to analyze a single anterior midline region. A ratio between trabecular and BMD to cortical BMD for each QCT study was determined, to compare mineral accretion over time Results: 91.2% were prepubertal (Tanner I) at diagnosis of ALL, 75.4% in late puberty (Tanner 4 and 5) at entry in study I, and all have been Tanner Stage 4 and 5 by entry in study II. BMD in study I: Z-score below the mean (<0) 57.9%, 1 SD below the mean 10.5% BMD in study II: Z-score below the mean 59.6%,	Strengths: -Homogenous group for treatment and methodology single institution Limitations: -Number of participants rather small -Follow-up period short (mean 3.5 years) **Risk of bias** A. Selection bias: Unclear Reason: the number of participants in study II is much smaller than in study I B. Attrition bias: High risk Reason: study II less than 50 % of study I C. Detection bias: Low risk Reason: low BMD by DXA is a hard end-point, not susceptible to subjectivity of the assessor D. Confounding: Unclear Reason: it is not clear why patients were not included in study 2, aside from likely lack of long-term follow-up. Although

	Study II: median age 3.4 (0.9-17.4) <u>Age at follow-up:</u> at least 4 years after completed therapy <u>Other characteristics:</u> Study I: 16 of 57 are receiving hormone replacement Study II: 28 receiving hormone replacement (P=0.003), significant change: increasing number received thyroid hormone replacement Tobacco and alcohol increased between study I and II (P=0.030 for both factors) little change in exercise frequency, significant change in exercise-related energy expenditure: significantly lower in study II (P=0.036) <u>Controls:</u> No		1 SD below the mean 19.3% Between study 1 and study 2, there was an increase in trabecular BMD of 9.3mg/cc (P=0.003)and an increase of mean BMD Z-score of 0.21 (P=0.035). Cortical BMD was measured in 40 survivors at study I and in 52 survivors in study II; 38 survivors received both studies. Cortical BMD increased significantly between the two studies (P=0.0003). Cortical BMD had a significantly greater gain than trabecular BMD (P=0.045). Cranial radiation: The change in BMD study I to study II was not significant in survivors with treated with < 2400 cGy or in those treated with > 2400 cGy. No effect in survivors with chemotherapy alone, who had high versus low anti metabolite treatment. But the groups are small, therefore the interpretation has to be seen under this aspect. Variables in study associated with low BMD were: male sex (P=0.051), Caucasian race (P0.003), trend for lower body weight (P=0.067). Variables in study II associated with low BMD were: male sex (P=0.018), Caucasian race(P=0.001), use of nutritional supplementation (P=0.019), Increase of BMD associated with younger age at diagnosis of ALL	there was statistical modeling to try to account for this, it is certainly possible that the patients in Group 2 were different than Group 1 and therefore may have had differences in outcomes

			(P=0.001),and absence of nutritional supplementation (P=0.032). Gain of BMD was positively related to increasing stage of puberty in the whole group. Pat at Tanner 5 in study I showed no significant change to BMD in study II. The per year change observed in this group ranged widely in this subset, from an increase of 14.90 mg/cc/year to a loss of 7.94 mg/cc/year. The same for Z-score: the mean did not change significantly, but pat at least age 18 in study had a decrease in mean BMD and significant change when BMD was adjusted for duration between the 2 examinations study I and study II. The mean Z-score decreased, but was not significant. Alcohol was associated with significant adverse change in BMD (P=0.009), tobacco no adverse change.	

Abbreviations: ALL=acute lymphoblastic leukemia; BMD=bone mineral density; BMI=body mass index; GH=growth hormone; NR=not reported; QCT=quantitative computed tomography; SCT=stem cell transplantation; SD=standard deviation.

Who needs BMD surveillance?				
Kaste et al. Pediatric Hodgkin Lymphoma survivors at Negligible Risk for Significant Bone Mineral Density Deficits, Pediatr Blood Cancer 52: 516-521: 2009.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Retrospective cohort study of consecutive patients with HL Treatment era: 1990-2002 Follow-up: Median 7.5 yrs (5.8-20.7 yrs) from diagnosis to QCT; median 9.5 yrs (5.1–13.0 years) from diagnosis to last follow-up	Type and number of non-participants: 24 HL survivors who did not have a QCT Type and number of participants: 109 HL survivors who underwent QCT. Participants vs. no participants (proportions): - females: 54/109 (49.5%) vs. 4/24 (16.7%), p=0.003; - hypothyroidism: 65/109 (59.6%) vs. 9 (37.5%), p=0.048; - cyclophosphamide: 74/103 (67.9%) vs. 11/24 (45.8%), p=0.042 No differences in: Race, Years from diagnosis to QCT, age at diagnosis, Age at QCT, histology, risk, Radiation to lumbar spine Yes vs. No, Procarbazine Yes vs. No, Cyclophosphamide Yes vs. No, Methotrexate (mg/m2) >120 vs. ≤120 1.11, Prednisone (mg/m2) >1,680 vs.≤1,68, hypogonadism, relapse. Other cohort characteristics: clinical and/or laboratory evidence of hypogonadism: 19/109 (17.4%, 3 females and 16 males) - 3 males received pelvic/inguinal radiation; 1 female received abdominal/pelvic radiation - HRT: 3 females and 2 males Diagnoses: HL	Chemotherapy: 69 (63.3%) procarbazine; 74 (67.9%) cyclophosphamide; 69% methotrexate 65% prednisone Methotrexate (mg/m2) <150 (%) 77/109 (70.6%) >150 (%) 32/109 (29.4%) Prednisone (mg/m2) <2.000 (%) 72/109 (66.1%) >2.000 (%) 37/109 (33.9%) Radiotherapy: 31/109 (28.4%) RT of lumbar spine 8/133 (6%) pelvic radiation SCT: NR Limb amputation: NA Other: 19/109 (17.4%) patients (3 females and 16 males) had clinical and/or laboratory evidence of hypogonadism -3 males received pelvic/inguinal radiation; 1 female abdominal/pelvic radiation -HRT: 3 females and 2 males	Outcome definitions: L1-L2 BMD QCT Z-score <- 1.5 used for the risk analyses to reflect the clinical practice patterns pertaining to patient referral for interventions to improve BMD subsets. Z-scores using sex/aged matched reference data (ref 42) BMD measurement modality: QCT imaging of L1-L2 vertebral bodies (BMD was determined using an offline personal computer equipped with Mindways QCT Pro software) Results: Proportion of survivors with BMD below expected mean not differ from CCS with low BMD Z-score vs. in age- and sex-matched general population (ref 42) < 1.5 SD: 14.7% vs.6.7%, p<0.001 <-2.0 SD: 7.3% vs. 2.3%, p<0.001 Restricted to white race: < 1.5 SD: 12.0% (95% CI: 6.5–17.6%) <-2.0 SD: 6.0% (95% CI: 2.0–10.1%). **Association with hormone defects (cited in the discussion section):**	**Strengths:** -Measurement techniques were well described and are valid; -All pts were at least 5 years from therapy, providing long-term look at bone health. **Limitations:** -Small population size; -Most participants were white, and all those with Z-scores <1.5 were white (true impact of race or reflect study population?); -Retrospective, so limited availability of laboratory data on gonadal function (17% of pts had clinical and/or laboratory evidence of hypogonadism); -No data on incidence of fracture; -No information regarding non-treatment related risk factors impacting bone health (e.g., genetic predisposition, diet, physical activity). **Risk of bias** A. Selection bias: Low risk Reason: consecutive pts with HL assessed with QCT, random sample of treatments received; 82% of the cohort analyzed. B. Attrition bias: Low risk Reason: all the included patients had QCT

	Age at diagnosis: Median 15.1 yrs (3.1-20.7 yrs) Male median 14.1 yrs (3.1-19.7 yrs) Female median 16.2 yrs (5.8-20.7) Age at follow-up: NR Controls: N/A		-over-treatment with L-thyroxin: 8/65 (12.3%) patients had subnormal TSH levels but normal BMD Z-score: 0.31 (range -0.61 - 2.55) - hypogonadism: not observed BMD deficits <- 1.5 SD (*specific number of patients tested n=19? Patients with and without HRT? BMD values NR*) **Univariate analyses: association with BMD <-1.5 z-score:** -Sex Male vs. female: OR 3.49 (95% CI: 1.05–11.61), p=0.042 - males more likely than females to have Z-scores <1.5, when diagnosed at age 14 years: OR 6.5(95% CI: 1.24–34.14; p=0.027. -BMI (kg/m2) Normal + underweight vs. overweight+ obesity: 2.67 (95% CI: 0.86–8.30), P=0.089 No significant associations: Race White, Years from diagnosis to QCT, age at diagnosis, Age at QCT, Radiation to lumbar spine Yes vs. No, Procarbazine Yes vs. No, Cyclophosphamide Yes vs. No, Methotrexate (mg/m2) >120 vs. ≤120 1.11, Prednisone (mg/m2) >1,680 vs.≤1,68 **Multivariable logistic regression analyses: BMD <-1.5 Z-score prediction** (factors with a p<0.10 in univariable models were included in the multivariable models)	C. Detection bias: High risk Reason: no blinding, paucity of QCT reference data. D. Confounding: Low risk Reason: prediction models corrected for gender and BMI.

			-Sex Male vs. female: OR 3.58 (95% CI:1.06–12.10, p=0.040* after correction for BMI -BMI (kg/m2) Normal + underweight vs. overweight+ obesity: OR 2.76 (95% CI:0.87–8.76), p= 0.086	

Abbreviations: BMD=bone mineral density; BMI=body mass index; CCS=childhood cancer survivors; CI=confidence interval; HL=Hodgkin's lymphoma; HRT=hormone replacement therapy; NA=not applicable; NR=not reported; OR=odds ratio; QCT=quantitative computed tomography; SCT=stem cell transplantation; SD=standard deviation; TSH=thyroid stimulating hormone.

Who needs BMD surveillance?				
Kaste et al. Calcium and cholecalciferol supplementation provides no added benefit to nutritional counseling to improve bone mineral density in survivors or childhood ALL. Pediatr Blood Cancer 61:885-893, 2014.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Prospective, randomized, double-blind Treatment era: 1984-1997 Follow-up: Median 8.4 yrs (4.6-19.1) from completion of ALL therapy to entry into study (intervention) Females 9.0 yrs (4.6, 18.6) Males 7.9 yrs (4.7, 19.1 Pts evaluated 2 yrs after study entry	Type and number of non-participants: n=348 (lost to follow-up, unable to contact, declined, ineligible) Type and number of participants: n=772 eligible Participants at the baseline QCT study: n=424 n=149 not included (Z-score 0 or greater) n=275 Randomized: Z-score <0 Randomization: -n=141 nutritional counseling and supplements (97 completed QCT at 24 months) -n=134 nutritional counseling and placebo (91 completed QCT at 24 months) n=213 (77%) took their medication over the entire 2 years n=188 (68.3%) completed the 24month QCT scan Diagnosis: childhood ALL Age at diagnosis: Median 4.6 yrs (0.2-18.8 yrs) Male median 4.6 yrs (0.2-18.8 yrs) Female median 16.2 yrs (0.6-18.7 yrs) Age at study entry: Median 17.0 yrs (9.0-36.1 yrs) Male median 17.1 yrs (9.0-35.4 yrs) Female median 17.0 yrs (9.4-36.1)	Chemotherapy: TXI-TXIII *Cyclophosphamide* <7500 mg/m^2, n (%) 196 (46.2%) Male 92 (42.2%) Female 104 (50.5%) More than 7500 mg/m^2, n (%) 228 (53.8%) Male 126 (57.8%) Female 102 (49.5) *Glucocorticoids* <5000 mg/m^2, n (%) 85 (20.0%) Male 44 (20.2%) Female 41 (19.9%) ≥ 5000 mg/m^2, n (%) 339 (80.0%) Male 174 (79.8%) Female 165 (80.1%) *Methotrexate* <10,000 mg/m^2, n (%) 150 (35.4%) Male 71 (32.6%) Female 79 (38.3%) 10,000-19,999 mg/m^2, n (%) 89 (21.0%) Male 46 (21.1%) Female 43 (20.9%) ≥20,000 mg/m^2, n (%) 185 (43.6%) Male 101 (46.3%) Female 84 (40.8%) Radiotherapy: 1-23 Gy 118 (27.8%) Male 57 (26.1%)	Outcome definitions: Z-scores using sex/aged matched reference data BMD measurement modality: QCT imaging of lumbar spine [Siemens Somatom-Plus spiral CT scanner (Siemens, Iselin, NY) and Mindways QCT calibration phantoms and software (Mindways Software, Inc., Austin, TX)] Results: "no significant difference in LS BMD Z-score at the end of the study between those given supplements and those with placebo" **Baseline LS-BMD Z-score, median, range** Females: -0.3 (-3.7 to 3.2) Males -0.6 (-3.9 to 5.1) Placebo -0.95 (-3.09, -0.05) Supplementation -0.97 (-3.94, -0.04) P NS **LS-BMD <-2 Z-score:** n=29/424 (6.8%) **LS-BMD -1 to -2 Z-score:** n=102/424 (42.1%) Placebo vs Supplement Radiation dose **P=0.07** >24Gy 11 (8.2%) vs 13 (9.2%)	Strengths: -Measurement techniques were well described and are valid; -The cohort is very well described. Randomized controlled intervention trial; -Multivariate analyses are robust; -Besides the RCT design, the study gives insights on the baseline QCT LS BMD 8,4 and 10.4 yrs after off-therapy in a large cohort of ALL survivors: many risk factors taken into account. Limitations: -Most participants were white, limiting applicability of results to pts of other races; -23% of participants stopped taking their supplement or placebo; -68% of participants completed QCT at 24 months, including some who were non-compliant with the intervention; -No increase in vitamin D supplement for those found to be insufficient or deficient at the start of the study; -No data on incidence of fracture. **Risk of bias** A. Selection bias: High risk Reason: 54,9% of the initial cohort analyzed (424 pts out of 772) B. Attrition bias: High risk

	Tanner stage I 26 (6.1%) Female 6 (2.9%) Male 20 (9.2%) II 26 (6.1%) Female 11 (5.3%) male 15 (6.9%) III 36 (8.5%) Female 22 (10.7%) Male 14 (6.4%) IV 76 (17.9%) Female 39 (18.9%) Male 37 (17.0%) V 260 (61.3%) 128 (62.1%) male 132 (60.6%) Controls: NR	Female 61 (29.6%) More than 24 Gy 35 (8.3%) Male 22 (10.1%) Female 13 (6.3%) <u>SCT</u>: NR <u>Limb amputation</u>: NA <u>Other</u>: Endocrine late effects Placebo vs Supplementation Somatotropin deficiency 5 (3.7%) vs 9 (6.1 %) P= 0.36 Hypothyroidism 3 (2.2%) vs 12 (8.1%) P= 0.03 Adrenal insufficiency 1 (0.7%) vs 2 (1.4%) P=0.62	1–23Gy 23 (17.2%) vs 40 (28.4%) None 100 (74.6%) vs 88 (62.4%) Hypothyroidism **P=0.03** 3 (2.2%) vs 12 (8.1%) No differences between the two groups by gender, race, Tanner stage, original treatment protocol, treatment modality or dose, other hormone defects, or by smoking or physical activity status. **Multivariate analyses for LS-BMD QCT Z-Scores at Baseline, β (95% CI)** Intercept -2.13 (-2.9, -1.36), **P<0.0001; adjusted R^2 0.2** Survival time (years) 0.01 (-0.05, 0.06) P NS Age at study entry, years 0.01 (-0.01, 0.04) P NS Gender: female vs. male 0.38 (0.15, 0.6) **P=0.001** Race: non-White vs. White 0.58 (0.28, 0.89) P**=0.0002** BMI (kg/m2) 0.05 (0.03, 0.07) **P<0.0001** Tanner stage -0.05 (-0.17, 0.07) P NS Smoking (no vs. yes) 0.23 (-0.08, 0.54) P NS Moderate/vigorous physical activity, minutes/week 0.0007 (-0.0001, 0.0015) P NS CRT <24 vs. ≥24 Gy 0.3 (-0.08, 0.69) P NS Cyclophosphamide dose (mg/m2): <7,500 vs. ≥7,500 -0.29 (-0.55, -0.05) **P=0.02** GCs dose (mg/m2): <5,000 vs. ≥5,000 0.72 (0.29, 1.14) **P=0.001**	Reason: 68% of the s cohort (188) concluded the 24 months study (IInd QCT) <u>C. Detection bias:</u> Low risk Reason: blinding <u>D. Confounding:</u> Low risk Reason: many factors impacting bone health were taken into account (height/weight is not so important as QCT gives true values of volumetric BMD and not areal BMD as DXA)

			MTX dose (mg/m2): P NS <10,000 vs. 10,000–19,999 -0.08 (-0.57, 0.4) 20,000 vs. 10,000–19,999 -0.29 (-0.69, 0.11) **Multivariate analyses for LS-BMD QCT Z-Scores at 24 months, β (95% CI)** Intercept 0.22 (-0.43, 0.88), **P =0.50; adjusted R^2 0.62** LS-BMD QCT Z-score at baseline 0.85 (0.74, 0.96) **P<0.0001** Supplement vs. placebo 0.008 (-0.15, 0.16) P NS Age at study entry (years) **P=0.003** 9–12 vs. 22–35 yrs 0.17 (-0.17, 0.51) 13–17 vs. 22–35 yrs -0.26 (-0.51, 0.00) 18–21 vs. 22–35 yrs -0.28 (-0.55, -0.01) Gender: female vs. male 0.15 (-0.01, 0.32) P=0.07 After correction for survival time, race, Tanner stage, physical activity, CRT dose, Ciclophosphamide dose, GCs dose, MTX dose **Multivariate analyses for LS-BMD QCT Z-Score Change at 24 Months, β (95% CI)** Intercept 0.38 (-0.28, 1.04), **P=0.26; adjusted R^2 0.16** Age at study entry (years) **P=0.01** 9–12 vs. 22–35 yrs 0.15 (-0.2, 0.49)	

			13–17 vs. 22–35 yrs -0.23 (-0.49, 0.03) 18–21 vs. 22–35 yrs -0.25 (-0.52, 0.03) Gender: female vs. male 0.14 (-0.02, 0.31) P 0.09 After correction for LS BMD at baseline, placebo vs supplement, survival time, race, Tanner stage, physical activity, CRT dose, Cyclophosphamide dose, GCs dose, MTX dose **Additional models:** taking into account baseline values of dietary vitamin D and calcium did not change the association between treatment group (calcium and cholecalciferol supplementation vs. placebo) and LS-BMD QCT Z-score at 24 months (P=0.60). including a history of hypothyroidism in the model, its effects were not significant (P=0.46). **In pts with baseline Z-scores <-2,** the supplemented ones had a bigger increase in BMD (n=14; median change +13.50 mg/cm3; range 1.1–45.9) than those who received the placebo (n=15, median change +3.05 mg/cm3; range -15.4 to 28.4; P=0.15).	

Abbreviations: ALL=acute lymphoblastic leukemia; BMD=bone mineral density; BMI=body mass index; CI=confidence interval; CRT=cranial radiotherapy; GCs=glucocorticoids; LS=lumbar spine; MTX=methotrexate; NA=not applicable; NR=not reported; NS=not significant; QCT=quantitative computed tomography; SCT=stem cell transplantation; SD=standard deviation.

Who needs BMD surveillance?				
Latoch et al. A long-term trajectory of bone mineral density in childhood cancer survivors after discontinuation of treatment: retrospective cohort study. Arch Osteoporos. 2021 Feb 26;16(1):45.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Retrospective cohort study Treatment era: 1987 to 2015 Follow-up: Median (range) 6.12 (4.0-22.0) years since end of treatment	Type and number of non-participants: Of the 773 childhood cancer survivors who visited oncology outpatient's clinic between 1990 and 2016 for late effects, 326 (42%) had at least one DXA scan after cessation of treatment Type and number of participants: N=326 childhood cancer survivors diagnosed with cancer under 18 years of age with a DXA scan available after cessation of treatment, who had no history of conditions which may have affected bone mineral density and content (i.e., apparent endocrine or renal disorders). Patients with relapse were excluded from the analysis. N=123 survivors had multiple DXA measurements Diagnoses: Multiple types of childhood cancer (excluding brain and bone tumor survivors) Acute lymphoblastic leukemia (ALL) n=138 (42.3%) Acute myeloblastic leukemia (AML) n=12 (3.7%) Chronic myeloblastic leukemia (CML) n=3 (0.9%) Hodgkin lymphoma n=48 (14.7%)	Chemotherapy: Corticosteroids: n=232 (71.2%) Median (IQR) prednisone equivalent dose: 2081 (1600-3081) mg/m2; mean (SD): 3126 ± 2000 mg/m2 MTX: n=166 (50.9%) Median (IQR) MTX dose: 2 (1-5) g/m2; mean (SD): 3.057 ± 1.89 g/m2 Radiotherapy: CRT: n=83 (25.5%) Median (IQR) CRT dose: 18 (12-18) Gy TBI: n=13 (4.0%) Abdominal: n=54 (16.7%) SCT: N=23 (7%) Limb amputation: NR Other:	Outcome definitions: Low BMD: Z-score ≤ − 1.0, Very low BMD: Z-score ≤ − 2.0 BMD measurement modality: DXA of the lumbar spine (L1-L4) and total body (DPX-L, GE-Healthcare Lunar, Madison, WI) Results: **Prevalence** Low BMD TB: 24% Low BMD LS: 20% Very low BMD LS and/or TB: 8% **Multivariable model** Low TB BMD: Age at diagnosis (increase per 1 year): OR=0.97, 95%CI 0.91–1.04, p=0.439 Age at DXA scan (increase per 1 year): OR=0.95, 95%CI 0.87–1.03, p=0.215 BMI at DXA scan (underweight n = 17 vs. normal n = 246) OR=3.16, 95%CI 1.1–9.07, p=0.032 Radiotherapy to the head and neck (yes n = 165 vs. no n = 161): OR=1.74, 95%CI 0.92–3.32, p=0.089 Stem cell transplantation (yes n = 23 vs. n = 303, majority had TBI): OR=3.13, 95%CI 1.02–9.63, p=0.046 Low LS BMD:	Strengths: -Longitudinal DXA measurements Limitations: -Very selective cohort -Possible selection of the survivors with two DXA measurements. Only 123 of 326 (38%) participants had two assessments. It is unknown whether this is a selective cohort or not. **Risk of bias** A. Selection bias: High risk Reason: Only 42% of the survivors seen at the late effects clinic had a DXA scan B. Attrition bias: Low risk Reason: all included survivors had a DXA scan and were included in the analysis High risk for the longitudinal analysis Reason: Only 38% of the included survivors had longitudinal DXA measurements C. Detection bias: Low risk Reason: low BMD by DXA is a hard end-point, not susceptible to subjectivity of the assessors

	Non-Hodgkin lymphoma n=28 (8.6%) Wilms tumor n=39 (12.0%) Soft tissue sarcoma n=19 (5.8%) Neuroblastoma n=13 (4.0%) Germ cell tumor n=13 (4.0%) Langerhans cell histiocytosis n=7 (2.1%) Hepatoblastoma n=3 (0.9%) Melanoma n=2 (0.6%) Retinoblastoma n=1 (0.3%) <u>Age at diagnosis:</u> Median (IQR) 7.27 (4.41–10.06) years <u>Age at follow-up:</u> Median (IQR) 16.0 (12.92-19.0) years <u>Controls:</u> Normative values from the DXA manufacturer		Sex (male n = 179 vs. female n = 147): OR=1.84, 95%CI 1.00–3.41, p=0.050 Age at diagnosis (increase per one year): OR=0.94, 95%CI 0.88–1.01, p=0.175 BMI at DXA scan (underweight n = 17 vs. normal n = 246): OR=3.57, 95%CI 1.24–10.23, p=0.004 Radiotherapy to the head and neck (yes n = 165 vs. no n = 161): OR=2.54, 95%CI 1.32–4.90, p=0.016 **Longitudinal BMD course** Mean time between the second (DXA2) and first (DXA1) densitometry was 5.54 years (mean age, 17.11 ± 3.67 vs. 11.57 ± 4.03 years Mean Z-scores between DXA1 and DXA2: TB: −0.176 vs. −0.262, p=0.293 LS: −0.277 vs. −0.180, p=0.842 Number of patients with TB BMD Z-score <−2 was 18 vs. 6, and that with Z-score <−1 and ≥ −2 was 23 vs. 19; LS BMD Z-score <−2 was 9 vs. 6 and Z-score <−1 but > − 2 was 28 vs. 14 patients	<u>D. Confounding:</u> Low risk Reason: the analyses were adjusted for all possible confounders

Abbreviations: BMD=bone mineral density; BMI=body mass index; CI=confidence interval; CRT=cranial irradiation; DXA=dual-energy X-ray absorptiometry; IQR=interquartile range; LS=lumbar spine; MTX=methotrexate; NR=not reported; RT=radiotherapy; SCT=stem cell transplantation; TB=total body; TBI=total body irradiation

Who needs BMD surveillance?				
Lemay et al. Prevention of Long-term Adverse Health Outcomes With Cardiorespiratory Fitness and Physical Activity in Childhood Acute Lymphoblastic Leukemia Survivors. Pediatr Hematol Oncol 2019;41:e450–e458.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Cross-sectional study Treatment era: 1987 and 2010 Follow-up: Median time since diagnosis 15.2 (5.4-28.2) yrs	Type and number of non-participants: Not described Type and number of participants: N=246 Eligible: All childhood ALL survivors who were diagnosed between 1987 and 2010 and treated according to DFCI-ALL 87-01 to 05-01 protocols13 at Sainte-Justine University Health Center (SJUHC), Montreal (Quebec), Canada, no history of refractory or recurrent diseases, did not receive a hematopoietic stem cell transplant. Were almost exclusively of French Canadian descent (>95%). For this study, participants were restricted to those who were <19 years of age at diagnosis and >12 years of age at the moment of interview. Subjects who had suffered from congenital bone disease or who had received osteotoxic drugs for non-ALL disease were excluded. Diagnoses: ALL Age at diagnosis:	Chemotherapy: Corticosteroids: n=241 Median (range): 9088 (4029-30,205) GCs> 134,13.93 mg/m2 (N=60: (24.9%) Methotrexate: n=241 Median (range): 6578 (854-12,784) MTX>7222 mg/m2 (N=60 (24.9%) Doxorubicin: n=241 Median (range) 225 (42-473) Dexrazoxane: n=241 Yes: n=72 (29.9%) No: n=169 (70.1%) Radiotherapy: CRT exposure: n=147 (40.2%) SCT: 0, this was an exclusion criteria Limb amputation: not mentioned but not expected Other: NA	Outcome definitions: Low LS BMD Z-score ≤−1 Vertebral fracture (VF): presence or not BMD measurement modality: Lumbar spine bone mineral density (LS BMD) was measured using the GE Lunar Prodigy (GE Lunar Corporation, Madison, WI) dual-energy X-ray absorptiometry. The presence or absence of vertebral fractures was assessed from anterior and lateral thoracolumbar spine radiographs. Two pediatric radiologists scored the spine radiographs from T4 to L4 vertebrae using the modified Genant semiquantitative method. Results: Prevalence of low BMD and VF Low LS BMD: n=54 (22%) VF: n=57 (23.2%) Risk factors: Low cardio fitness (VO2max): LS BMD: n=44 (23.9%); VF: n=40 (21.7%) High cardio fitness: LS BMD: n=6 (15%); VF: 9 (23.1%) Adjusted preventive fractions (1-OR) (95% CI) for cardio fitness	Strengths: Both possible determinants (physical activity) and outcome were validly assessed Vertebral fractures were assessed with radiographs and assessed by two pediatric radiologists Large study sample Clear and well-written paper Limitations: Selection bias was not described, weight bearing physical activity was not taken into account **Risk of bias** A. Selection bias: Unclear Reason: There is no description of the selection at baseline; no comparison of respondents and non-respondents. B. Attrition bias: Low risk Reason: the outcome was assessed in all but one participants. C. Detection bias: Low risk

	Median: 4.8 (0.9-18.0) yrs <u>Age at follow-up:</u> Median: 21.8 (8.5-41.0) yrs <u>Controls:</u> NA		with LS BMD as outcome: 0.18 (−0.02-0.33) (NS) VF as outcome: 0.05 (−0.18 to 0.23) (NS) Low physical activity level (<150 MVLPA (moderate-to-vigorous leisure physical activities (MVLPA)) min per week): LS BMD: n=34 (27%); VF: n= 28 (22.2%) High physical activity level (>150 min per week): LS BMD: n=20 (16.7%); VF: n=29 (24.3%) Adjusted PF for physical activity with LS BMD as outcome:: 0.60 (0.20-0.80), p<0.01 VF as outcome: −0.05 (−1.01 to 0.45) (NS) Cardiorespiratory fitness induces a preventive fraction of 18% for LS BMD, while a preventive fraction of 60% (P<0.01) is observed for the physical activity level.	Reason: low BMD by DXA is a hard end-point, not susceptible to subjectivity of the assessor. <u>D. Confounding:</u> Low risk Reason: most important confounders were taken into account into multivariable models.

Abbreviations: ALL=acute lymphoblastic leukemia; BMD=bone mineral density; CI=confidence interval; CRT=cranial radiotherapy; LS=lumbar spine; NA=not applicable; NS=not significant; OR=odds ratio; SCT=stem cell transplantation; VF=vertebral fracture.

Who needs BMD surveillance?				
LeMeignen et al. Bone mineral density in adult survivors of childhood acute leukemia: impact of hematopoietic stem cell transplantation and other treatment modalities. Blood 118: 1481-1489, 2011.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Cross-sectional study Treatment era: 1980-2008 Follow-up: Mean time from diagnosis to DXA 14.66 ± 0.44 yrs	Type and number of non-participants: N=61 Type and number of participants: n=159 (138 with ALL, 29 with AML), 49.7% males -No significant differences between non-participants and participants for: sex, type of leukemia, age at diagnosis, duration of follow-up, type of treatment (chemotherapy alone, chemotherapy and CNS irradiation, chemotherapy and HSCT), or treat-related complications (data not shown) - No significant differences between HSCT participants vs. HSCT non participants for: age, disease status at transplantation (first complete remission vs more advanced), type of transplantation (allograft vs autograft, donor type), conditioning regimen (TBI or not), and occurrence of GVHD or late endocrine complications (data not shown). Diagnosis: childhood ALL (n=131, 81.8%) and AML (n=29, 18.2%) HSCT group: 54 (34%) CHT group (only chemotherapy): 105 (66%) In the HSCT group AML pts (n=20; 37%) and pts who experienced relapse	Chemotherapy: according to various French multicentric protocols (ie, French Acute Lymphoblastic Leukaemia, European Organisation for Research and Treatment of Cancer, Leucemie Aigue Myeloblastique Enfant, ELAM), depending on the period of the treatment and the type of leukemia (ref 22-25) **Total cohort:** -GCs 137 (86.2%) -mean total dose of GCs: 4534 ± 229 mg/m^2 * -CNS CRT 30 (18.9%) **CHT group**: - GCs 96 (91.4%) - mean GCs dose: 4488 ± 224 mg/m2 Radiotherapy: - CNS RT: 28 (26.7%) - CNS RT dose: 18 Gy in 22 cases, 24 Gy in 6 pts - testis RT: 1 pt **HSCT group:** - mean age at HSCT 10.4± 0.74 yrs - Autograft 18 (33.3%) - Allograft 36 (66.7%) [matched related donors (n = 25; 69.4%), matched unrelated donors (n =4; 11.1%), mismatched related	Outcome definitions: A low BMD for age was defined as a Z-score of -2 or lower at 1 of the 2 sites. BMD measurement modality: DXA of lumbar spine (LS; L1 - L4) and left femoral neck (FN). BMD Z-scores using sex/aged matched reference data. No manufacturer specified. Results BMD <-2 Z-score, n (%) -All patients FN: 5 (3.2%) LS: 6 (3.8%) -CHT group vs HSCT group FN 2 (1.9%) vs 3 (5.8%) P NS LS 5 (4.8%) vs 1 (1.9%) P NS Mean BMD Z-score ± SEM -All patients FN -0.19± 0.08 LS -0.37 ± 0.08 -CHT group vs HSCT group FN -0.04±0.10 vs -0.49±0.15 **P=0.009** LS -0.39±0.11 vs -0.33±0.13, P NS **FN BMD: Univariate analyses, Mean ± SEM** -All patients	Strengths: -Measurement techniques were well described and are valid. -Some pts up to 15 years from treatment- allows assessment of long-term impact of treatments. -Many patient, disease characteristics, treatment modalities, and treatment-related complications were tested in both univariable and multivariable analyses. -The number of fractures are reported. Limitations: -Race of pts not noted; -Other factors impacting bone health not assessed; in particular height and weight or BMI were not taken into consideration in multivariable analyses. -The DXA manufacturer was not specified. -The site, timing and modality of the fracture outcome were not specified. **Risk of bias** A. Selection bias: Low risk Reason: all eligible pts with childhood acute leukemia in a coordinated program were eligible to be assessed with DXA B. Attrition bias: High risk

	(n=25; 46.3%) were higher than in the CHT group (p NS) 134 received nutritional counseling and placebo (91 completed DXA at 24 months) <u>Age at diagnosis:</u> Mean 8.33 ± 0.38 yrs <u>Age at study entry:</u> Mean 23.05 ± 0.38 yrs Controls: NA	donors (n= 2; 5.6%), and cord blood (n=5; 13.9%)] - GCs 41 (75.9%), as part of CHT in 34 pts, after HSCT in 23 pts; - mean GCs dose: 4622± 517 mg/m^2)* <u>Radiotherapy</u>: CRT: 2 Testis RT: 1 before HSCT TBI: n=38 (70.4%), as 2 Gy fractions twice daily during 3 days for a total dose of 12 Gy with lung shielding at 8 Gy. GVHD 23 (42.6%) Acute 20 (37.1%) Chronic 13 (24.1%) Significant 17 (31.5%) Treatment for GVHD 19 (35.2%) Hormonal defect, n (%): Hypogonadism 30 (18.9%), CHT group 2 (1.9%) vs HSCT group 28 (51.9%). Compensated hypogonadism:18 (11.3%); CHT group 1 (0.9%) vs HSCT group 17 (31.5%); Uncompensated hypogonadism 12 (7.5%); CHT group 1 (0.9%) vs HSCT group 11 (20.4%) GHD 6 (3.8%): CHT group 1 (1%) vs HSCT group 5 (9.3%) -Limb amputation: NA	Female vs male gender -0.34±0.10 vs -0.03±0.13, P=0.07 HSCT No vs Yes -0.04±0.10 -0.49±0.15, **P=0.009** No significant difference between ALL vs AML, CGs therapy yes vs no, dexamethasone yes vs no, age at diagnosis, length of follow up -CHT group Age at diagnosis P=0.04 (older) No significant difference between females vs males, ALL vs AML, CGs therapy yes vs no, dexamethasone yes vs no., age at diagnosis, length of follow up -HSCT group Female vs male gender -0.87±0.14 vs -0.22±0.23, P=0.03 Age at diagnosis P=0.09 (older age lower BMD) Age at HCST P=0.09 (younger age, lower BMD) Compensated vs non compensated hypogonadism -0.59±0.18 vs -1.37±0.26, P=0.004 No significant difference between ALL vs AML, CGs therapy yes vs no, dexamethasone yes vs no., length of follow up, TBI yes vs no, type of graft, post HCST GCs therapy, hypogonadism yes vs no, GHD yes vs no. **<u>LS BMD: Univariable analyses</u>** Any influence of patient and disease characteristics, treatment	Reason: 72.3% of pts had DXA <u>C. Detection bias:</u> High risk Reason: no blinding <u>D. Confounding:</u> High risk Reason: other factors impacting bone health were not taken into account

			modalities, and treatment-related complications on LSBMD **<u>Multivariate analyses, β-coefficient, P</u>** -All patients <u>FN BMD prediction</u> Sex <u>β</u> 0.18, P=0 .03 HSCT <u>β</u> -0.24, P=0 .006 After correction for initial diagnosis, Age at diagnosis, length of Follow-up, Corticotherapy <u>LS BMD prediction</u> The model including sex, initial diagnosis, Age at diagnosis, length of Follow-up, Corticotherapy, HSCT was not predictive -CHT group The model including sex, initial diagnosis, Age at diagnosis, length of Follow-up and CNS radiation was not predictive of both LS and FN BMD. -HSCT group <u>FN BMD prediction</u> Age at HCST β 0.3, P=0 .07 Hypogonadism β -0.32, P=0 .04 After correction for sex, length of Follow-up, TBI and significant GVHD (grade II or above or chronic GVHD). <u>LS BMD prediction</u> Age at HCST β 0.38, P=0.03	

			After correction for sex, length of Follow-up, TBI, significant GVHD and Hypogonadism. **Fractures:** total 6 fractures reported (4 in the HSCT group, 2 in the CHT group). Patients with previous fractures had lower FN BMD (FN Z-score, -1.26 ± 0.34 vs -0.10±0.09; P=0.008). No difference in LS BMD was identified.	

Abbreviations: ALL=acute lymphoblastic leukemia; AML=acute myeloid leukemia; BMD=bone mineral density; BMI=body mass index; CNS=central nervous system; CHT=chemotherapy; CRT=cranial radiotherapy; DXA=dual-energy X-ray absorptiometry; FN=femoral neck; GCs=glucocorticoids; GHD=growth hormone deficiency; GVHD=graft versus host disease; HSCT=hematopoietic stem cell transplantation; LS=lumbar spine; NA=not applicable; SEM=standard error of the mean.

Who needs BMD surveillance?				
Leung et al. A Prospective Cohort Study of Late Sequelae of Pediatric AlloHST. Medicine, 86 (4) 2007, pages 215 – 224.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Prospective cohort study over 10 years Treatment era: 1990-2003 Follow-up: Median 9 yrs from HSCT (range 3 to 10 years)	Type and number of non-participants: N=204 pts eligible to start monitoring one year after HSCT. All agreed but one, who declined for unstated reasons. N=155 pts were >3 yrs after HSCT and were included in this study. Type and number of participants: n=155 Diagnoses: 54% myeloid malignancy; 26% lymphoid malignancy; 20% non-malignant Age at HSCT: Median 9.7 years (range 0.5 to 21.4) Age at follow-up: Median 18.5 years (range 4.6 to 36.1) Controls: NA – this was a descriptive, phenotype study	Chemotherapy: Alkylator-based conditioning pre-HSCT in 21% Radiotherapy: TBI-based conditioning in 79%; 41% 8 to 12 Gy; 38% 14.4 Gy. SCT: Yes (100%) Limb amputation: None	Outcome definitions: Osteopenia was defined as BMD > 1 SD below the mean relative to age- and sex-matched reference data BMD measurement modality: Computed tomography; it is not stated how, at what skeletal site and by what machine BMD was measured. Results: 61 cases, 39% had a BMD that was worse than 1 SD below the mean The cumulative incidence of osteopenia by the above definition at 10 years was 47.7% (95% CI 38.4 to 58). TBI predicted osteopenia (HR 1.96; 95% CI 1.1-3.07, p=0.022; as did female sex (HR 1.94, 95% CI 1.38 to 2.72, p=0.010) in a multivariable model.	Strengths: -Frequent and long (10 year) follow-up Limitations: -BMD skeletal site, machine not stated. "Impaired BMD definition" not logical, as 1 SD below the mean is within the normal range, and can vary depending on the normative data that is used (osteoporosis not measured). **Risk of bias** A. Selection bias: Low Risk Reason: all but one eligible pts participated in the study, all pts >3 yrs from HSCT were included in the analysis for this paper. B. Attrition bias: Low risk Reason: only n=7 lost to follow-up due to death. C. Detection bias: Unclear Reason: it is not stated how, at what skeletal site and by what machine BMD was measured. D. Confounding: High risk

				Reason: BMD was adjusted for age and sex, but not BMI and Tanner stage.

Abbreviations: BMD=bone mineral density; BMI=body mass index; CI=confidence interval; HR=hazard ratio; HSCT=hematopoietic stem cell transplantation; NA=not available; SD=standard deviation; TBI=total body irradiation.

Who needs BMD surveillance?				
Liuhto et al. Diseases of renal function and bone metabolism after treatment for early onset cancer: A registry-based study. International Journal of Cancer 2020; 146: 1316-1324.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Cohort study from Finnish Cancer Registry, compared with healthy siblings Treatment era: January 1975- December 2004 Follow-up: NR The aim of this study was to investigate pediatric and young adult cancer survivors' morbidity due to renal and bone metabolism disease and especially to study bone metabolism in cancer survivors with renal disease	Type and number of non-participants: 0 Type and number of participants: 13,860 5-year survivors of cancer diagnosed <35 years in the Finnish Cancer Registry Healthy siblings were the comparison cohort Diagnoses: Pediatric cohort (PC): aged 0-19 years at cancer diagnosis (n=4459, 32% of the entire cohort) Young adult cohort (YA cohort): aged 20-34 years at diagnosis **Total cohort** Leukemia: 9.1% Lymphoma: 15.4% CNS tumors: 13.7% Solid tumors: 53.3% Other: 8.5% **PC females** Leukemia/other hematological: 24.3 % Lymphomas: 13.6% CNS tumors: 20.0% Solid: 38.9% Other 3.2% **PC males** Leukemia: 22.6% Lymphoma: 17.4% CNS tumors: 22.8% Solid tumors: 34.9 % Other: 2.3% Age at diagnosis: Between 0-34.9 years	No treatment data in this paper, noted by authors to be a significant limitation	Outcome definitions: Osteoporosis and fractures outcomes were defined by billing codes Results: HR of bone and renal outcomes: Osteoporosis: 5.2 (2.4-11.4) in entire group (n=13); 13.1 (4.3-39.7) in PC (n=9) Fractures: 1.3 (1.2-1.5) in total cohort (n=324), 1.3 (1.1-1.6) in PC (n=107); For fractures, the HR was elevated in all female survivors 1.5 (1.2-1.8) but not male survivors Cancer survivors with any renal outcomes (nephritis, nephrotic syndrome, kidney failure, obstructive and reflux nephropathy) had an increased risk of fractures [HR 3.1 (1.6-6.0, P=0.0008], but there was no increased HR for osteoporosis when looking specifically at patients with a renal outcome; the authors conclude that underlying renal disease is a risk factor for bone health problems later in life HR of bone outcomes by cancer type (PC):	Strengths: -Large national registry Limitations: -Used only billing codes; definition of osteoporosis not well-defined and no measurement obtained other than billing code; no details about fractures; no treatment details; length of follow-up unclear; codes obtained from hospitalizations and not from community health centers; the actual number of patients with osteoporosis is very low (range 0-4 based on diagnosis). **Risk of bias** A. Selection bias: Low risk Reason: comprehensive registry that includes all patients within one country for 29 years B. Attrition bias: High risk Reason: it is not clear how many were lost from this registry, due perhaps to moving or being lost to follow-up C. Detection bias: High risk Reason: using ICD10 codes without systematically testing for bone outcomes is likely to

	PC: 0-19 years Age at examinations: Registry data – at least 5 years post diagnosis and not having a second malignancy within the first 5 years; no other data given Other characteristics: 55% female Age at follow-up: not specifically listed Controls: Sibling controls; follow-up began at age 5 for the pediatric cohort and 25 for the YA cohort		Osteoporosis: Leukemia HR 26.6 (6.6-107), n=4 Lymphoma: HR N/A, n=0 CNS tumor: HR 7.1 (0.8-61.3), n=1 Solid tumors: HR 16.3 (4.5-59.5), n=4 Fractures: Leukemia: HR 1.1 (0.7-1.7), n=23 Lymphoma: HR 0.9 (0.5-1.7), n=11 CNS tumors: HR 1.2 (0.8-1.8), n=22 Solid tumors: HR 1.5 (1.1-2.0), n=48 Other: HR 1.4 (0.4-4.2), n=3	underdetect those who were not systematically screened; alternatively, this method could lead to an overestimation due to misinterpretation of screening DXA scans, resulting in patients with mild abnormalities in z-scores mislabeled as having osteoporosis; In addition, fractures are not characterized, leading perhaps to missing data (not recorded by ICD10 codes); no way to determine whether individual patients had multiple fractures. Will miss these outcomes if fractures are treated at community health centers as the data are based upon hospitalizations D. Confounding: High risk Reason: HRs were calculated for cancer diagnosis or renal outcomes or RT y/n, but no multiple regression analyses were performed

Abbreviations: CNS=central nervous system; HR=hazard ratio; PC=pediatric cohort; YA=young adult.

Who needs BMD surveillance?				
Mandel et al. Skeletal Morbidity in Childhood ALL. J Clin Oncol, 22(7), 2004 pages 1215-1221.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Cross-sectional study Treatment era: 1983 to 1998 Follow-up: Average time since diagnosis 10.1 years (range 5.5 to 15.4 years), the time since completion of therapy ranged from 2.5 to 12.4 years.	Type and number of non-participants: N = 248. There were no significant differences between those studied and those not studied for sex, age, age at diagnosis or years since diagnosis. Type and number of participants: 113 patients were studied, 62F and 44M. Patients were divided into High risk (girls over 9 and boys over 11) and low risk (under these ages) Diagnoses: ALL (100%) Age at diagnosis: Mean 5.8 years (range 1.0 to 17.1 years) Age at follow-up: Mean 15.9 years (range 7.8 to 30.6) Controls: No; published reference data for BMD comparisons were used instead	Chemotherapy: Hospital for Sick Children in-house protocols A (low risk), B (intermediate risk), C (high risk). Protocol A (n=18): No radiation, no anthracyclines, 7,920 mg/m2 corticosteroid dose (?prednisone equivalents – unknown), no high dose MTX Protocol B (n=15): -less than 5 years of age: No radiation, no anthracyclines, 7,920 mg/m2 corticosteroid dose, and high dose MTX. -over 5 years of age: yes radiation (18 Gy), No anthraclyclines, corticosteroid dose 7,920 mg/m2, and no high dose MTX Protocol AB (n=10): No radiation, no anthracyclines, 7,920 corticosteroid dose (mg/m2), no high dose MTX Protocol C (n=63): -less than 5 years of age: no radiation, yes anthracyclines, 9,080 mg/m2, yes high dose MTX -greater than 5 years of age: yes radiation (18 Gy), Yes anthracyclines, corticosteroid dose 9,080 mg/m2 and no high-dose MTX	Outcome definitions: Spine BMD Z-score -1 SD below the mean. Femoral neck BMD less than 89%. *(However, it is unclear, given that different reference databases generate different Z-scores, how this reference data's results compare to those of other reference data results. Therefore, it should be recognized that this -1 assignment is completely arbitrary, and not comparable to any other studies in this review that used different reference data.)* BMD measurement modality: L2-4 areal BMD and femoral neck areal BMD by DXA – Lunar DPX, Software version 4.6. Results compared to reference data provided by the manufacturer (i.e. intrinsic to the software) Results: LS BMD below -1 SD: 15 females and 8 males (23/106 = 21%). Mean LS BMD Z-score=0.019 (SD=1.29, range: -2.9-5.2) When data were analyzed by AAD, sex, low or high osteoporotic risk using ANOVA,	Strengths: Femoral neck BMD, a trabecular site and therefore theoretically sensitive to adverse effects of chemotherapy, in addition to the traditional spine Limitations: -Cross-sectional study, therefore unable to assess change from baseline as an index of recovery, nor prospective, longitudinal predictors of low BMD -Definition of low BMD is not logical, given that the proportion of BMDs below the outcome measure cut-off are similar to what would be expected in a healthy population of children -Prediction models did not include height as a confounding variable, a methodological omission. ***Without controlling areal BMD for height, and without a more conservative definition of "impaired BMD", my assessment is that these results are not valid when looking at the frequency and predictors of "impaired BMD".* **Risk of bias** A. Selection bias: High risk

		SCT: None Limb amputation: None Other: -	there was no difference between the study group and age-matched normal controls (Table 3 of manuscript). Femoral neck BMD less than 89% of the healthy average: 22/106 = 20%. When data were analyzed by AAD, sex, low or high risk using ANOVA, there was no difference between the study group and age-matched normal controls (Table 3 of manuscript). Those "low BMD sub-groups for spine and FN" did not differ from the remainder of the group with respect to age, AAD or YSD. Similarly, radiation and corticosteroids were not related to spine or femoral neck BMD. MTX showed no relationship with spine BMD. However, patients without a history of radiation exposure but who had received very high doses of MTX more frequently had femoral neck BMDs less than 90% of the healthy average. Patients with femoral neck BMD less than 90% were also more likely to have received protocol C with higher doses of corticosteroids, controlled for age (OR 2.81, p = 0.049).	Reason: High – Only 113 out of 361 patients participated B. Attrition bias: Low risk Reason: cross-sectional study – everyone who consented, participated. C. Detection bias: High risk Reason: High – definition of 'impaired BMD" not appropriate (not sufficiently conservative) D. Confounding: High risk Reason: High – no attempt to control for height Z-score

Abbreviations: AAD=age at diagnosis; ALL=acute lymphoblastic leukemia; BMD=bone mineral density; DXA=dual-energy X-ray absorptiometry; FN=femoral neck; LS=lumbar spine; MTX=methotrexate; OR=odds ratio; SCT=stem cell transplantation; SD=standard deviation; YSD=years since diagnosis.

Who needs BMD surveillance?				
Miyoshi et al. Endocrinological Analysis of 122 Japanese Childhood Cancer Survivors in a Single Hospital. Endocrine Journal, 2008, 55 (6): 1055-1063.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Retrospective cross-sectional study Treatment era: NR. FU between Jan 1997-Dec 2007, so estimated treatment era 1989-1999. Follow-up: Time since therapy from 2 to 30 years (mean 8.8; median 8.0)	Type and number of non-participants: 151 subjects CCS >2 years after therapy. 29 excluded (not referred to Oncologist) Type and number of participants: **122 CCS** (62 males and 60 females) in remission and referred to oncologist survived more than 2 years after cancer treatment Diagnoses: 67 hematological diseases: -34 ALL, 12 AML, 8 non Hodgkin lymphoma, 3 chronic myelocitic leukemia, 2 juvenile myelomonocytic leukemia, 2 Hodgkin Lymphoma, 1 myelodysplastic syndrome, 3 aplastic anemia, 1 Wiskott-Aldrich syndrome, 1 leukosite adhesion deficiency. 26 brain tumors: -11 germinomas, 9 medulloblastomas, 6 craniopharyngiomas 29 solid tumors: -7 neuroblastomas, 8 rhabdomyosarcoma, 4 hepatoblastoma, 2 primitive neuroectodermal tumor, 2 Wilm's Tumor, 1 germinoma, 1 upper pharyngeal tumor, 1 teratoma, 1 eosinophilic granuloma, 1 ovarian undifferentiated germinoma, 1 granulosa cell tumor of the ovary	Chemotherapy: 116 pts (95%) Radiotherapy: 72 pts (59%) -3-24 Gy to whole brain for hematological disease -10-54 Gy to local cerebral and 18-30 Gy to whole brain and 18-32 Gy to spine for brain tumors -20-45 Gy to local lesion for solid tumors SCT: 65 pts (53%) (25 pts with hematological disease received conditioning radiation. TBI at 8-12 Gy, TBI without cranial irradiation at 6-10 Gy, 40 non-TBI): -33 allogenic and 32 autologous -5 pts two transplant and 1 pts three transplants Limb amputation: NA Other: Surgery 57 pts (47%) Hypogonadism 60 (49%) Thyroid dysfunction 26 (21%) Adrenocortical dysfunction 9 (7%) Central diabetes insipidus 11 (9%)	Outcome definitions: Endocrine abnormalities of CCS and BMD abnormalities after 2 yrs since therapy (Lumbar BMD Z-score between 1.7-2.6 SD below the mean= osteopenia; Lumbar BMD Z-score < -2.6 SD= osteoporosis) BMD measurement modality: Measured in 98 pts. Lumbar (L2-L4) BMD (g/cm2) by DXA scan (LUNAR until march 2006 and HOLOGIC DISCOVERY QDR 1000 after april 2006 using conversion formula 0.827 x [DPX-L] + 0.042). Z-scores generated according to Tanaka et al. Results: Low BMD: 41 pts (42%): -osteopenia 30 (31%; 14 females) -osteoporosis 11 (11%; 9 females) - 9/25 (36%) of adults showed low BMD One male with GVHD showed compression fracture of lumbar spine LOW BMD: -23/54 Hematological (7 osteoporosis) -11/24 brain tumor (3 osteoporosis) - 7/20 solid tumors (1 osteoporosis)	Strengths: -Single hospital -Pretty large number Limitations: -Retrospective design -Small number analyzed for BMD and very different diagnosis -Non stratified for treatment (chemo vs radio) -No multivariable or correlation analysis **Risk of bias** A. Selection bias: Low risk Reason: the number was 80% of the sample all referred to oncologist and there was no difference in diseases/age or sex among the groups B. Attrition bias: Low risk Reason: outcome was assessed for 90% of the sample C. Detection bias: Low risk Reason: DXA was used to define BDM values and data were adjusted for age, sex and Device software D. Confounding: High risk Reason: only univariable analysis.

	Age at diagnosis: 6.4 years (range 0-15 years) Age at follow-up: Mean 17.3 yrs (range 4-36 yrs; median 17.0 yrs); 38 pts reached adulthood (31%) Controls: NA		- 21/36** pts with growth disturbance (9 osteoporosis*); 7/12 with GHD (5 osteoporosis*); 25/53 with hypogonadism (10 osteoporosis**) **p<0.01, **p<0.001* Risk only! (only univariable RF analysis)	osteoporosis and osteopenia were used in children and not low BMD vs normal BMD. Fractures were not considered as diagnosis or stratification

Abbreviations: ALL=acute lymphoblastic leukemia; AML=acute myeloid leukemia; BMD=bone mineral density; CCS=childhood cancer survivors; DXA=dual-energy X-ray absorptiometry; FU=follow-up; GVHD=graft versus host disease; NA=not available; NR=not reported; TBI=total body irradiation; SCT=stem cell transplantation; SD=standard deviation.

Who needs BMD surveillance?				
Molinari et al. Assessment of the late effects on bones and on body composition of children and adolescents treated for acute lymphocytic leukemia according to brazilian protocols. Rev Paul Pediatr. 2017;35(1):78-85.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Cross-sectional study Treatment era: The Brazilian Cooperative Group of Treatment of Lymphoblastic Leukemia in Childhood (GBTLI) LLA-93 and LLA-99. 1994-2006. Follow-up: At least 5 years.	Type and number of non-participants: Out of the 242 patients treated for ALL, 76 died due to various causes and 65 of them were excluded from the study due to one or more predetermined criteria. This led to a total of 101 patients. Type and number of participants: N=101 Diagnoses: ALL (100%) Age at diagnosis: Mean 5.2 ± 3.6 years Age at follow-up: Mean 17.2±4.9 years Controls: NA	Chemotherapy: Cumulative doses: Prednisolone: GBTLI LLA-99 1,169±160 Dexamethasone: GBTLI LLA-93 vs GBTLI LLA-99 597±265 vs 268±63 Methotrexate: GBTLI LLA-93 vs GBTLI LLA-99 10,373±331 vs 9,879±2,150 Alkylating Agents GBTLI LLA-99 6,197±4,623 6-mercaptopurine GBTLI LLA-93 vs GBTLI LLA-99 36,145±4,936 vs 32,898±539 Radiotherapy: Prophylactic (12 Gy): 18 Therapeutic: (24 Gy): 6 SCT: NR Limb amputation: NR Other:	Outcome definitions: Patients <20 years Low BMD: Z-score <-2 At risk for low BMD: Z-score between -1.1 and 1.9. Patients >20 years Osteoporosis: T-score <-2.5 Osteopenia: T-score between -1 and -2.5 BMD measurement modality: BMD of the lumbar spine segment L1-L4, whole body and femur, through DXA, using the Lunar DPX (GE Lunar Corporation®) instrument Results: The patients presented a frequency of fractures of 2%, of osteonecrosis, 2%, and of low BMD, 2.9%. In the group of 79 patients under 20 years of age, three had low BMD. The 16 that presented risk for low BMD, demonstrated lower values in lumbar vertebrae L1–L4 (p=0.01) and whole body (p=0.005), and smaller values of lean body mass (p=0.03). In the group of 22 patients over 20 years of age, ten had osteopenia.	Strengths: -Non-white study population -Reasonable sample size Limitations: -Only univariable risk factor analysis **Risk of bias** A. Selection bias: High risk Reason: Only 101 of 242 (42%) patients included, predetermined exclusion criteria not specified. B. Attrition bias: Low risk Reason: All included patients had a DXA scan. C. Detection bias: Low risk Reason: BMD by DXA is a hard end-point and reasonable cut-points for low BMD were used. D. Confounding: NA Reason: this study will only be used to assess the risk of low BMD, not risk factors.

Abbreviations: ALL=acute lymphoblastic leukemia; BMD=bone mineral density; DXA=dual-energy X-ray absorptiometry; FU=follow-up; NA=not available; NR=not reported; SCT=stem cell transplantation.

Who needs BMD surveillance?				
Mostoufi-Moab et al. Bone Density and Structure in Long-Term Survivors of Pediatric AlloHST. JBMR, 27 (4), 2012, pages 760 – 769.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Cross-sectional study Treatment era: Not stated Follow-up: At least a 3 year interval from alloHSCT (median 6.8 years, range 3.0 to 16.4)	Type and number of non-participants: 73 eligible, 55 enrolled. Non-participants did not differ in AAD, age at alloHST, conditioning regimen, type of marrow donor, frequency of GVHD, or frequency of endocrinopathies Type and number of participants: 55 participants, over 5 years of age, at least 3 years from alloHST, excluded if a history of diseases known to affect bone health (such as neuromuscular diseases, active malignancy etc). AlloHST was carried out for leukemia and bone marrow failure syndrome. Diagnoses: AML n=23 (42%) ALL n=12 (22%) CML n=6 (11%) MDS n=5 (9%) JMML n=5 (9%) Aplastic anemia n=2 (4%) Bone marrow failure syndrome n=2 (4%) Age at diagnosis: Median 5.7 years (range 0 to 20 years) Age at transplant: Median 6.7 years (range 0.1 to 21.1 years)	Chemotherapy: Yes, for the 92% of patients with leukemia. Specific regimens not stated. Conditioning regimen: Cyclophosphamide + thiotepa (69%) Busulfan + cyclophosphamide (unknown %) Busulfan + Cytoxan ± melphelan or fludarabine (unknown %) Radiotherapy: TBI conditioning regimen, 1200 to 1320 Gy (69%) SCT: Yes (100%) Limb amputation: None Other: 53% of patients had treatment with GCs following HSCT; 47% had GVHD, 89% had an endocrinopathy (GHD [29%, treated in 50%], hypothyroidism [36%, treated in 100%], gonadal failure [45%, treated in 100%])	Outcome definitions: No definitions of impaired skeletal health were established a priori. Outcomes measures at the tibia included: Trabecular vBMD, cortical vBMD, cortical dimensions, and polar section modulus, plus muscle and fat cross-sectional area (CSA). BMD measurement modality: pQCT by a STRATEC SCT2000 (Orthometrix, White Plains, NY, USA). Results: Patients' Z-scores relative to healthy controls (beta and 95% confidence interval, with p value compared to the healthy population) Trabecular vBMD -1.05 (-1.33 to -0.78) p<0.001 Cortical vBMD -0.20 (-0.48 to 0.08) p=NS Section modulus -0.63 (-0.91 to -0.35) p <0.001 Cortical CSA -0.71 (_0.99 to -0.43) p<0.001 Periosteal circumference -0.53 (-0.78 to -0.27) p<0.001 Endosteal circumference -0.16 (-0.44 to -0.12) p=NS Muscle CSA -1.01 (-1.30 to -0.72) p<0.001	Strengths: This is an outstanding paper methodologically, which presents TRUE volumetric trabecular BMD results at the tibia, and which appropriately corrects size-dependent measures of bone/muscle/fat geometry for tibia length. This paper therefore provides information that is superior to DXA-based papers, particularly those that do not endeavor to correct for body size. Limitations: None identified **Risk of bias** A. Selection bias: low risk Reason: no difference between participants and non-participants B. Attrition bias: Low risk Reason: cross-sectional study (everyone enrolled underwent testing) C. Detection bias: Low risk Reason: this paper is of superior quality methodologically (to DXA, particularly when DXA is not

	Age at follow-up: Median 15.1 years (range 5.1 to 25.5) Controls: 985 healthy reference participants ages 5 to 30 years recruited from pediatric and internal medicine clinics in the Philadelphia area and through community advertisements to characterize bone health and body composition in healthy subjects		Fat CSA 0.82 (0.54 to 1.11) p<0.001 Adjustment for muscle deficits eliminated section modulus (an index of bone strength) deficits in alloHSCT. Total body irradiation (TBI) was associated with lower trabecular vBMD Z-scores (-1.30 ± 1.40 versus -0.49 ± 0.88; p=0.01) and lower muscle CSA Z-scores (-1.34± 1.42 versus -0.34± 0.87; p<0.01). Growth hormone deficiency (GHD) was associated with lower Section Modulus Z-scores (-1.6± 2.47 versus -0.28± 1.24; p=0.05). Muscle CSA differences were not significant in those with GHD compared to those without (-1.69± 1.84 versus -0.78± 1.01; p=0.09). History of graft versus host disease was not associated with any of the pQCT outcomes. *The BMD results are true (size-independent) values. Muscle, fat and bone geometry Z-scores are size-dependent and were appropriately adjusted for tibia length Z-scores.*	appropriately controlled for body size) D. Confounding: Low risk Reason: no other confounders identified other than the adjustments made as discussed. **These volumetric BMD results are "true true" given the lack of need for body size adjustment, and the geometry measures have been appropriately scaled to tibia length

Abbreviations: AAD=age at diagnosis; ALL=acute lymphoblastic leukemia; AML=acute myeloid leukemia; CML=chronic myeloid leukemia; CSA= cross-sectional area; BMD=bone mineral density; GCs=glucocorticoids; GHD=growth hormone deficiency; HSCT=hematopoietic stem cell transplantation; JML=juvenile myelomonocytic leukemia; MDS=myelodysplastic syndrome; NS=not significant; pQCT=peripheral quantitative computed tomography; TBI=total body irradiation.

Who needs BMD surveillance?				
Mueller et al. Hospitalization and mortality among pediatric cancer survivors: a population-based study. Cancer Causes & Control 2018; 29: 1047-1057.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Cohort study from Washington State Treatment era: 1982-2008 Follow-up: Median 9.1 years (range 0.1-27 years) The aim of this study was to investigate serious long-term outcomes among CCS using population-based data; in particular, they used linked population-based health registry data to compare the occurrence of hospitalization or death among childhood cancer cases in Washington State to that among children without cancer born in the same years, evaluating outcomes by cancer types and selected personal and family characteristics	Type and number of non-participants: 0 Type and number of participants: 3152 5+-year survivors of cancer diagnosed <20 years in Washington state; comparison cohort was birth cohorts; for each case, 10 comparison subjects were selected from birth records, matched on birth year and sex Diagnoses: Leukemia: 26% Lymphoma: 14% CNS tumors: 20% Neuroblastoma 7% Retinoblastoma 3% Wilms Tumor: 5.5% Hepatoblastoma 1.2% Bone tumors: 3.5% Soft Tissue sarcomas: 6.4% Germ cell tumors: 5.3% Other epithelial malignant: 8.5% Other 0.5% Age at diagnosis: 0=<20 years Age at examinations: NR Other characteristics: 48% female 5% non-white Age at follow-up: Median age at last follow-up was 23.8 years Controls: For each case, 10 comparison subjects were selected from birth records,	No treatment data in this paper	Outcome definitions: Hospitalization rate All-cause death rate Outcomes were defined by billing codes (cause-specific hospitalization/ death) Of interest/possible interest: fractures, endocrine/metabolic and musculoskeletal outcomes. Results: Survivors had an HR of 2.7 (2.4-3.0) for all-cause hospitalization compared with comparison group Any-cause death HR was 14.7 (11.3-19.1) compared with comparison group Fractures: HR was 1.6 (1.1-2.3) compared with comparison group When broken down into 5-<10 year post-index date compared with only events >10 years post-index date, the HR decreased slightly for fractures (was 1.7 (1.0-3.1) during the earlier years and was 1.6 (1.0-2.5) during the later years.	Strengths: -State registry Limitations: -This study used only billing codes; no details about fractures; no treatment details; only looked at hospitalizations, and most patients with fractures are not hospitalized **Risk of bias** A. Selection bias: Low risk Reason: comprehensive registry that includes all patients within one state for 16 years B. Attrition bias: High risk Reason: it is not clear how many were lost from this registry, due perhaps to moving or being lost to follow-up C. Detection bias: High risk Reason: using ICD9 or ICD10 codes for fractures may lead to under- or over-detection; this is particularly true for this study, when only reasons for hospitalization are being evaluated; most patients will be not hospitalized for fractures; therefore, fractures may be underestimated. However, I am a

	matched on birth year and sex, excluding those known to have died before their case's index date			bit concerned that perhaps these cancer survivors may have additional health concerns that might make them more likely to be hospitalized for a fracture than a comparison group. This would actually lead to overdetection of fractures using these methods <u>D. Confounding:</u> High risk Reason: I think the study as a whole is at high risk for confounding variables. For example, "musculoskeletal disorders" may actually be related to fractures; endocrine deficiency may be related to fractures. No multiple regression analyses undertaken.

Abbreviations: CCS=childhood cancer survivors; HR=hazard ratio; NR=not reported.

Who needs BMD surveillance?				
Muszynska-Roslan et al. Body Composition and Bone Mass in Survivors of Childhood Cancer. Pediatr Blood Cancer 2007;48:200–204.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Cross-sectional study Treatment era: Not reported (probably around 1985-1995) Follow-up: Time since end of cancer-directed treatment ranged from 5.5 -21.4 years Reported as: 8.1 ± 2.9 years for males, 7.5 ± 3.4 years for female survivors	Type and number of non-participants: NR Type and number of participants: -68 young-adult CCS, ≥ 5 years from completion of cancer therapy. -31 (46%) females, 37 (54%) male -All subjects post-pubertal (Tanner stage 5) at study follow-up. -2 patients excluded for growth hormone deficiency Diagnoses: Leukemia: 30 (44.1%) Lymphoma: 28 (41.2%) Solid tumors: 10 (14.7%) Age at diagnosis: Females: 10.4 years Males: Mean age 9.6 years (other details not reported) Age at follow-up: Range 15.5–27 years; Females: Mean age 19.6± 3.3 years Males: Mean age 19.8± 2.4 years Controls: NA	Chemotherapy: -Corticosteroid 58/68 (85.3%) (all leukemia/lymphoma patients Radiotherapy: -Cranial radiation: 26/68 (38.2%); (10 patients 12Gy; 16 patients 18Gy) -Mediastinal RT: 17/68 (25%); (20Gy) -Abdominal RT: 20/68 (29.4%); (20Gy) SCT: NR Limb amputation: NR	Outcome definitions: Stated aim was to examine association between body composition and bone mineral content (BMC) in CCS. Outcome was correlation between Spine or Total BMC and lean mass or fat mass. BMD measurement modality: DXA (lunar) of total body and lumbar spine (L2-L4). Unclear which reference values were used. Total Body BMC correlations: -BMI correlated positively with Total Body BMC (males r=0.56; females r=0.66; P<0.001) -Total body BMC correlated strongly with Lean Mass (males r=0.9, females r=0.76; P<0.0001) and with Fat Mass (males r=0.54; P<0.01; females r=0.8; P<0.00001). Spine BMC correlations: -BMI correlated positively with Spine BMC (males r=0.42; P<0.01; females r=0.52; P<0.0001) -Spine BMC correlated with Lean mass (males r=0.77, females r=0.64; P<0.0001); and with fat mass only in females (p=0.03)	Strengths: -Provides details on associations between total body/spine BMC and body composition (lean mass/fat mass, BMI) by sex Limitations: -Relatively small study sample -BMD Z/T scores not reported **Risk of bias** A. Selection bias: High risk Reason: information on non-participants not reported, and mean age at diagnosis rather old for these tumor types. B. Attrition bias: Low risk Reason: outcomes appear to have been assessed in full study group (no multiple/ longitudinal assessments) C. Detection bias: Low risk Reason: BMC and body composition parameters were not subjective assessments D. Confounding: Low risk Reason: age, sex, BMI considered in analysis; height not commented upon, but of note all subjects

			Multiple regression analysis: (variables age, sex, fat mass, and mean mass) -Total body BMC in males was associated with lean mass and and Fat Mass with “stronger” association for Lean Mass. -Total body BMC in females, reported “similar associations” but “stronger” for Fat Mass than Lean Mass.”	were post-pubertal at time of assessment.

Abbreviations: BMI=body mass index; BMC=bone mineral content; CCS=childhood cancer survivors; DXA=dual-energy X-ray absorptiometry; NA=not applicable; NR=not reported; RT=radiotherapy; SCT=stem cell transplantation.

Who needs BMD surveillance?				
Muszynska-Roslan et al. Is the Treatment for Childhood Solid Tumors Associated with Lower Bone Mass than that for Leukemia and Hodgkin Disease? Pediatric Hematology and Oncology, 26:1, 36-47, 2009.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Longitudinal study Treatment era: Not reported Follow-up: Two assessment time points: Mean time from end of therapy to 1st assessment (which was reported by diagnosis category): -ALL: 2.4 ± 1.9 years -Hodgkin lymphoma: 2.8 ± 2.1 years -Solid tumor: 3.7 ± 4.6 years Mean time from end of therapy to 2nd assessment: -ALL: 5.8 ± 3.4 years -Hodgkin lymphoma: 6.3 ± 2.9 years -Solid tumor: 6.9 ± 4.6 years	Type and number of non-participants: NR Type and number of participants: 114 CCS treated for ALL, Hodgkin lymphoma, and solid tumors. Diagnoses: ALL: 43 (37.7%) Hodgkin lymphoma (HL): 35 (30.7%) Solid Tumor: 36 (31.6%) Age at diagnosis: Median age at diagnosis 8.4 years (range 1.4-17 years) Age at follow-up: Two assessment time points: Median age 12.8 years (range 5.1–23.5) at 1st assessment and 16.4 years (range 7.3–27.2) at 2nd assessment Controls: Reference data from 473 age and sex-matched healthy controls.	Chemotherapy: Corticosteroid: -Overall: 78/114 (68.4%) -ALL: 43/43 (100%); median cumulative dose 2950mg prednisone/m2 (range 1680-5540mg/m2) -Hodgkin lymphoma: 35/35 (100%); median cumulative dose 1200mg prednisone/m2 (range 800-1600mg/m2) -Solid tumor: 0/36 (0%) Methotrexate: -Overall: 43/114 (37.7%) (100% of ALL patients, no HL or ST patients) Radiotherapy: -Cranial radiation: 28/114 (24.6% of full cohort, 65.1% of ALL cohort); (1200Gy) -Mediastinal RT: 32/114 (28.1% of full cohort, 91.4% HL cohort); (20Gy) -Abdominal RT: 41 (36%) -Extra-abdominal local radiation: 4/114 (3.5%) SCT: NR Limb amputation: NR	Outcome definitions: Low BMD Z-score <-2 BMD measurement modality: DXA (lunar) of total body and lumbar spine (L2-L4) Low BMD: (1st; 2nd assessment): ALL: 10.5%; 8.7% HL: 6.9%; 6.9% Solid Tumor: 30.5%; 16.6% Median TB BMD Z-score* (1st, 2nd assessment): ALL: 0.26 ± 1.7; 0.12± 1.5 HL: 0.11±0.9; -0.09±1.2 Solid Tumor: -1.14±1.2**; -0.40±0.6 (** p=0.00001, difference between examined and reference group) Median Spine BMD Z-score* (1st, 2nd assessment): ALL: 0.23 ± 1.3; 0.15± 1.6 HL: 0.23±1.1; -0.09±0.8 Solid Tumor: -1.13±1.1**; ? ±0.8 (** p=0.00002, difference between examined and reference group) *Age and sex-adjusted Z-score, 21 patients with height Z-score <-1 assess according to bone age Multiple regression analyses:	Strengths: -Highlights potential risk for low BMD in those treated for Solid Tumors -Large reference group Limitations: -Relatively small study sample -Fracture not reported **Risk of bias** A. Selection bias: High risk Reason: information on non-participants not reported, and mean age at diagnosis rather old for these tumor types. B. Attrition bias: Low risk Reason: outcomes appear to have been assessed in full study group (although not definitively stated) C. Detection bias: Low risk Reason: low BMD by DXA hard end-point (not subjective assessments) D. Confounding: Unclear Reason: analyses do not appear adjusted for height SDS, but patients with height Z-score <-1 assessed according to bone age.

			"Increasing age and male sex were independently associated with higher *Z*-scores of total BMD (p = .054 and p = .021, respectively) and spine BMD (p <.0001 and p = .03)." (no additional details reported)	

Abbreviations: ALL=acute lymphoblastic leukemia; BMD=bone mineral density; DXA=dual-energy X-ray absorptiometry; HL= Hodgkin lymphoma; NR=not reported; RT=radiotherapy; SCT=stem cell transplantation.

Who needs BMD surveillance?				
Nysom K et al, Bone Mass After Treatment for Acute Lymphoblastic Leukemia in Childhood. J Clin Oncol 1998: 16; 3752-3760.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Cross-sectional study Treatment era: 1970-1990 Follow-up median (range): Median 10.7 yrs after diagnosis (3.4-23.4) Median 7.6 yrs after off-therapy (1.2-18.3)	Type and number of non-participants: Eligible cohort 162 ALL CCS: 32 declined 1 pregnant 1 relapsed before study Out of 128 (79%) that gave consent the following were excluded: -24 for previous relapse -1 second malignancy -6 previous BMT or mediastinal irradiation -2 to young (no references for bone parameters) Type and number of participants: 95 survivors of childhood ALL in first remission (50 males, 45 females) Diagnoses: ALL (100%) Age at diagnosis median (range): 4.0 yrs (range 3.5-19.5) Age at follow-up median (range): 16.2 yrs (range 6.1-34.2) Controls: 396 local controls *(ref 17)* Children/adolescents: 343/396 (age range 6-19 yrs) Adults: 53/396 (21 men, age range 20-29 yrs)	Chemotherapy: (reported in *ref 19)* Median (range): 95/95: MTX 1.8 g/m^2 (0.3-3.2) 67/95 intermediate/high dose MTX infusion (doses NR) Corticosteroids median cumulative dose (range): 5.9 g/m2 of prednisone (2.3-31.9). Radiotherapy: 39/95: CRT -Doses: 3/39: 15 Gy 19/39: 18 Gy 17/39: 24 Gy -Fraction size: 1.5 Gy (n = 2) 1.9 Gy (n = 2) 2 Gy (n = 34) 2.25 Gy (n = 1) SCT: None Limb amputation: NR Other: At study entry: Oral contraceptives: 12 females GH therapy: 3 Hypothyroidism: 1/3 GHD pts	Outcome definitions: Bone parameters Z-scores less than -1,96: significantly reduced BMD measurement modality: DXA (Hologic 1000/W) of the TB, LS_{TB} subregion obtained from TB scan and $LS_{(L1-L4)}$ (dedicated scan). TB values were compared to the control group mentioned in the 2nd column. $LS_{(L1-L4)}$ values were compared to ref. values supplied by manufacturer. Bone parameters: TB: BMC Z-score, BMD Z-score and 3 step approach *(ref 13 for children/adolescents, ref 16 for young adults)* -Height/age Z-score -Bone area/height Z-score -BMC/bone area Z-score LS_{TB} BMC Z-score, BMD Z-score $LS_{(L1-L4)}$ BMD Z-score Significance *P<0.05 for mean different from 0 †P<0.05 for differences between means Results: **Total cohort Z-score, mean (range)** Height - 0.57* (- 4.04-2.33) TB	Strengths: -Quite large homogeneous cohort (95 ALL in first remission and irradiated only at the cranial field); -Long follow-up; -Multiple linear regression analyses were performed; -Information on the overall prevalence of fractures by age groups. Limitations: -Treatment era was wide (20 yrs span); i.e. differences between pts >19 o < 19 yrs could be due to different treatment protocols; -Significant differences in important variables between CCS participants and non-participants are not stated. **Risk of bias** A. Selection bias: Low risk Reason: 79% of the initial cohort (n=162) gave informed consent (95/162 pts were finally included based on inclusion criteria (56.5% of the initial cohort)); Significant differences in important variables between CCS participants and non-participants are not stated. B. Attrition bias: Low risk

			Bone area/height 0.09 (- 3.23-2.87) BMC/bone area - 0.17 (- 2.90-2.80) BMC - 0.37* (- 3.33-2.64) Bone area - 0.34* (- 3.70-2.67) BMD - 0.39* (- 3.18-2.44) $\underline{LS_{TB}}$ BMC - 0.45* (- 3.73-2.12) BMD - 0.47*(- 3.16-2.01) $\underline{LS_{(L1-L4)}}$ BMD - 0.55*(- 2.99-1.84) **No CRT vs CRT pts (n=56 vs. n=39), mean (range)** Height - 0.25 vs.- 1.04*† TB Bone area for height 0.09 vs. 0.09 BMC for bone area - 0.24 vs. - 0.08 BMC - 0.12 vs. - 0.73*† Bone area - 0.06 vs. - 0.75*† BMDA - 0.20 vs. - 0.66*† $\underline{LS_{TB}}$ BMC - 0.20 vs. - 0.80*† BMD - 0.29* vs. - 0.72*† $\underline{LS_{(L1-L4)}}$ BMD - 0.45* vs. - 0.69* **No GHD vs. GHD pts (n=72 vs. n=18), mean (range)** Height -0.51*vs. - 0.81* TB Bone area/height 0.05 vs. 0.31 BMC/bone area -0.22 vs. - 0.01 BMC - 0.33* vs. - 0.50 Bone area - 0.29 vs. - 0.52 BMD -0.39* vs. - 0.39 $\underline{LS_{TB}}$	Reason: the outcomes were assessed for all the 95 patients C. Detection bias: Low risk Reason: low BMD/BMC by DXA is a hard end-point, not susceptible to subjectivity of the assessor. TB was also analyzed by a 3 step approach, also including hard end-points (height/age/bone area by DXA). D. Confounding: High risk Reason: most analyses were adjusted for height SDS, and height was included in the 3 step approach. Weight or fat mass/lean mass and Tanner stage were not included in multivariable analyses (DXA results might have been underestimated in under-weighted patients and overestimated in over-weighted ones).

			BMC -0.39* vs. - 0.67* BMD - 0.44* vs. - 0.59* $\underline{LS_{(L1-L4)}}$ BMD - 0.57* vs. - 0.42 **Estimates of gender difference in 95 CCS (95% CI)** TB MC/Bone area reduced in females 0.42 (95% CI -0.05 to 0.89) BMC/Bone area controlled for RT reduced in females 0.41 (95% CI -0.06 to 0.88) $\underline{LS_{TB}}$ BMC reduced in males: 0.46 (95% CI, 0.01 to 0.91) controlled for RT: 0.40 (95% CI, -0.04 to 0.85) $\underline{LS_{(L1-L4)}}$ BMD reduced in males: 0.39 (95% CI, -0.01 to 0.78) controlled for RT: 0.37 (95% CI, -0.03 to 0.76). **62/95 CCS <19 yrs (38 males), mean (range)** Height - 0.41*(- 2.73-2.33) TB Bone area/height 0.44*(-2.48-2.87) BMC/bone area - 0.02 (-2.90-2.80) BMC - 0.09 (-2.60-2.64) Bone area - 0.09 (- 2.62-2.67) BMD - 0.15 (- 3.18-2.44) $\underline{LS_{TB}}$ BMC - 0.48* (-3.73-2.12) BMD - 0.37* (-3.16-2.01) $\underline{LS_{(L1-L4)}}$ BMD- 0.62* (-2.99-1.33)	

			No CRT vs. CRT CCS (n=33 vs. n=29) <19 yrs, mean (range) Height - 0.05 vs. - 0.83*† <u>TB</u> Bone area/height 0.38* vs. 0.51* BMC/bone area - 0.07 vs. 0.03 BMC 0.23 - 0.45*† Bone area 0.23 - 0.45*† BMD 0.14 vs. - 0.47*† <u>LS_{TB}</u> BMC - 0.24 vs. - 0.74* BMD - 0.19 vs. - 0.58* <u>$LS_{(L1-L4)}$</u> BMD - 0.57*vs. - 0.69* **33/95 CCS >19 yrs (12 males), mean (range)** Height - 0.87* (- 4.04-1.49) <u>TB</u> Bone area/height - 0.57* (-3.23-1.73) BMC/bone area - 0.47* (-2.53-2.05) BMC - 0.91*(-3.33-1.27) Bone area - 0.82* (-3.70-1.66) BMD - 0.84* (-3.15-1.86) <u>LS_{TB}</u> BMC - 0.39* (-2.11-1.43) BMD - 0.64* (-2.82-1.30) <u>$LS_{(L1-L4)}$</u> BMD - 0.41*(-2.53-1.84) **No CRT vs. CRT CCS (n=23 vs. n=10) >19 yrs, mean (range)** Height - 0.53* vs. - 1.65*† <u>TB</u> Bone area/height - 0.32 vs.- 1.13*† BMC/bone area - 0.49*vs. - 0.42 BMC - 0.64* vs. - 1.53*†	

			Bone area - 0.48 vs. - 1.61*† BMD - 0.67*vs. - 1.21* $\underline{LS_{TB}}$ BMC - 0.15 vs. - 0.96*† BMD - 0.43* vs. - 1.14*† $\underline{LS_{(L1-L4)}}$ BMD - 0.29 vs. - 0.68 **Estimates differences between CCS < or > 19 yrs (95% CI) after controlling for RT** *(stated all significant, but P's NR)* TB BMC reduced >19 yrs: 0.95 (95% CI 0.49-1.40) TB Bone area reduced >19 yrs: 0.87 (95% CI 0.36-1.37) TB BMD reduced >19 yrs: 0.79 (95% CI 0.33 to 1.24) Height/age reduced >19 yrs: 0.60 (95% CI 0.13 to 1.07) TB Bone area/height reduced >19 yrs: 1.04 (95% CI 0.60 to 1.48) Trend for difference TB BMC/area reduced >19 yrs: 0.43 (95% CI -0.07 to 0.93) **Risk factors for reduced TB BMC/bone area in CCS >19 yrs** After controlling for gender: - cumulative MTX dose (P=0.90) - cumulative GCs dose (P=0.22) - CRT (P=0.91) - age at diagnosis, age at follow-up, lenghts of follow-up, calcium intake, or endocrine defects at follow-up (P's 0.13 to 0.97) **Previous fractures (incl. during therapy):** % patients with fractures vs. % controls with fractures by ae group:	

			age 6-9 yrs: 33% (6/18) vs. 8% (7/84) **(P=0.02)** age 10-14 yrs: 22% (9/24) vs. 38% (31/139) age 15-18 yrs: 31% (8/20) vs. 40% (15/48) age 19-23 yrs: 39% (9/23) age 24-29 yrs: 67% (4/6) age 29+ yrs: 100% (4/4) n=5 had 2 fractures n=1 had 1 fracture **Conclusion:** Whole-body bone mass, but not whole body bone mass for bone area, was significantly reduced in survivors of childhood ALL because of shorter height and bone size after CRT. In pts older than 19, also BMC for bone area was significantly reduced. Reduced size-adjusted bone mass in young adults was not significantly related to previous therapy, calcium intake, or endocrine status at follow-up.	

Abbreviations: ALL-acute lymphoblastic leukemia; CCS=childhood cancer survivors; CI=confidence interval; CRT=cranial radiotherapy; BMC=bone mineral content; BMD=bone mineral density; BMT=bone marrow transplantation; DXA=dual-energy X-ray absorptiometry; GCs=glucocorticoids; GHD=growth hormone deficiency; LS=lumbar spine; MTX=methotrexate; NR=not reported; TB=total body; SCT=stem cell transplantation.

Who needs BMD surveillance?				
Pietila et al. Bone mineral density is reduced in brain tumour patients treated in childhood. Acta Pædiatrica, 2006; 95: 1291-1297.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Cross-sectional study Treatment era: NR Follow-up: 6.4 yrs (range 1.4-14.8 y) after off-therapy Follow –up era: 1998-2000	Type and number of non-participants: Five out of 80 brain CCS were excluded because the study protocol was considered too demanding for them. 75/80 brain CCS were invited; Reasons for no participation: 9/75 for long distance from the hospital; 2/75 wanted to forget about their disease; 1/75 parent's refusal due to demanding follow-up; 11/75 not interested, no specific reason. Out of the remaining 52 pts, 6 did not undergo DXA analyses due to cooperation, schedule/ technical problems. Type and number of participants: 52/75 (65.0% of CCS) participated; Final cohort: 46/52 (22 females, 24 males) aged from 3.8 to 28.7 yrs (mean 14.9 yrs) underwent a DXA analyses Diagnoses: Astrocytic tumour 25/46 Oligodendroglioma 1/46 Mixed glioma 3/46 Ependymoma 2/46 Choroid plexus tumour 2/46 Ganglioglioma 2/46	Surgery: -Resection 45/46 -Biopsy 1/46 Chemotherapy: 11/46 Steroids: -Dex: 5 to 8 days in conjunction with surgery -Dex 2-4 mg/m2 /day during RT for 4 -12 wks: most pts - GCs (dose and number of pts NR) occasionally during cytostatics; Radiotherapy: -Cranial 10/46 -Craniospinal 5/46 Combination of CRT and chemotherapy 9/46 SCT: no Limb amputation: no Other therapies: -Methotrexate 1/week for rheumatic disease: 1/46 -antiepileptic medication: 5/46	Outcome definitions: Total body bone mineral density (TBBMD) Z-score < -2.0: low bone mineral density Reference data: <20 yrs: age- and gender-specific TBBMD data *(based on ref 14)* >20 yrs (8 pts): reference values for 18-20-yrs-olds were used BMD measurement modality: Total body DXA (XR-26, software 2.5.2., Norland Corp., Fort Atkinson, WI, USA) for: -bone mineral density (TBBMD) -lean body mass (LBM) -fat mass (FM) *TBBMD Z-score differences were analyzed by analyses of covariance (ANCOVA), using LBM and Height SDS as covariates. ** Height SDS differences were analyzed by analyses of variance (ANOVA). **Results:** TBBMD Z-score <-2: 33% (n=15) TBBMD Z-score <-2 (n=15) vs. >-2 (n=41), mean (range): -Height SDS -0.4 (-4,6 - +2.6) vs. +0.2 (-2,6 - +2.8), p=0.151; -FM% 33.7 (13.4 -53.1) vs. 34.2 (8.3 -53.7), p=0.289 (ANCOVA);	Strengths: -Many risk factors are analyzed and differences in TBBMD Z-score between subgroups with different risk factors are corrected for LBM and height SDS; -Multivariable analyses are undertaken. Limitations: -Relative small cohort: different tumor diagnoses are combined together, that bear different risk factors for poor bone health (i.e. central endocrine defects vs. ataxia) -Final multivariable analyses model is not showed nor specified descriptively (not known which final covariates were tested). **Risk of bias** A. Selection bias: High risk Reason: 61.3% of the initial cohort underwent a DXA analyses. B. Attrition bias: Low risk Reason: cross-sectional study; no loss to FU. C. Detection bias: Low risk Reason: low BMD by DXA is a hard end-point, not susceptible to subjectivity of the assessor. Z-

	Embryonal tumour (medulloblastoma) 2/46 Germ-cell tumour 4/46 Meningioma 1/46 Craniopharyngioma 2/46 Pituitary adenoma 1/46 Tumour-like lesion (hamartoma) 1/46 Tumour grade I-II (n=36) >III (more malignant) (n=9) Tumour site -infratentorial n=22 -supratentorial n=24 After surgery: Hydrocephalus 26/46 →Shunt revisions 11/26 <u>Age at diagnosis:</u> Mean age at diagnosis (range), 7.4 yrs (0.5-15.5) <u>Age at follow-up:</u> Mean age at evaluation (range), 14.9 yrs (3.8 - 28.7) Younger than 18 yrs: 30/46 At least 1 hormone defect 8/46 >1 hormone defect 5/46 Pubertal phase: Prepubertal 14/46 Normal puberty 27/46 Precocius puberty 1 female at 7.8 yrs Hypogonadism (HH) 4/46 (age at therapy 12.9 and 15.7 yrs (girls), a boy at 15.9 y; GH therapy 2/46 *(9 pts GHD)*		-shunt revisions, median (range): 0 (0-8) vs. 0 (0-6), p=0.093; **<u>TBBMD Z-score, mean (range)</u>** - Total cohort: -1.7 (-5.7 - +0.6) ***<u>1.Based on brain CCS characteristics*</u>*** *<u>P's<0.2 are reported</u>* - Males (n=24) vs. females (n=22): -1.9 (-5.7 - +0.6) vs. -1.6 (-3.9 - -0.1), NS (p=0.109); - Tumour grade I-II (n=36) vs. >III (n=9): -1.6 (-5.7 - +0.6) Vs. -2.3 (-3.9 - -0.5), NS; - infratentorial (n=22) vs. supratentorial (n=24): -2.0 (-3.9 - +0.2) vs. -2.5 (-5.7 - +0.6), NS (p=0.221); - Hydrocephalus yes (n=26) vs. no (n=20): -2.1 (-5.7 - -0.1) vs. -1.3 (-3.4 - +0.6), NS (p=0.09); -CRT yes (n=15) vs. no (n=31): -1.7 (-3.9 - +0.1) vs. -1.7 (-5.7 - +0.6), NS; - CSRT (n=5) vs. CRT alone (n=10) vs. none (n=31): -3.0 (-3.9 - -1.8) vs. -1.1 (-2.4 - +0.1) vs. -1.7 (-5.7 - +0.6), NS (p=0.088); -Chemotherapy yes (n=11) vs. no (n=35): -2.2 (-3.9 - -0.3) vs. -1.6 (-5.7 - +0.6), NS; -Radiotherapy and Chemotherapy both (n=9) vs. either/or (n=8) vs. neither (n=29): -2.0 (-3.9 - -0.3) vs. -1.7 (-3.4 - +0.1) vs. -1.7 (-5.7 - +0.6), NS; -Severe surgery complications yes (n=12) vs. no (n=34): -1.9 (-5.7 - -0.2) vs. -1.7 (-3.9 - +0.6) NS;	score <-2 is a reasonable cut-point. <u>D. Confounding:</u> Low risk Reasons: in multiple regression analyses, important prognostic factors were taken adequately into account: both patients characteristics and treatment factors. Analyses were adjusted for height SDS, LBM age and Tanner stage, however without consideration of the fat mass impact. -in multiple regression analyses for TBBMD Z-score prediction only the significant covariate was cited, i.e. CSRT; no values for R^2, nor the list of the other prognostic factors/covariates considered in the models were specified. -In ANOVA analyses only LBM and height SDS were considered (fat mass not considered, nor BMI). An over-estimation of TBBMD by DXA could be expected as FM% is reported high.

	ACTHD 4/46 Thyroxin therapy 6/46 <u>Controls:</u> not available (for DXA ***ref 14***)		-Treatment at the time of puberty yes (n=13) vs. no (n=33): -1.4 (-5.7 - -0.2) vs. -1.9 (-3.9 - -0.1) NS; -Impaired mobility yes (n=12) vs. no (n=34): -2.0 (-5.7 - -0.5) vs. -1.6 (-3.9 - +0.6), NS. **<u>2.Based on medications, endocrine and metabolic characteristics of brain CCS *</u>** TBBMD Z-score values are shown if differences with P's <0.2 where found: -Thyroxin medication yes (n=4) vs. no (n=40): -2.4 (-5.7 - -0.5) vs. -1.6 (-3.5 - +0.6), NS p=0.198; -GHD yes (n=9) vs. no (n=37): -1.6 (-3.9 - -0.5) vs. -1.8 (-5.7 - +0.6), NS p=0.193; -Low dietary calcium intake yes (n=7) vs. no (n=39): -1.2 (-2.2 - +0.1) vs. -1.8 (-5.7 - +0.6), NS p=0.155; NS differences (P'2 >0.2) were found between the following groups: - Antiepileptic medications yes vs. no; -GCs replacement yes vs. no; -Sex hormone defect yes vs. no; -Hyperprolactinemia yes vs. no; -Hypomagnesemia yes vs. no; -25-hydroxycholecalciferol <38 nml/L yes vs. no; PTH ≤2.9 pmol/L vs. 2.9≤PTH≤4.9 pmol/L vs. ≥5 pmol/L. **Correlations between TBBMD Z-score and**: - hours of physical activity r=0.30 (n=40), p NR;	

			- age at evaluation r=0.14, NS; - age at close treatment r=0.15; - height SDS r=0.27, NS; - Tanner stage r=0.03, NS; -%FM r=-0.01, NS. **Multiple regression analyses for TBBMD Z-score prediction** (*the method for final regression model building is specified in the statistical analyses section, but no models are shown with final covariates included*) CSRT, R^2 NR, p=0.034 CRT, R^2 NR, p=0.100	

Abbreviations: C(S)RT=cranial(spinal) radiotherapy; BMD=bone mineral density; DXA=dual-energy X-ray absorptiometry; GHD=growth hormone deficiency; NR=not reported; NS=not significant; SCT=stem cell transplantation; SDS=standard deviation score.

Who needs BMD surveillance?				
Pluskiewicz et al. Skeletal status in survivors of childhood acute lymphoblastic leukemia assessed by quantitative ultrasound: a pilot cross-sectional study. Ultrasound in Med. & Biol., 2002, Vol. 28, No. 10, pp. 1279–1284.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Cross-sectional study Treatment era: 1991 to 2000 Cohort from Poland Follow-up: Mean 4.6 years ± 3.4 SD	Type and number of non-participants: NR Type and number of participants: 54 randomly selected survivors of childhood ALL Diagnoses: ALL The low-risk (LR) subgroup comprised 7 subjects (4 boys and 3 girls), moderate-risk (MR) subgroup comprised 26 subjects (9 boys and 17 girls) and in the high-risk (HR) subgroup were 21 subjects (10 boys and 11 girls). Age at diagnosis: Mean age at diagnosis was 5.5 ± 3.5 years (girls: 5.3 ±3.0; boys: 5.7 ± 4.1) Age at follow-up: Mean 13.0 ± 3.3 years. (girls: 12.3 ± 3.4; boys: 13.8 ± 3.0) Controls: 1020 healthy children (512 boys and 508 girls) without past fractures. Patients and controls did not differ significantly in regard to age, height, or weight.	Chemotherapy: Children with low or moderate risk were treated according to the Berlin–Frankfurt–Munster (BFM-95) program (Reiter et al. 1994), and subjects with high risk were treated using the New York program (Steinherz et al. 1986). Therapy consisted of several chemotherapeutics daunorubidomycin, endoxan, vincristine, PEG-asparaginase, prednisone, methotrexate, 6-thioguanine) Radiotherapy: In the HR subgroup, additionally cranial irradiation was performed (dose 18 to 24 Gy) SCT: NR Limb amputation: None Other: -	Outcome definitions: Measures amplitude dependent speed of sound (**Ad-SoS, m/s**) BMD measurement modality: Quantitative ultrasound (US) at right (dominant) hand second to fifth phalanges using DBM Sonic 1200 (IGEA, Carpi, Italy) Results: No fractures due to minimal trauma occurred. Mean Ad-SoS values (2018 ±73 m/s in patients and 2003 ±80 m/s in controls) did not differ significantly between patients and controls. In the moderate- and high-risk subgroups, Ad-SoS values tended to be lower than in the low-risk subgroup, but differences did not achieve significance. Ad-SoS correlated significantly with age in patients (r value ranged from 0.63 to 0.77, $p < 0.01$) and controls (r value ranged from 0.79 to 0.84, $p < 0.0001$) In multiple forward regression analysis, the following equation was obtained: Ad-SoS(m/s) = 1878	Strengths: -ALL patients alone -All measurements were carried out by the same operator Limitations: -Sample size -Technology operator dependent **Risk of bias** A. Selection bias: Unclear Reason: no data on non-participants B. Attrition bias: Low risk Reason: all included patients underwent QUS. C. Detection bias: Low risk Reason: All measurements were carried out by the same operator. Precision was based on 75 measurements made in each of 15 healthy children (8 boys and 7 girls) by the same operator. Root mean square (RMS)_CV% was 0.43% D. Confounding: Low risk Reason: adjustment for sex, height, weight and Tanner stage

			(m/s) + 11.4 x age at the study (y) + 4.0 x period after therapy completion (y) - 9.5 x duration of the therapy (y).	not needed since variables were comparable in pts and controls

Abbreviations: AD-SoS=amplitude dependent speed of sound; ALL=acute lymphoblastic leukemia; NR=not reported; QUS=quantitative ultrasound; SCT=stem cell transplantation; SD=standard deviation.

Who needs BMD surveillance?				
Polgreen et al. Modifiable risk factors associated with bone deficits in childhood cancer survivors. BMC pediatr. 2012;12:40.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Cross-sectional study Treatment era: NR Follow-up: Average time since treatment (±SE) 10.1 ± 0.2 years (range 4.3-17.8)	Type and number of non-participants: Eligible cohort 723 CCS. 66 were not able to be contacted; of the remaining 657: 319 (49%) agreed to participate. There were no significant differences in important variables between CCS participants and non-participants Type and number of participants: 319 CCS in remission and surviving ≥ 5 yrs after cancer diagnosis Diagnoses: Leukemia 110 (34.5%), Solid tumors 127 (39.8%), CNS tumors 82 (25.7%) Age at diagnosis: Mean(±SE) 4.5 ± 0.2 years (range 0-12.5) Age at follow-up: Mean(±SE) 14.5 ± 0.1 years (range 9-18) Controls: 208 healthy siblings of CCS (97 females) Age at follow-up: 13.7 ± 0.2 for controls	Corticosteroid: 134/319 (42.0%); median dose: 7,520 mg/kg/day prednisone equivalents (range 200-15,250) Radiotherapy: 74/319 (23.2%); RT field: cranial (CNS) 31 (9.7%), other 43 (13.5%); Median RT dose: cranial (CNS) 2370 cGY (range 1800-5580) SCT: 0/319 (0%)	Outcome definitions: Low BMD: Z-score ≤-1 Very low BMD: Z-score ≤-2 BMD measurement modality: DXA (Lunar) of the total body (including head) and lumbar spine (L2-L4) Low BMD: Prevalence TB BMD CCS 11% vs. controls 3%, OR* 3.3, 95%CI: 1.4-7.8, p=0.007. Prevalence LS BMD CCS 23% vs. controls 13%, OR* 1.7,95%CI 1.0-2.7, p=0.003. Very low BMD: Prevalence CCS TB 7/319 (2.3%), LS 11/319 (3.5%); controls TB 0/208 (0%), LS 0/208 (0%) After adjusting for height SDS there was no difference in whole body or lumbar spine BMD Z-scores. Risk factors low TB BMD: **Model 1 (without height SDS)*[1]** Hypogonadism (yes vs. no), OR 9.1, 95%CI 3.3-25.3, **p<0.001**; Hypothyroidism, IGF-1 SDS, NS **Model 1 (with height SDS)*[1]** Hypogonadism (yes vs. no), OR 11.2, 95%CI 3.7-35.8, **p<0.001**; Hypothyroidism, IGF-1 SDS, NS **Model 2**	Strengths: -Large study sample -Long follow-up period -CCS versus controls Limitations: -Only risk factors for low BMD were assessed **Risk of bias** A. Selection bias: low risk Reason: the study group consisted of less than 75% of the original cohort, but there were no significant differences in important variables between CCS participants and non-participants B. Attrition bias: Low risk Reason: the outcome was assessed for more than 75% of the study group C. Detection bias: Low risk Reason: low BMD by DXA is a hard end-point, not susceptible to subjectivity of the assessor D. Confounding: Low risk Reason: all important prognostic factors were taken adequately into account. Most analyses were not adjusted for height SDS, but height was normal among the CCS, so a significant

			Age at study (>16 yrs vs. ≤16 yrs), OR 2.5, 95% CI 0.8-8.1, p=0.125; Ethnicity (white non-Hispanic vs. other), OR 1.7, 95%CI 0.5-6.9, p=0.420; Tanner stage 1-5 (one stage increase), OR 2.2, 95%CI 1.3-3.8, **p=0.006;** Sex (male vs. female), OR 2.6, 0.8-10.0, p=0.137; Percent body fat (1% increase), OR 0.95, 95%CI 0.9-1.0, p=0.070; Lean body mass (1kg increase), OR 0.85, 95%CI 0.8-0.9, **p<0.001**; Years since diagnosis (>9.0 yrs vs. 5-9 yrs), OR 2.3, 95%CI 0.9-6.3, p=0.080; IL-6 (>2.5 ng/dl vs. ≤2.5 ng/dl), OR 4.4, 95%CI 1.5-12.9, p=0.007; Screen time (≥2h/day vs. 0-1h/day), OR 4.1, 95%CI 1.3-18.6, **p=0.033;** Adiponectin, physical activity score, NS M**odel 3*** Protein (p=0.055); Milk, fruits/vegetable and daily total caloric intake, NS **Model 4*** Protein, vitamin D, zinc, calcium, omega-3 and daily total caloric intake, NS **Model 5** Age at study (>16 yrs vs. ≤16 yrs), OR 2.0, 95%CI 0.8-5.3, p=0.177; Ethnicity (white non-Hispanic vs. other), OR 0.9, 95%CI 0.3-2.9, p=0.800;	underestimation of BMD by DXA was not expected

			Tanner stage 1-5 (one stage increase), OR 0.9, 95%CI 0.6-1.4, p=0.666; Sex (male vs. female), OR 1.2, 95%CI 0.5-2.5, p=0.704; Radiation exposure (CNS vs. none), OR 7.9; 95%CI 3.0-20.8, **p<0.001**; Radiation exposure (other vs. none), OR 5.7, 95%CI 2.3-13.9, **p<0.001;** Steroid exposure, NS <u>Risk factors low LS BMD:</u> **Model 1 (without height SDS)*[1]** Hypogonadism (yes vs. no), OR 4.4, 95%CI 1.7-11.4, **p=0.002**; Hypothyroidism (yes vs. no), OR 2.9, 95%CI 1.3-6.6, **p=0.012**; IGF-1 SDS, NS **Model 1 (with height SDS)*[1]** Hypogonadism (yes vs. no), OR 4.3, 95%CI 1.6-11.8, **p=0.003**; Hypothyroidism (yes vs. no), OR 2.8, 95%CI 1.2-6.7, **p=0.017** IGF-1 SDS, NS **Model 2** Age at study (1 yr increase), OR 2.2, 95%CI 1.7-3.0**, p<0.001**; Ethnicity (white non-Hispanic vs. other), OR 2.6, 95%CI 0.9-9.1, p=0.104; Tanner stage 1-5 (one stage increase), OR 0.4, 0.2-0.7, **p<0.001**; Sex (male vs. female), OR 1.6, 95%CI 0.7-3.4, p=0.270; Lean body mass (≤35kg vs. >35kg), OR 4.1, 95%CI 1.8-9.6, **p<0.001**; Percent body fat (1% increase), OR 0.97, 0.94-1.0, 0.088;	

			Physical activity score (1U increase), OR 0.99, 95%CI 0.99-1.0, **p=0.042**; Years since diagnosis, IL-6, adiponectin and screen time, NS M**odel 3*** Protein, milk, fruits/vegetable and daily total caloric intake, NS **Model 4*** Protein, vitamin D, zinc, calcium, omega-3 and daily total caloric intake, NS **Model 5** Age at study (>16 yrs vs. ≤16 yrs), OR 3.1, 95%CI 1.4-7.1, **p=0.006**; Ethnicity (white non-Hispanic vs. other), OR 2.2, 95%CI 0.9-6.7, p=0.135; Tanner stage 1-5 (one stage increase), OR 0.7, 95%CI 0.5-0.9, **p=0.015**; Sex (male vs. female), OR 1.1; 95%CI 0.6-1.9, p=0.732; Radiation exposure (CNS vs. none), OR 2.5; 95%CI 1.0-5.7**, p=0.040**; Radiation exposure (other vs. none), OR 2.4; 95%CI 1.0-5.5, **p=0.041;** Steroid exposure (yes vs. no), OR 1.9, 95%CI 1.0-3.5**, p=0.042**	

Abbreviations: BMD=bone mineral density; CCS=childhood cancer survivors; CNS=central nervous system; DXA=dual-energy X-ray absorptiometry; LS=lumbar spine; NS=not significant; OR=odds ratio; SCT=stem cell transplantation; SDS=standard deviation score; SE=standard error; TB=total body.

Who needs BMD surveillance?				
Remes TM et al. Bone mineral density is compromised in very long-term survivors of irradiated childhood brain tumor. Acta Oncologica. 2018; 57:665-674.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Cross-sectional study Treatment era: Finland Survivors 1970-2008 Follow-up: Average time since cessation of tumor therapy (mean±SD): 18.9 ± 6.1 years	Type and number of non-participants: Eligible cohort of 127 irradiated childhood brain tumor survivors. 40 refused to participate 13 were not reached At the time of the study there were no significant differences in important variables (sex, age at diagnosis or at the time of study, time since treatment, type of treatment) between participants and non-participants (total 53, 41.7%). Type and number of participants: 74 irradiated childhood brain tumor survivors in remission and surviving ≥ 5 yrs since the cessation of therapy Diagnoses NR Location of the tumor: Posterior fossa 34 (46%) Middle brain 22 (29.7%) Hemispheric 12 (16.2%) Intraventricular 2 (2.7%) Pons 4 (5.4%) Age at diagnosis: Mean(±SD) 8.3 (±4.3) years Age at follow-up: Mean(±SD) 28.4 (±6.8) years Controls: NA	Chemotherapy: Yes: 47 (63.5%) No: 27 (36.5%) Most commonly used protocols: -eight-in-one protocol *[ref 20,21]* -three-drug protocol (involving cisplatin, vincristine, and lomustine for medulloblastoma) *[ref 22,23]* Radiotherapy: Local irradiation: 39 (52.7%) Craniospinal with local boost to the tumor bed: 30 (40.5%) Cranial with local boost to the tumor bed: 3 (4.1%) Stereotactic: 2 (2.7%) SCT:NR Limb amputation: NR Other: operation in 95.9% -partial resection: 32 (43.2%) -total resection: 29 (39.%2) -biopsy: 10 (13.5%) -no operation: 3 (4.1%) Reoperation -yes 19 (26.8%) -no 52 (73.2%) Ventriculoperiotoneal shunt -yes 44 (59.5%) -no 30 (40.5%)	Outcome definitions: Low BMD: LS BMD and/or FN BMD and/or Total Hip Z-score ≤-2.0 BMD measurement modality: DXA (Lunar Prodigy in Oulu; Lunar Prodigy Advance in Kuopio; Lunar iDXA in Tampere; Hologic Discovery A in Helsinki; Hologic QDR 4500 C in Turku) of the LS (L1-L4) and four femoral sites (femoral necks and total hips) Results: Low BMD: 23.6% of the patients had low sex- and age- normalized Z-scores (NR if at one or at all DXA measurement sites). BMD total cohort, mean (SD): LS BMD -0.83 (1.15) Z-score FN BMD: -right: -0.91 (0.93) Z-score left: -0.82 (1.93) Z-score Hip BMD: -right: -0.77 (1.08) Z-score -left: -0.69 (1.16) Z-score **Compared groups [student T-test]: mean difference, 95% CI, p** Males vs. females -lower LS BMD Z-score: 0.57, 95% CI 0.01–1.12, p<0.05; -lower right FN: 0.50, 95% CI 0.06–0.95, P=0.028;	Strengths: -Long follow up time -Robust statistics -Data on the prevalence of fractures of the long bones. Limitations: -Lack of a control group; -Use of different DXA techniques in different hospitals (data were not transformed in order to convert Hologic data to Lunar or viceversa); -No informations about hormone defects yes/no, type of hormone defects and eventual substitutive hormonal treatment doses are provided (high risk cohort). **Risk of bias** A. Selection bias: High risk Reason: although no significant differences were found in all the important variables considered between participants and no participants, the study group consisted of only 58% of the original cohort of cancer survivors which is considered too small. B. Attrition bias: Low risk Reason: the outcome was assessed for 98.6% of the study group

			-lower left FN 0.54, 95% CI (0.04–1.03, P=0.033. -trend towards a lower BMI in males (p=0.055) <u>Previous fractures in long bones (n=16) vs. no fractures (n=56)</u> -lower right FN BMD Z-score: -0.55, 95% CI -1.07 – -0.04, p=0.036; -lower total right hip BMD Z-score: -0.70, 95% CI -1.29 – -0.10, p=0.023; -lower total left hip BMD Z-score: -0.75, 95% CI -1.40 – -0.10, p=0.025; -lower LS BMD Z-score: -0.71, 95% CI -1.35 – -0.08, p=0.028. <u>Infratentorial tumor (n=38) vs. supratentorial tumors (n=34):</u> -lower left FN BMD Z-score: -0.63, 95% CI -1.10 – -0.16, p=0.009; -lower total right hip BMD Z-score: -0.64, 95% CI -1.15 – -0.14, p=0.013; -lower total left hip BMD Z-score: -0.69, 95% CI -1.22 – -0.69, p=0.011; <u>CSRT (n=29) vs no CSRT (n=43):</u> -lower total left hip BMD Z-score: 0.66, 95% CI 0.12– 1.20, p=0.017; <u>ventriculoperitoneal shunt (n=43) vs. no ventriculoperitoneal (n=29):</u> -lower right FN BMD Z-score: -0.58, 95% CI -1.01 – -0.15, p=0.009; -lower left FN BMD Z-score: -0.55, 95% CI -1.03 – -0.07, p=0.026;	<u>C. Detection bias:</u> Unclear Reason: low when considered BMD Z-score a hard endpoint; unclear as data seem not transformed in order to convert Hologic data to Lunar or viceversa. <u>D. Confounding:</u> Low risk Reason: extensive univariate, stepwise regression analyses and multivariate analyses were undertaken; sex, BMI, tumor, cancer treatment and hormone variables were taken adequately into account.

			-lower total right hip BMD Z-score: -0.68, 95% CI -1.18 – -0.18, p=0.009; -lower total left hip BMD Z-score: -0.55, 95% CI -1.10 – -0.01, p=0.047. No difference between pituitary/hypothalamus location yes/no, chemotherapy yes/no, high impact sport yes/no. **Univariate linear regression analyses (**β, 95%CI, p) Age at diagnosis positive association with: -right FN BMD Z-score: β 0.05; 95% CI 0.002– 0.10, p=044; -left FN BMD Z-score: β 0.06; 95% CI 95% 0.001–0.11, P=0.045; Age at the follow-up visit positive association with LS BMD Z-score: β 0.06; 95% CI 0.02–0.10, p=0.002; Follow-up time: positive association with LS BMD Z-score: β 0.05; 95% CI 0.004–0.09, p=0.031; BMI: positive association with -BMD Z-score at all DXA sites (β between 0.06 and 0.010, 95%CI between 0.02 and 0.014, all p's<0.01; FSH negative association with: -bilateral FN BMD Z-scores and left hip BMD Z-score in females (β between -0.09 and -0.13, 95%CI between -0.23 and -0.003, p's<0.05); LH negative association with: -LS BMD Z-score in females (β-0.07, 95%CI -0.14 - -0.001, p=0.46);	

			Ft4 negative association with: -left FN BMD Z-score, bilateral total hip BMD Z-score and LS BMD Z-score (β between -0.08 and -0.10, 95% CI between -0.19 and -0.001, all p's<0.05); TSH, IGF-1, IGFBP3, Estradiol, testosterone, cumulative GCs dose in prednisolone during brain tumor treatment were not associated to BMD Z-scores, nor FSH and LH levels in males. The number of patients on hormonal substitutive therapy, nor their doses are reported. Replacement therapy for thyroid, growth hormone, or gonadal dysfunction did not increase the BMD Z-scores (data NR). **Prediction model low BMD:** [Multivariable regression analyses for BMD Z-scores] I model (candidate variables tested: ventriculoperitoneal shunt, cranial irradiation with or without CSRT, chemotherapy and supratentorial or infratentorial tumor, BMI, dose of radiation to the thalamic area, and total dose of GCs during the tumor treatment) 1) Femoral necks and total hips **Ventriculoperitoneal shunt** -right FN β 0.73 (95% CI 0.31-1.14), p=0.001; - left FN β 0.60 ((95% CI 0.12-1.07), p=0.015;	

			- right total hip: β 0.70 ((95% CI 0.24-1.14), p=0.003; - left total hip: β 0.62 ((95% CI 0.12-1.11), p=0.015; **BMI** -right FN β 0.07 ((95% CI 0.04-0.11), p<0.001; -left FN β 0.08 ((95% CI 0.04-0.12), p<0.001; -right total hip: β 0.09 ((95% CI 0.05-0.13), p<0.001; -left total hip: β 0.10 ((95% CI 0.06-0.15), p<0.001; <u>2) Lumbar spine</u> **BMI** β 0.07 ((95% CI 0.02-0.11), p=0.006 <u>II model (candidate variables tested: IGF1; IGFBP3; fT4, testosterone and BMI)</u> <u>Femoral necks and total hips</u> **<u>BMI</u>** -left FN β 0.09 (95% CI 0.03-0.15), p=0.005; -right total hip: β 0.08 (95% CI 0.03-0.14), p=0.003; -left total hip: β 0.11 (95% CI 0.05-0.17), p<0.001; **<u>Testosterone</u>** -left FN β 0.05 (95% CI 0.007-0.009), p=0.025; -right total hip: β 0.05 (95% CI 0.009-0.09), p=0.018; -left total hip: β 0.06 (95% CI 0.02-0.10), p=0.007.	

Abbreviations: BMD=bone mineral density; BMI=body mass index; CI=confidence interval; CSRT=craniospinal radiotherapy; FN=femoral neck; LS=lumbar spine; NA=not applicable; NR=not reported; SCT=stem cell transplantation; SD=standard deviation.

Who needs BMD surveillance?				
Ruza E et al. Bone mineral density and bone metabolism in children treated for bone sarcomas. Pediatr Res. 2006; 59:866-871.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Cross-sectional study Treatment era: NR Follow-up: Mean duration of remission was 6.12 years (SD 3.67) in patients with osteosarcomas and 6.11 years (SD 3.73) for Ewing's sarcoma patients	Type and number of non-participants: 12 patients with osteosarcoma and 4 with Ewing's sarcoma were excluded because they had other diseases or they have incomplete information about treatment protocol, evolution and/or complications Type and number of participants: 59 patients with osteosarcoma and 36 with Ewing's sarcoma. 38 patients (20 females, 18 males) with osteosarcoma and 25 (11 females, 14 males) with Ewing's sarcoma were evaluated by DXA 59 patients with osteosarcoma and 36 with Ewing's sarcoma were evaluated by blood tests Diagnoses: 59 patients with osteosarcoma 36 with Ewing's sarcoma Age at diagnosis of patients that underwent DXA: Osteosarcoma median (IQR) 13.79 yrs (11.58;15.08); Ewing's sarcoma mean (SD) 12.06 yrs (3.78) Age at follow-up: Osteosarcoma 20.65 (4.42); Ewing's sarcoma 19.13 (4.20)	Chemotherapy: In Osteosarcoma MTX median (IRQ): 62.77 g/m2 (41.15;90.10) Cyclophosphamide (mean (SD): 4.47 g/m2 (2.20) Bleomicin (mean (SD): 100.10 mg/m2 (45.60) Cisplatin (mean (SD): 477.60 mg/m2 (131.70) Adriamycin (mean (SD): 424.21 mg/m2 (114.37) Actinomycin D (mean (SD) (mg/m2) 4.96 (2.06) Vincristine 6.43 mg/m2 (3.12;8.49) In Ewing's sarcoma MTX median (IQR): 0.23 g/m2 (0.21; 0.28) Cyclophosphamide (mean (SD): 17.71 g/m2 (14.66;21.78) Bleomicin (mean (SD): 173.95 mg/m2 (56.94) Adriamycin (mean (SD): 432.08 mg/m2 (134.03) Actinomycin D: (mean (SD) (mg/m2) 9.20 (2.91) Vincristine median (IQR): 21.49 mg/m2 (17.79;32.18) Limb amputation: 3 after fractures	Outcome definitions: Low BMD: BMD Z-score ≤-2.0; considered also BMD between -1 and -2 Z-score. Areal bone mineral density (areal-BMD) BMD measurement modality: DXA (Hologic QDR 4500W v9.8 Elite, Woltham, MA) of the LS (lumbar spine, L2-L4) and the FN (femoral neck; right side; left if primary location was on the right). All data were transformed based on *ref 14* in order to convert Hologic data to Lunar data (reference Spanish population available for Lunar). Results: Low LS BMD: 9.7%; Low FN BMD: 17.5% LS BMD between -1 and -2 Z-score: 33.9% FN BMD between -1 and -2 Z-score: 25.4% BMD Lunar (Z-score) compared to Spanish reference population: Osteosarcoma LS BMD: **-0.76 (0.96) p < 0.001** Females **-0.46 (0.82) p = 0.020** Males: **-1.11 (1.02) p < 0.001** FN BMD: **-0.88 (1.10) p < 0.001**	Strengths: -Homogeneous group of cancer diagnosis (bone sarcomas) Limitations: Small number of patients; Heterogeneity of treatments; Occurrence of clinical complications; different databases for calculation of BMD Z-scores; Flow chart of the study design not included. **Risk of bias** A. Selection bias: High risk Reason: the study group analyzed by DXA consisted of 66.3% of the initial cohort B. Attrition bias: High risk Reason: the outcome (DXA) was assessed for less than 75% of the study group C. Detection bias: Low risk Reason: BMD is a hard endpoint D. Confounding: Low risk Reason: sex, height, weight and BMI were taken into account, together with chemotherapy

	Remission time: Osteosarcoma 6.12 (3.67); Ewing's sarcoma 6.11 (3.73) <u>Controls:</u> NA		Females: **-0.85 (1.20) p = 0.005** Males: **-0.91 (1.01) p = 0.001** Ewing´s sarcoma LS BMD: **- 0.84 (1.05) p = 0.001** Females: -0.74 (1.20) p = 0.068 Males: **-0.92 (0.95) p = 0.003** FN BMD: **-0.76 (1.15) p = 0.003** Females: **-0.90 (1.14) p = 0.025** Males: -0.64 (1.18) p = 0.063 Fractures: 17 patients (for tumor location or therapy). No differences in DXA bone parameters (data NR). *Markers of bone metabolism were throughout lower than reference values* Univariate analyses for areal BMD prediction: At the LS: Months in clinical remission: p=0-017 At the FN: duration of hospitalization negative trend: p=0.065 **<u>Multivariate prediction model low BMD:</u>** **<u>1)Lumbar BMD**</u>** **Sex** (p< 0.002 for areal BMD, p=0.12 for BMD Z-score) BMD higher in women than in men **Age at diagnosis** (p=0.035 for areal BMD). BMD increasing with older age **Weight** (p=0.016 for areal BMD). Positive effect **BMI** (p=0.038 for BMD Z-score). Positive effect	regimens. However, it is not entirely clear how the models were exactly created.

			Age at DXA (p<0.001 for BMD Z-score). BMD increasing with older ages **<u>2) Femoral BMD**</u>** **Weight** (p=0.001 for areal BMD). Positive effect **BMI** (p=0.001 for BMD Z-score). Positive effect **Vincristine dose** (p=0.03 for areal BMD). Negative effect <u>**it is not clear if all the variables were tested together</u>	

Abbreviations: BMD=bone mineral density; BMI=body mass index; CSRT=craniospinal radiotherapy; FN=femoral neck; IQR=interquartile range; LS=lumbar spine; MTX=methotrexate; NA=not applicable; NR=not reported; SCT=stem cell transplantation; SD=standard deviation.

Who needs BMD surveillance?				
Sawicka-Zukowska et al. Does Q223R Polymorphism of Leptin Receptor Influence on Anthropometric Parameters and Bone Density in Childhood Cancer Survivors?. International Journal of Endocrinology, Volume 2013, Article ID 805312, 9 pages.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Cross-sectional study Treatment era: 2000-2006 Follow-up: Average age at the beginning of treatment was 6.3 +/- 3.7 years, post-treated was 8.9 +/- 3.5 years, and at the time of analysis was 15.4 +/- 2.6 years Not specifically stated, but the average time at the time of analysis post treatment completion would be 6.6 years	Type and number of non-participants: NR Type and number of participants: 74 cancer survivors (42M) > age 10 years Diagnoses: ALL n = 64 Lymphomas n = 10 Age at diagnosis: 6.292 ± 3.685 Age at follow-up: 15.473 ± 2.643 Controls: Hospitalized for non-neoplastic disease. Non-obese N=51 (34M) 14.77 ± 3.643 > age 10 years	Chemotherapy: NR Radiotherapy: N=16 (5F) cranial RT (12Gy x13, 18Gy x3) SCT: NR Limb amputation: NR Other:	Outcome definitions: The study sought to evaluate correlations between serum leptin concentrations, Q223R (leptin receptor gene), anthropomorphic parameters and BMD by DXA BMD measurement modality: DXA (GE-Lunar) measurement of BMD and BMC, fat, and lean tissue. Results: BMD total Z-score -0.0132 BMD spine Z-score -0.2610 BMC Z-score 0.3244 No correlations between serum leptin concentrations and anthropometric parameters nor BMD Serum leptin concentrations significantly lower in cancer survivors compared with controls; Q223R polymorphism of leptin receptor not associated with higher leptin levels, BMI, BMD, body fat or lean tissue.	Strengths: -None identified Limitations: -Small patient numbers -Wide age range -Treatment regimens not documented **Risk of bias** A. Selection bias: Unclear Reason: small cohort, and selection of cases not well defined in manuscript. B. Attrition bias: Unclear Reason: unclear if study cohort is part of a larger cohort C. Detection bias: Low risk Reason: low risk as simple cross-sectional data D. Confounding: Low risk Reason: it appears that confounding variables were evaluated

Abbreviations: ALL=acute lymphoblastic leukemia; BMC=bone mineral content; BMD=bone mineral density; BMI=body mass index; DXA=dual-energy X-ray absorptiometry; NR=not reported; RT=radiotherapy; SCT=stem cell transplantation.

Who needs BMD surveillance?				
Siegel et al. Risk factors and surveillance for reduced bone mineral density in pediatric cancer survivors, Pediatr Blood Cancer. 2017;64:e26488.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Retrospective cross-sectional study, single center Treatment era: Survivors seen between March 1, 2003 to July 1, 2010 Follow-up: Mean (SD) 5.4 +/- 4.3years	Type and number of non-participants: 58 no DXA as (1) lack of insurance approval (2) missed DXA appointment (3) evaluation with different methodology at an outside institution Type and number of participants: 475 pediatric blood cancer and non CNS solid tumor survivors At least 1 year removed from therapy. Aged 6–21 DXA scans completed >1 year after end of therapy Diagnoses: ALL n=283 AML n=35 Hodgkin n=29 NHL n=68 Neuroblastoma n=22 Renal tumour n=6 Sarcoma n=29 Other n=3 Age at diagnosis: Mean (SD) 6.3 +/- 4.2 years Age at follow-up: Mean (SD) 13.8 +/- 4.0 years Controls: DXA Z-score adjusted for age, gender, and ethnicity from NHANES data	Chemotherapy: Steroids n=396 (83.4%) Methotrexate n=366 (77.2%) Radiotherapy: Cranial / craniospinal n=63 (13.3%) TBI n=47 (9.9%) SCT: n=85 (17.9%) Limb amputation: NR Other: Dexamethasone n=231 Prednisolone n=288	Outcome definitions: Low BMD defined as ≤–2.0 Mild BMD deficit defined as Zscore ≤–1.0 but >–2.0. BMD measurement modality: BMD assessed using Lunar Prodigy Advance DXA system (General Electric Co, Fairfield, CT) based upon COG -LTFU guidelines Results: Mean DXA Z-score –0.1 +/- 1.2 for whole body and lumbar spine. DXA Z-scores ≤–1.0 but >-2.0 at whole body or LS 100 (21.1%); at LS 73 (15.4%); at whole body 85(17.9%) 8.2% (39/475) low BMD (Z-score ≤–2.0) at whole body or LS; 7.4% (35/474) at LS; and 4.0% (19/475) for whole body. For leukemia or lymphoma survivors 6.5% (27 of 415) had low BMD vs. 20.0% (12 of 60) of solid tumors survivors. Multivariate analysis associated low BMD with (1) male gender (OR 3.4, 95% CI, 1.3–9.0) (2) exposure to TBI, cranial, or craniospinal radiation (OR 5.2, 95% CI, 1.8–14.9), (3) gonadal dysfunction (OR 4.3, 95% CI, 1.4–13.0).	Strengths: -Large cohort -One DXA machine Limitations: -Included only patients who had DXA scan as part of their long-term follow-up - ?selected cohort (per current guidelines) -No data on n=58 **Risk of bias** A. Selection bias: Low risk Reason: although missing data in n=58 demographics of those scanned and not scanned are similar. B. Attrition bias: Low risk Reason: >80% of cohort underwent DXA C. Detection bias: Low risk Reason: low risk as simple cross-sectional data D. Confounding: High risk Reason: DXA values not adjusted for height.

			No association with methotrexate exposure Hematopoietic cell transplant (HCT) reduced risk of low BMD (OR 0.2, 95% CI, 0.1–0.9)	

Abbreviations: ALL=acute lymphoblastic leukemia; AML=acute myeloid leukemia; BMD=bone mineral density; CNS=central nervous system; COG=children's oncology group; LS=lumbar spine; NHL=non-Hodgkin's lymphoma; OR=odds ratio; SCT=stem cell transplantation; SD=standard deviation; TBI=total body irradiation.

Who needs BMD surveillance?				
Siviero -Miachon et al. Visfatin is a positive predictor of bone mineral density in young survivors of acute lymphocytic leukemia. J Bone Miner Metab (2017) 35:73–82.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Cross-sectional study Treatment era: May 1991 to June 2003 Follow-up: Mean (SD) 8.5+/-3.5 yrs	Type and number of non-participants: NR Type and number of participants: 56 (32F) survivors aged 15 - 24 years Randomly selected sample >2years In remission Completed pubertal development Diagnoses: ALL Age at diagnosis: Mean (SD) 7.5+/-3.9 yrs Age at follow-up: Mean (SD) 18.6+/-2.5 yrs Controls: NHANES (1999 to 2004)	Chemotherapy: GBTLI protocol Radiotherapy: 44.6% (25) received cranial radiotherapy (18Gy, 76%;24 Gy, 24%) at age 8.0+/-4.0 yrs Spinal RT x 1 24Gy Testicular RT x 2 SCT: SCT was an exclusion criterion Limb amputation: Other:	Outcome definitions: L1–L4 and total body BMD Z-scores stratified into groups: (1) Low BMD for chronological age, Z-scores < or equal to −2.0. (2) BMD within the inferior limit of normality, comprising Z-scores −1.0 and −2.0. (3) Normal BMD, regarding Z-scores > or equal to −1.0. BMD measurement modality: L1–L4 BMD, according to sex, age, and ethnicity/race (Hologic, 2005), and total body BMD, based on data from the NHANES (1999 to 2004), evaluated by DXA (Hologic Discovery 4500). Results: L1–L4 and total body BMD positively correlated with visfatin (p =0.007). No correlation between LS BMD and XRT. Lean mass index positively correlated, while waist-to-height ratio negatively correlated with LS BMD (p < 0.010). Total body BMD correlated positively with visfatin and lean mass index; and negatively with waist ratio. Low BMD for chronological age was detected in 5.4 % of patients	Strengths: -None identified Limitations: -Details of random selection of patients not stated -Small cohort **Risk of bias** A. Selection bias: High risk Reason: unclear how patients were selected to enter the study B. Attrition bias: Low risk Reason: DXA in all patients within selected cohort C. Detection bias: Low risk Reason: not blinded, but data purely observational. D. Confounding: Low risk Reason: data corrected for confounders except height (height may have an impact but looking at the age it is not a huge thing).

			in total body, and 8.9 % at the lumbar spine. BMD -2.0 to -1.0 detected in 22(39.3%) at LS and 17(30.4%) at total body. Mean LS and total body BMD Z-score in irradiated patients – 0.78(+/-1.04) & -0.89(+/-1.0) respectively. In non-irradiated patients -0.79(+/-0.91) & -0.37(+/-0.79) respectively.	

Abbreviations: ALL=acute lymphoblastic leukemia; BMD=bone mineral density; DXA=dual-energy X-ray absorptiometry; LS=lumbar spine; NR=not reported; RT=radiotherapy; SCT=stem cell transplantion; SD=standard deviation.

Who needs BMD surveillance?				
Sloof et al. The Impact of Physical Activity on the Health of Young Adult Survivors of Childhood Cancer: An Exploratory Analysis. J Adolesc Young Adult Oncol. 2019 Oct;8(5):602-609.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Retrospective cohort study Treatment era: NR Follow-up: NR	Type and number of non-participants: NR Type and number of participants: n=253, patients aged 18-39 years enrolled in the aftercare program at McMaster, diagnosed with malignancies before the age of 18, who were treated at McMaster Children's Hospital, Hamilton, Canada, or who were transferred from another pediatric cancer center, and subsequently enrolled in the AfterCare program and who have attended a follow-up appointment in the last 5 years. Neuro-oncology patients and those patients without complete treatment information were excluded. n=240 had complete data. Diagnoses: ALL: n=118 (46.6%) AML: n=11 (4.4%) Ewing sarcoma: n=9 (3.6%) Germ cell tumor: n=4 (1.6%) Hodgkin disease: n=36 (14.2%) Hepatoblastoma: n=3 (1.2%) Neuroblastoma: n=10 (4.0%) Non-Hodgkin lymphoma n=26 (10.3%) Osteosarcoma: n=8 (3.2%) Rhabdomyosarcoma: n=5 (2.0%)	Chemotherapy: NR Radiotherapy: Radiation therapy dose ≥1500 cGy (any site) n=120 (47.4%) Cranial radiotherapy 91 (36.0) SCT: 0% Limb amputation: 0% Other: -	Outcome definitions: Osteopenia was defined as a z-score between -1.0 and -2.5, and osteoporotic as a z-score <-2.5 One category for analysis: osteopenic/osteoporotic: Z-score <-1.0. BMD measurement modality: DXA (site and manufacturer not reported) Results: BMD Z-score <-1: 25.4% *Risk factors of low BMD* Multivariable model (BMD Z-score <-1): Age at diagnosis <10 years: OR 1.39, 95%CI 0.68–2.82, p=0.37 Female: OR 1.64, 95%CI 0.80–3.35, p=0.18 Any physical activity OR 0.38, 95%CI 0.16–0.88, **p=0.03** No smoking: OR 0.60, 95%CI 0.21–1.69, p=0.34 Ideal BMI: OR 2.62, 95%CI 1.22–5.62, **p=0.01** Normal blood pressure: OR 9.51, 95%CI 0.53–172.16, p=0.13 No relapse: OR 0.40, 95%CI 0.11–1.42, p=0.16	Strengths: -Relatively large sample size Limitations: -Retrospective study design -Follow-up time and site and apparatus of BMD measurement not reported -Reference categories in multivariable analyses not described -Non-response not described **Risk of bias** A. Selection bias: Unclear Reason: unclear if and how many survivors attended the aftercare clinic. Attenders and non-attenders were not compared on baseline characteristics. B. Attrition bias: Low risk Reason: the outcome was assessed for 95% of the study group. C. Detection bias: Unclear Reason: retrospective study, unclear whether assessors were blinded for BMD when assessing physical activity levels D. Confounding: Unclear

	Wilms tumor: n=16 (6.3%) Other: n=7 (2.8%) <u>Age at diagnosis:</u> <18 years (mean/median age at diagnosis not reported) <u>Age at follow-up:</u> Between 18-39 years, 77.5% <30 years (mean/median age at follow-up not reported) <u>Controls:</u> NA			Reason: site, manufacturer and method of Z-score calculation not described. Furthermore, the analyses were not adjusted for attained age. This was probably because it was not significant in univariable analysis, but this is not described.

Abbreviations: ALL=acute lymphoblastic leukemia; AML=acute myeloid leukemia; BMD=bone mineral density; BMI=body mass index; CI=confidence interval; DXA=dual-energy X-ray absorptiometry; NA=not applicable; NR=not reported; OR=odds ratio; SCT=stem cell transplantation.

Who needs BMD surveillance?				
Staba Hogan et al. *New Health Conditions Identified at a Regional Childhood Cancer Survivor Clinic Visit.* Pediatr Blood Cancer 2013;60:682-687.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Observational, retrospective study Single institution Treatment era: Not specifically stated; however, patients were a mean of 7 years of age at diagnosis, and were on average 11 years post-diagnosis (but the range was from 3-32 years; study visits took place 2003- 2009 (therefore it is possible that the treatment era ranged from 1971- 2000, but this is certainly not stated) Follow-up: More than 3 years after cancer diagnosis the follow up takes place in a special survivorship clinic at Yale university (HEROS: Health, Education, Research, Outcomes for Survivors) according to the COG guidelines for long term follow up.	Type and number of non-participants: NR Type and number of participants: 213 participants, 117 female (54.9%) 96 male (45.1) Non-Hispanic Caucasian 172 (80.8%) Diagnoses: Leukemia 80 (37.6%) Non-CNS solid tumor 71 (33.3%) Lymphoma 43 (20.2%) CNS tumor 19 (8.9%) Age at diagnosis: Under age of 21; median age 5.4 years (0-19) Age at follow-up: At least 1 year after last cancer therapy, at least 3 years after cancer diagnosis, in remission; median age 18.1 years Controls: NA Included patients: Evaluated at HEROS between Feb 2003 and Dec 2009	Chemotherapy: Aklylating agents 136 (63.8%) Not otherwise stated Radiotherapy: Any radiation: 104 (48.8%) Chest radiation 81 (38%) Cranial radiation 58 (27.2%) SCT: 30/213 (14.1%) Limb amputation: NR Other: The detailed treatment is not part of the study	Outcome definitions: To determine the effectiveness of a survivorship clinic visit beyond the usual medical care, newly identified therapy-related late effects in childhood cancer survivors. One aspect of this is BMD. BMD measurement modality: BMC and BA were measured using GE Lunar Prodigy 10326 Scanner or Hologic 4500 scanner 1 standard deviation below age-, gender- and height- appropriate norms were categorized as abnormally BMD calculated as BMC/BA by 1 radiologist Results: 149 patients were screened: 30 had reduced BMD, 3 previously known, 26 newly diagnosed (CTCAE score: 24 Grade I, 2 Grade II.) In a comprehensive survey of Childhood Cancer Survivors it is reasonable to include BMD measurement	Strengths: -To look if it is necessary to screen Childhood cancer survivors beside their regular medical care Limitations: -Small sample size, no treatment information **Risk of bias** A. Selection bias: Unclear Reason: it is unclear what percentage of patients who are cancer survivors attend this clinic; it is also unclear how many had DXA scans B. Attrition bias: Unclear Reason: it is unclear what percentage of patients who are cancer survivors attend this clinic; it is also unclear how many had DXA scans C. Detection bias: Low Risk Reason: no reason to think that these patients would systematically have a different outcome in terms of DXA scan results; low BMD by DXA is a hard end-point, not susceptible to subjectivity of the assessor D. Confounding: High risk

				Reason: there are many unknown variables, including steroid dosing, whether patients had an SCT, etc.

Abbreviations: BA=bone area; BMC=bone mineral content; BMD=bone mineral density; CNS=central nervous system; COG=children's oncology group; DXA=dual-energy X-ray absorptiometry; NA=not applicable; NR=not reported; SCT=stem cell transplantation.

Who needs BMD surveillance?				
van Atteveld et al. Prediction of Low and Very Low Bone Mineral Density Among Adult Survivors of Childhood Cancer. J Clin Oncol 2019;37:1-9.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Cross-sectional study (prediction model development and validation) Treatment era: SJLIFE before 2006 Dutch survivors 1965-2003 Follow-up: SJLIFE (model development) 21.6 yrs (range 10.4-40.6) Dutch survivors (model validation) 15.1 yrs (range 5.1-39.8)	Type and number of non-participants: SJLIFE (development): eligible cohort 2167 CCS, 135 non-participants (6%, 32 amputation + 103 no DXA) Dutch survivors (validation): eligible cohort 537 CCS, 134 non-participants (25%, no DXA). Participants tended to be older at both primary cancer diagnosis and at follow-up, and more likely to be treated with corticosteroids Type and number of participants: SJLIFE (development): 2032 white survivors of childhood cancer between 18-40 yrs of age and ≥10 yrs from diagnosis Dutch survivors (validation): 403 survivors of childhood cancer between 18-40 yrs of age and ≥5 yrs from cancer treatment Diagnoses: SJLIFE: ALL 741 (36.5%), Other leukemia 86 (4.2%), HL 205 (10.1%), NHL 150 (7.4%), CNS tumor 265 (13.0%), Renal tumor 122 (6.0%), Neuroblastoma 98 (4.8%), Soft tissue sarcoma 113 (5.6%), Bone tumor 78 (3.8%), Other 174 (8.6%)	Chemotherapy: SJLIFE Alkylating agent 1149 (56.6%), MTX 1095 (53.9%), GCs 1095 (53.9%) Dutch survivors Alkylating agent 204 (50.6%), MTX 244 (60.5%), GCs 282 (70.0%) Radiotherapy: SJLIFE Cranial 688 (33.9%), Abdominal 441 (21.7%) Dutch survivors Cranial 91 (22.6%), Abdominal 26 (6.5%) SCT: NR Limp amputation: NR	Outcome definitions: Low BMD: BMD_{LS} and/or BMD_{TB} Z-score ≤-1 Very low BMD: : BMD_{LS} and/or BMD_{TB} Z-score ≤-1 Z-score ≤-2 BMD measurement modality: DXA (SJLIFE Hologic, Dutch survivors Lunar) of the LS (L1-L4) and TB Low BMD: SJLIFE 51.5% (LS 25.1%, TB 48.0%) Dutch survivors 44.7% (LS 27.3%, TB 37.0%) Very low BMD: SJLIFE 20.2% Dutch survivors 10.2% Prediction model low BMD: β0 10.91 Sex β 1.12 (SE 0.14), OR 3.07, 95%CI 2.35-4.02; Height β -0.05 (SE 0.01), OR 0.95, 95%CI 0.93-0.96; Weight β -0.02 (SE <0.01), OR 0.98, 95%CI 0.97-0.98; Attained age β -0.03 (SE 0.01), OR 0.97, 95%CI 0.96-0.99; Current smoker β 0.39 (SE 0.11), OR 1.48, 95%CI 1.19-1.85; Cranial irradiation β 0.75 (SE 0.11), OR 2.11, 95%CI 1.69-2.63 SJLIFE **AUC 0.72**, 95%CI 0.70-0.75,	Strengths: -Large cohorts with a long follow-up time -Externally validated, clinically applicable prediction models were created -Easily measured predictors were used Limitations: -Dutch survivors received a DXA on the basis of physician referral -The models were developed in white survivors, so they require validation in survivors of other races **Risk of bias** A. Selection bias: Low risk Reason: broad representation, the SJLIFE cohort consisted of 100% of the eligible cohort. In the Dutch survivors this was the case in 74.1% B. Attrition bias: Low risk Reason: the outcome was assessed for all study participants C. Detection bias: Low risk Reason: low BMD by DXA is a hard end-point, not susceptible to subjectivity of the assessor

	Dutch survivors: ALL 184 (45.7%), Other leukemia 18 (4.5%), HL 46 (11.4%), NHL 50 (12.4%), CNS tumor 23 (5.7%), Renal tumor 48 (11.9%), Neuroblastoma 16 (4.0%), Soft tissue sarcoma 8 (2.0%), Bone tumor 10 (2.5%), Other 0 (0.0%) <u>Age at diagnosis:</u> SJLIFE 6.1 yrs (IQR 9.1, range 0-22.7) Dutch survivors 6.5 yrs (IQR 8.3, range 0-16.8) <u>Age at follow-up:</u> SJLIFE median 29.3 yrs (IQR 9.5, range 18.1-40.9) Dutch survivors 24.2 (IQR 9.2, range 18.0-40.9) <u>Controls:</u> NA		Dutch survivors AUC 0.69, 95%CI 0.64-0.75 <u>Prediction model very low BMD</u>: β0 9.98 Sex β 1.19 (SE 0.17), OR 3.28, 95%CI 2.37-4.54; Height β -0.06 (SE 0.01), OR 0.95, 95%CI 0.93-0.96; Weight β -0.03 (SE <0.01), OR 0.97, 95%CI 0.96-0.98; Attained age β -0.02 (SE 0.01), OR 0.98, 95%CI 0.96-1.00; Cranial irradiation β 0.73 (SE 0.13), OR 2.07, 95%CI 1.59-2.68; Abdominal irradiation β 0.48 (SE 0.14), OR 1.61, 95%CI 1.23-2.11 SJLIFE **AUC 0.76**, 95%CI 0.73-0.78, Dutch survivors AUC 0.75, 95%CI 0.67-0.83	<u>D. Confounding:</u> Low risk Reason: confounding does not play a role in prediction modelling

Abbreviations: ALL=acute lymphoblastic leukemia; AUC=area under the curve; BMD=bone mineral density; CCS=childhood cancer survivors; CNS=central nervous system; DXA=dual-energy X-ray absorptiometry; GCs=glucocorticoids; HL=Hodgkin lymphoma; IQR=interquartile range; LS=lumbar spine; MTS=methotrexate; NA=not available; NHL= non-Hodgkin lymphoma; NR=not reported; OR=odds ratio; SJLIFE=St. Jude Lifetime Cohort Study; SCT=stem cell transplantation; SE=standard error; TB=total body.

Who needs BMD surveillance?				
Van Beek et al. No difference between prednisolone and dexamethasone treatment in bone mineral density and growth in long term survivors of childhood acute lymphoblastic leukemia. Pediatric blood and cancer 2006;46:88-93.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Cross-sectional single center study Treatment era: Estimated 1975-2004, not explicitly stated Follow-up: Mean 12.7 yrs after dx (2.0-29.7)	Type and number of non-participants: NR Type and number of participants: N=90 Diagnoses: ALL (100%) Age at diagnosis: Mean 7.0 yrs (range: 0.9-15.9 yrs) Age at follow-up: Mean 21.2 yrs (range: 8.6-38.5 yrs) Controls: Dutch normative values	Chemotherapy: N=47 pred (1,225-22,225 mg/m2) N=43 dex (1,244-1,444 mg/m2) N=64 MTX (mean ~10g) Radiotherapy: N=19 received cranial irradiation SCT: None Limb amputation: None Other: NA	Outcome definitions: BM(A)D lumbar spine and total body Hx of fracture by self-report BMD measurement modality: DXA (Lunar) Results: 17 fractures in 14 subjects (none vertebral). No association between fractures and lower BM(A)D. BM(A)D was normal in the survivors compared to the controls. BMD normal in group not receiving radiotherapy, low in CRT group (P<0.05). When adjusted for height, this difference was no longer significant. No difference in BM(A)D dex vs. pred	Strengths: -Equal ascertainment in all evaluated patients Limitations: -Limited description of evaluated and unevaluated patients, relatively small size, unclear biases (below) **Risk of bias** A. Selection bias: Unclear Reason: selection methods of patients not described. B. Attrition bias: Low risk Reason: not applicable - cross-sectional study – everyone who consented, participated. C. Detection bias: Low risk Reason: BMD is a hard end-point. Reference group is clearly described and seems appropriate. D. Confounding: Low risk Reason: appropriate covariates considered (although tanner stage not stated, mean age of 21 should address this)

Abbreviations: ALL=acute lymphoblastic leukemia; BM(A)D=bone mineral (apparent) density; CRT=cranial radiotherapy; DXA=dual-energy X-ray absorptiometry; MTX=methotrexate; NA=not applicable; NR=not reported; SCT=stem cell transplantation.

Who needs BMD surveillance?				
Van Iersel et al. Hypothalamic-Pituitary Disorders in Childhood Cancer Survivors: Prevalence, Risk Factors and Long-Term Health Outcomes. J Clin Endocrinol Metab, December 2019, 104(12):6101–6115.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Retrospective cross-sectional study Treatment era: NR (ref 11,12) Follow-up: Average time since treatment 24.1 (range,6.8 to 51.1) years	Type and number of non-participants: Eligible SJLIFE cohort: 5304 CCS. 2163 non participants: 1066 (20.1%) lost to follow-up or declined participation, 1097 pending. Type and number of participants: 3141 (74.1%) CCS surviving ≥ 5 yrs after cancer diagnosis Compared with nonparticipants, participants were more: -female (47.9% vs 43.4%, p =0.001); -white (81.7% vs 78.3%, p =0.004); -leukemia survivors (37.2% vs 32.1%, p<0.0001); -diagnosed at an older age (p<0.0001) Participants received more frequently: -chemotherapy (85.2% vs 81.2%, p=0.0001); -alkylating agents (58.8% vs 54.8%, p=0.004); -intrathecal chemotherapy (40.5% vs 37.1%, (p=0.01); - radiotherapy including the HP region (34.6% vs 29.1%, p<0.0001); Diagnosis: Leukemia 1167	Corticosteroid: NR (however in table 7 prednisone equivalent dose is reported as independent variable in multivariable regression models for BMD prediction) Chemotherapy Any 2676 (85.2%) Intrathecal 1273 (40.5%) Alkylating agents in 1847 (58.8%) Radiotherapy: HP RT dose, Gy: No cranial RT 2055 (65.4%) 1–19.9 Gy 399 (12.7%) 20–30 Gy 388 (12.4%) >30 298 (9.5%) Dose unknown 1 (0.03%) HP radiotherapy in 1086 (34.6%) SCT: NR Other risk factors Hydrocephalus with shunt placement 95 (3.0%)	Outcome definitions: Low BMD: Z-score ≤-2 BMD measurement modality: DXA (model not specified; as explained in the additional remarks it seems that it was actually **QCT** and not DXA) average volumetric trabecular BMD for lumbar vertebrae L1 and L2 (available for 2035 patients, 64.8% of participants, 38.4% of the initial cohort) **Low volumetric LS BMD:** 521/2035 (25.6%) **Multivariable regression analyses:** Risk factors low lumbar BMD: *adjusted for body mass index 30 kg/m2, prednisone equivalent dose, and TB irradiation **GHD** 164 (40.5%) vs no GHD 357 (21.9%) OR 2.16, 95CI 1.68 to 2.78, **p=0.0001** **Untreated LH/FSHD** 32 (55.2%) vs no LH/FSHD 489 (24.7%) OR 2.4 95CI 01.35 to 4.26, **p=0.003** **TSHD** 49 (47.6%) vs no TSHD 472 (24.4%), OR 1.54, 95CI 0.98 to 2.42, p=0.06	Strengths: - Large study sample - Long follow-up period - Multivariable analyses for low BMD were adjusted for obesity (BMI>30kg/m2) Limitations: -The focus of the paper was assessing risk factors for HP hormone defects; as a consequence, HP hormone defects were assessed as risk factors for low BMD. -DXA model not available -Large follow-up interval: different software could have been used -A low volumetric BMD is declared as bone outcome, however BMD by DXA is always areal, unless corrected as BMAD. -The definition of low BMD is referenced by paper n.15 (Cann CE et al. Quantitative computed tomography for prediction of vertebral fracture risk. Bone. 1985; 6(1):1–7) meaning that the reference is based on QCT and not on DXA. **Risk of bias** A. Selection bias: High risk Reason: the group analyzed for BMD consisted of 38.4% of the original cohort; moreover, CCS

	Lymphoma 558 CNS tumor 352 Craniopharyngioma 26 Ependymoma 38 Glial cell tumor 174 Medulloblastoma 87 Other CNS tumor 27 Non-brain solid tumor of head and neck 203 Other solid tumor 795 Other 66 (CNS tumors of the HP region: 77) <u>Age at diagnosis:</u> Median 6.8 (range 0–18.0) years <u>Age at follow-up:</u> Median 31.7 (range, 7.5 to 65.1) years <u>Controls</u>: NA			participants and no participants differed significantly for demographics and treatment risk factors. <u>B. Attrition bias:</u> High risk Reason: the outcome was assessed for 64.8% of the study group <u>C. Detection bias:</u> Low risk Reason: low BMD by DXA is a hard end-point, not susceptible to subjectivity of the assessor <u>D. Confounding:</u> Unclear Reason: BMI (partial correction for dimensions, but risk of overestimating BMD in obese patients), prednisone dose and TBI were taken into account, however as the focus was analyzing associations with HP hormone defects, many risk factors were considered for those endocrine outcomes and not included in Multivariable analyses for low BMD prediction.

Abbreviations: BMD=bone mineral density; CCS=childhood cancer survivors; CI=confidence interval; CNS=central nervous system; DXA=dual-energy X-ray absorptiometry; GHD=growth hormone deficiency; HP=hypothalamic-pituitary; LH/FSHD=central hypogonadism; LS=lumbar spine; NA=not applicable; NR=not reported; OR=odds ratio; QCT=quantitative computed tomography; SCT=stem cell transplantation; SJLIFE=St Jude Lifetime Cohort Study; TB=total body; TSHD=central hypothyroidism.

Who needs BMD surveillance?				
van Iersel et al. Clinical impact of hypothalamic-pituitary disorders after conformal radiation therapy for pediatric low-grade glioma or ependymoma. Pediatr Blood Cancer. 2020 Dec;67(12):e28723.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Cross-sectional single center cohort study Treatment era: 1996 to 2016 Follow-up: Median duration since RT 10.1 (range, 0.1-19.6) years	Type and number of non-participants: Of 385 potentially eligible survivors, 30 were excluded because they received spinal RT (n=6), received proton RT (n=19) or received initial RT outside the institution (n=5) Type and number of participants: 355 survivors diagnosed with ependymoma or low-grade glioma before age 25 years and treated with conformal and intensity-modulated RT using photons were included in the GHD analysis. Numbers were slightly lower for other endocrine defects (n=262-330) Diagnoses: Ependymoma (n=193; 54%) Low-grade glioma (n=162; 46%) Age at diagnosis: Median 4.6 (range, 0.20-24.6) years Age at follow-up: Median 17.8 (range, 2.0-40.5) Controls: NA	Chemotherapy: Yes: 35% Alkylating agents: 16% Radiotherapy: C(S)RT: 100% -Cranial RT n=343; 96.6% -Craniospinal RT n=12 3.4% Median dose 54 (range, 50.4-59.4) Gy SCT: 0% Limb amputation: NA Other: GHD: 37.2% (95% CI 32.1-42.4) LH/FSHD: 17.7% (95% CI 13.2-23.0) TSHD: 14.9% (95% CI 11.2-19.2) ACTHD: 10.3% (95% CI 7.3-14.1) CPP: 12.6% (95% CI 8.8-17.2) 63.3% of survivors with GHD received GH replacement therapy.	Outcome definitions: Low BMD: Z-score ≤-2 BMD measurement modality: Volumetric BMD (L1 and L2) by quantitative computed tomography with GE VCT Lightspeed 64-detector (GE Healthcare) and quantitative CT calibration phantoms and software (Mindways) Results: Prevalence of low BMD NR **Multivariable model** GHD: OR=3.47, 95%CI 1.16-10.40, p=0.03 TSHD: OR=1.72, 95%CI 0.48-6.17, p=0.40 ACTHD: OR=2.53, 95%CI 0.64-10.06, p=0.19 N.B.: *After excluding patients with untreated GHD from analysis, GHD was not significantly associated with low BMD (OR 2.98; 95% CI 0.84-10.57) anymore.*	Strengths: -This paper describes endocrine disorders and their latency time in this at-risk group in detail Limitations: -Limited information available about the prevalence and multivariable model for low BMD **Risk of bias** A. Selection bias: Low risk Reason: the study group consisted of more than 75% of the original cohort of childhood cancer survivors B. Attrition bias: Unclear Reason: unclear how many of the included participants had a BMD evaluation C. Detection bias: Low risk Reason: low BMD by QCT is a hard end-point, not susceptible to subjectivity of the assessor D. Confounding: High risk Reason: analyses were not adjusted for sex, age, and weight. Height adjustment was not needed (vBMD)

Abbreviations: ACTHD=adrenocorticotropic hormone deficiency; BMD=bone mineral density; BMI=body mass index; CI=confidence interval; C(S)RT=Cranial(spinal) irradiation; CPP=central precocious puberty; GHD=growth hormone deficiency; LH/FSHD=luteinizing hormone/follicle stimulating hormone deficiency; NA=not applicable; NR=not reported; OR=odds ratio; QCT=quantitative computed tomography; RT=radiotherapy; SCT=stem cell transplantation; TSHD, thyroid-stimulating hormone deficiency

Who needs BMD surveillance?				
Van Santen et al. Fractures, Bone Mineral Density, and Final Height in Craniopharyngioma Patients With a Follow-up of 16 Years. J Clin Endocrinol Metab. 2020 Apr 1;105(4):e1397-e1407.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Cross-sectional retrospective study Treatment era: 1987-2019 Follow-up: Median 16 years (range 1-62)	Type and number of non-participants: NR Type and number of participants: 177 craniopharyngioma survivors. A DXA was available in 117 participants. Patients with a DXA scan available had a higher percentage of diabetes insipidus (68% vs. 51%, P = .03), of growth hormone deficiency (GHD) (93% vs. 72%, P < .001) and of TSH deficiency (95% vs. 86%, P = .06) than patients with no DXA scan, and less often epilepsy (13% vs. 27%, P = .03) or a hydrocephalus (23% vs. 40%, P = .03). There was no difference in fractures (18% vs. 18%, P = .95). Diagnoses: Craniopharyngioma 100% Age at diagnosis: Median age 23 years (range 0-79) Age at follow-up: Median age 45 years (range 15-92) Controls: -	Chemotherapy: None Radiotherapy: Radiation: 90 (51%) ^{90}Yttrium brachytherapy: 23 (13%) SCT: None Limb amputation: None Other:	Outcome definitions: Low BMD: T- or Z-score below -1 Osteoporosis: T-score below -2.5 or Z-score below -2. Osteopenia: T- or Z-score between -1 and -2.5 or -2 Incidence of fractures BMD measurement modality: DXA (Lunar DPXL, Lunar iDXA, and Lunar Prodigy) of the FN, LS (L2-L4) or TB Results: Fractures: 31 (18%), over time (5.8 fractures per 1000 person-years) Mean TB BMD Z-score: 0.1 ± 1.5 (range, -4.1 to 3.5) Mean FN BMD Z-score: -0.1 ± 1.3 (range, -2.7 to 4.7), Mean LS BMD Z-score: 0.0 ± 2.0 (range, -3.5 to 6.8) Low BMD: 47 (50%) Osteopenia: 43 (46%) Osteoporosis: 22 (24%) Multivariable logistic regression model: Fractures: female sex OR 0.3 (95%CI 0.1-0.7), p=0.004; Previous surgery OR 0.1 (95%CI 0.0-0.6), p=0.009 Medication for epilepsy OR 3.0 (95%CI 0.9-10.0), p=0.07	Strengths: -Large study that assessed fractures in CP survivors, and the relationship between BMD and fractures Limitations: -Retrospective study design **Risk of bias** A. Selection bias: High risk Reason: retrospective study, eligible cohort unknown; patients were only included if data were available on fractures, BMD or final height. B. Attrition bias: High risk Reason: the outcome was assessed for less than 75% of the study group (66%) C. Detection bias: Low risk for BMD, high risk for fractures Reason: BMD is a hard end-point. Fracture ascertainment differed in the Dutch (inpatient and outpatient fractures) and the Swedish cohort (only inpatient fractures) and was retrospectively registered. D. Confounding:

			Multivariable Cox regression model: Fractures: female sex HR 0.4 (95%CI 0.2-0.8), p=0.02; Previous surgery HR 0.3 (95%CI 0.1-0.8), p=0.02 Medication for epilepsy HR 2.7 (95%CI 1.1-6.7), p=0.03 Multivariable logistic regression model: Very low BMD/osteoporosis: attained age OR 1.03, (95%CI 1.0-1.06), p=0.03 Obstructive sleep apnea syndrome NS Hydrocortisone dose NS Low BMD values based on either T- or Z-scores were found in 11 patients (65%) with fractures as opposed to 32 patients (42%) without fractures in their history (P = .08). In a univariable logistic regression model for fractures, osteopenia showed an OR of 2.6 (95%CI 0.9-7.7), p=0.09; osteoporosis 2.1 (95%CI 0.7-6.4), p=0.21	High risk Reason: BMD model did not include sex and BMI, fracture model did not include age and BMI

Abbreviations: BMD=bone mineral density; BMI=body mass index; CI=confidence interval; CP=craniopharyngioma; FN=femoral neck; HR=hazard ratio; LS=lumbar spine; NS=not significant; OR=odds ratio; SCT=stem cell transplantation; TB=total body.

Who needs BMD surveillance?				
Watsky et al. Bone Turnover in Long-Term Survivors of Childhood Acute Lymphoblastic Leukemia. Pediatr Blood Cancer 2014;61:1451-1456.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Cross-sectional, observational, retrospective, single institution Treatment era: 1984-1997 Follow-up: More than 5 year survivors of ALL. Median time from completion of treatment of ALL was 8.5 years (range, 4.5–19.1 years).	Type and number of non-participants: 6 patients, excluded because they were not white or black Type and number of participants: N=418 female 203, male 215 Diagnoses: ALL Age at diagnosis: Median female 4.6 yrs (range: 0.6, 18.7) Median male 4.6 yrs (range: 0.2, 18.8) Age at follow-up: Median 17.0 yrs (9.0-36.1) Controls: None Other: Not taking supplemental calcium or vitamin D within 3 months of entering the study	Chemotherapy: IRB-protocols Total Therapy TXI-XIII patients divided into intermediate and high risk / and low risk. Corticosteroids 100% MTX 100% Cyclophosphamide 100% Radiotherapy: CRT >24Gy (8.4%), 1-23 Gy, or none SCT: Excluded Limb amputation: None Other: Dietary intake of Ca and Vit D self-reported smoking status and physical activity	Outcome definitions: The authors investigated the effects of demographic, lifestyle (smoking and physical activity), cancer-related treatment factors and diet on bone turnover biomarkers as well as the relationship between bone turnover markers to bone mineral density Z-scores BMD measurement modality: LS BMD Z-score of L2 and L2 using GE Lightspeed QCT scanner Biomarkers: BALP, N-telopeptide, Osteocalcin Results: For females, 10 participants had LS-BMD Z-scores below -2; 39 had scores of -2 to -1, 76 had scores of -1 to 0, and 59 had scores >0. For males, 19 participants had LS BMD Z-score below -2, 61 had scores of -2 to -1, 76 had scores of -1 to 0, and 59 had scores >0 After adjustment for age, gender, tanner stage and BMI, the authors found no significant association of any biomarker with lifestyle related factors, ALL treatment and dietary intake. Cranial radiation has no impact on BMD , this treatment did not influence long-term bone turnover.	Strengths: -Large, well-defined cohort -Treated at a single institution -Treatment data are documented -Male and female are equal -Biomarkers and direct volumetric BMD measurement Limitations: -Sample size of other races than black and white -The questionnaire for physical activity was not validated for children, but most of the participants were older -Parental reports about smoking and physical activity were not reliable. -BMD was determined with QCT and not with DXA, therefore limits in comparison with other papers -Radiation group 24 Gy, and 1-23 Gy **Risk of bias** A. Selection bias: High risk Reason: specifically excluded patients who were not white or black (due to sample size) B. Attrition bias: Low risk Reason: baseline data from a clinical trial; no opportunity for drop-out

			Long-term bone turnover is not associated with prior treatment for ALL, factors that influence bone turnover are similar to healthy children.	C. Detection bias: Low risk Reason: low BMD by QCT is a hard end-point, not susceptible to subjectivity of the assessor; interpretation of biomarkers is also not subsect to subjectivity of the assessor D. Confounding: Low risk Reason: confounding variables accounted for in the analysis

Abbreviations: ALL=acute lymphoblastic leukemia; BMD=bone mineral density; DXA=dual-energy X-ray absorptiometry; LS=lumbar spine; MTX=methotrexate; QCT=quantitative computed tomography; SCT=stem cell transplantation.

Who needs BMD surveillance?				
Wei et al. Bone Mineral Density Corrected for Size in Childhood Leukaemia Survivors Treated with Haematopoietic Stem Cell Transplantation and Total Body Irradiation. Horm Res Paediatr 2018;89:246–254.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Cross-sectional study Treatment era: 2007-2012 Follow-up: Median time since HSCT-TBI, years 9.1 (2.3-16.6). NR for Chemotherapy-only participants 2 or more years since the com-pletion of all oncological treatments and who had undergone DXA scanning before the age of 21 years	Type and number of non-participants: NR Type and number of participants: A total of 49 childhood leukaemia survivors who have had 1 or more DXA scans before the age of 21 years were identified, which included 33 (18 males) treated with HSCT-TBI and 16 (5 males) with chemotherapy only. Diagnoses: The HSCT-TBI survivors included subjects with a primary diagnosis of acute lymphoblastic leukaemia (ALL) (*n* = 28);85% and acute myeloid leukaemia (AML) (*n* = 5); 15%. All subjects in the chemotherapy-only group had ALL. Age at diagnosis: HSCT-TBI survivors median 3.8 (0.85– 15.0) years and 5.6 (1.6–14.1) years of age in chemotherapy-only survivors. Age at follow-up: At the time of DXA scanning, the median age of HSCT-TBI survivors	Chemotherapy: NR, apart from Total dose of steroids (equivalent doses to Hydrocortisone, mg): HSCT-TBI group 20,469 mg (42–4,4578) and Chemotherapy- only group 29,870 (20, 513- 41,316) Radiotherapy: HSCT-TBI group: All patients received TBI (total from 10 to 14.4 Gy; single faction, *n* = 5 (15%); 6 fractions, *n* = 1 (3%) ; 8 fractions, *n* = 27 (82%)) and 11 patients (33.4%) were also treated with additional cranial irradiation. SCT: 33 patients Limb amputation: None Other: The total dose of steroids given was lower in the HSCT-TBI than in the chemotherapy-only group (*p* = 0.003)	Outcome definitions: -Primarily aims to compare size-adjusted volumetric BMD in childhood leukaemia survivors treated with and without HSCT-TBI with population references. -The secondary aim is to investigate risk factors associated with size-adjusted BMD in leukaemia survivors treated with HSCT-TBI. BMD measurement modality: All participants underwent DXA scanning -The DXA outputs needed for this study included BMC, projected vertebral area of lumbar vertebrae L1–L4, total fat mass, and total lean body mass (LBM).Bone mineral apparent density (BMAD) was calculated ac-cording to an adapted Carter methodology : Lumbar spine BMAD (g/cm3) = (BMC1 + BMC2 + BMC3 + BMC4) / (V1 + V2 + V3 + V4) Results: **Fractures**: HSCT-TBI participants (12%): 1 vertebral fracture, 1 avascular necrosis of hip, 1 aneurismal bone cyst and 1 osteoid osteoma. In chemotherapy group (18.75%): 1	Strengths: -The first study to report size-corrected BMD measurements from childhood leukaemia survivors treated with and without HSCT-TBI in the UK using the recently published national reference ranges, which are size, gender, and ethnically corrected. -All HSCT-TBI survivors with areal BMD-SDS <–2 had BMAD-SDS >–2 Limitations: -Small study sample -Demonstrated reduction in lean mass in HSCT-TBI survivors consistent with that previously reported, but a relationship between lean mass and BMAD was not found. This may be due to the limited duration of follow-up after HSCT-TBI and as reduction in lean mass continues with time, this may also have an effect on ongoing BMD reduction and should be further evaluated. **Risk of bias** A. Selection bias: Low risk Reason: the study group consisted of more than 75% of the original

	was 17.3 (10.5–20.9) years and that of chemotherapy-only survivors was 18.5 (16.1–20.9) years. Controls: UK population references		avascular necrosis of the hip and 2 accidental long bone fractures. **Height**: HSCT-TBI survivors were significantly shorter ($p < 0.001$) and lighter ($p = 0.02$) compared with the chemotherapy-only controls and population reference ranges. HSCT-TBI survivors had reduced sitting height compared with chemotherapy-only subjects ($p < 0.001$) and population references ($p < 0.001$). Chemotherapy-only subjects showed a trend towards reduced sitting height, although not statistically significant ($p = 0.06$). HSCT-TBI survivors showed significant reduction in lean mass for height-SDS compared with chemotherapy-only ($p < 0.001$) and population references ($p < 0.001$). ***BMD and BMAD*** HSCT-TBI survivors- significantly lower BMD-SDS ($p = 0.008$), but no differences in BMAD-SDS ($p = 0.25$) in comparison to population references. The chemotherapy-only survivors were not different to population references in terms of BMD-SDS ($p = 0.7$) and BMAD-SDS ($p = 0.93$). There were no differences in BMD-SDS and BMAD-SDS between the HSCT-TBI and chemotherapy-only group. In the HSCT-TBI group, the only 2 patients with BMD-SDS of <–2 had	cohort of childhood cancer survivors B. Attrition bias: Low risk Reason: the outcome was assessed for more than 75% of the study group C. Detection bias: Low risk Reason: low BMD by DXA is a hard end-point, not susceptible to subjectivity of the assessor D. Confounding: Low risk Reason: all important prognostic factors were taken adequately into account

			BMAD-SDS >–2 , Outcomes were unchanged when the analyses were repeated comparing all post pubertal (Tanner stage 5) subjects only. No significant associations between BMAD-SDS with age at primary diagnosis or HSCT-TBI, time since HSCT-TBI, sitting height-SDS, or lean mass-SDS. Multi-regression analysis did not show any differences in the relationship between BMAD-SDS and the risk factors (CRT, GVHD, hypothyroidism, gonadal failure or GHD).	

Abbreviations: ALL=acute lymphoblastic leukemia; BMC=bone mineral content; BM(A)D=bone mineral (apparent) density; CRT=cranial radiotherapy; DXA=dual-energy X-ray absorptiometry; GHD=growth hormone deficiency; GVHD=graft versus host disease; HSCT=hematopoietic stem cell transplantation; NR=not reported; SDS=standard deviation score; TBI=total body irradiation; V=volume.

Who needs BMD surveillance?				
Wilson et al. Fractures Among Long-Term Survivors of Childhood Cancer A Report From the Childhood Cancer Survivor Study. Cancer 2012;118:5920-8.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Observational retrospective study, CCSS Treatment era: 1970-1986 Follow-up: Median length of follow-up was 22.7 years (range, 15.6-34.2 years).	Type and number of non-participants: 9769 emailed 2007 follow-up questionnaire (861 lost to follow-up, 772 refusals, 12 unavailable, 111deceased), 8013 completed 2007 questionnaire, but on 559 no treatment information Compared with nonparticipants, survivors were more likely to be female (51% vs 42%, p<0.001) and of white, non-Hispanic descent (91% vs 80%, p<0.001). In addition, a higher proportion of survivors had received glucocorticoids (47% vs 35%) or methotrexate (44% vs 31%) than nonparticipants. Type and number of participants: N=7414 Diagnoses: Leukemia 2559, HL 962, NHL 552, CNS malignancy 905, Kidney tumor 685, NBL 494, STS 650, Bone tumor 607 Age at diagnosis: The median age was 6.9 years (range, 0-21 years) Age at follow-up: Median among survivors and siblings were 36.2 years (range, 21.2-58.8 years) and 38.1 years (range, 18.4-62.6 years),	Chemotherapy: Methotrexate 3232 (43.6%), Steroids 3469 (47%) Dexamethasone+/- Prednisone 355 (10% of those on steroids, 4.8% of total population), Prednisone only 3114 (90% of those on steroids, 42% of total population) Radiotherapy: Cranial RT 2285 (32%), Pelvic RT 970 (13%) SCT: None Limb amputation: NR Other:	Outcome definitions: The prevalence of fracture among long-term adult survivors of childhood cancer is similar to that of their siblings despite chemotherapy and radiation exposure known to disrupt bone metabolism during therapy. BMD measurement modality: No data (not included in the study) Results: Over a third of survivors (34.8%) and siblings (38.9%) reported the occurrence of 1 or more fractures during their lifetime. The most frequently reported site-upper limb both for survivors (54.9%) and for siblings (55.6%), Adjusted for attained age, ethnicity, smoking status, body mass index, and history of medications known to promote bone health, male survivors were less likely to report a fracture than their siblings (prevalence ratio, 0.87; 95% CI, 0.81-0.94; P < .001). Reported prevalence of fractures also lower among female survivors compared with their siblings was not statistically significant	Strengths: -Large cohort Limitations: -Based on self-report questionnaires -Absence of data on BMD, therefore no evaluating of potential associations between fracture risk and BMD in the study population **Risk of bias** A. Selection bias: High risk Reason: the greater proportion of females and individuals of white, non-Hispanic descent among survivors who completed the CCSS 2007 follow-up questionnaire may limit ability to generalize findings to males and to survivors of non-white descent. B. Attrition bias: Low risk Reason: the outcome was assessed for more than 75% of the study group C. Detection bias: High risk Reason: self-reported questionnaires is a weak end point, plus no data on BMD, therefore no evaluation of

	Controls: 2374 siblings		**Multivariable Analysis of the Risk of Fractures Among Survivors of Childhood Cancer Stratified by Sex** Male- In multivariable analyses, male survivors of non-white ethnic descent were less likely to report a fracture than white participants (prevalence ratio, 0.78; 95% CI, 0.66- 0.92; P=.004). Only prior smoking history (prevalence ratio, 1.24; 95% CI, 1.14-1.34; P < .001) was associated with an increased prevalence of fracture. Female survivors- association between increasing age at follow-up and an increased prevalence of fractures was observed: survivors between ages 40 and 49 years were 1.22 times (95% CI, 1.01-1.48; P=.044) and survivors aged >50 years were 1.48 times more likely (95% CI, 1.10-1.99; P=.009) to report a fracture than survivors between ages 18 and 29 years. Female survivors who reported difficulties with balance or equilibrium (prevalence ratio, 1.25; 95% CI, 1.05-1.48; P=.012) or who had received methotrexate treatment (prevalence ratio, 1.15; 95% CI, 1.03-1.27; P=.001) also reported an increased prevalence of fracture in multivariable analyses Among male survivors, a history of any diagnosis except non-Hodgkin lymphoma and	potential associations between fracture risk and BMD in this study D. Confounding: High risk Reason: a greater proportion of participants who received glucocorticoids and methotrexate also completed the CCSS 2007 follow-up questionnaire, these observations are difficult to interpret given the high number of nonparticipants for whom treatment information was unavailable.

			bone tumors was associated with a decreased risk of fracture compared with siblings. The observed prevalence of fracture was reduced significantly only among female survivors of kidney tumors (prevalence ratio, 0.76; 95% CI, 0.62-0.93; P=.009). The only diagnostic group that had an observed higher prevalence of fracture compared with the sibling control group was female survivors of bone tumors (prevalence ratio, 1.15; 95% CI, 0.97-1.36), although this finding was not statistically significant at P =.05.	

Abbreviations: BMD=bone mineral density; CCSS=childhood cancer survivor study; CI=confidence interval; CNS=central nervous system; HL=Hodgkin lymphoma; NBL=neuroblastoma; NHL=non-Hodgkin lymphoma; NR=not reported; RT=radiotherapy; SCT=stem cell transplantation; STS=soft tissue sarcoma.

Who needs BMD surveillance?				
Wilson et al. Modifiable Factors Associated With Aging Phenotypes Among Adult Survivors of Childhood Acute Lymphoblastic Leukemia. J Clin Oncol 2016. 34:2509-2515.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Cross-sectional study Treatment era: NR - St Jude Lifetime Cohort Study (SJLIFE) Follow-up: The median duration between diagnosis and follow-up was 25.1 years (range, 10.5 to 47.7 years).	Type and number of non-participants: **Survivors of ALL eligible for SJLIFE (N = 1,420):** Nonparticipants (n = 519) Active and passive refusals (n = 290), Lost to follow-up (n = 39) Campus visit pending (n = 113) Completed questionnaires (n = 77) **SJLIFE participants (n = 901):** No QCT/pregnant (n = 39) When compared with participants, a higher proportion of participants were women (p<0.01), of white, non-Hispanic descent (p<0.01), and had received cranial or craniospinal irradiation (p<0.05) Type and number of participants: 862 survivors of ALL >age 18 years >10 years post-diagnosis Diagnoses: ALL Age at diagnosis: Median age 5.0 years (range, 0.2 to 19.5 years) Age at follow-up: 31.3 years (range, 18.4 to 59.7 years). Controls:	Chemotherapy: HD Methotrexate 523 (60.7%); MTX dose 5461 (12-51367) mg/m2 Cyclophosphamide dose 9.278 (300-10889)mg/m2 Glucocorticoid dose 9529 (82-27360) mg/m2 Radiotherapy: None 337 (39.1%) CRT<22Gy 194 (22.5%) CRT>=22Gy 224 (26%), CRT+CS or TBI 107 (12.4%) SCT: NR Limb amputation: NR Other:	Outcome definitions: **1.*Low BMD*** was defined as an age- and sex-standardized Z-score <-1. **2.*The presence of frailty or pre-frailty*** was defined as having at least two of the following: low muscle mass, self-reported exhaustion, low energy expenditure, slow walking speed, and weakness **3.*Data on lifestyle habits*** were collected using a structured questionnaire completed at the time of the SJLIFE evaluation. Alcohol intake was based on number of alcoholic drinks consumed during a typical day. Men who consumed between one and four drinks daily and women who consumed between one and three drinks daily were classified as moderate drinkers. Men and women who consumed more than five or four drinks daily, respectively, were considered risky drinkers. Smoking status was classified as current, past, or never. BMD measurement modality: Quantitative computed tomography of L1 through L2 vertebrae. Results:	Strengths: -A large, well-characterized population of cancer survivors with data on BMD, strength, mobility, body composition, hormonal status, and lifestyle Limitations: -Interpretation of findings is limited by the cross-sectional design of this analysis -Limited by reliance on plasma IGF-1 levels for identifying GHD and not dynamic endocrine testing and assumption that all pre-existing hormonal deficits were valid and persistent at the SJLIFE assessment, which may have resulted in misclassification of exposure for some participants. -When compared with nonparticipants, a higher proportion of participants were women (P<01); of white, non-Hispanic descent (P ,<1); and had received cranial or cranio-spinal irradiation (P <05) **Risk of bias** A. Selection bias: High risk Reason: the greater proportion of females, white, non-Hispanics may limit the ability to generalize these findings to males and survivors of non-white descent.

			329 survivors (38.2%) with IGF-1 levels suggestive of GHD, only 4 (1.2%) were receiving replacement therapy. 11% of women had premature ovarian insufficiency, of whom 21.3% were taking hormone replacement therapy. Among men 24.2% had low testosterone, of whom 34% were receiving treatment. The mean BMD Z-score -0.64 (+/- SD 1.08) for men, and -0.04 (6 SD 1.18) for women. Among men, 36.6% had a BMD Z-score between -2.5 and -1, and 2.8% had Z-scores ≤ -2.5. Among women, 20.2% had BMD Z-scores between -2.5 and -1, and 0.7% had Z-scores ≤-2.5. After adjusting for BMI, men with GHD (OR, 1.59; 95% CI, 1.02 to 2.49) or who were current smokers (OR, 1.71; 95% CI, 1.02 to 2.85) had increased odds of low BMD compared with those without GHD or who were non-smokers. Women with GHD (OR, 2.18; 95% CI, 1.26 to 3.78) and who consumed moderate levels of alcohol (OR, 2.09, 95% CI, 1.14 to 3.83) had increased odds of low BMD compared with women without GHD or who were never drinkers. Survivors with low BMD did not have increased odds of having at least two components of the frailty phenotype compared with	<u>B. Attrition bias:</u> Low risk Reason: the outcome was assessed for all study participants <u>C. Detection bias:</u> Unclear Reason: there is paucity of reference data for QCT in children and adolescents, and established international definitions for reduced BMD including osteopo-rosis may not be applicable in the interpretation of QCT outcomes <u>D. Confounding:</u> Unclear Reason: the diagnosis of GHD is suspect and may be a confounder that has not been well-documented.

			survivors with normal BMD (p>0..05).	

Abbreviations: ALL=acute lymphoblastic leukemia; BMD=bone mineral density; BMI=body mass index; CI=confidence interval; CRT=cranial radiotherapy; GHD=growth hormone deficiency; HD=high-dose; NR=not reported; OR=odds ratio; QCT=quantitative computed tomography; TBI=total body irradiation; SCT=stem cell transplantation.

Who needs BMD surveillance?				
Woo Han et al. Poor Bone Health at the End of Puberty in Childhood Cancer Survivors. Pediatr Blood Cancer 2015; 62: 1838-1843.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Cross-sectional study Treatment era: NR Follow-up: Mean duration from cancer treatment to completion of BMD 9.2 yrs ± 5.4 yrs (assuming this is a SE although not actually stated)	Type and number of non-participants: Eligible (>age 16yrs) cohort: 315 out of 537 patients registered in the Yonsei University Long Term Follow-Up clinic 223/315 had an indication for DXA and were invited 131 did not participate (these non-participants had significant differences to participants:) **Lower mean age at diagnosis** (7.2±4.3 vs 8.7±4.5 yrs) **Longer FU duration** (11.1±10.7vs 9.2±5.4yrs) **Less ALL and NHL** ALL 32.1 vs 49.1% NHL - figures not clear 24.6 vs 24.1% ? **More brain tumour** 23.6%vs9.6% Type and number of participants: **92** CCS Age >16yrs Agreed to participate and DXA Had an indication for DXA (previous brain or NP cancer, head and neck radiotherapy, past corticosteroid use) Also included **16** others Age >16 yrs Who had had a DXA for reasons not in their indication list	Chemotherapy: N= 106/108 (98.2%) Radiotherapy: N=60/108 (55.6%) (Head and neck radiation: 49/108 (45%)- (assuming this is 49 out of the 60 who had radiotherapy but this is not explicit) SCT: 18/108 (16.7%) Limb amputation: NR Other: Corticosteroids: 76/108 (70%) Surgery (undefined): 33/108 (30.6%)	Outcome definitions: Normal bone health: Z- score ≥ -1 Moderate BMD deficit: Z-score <-1.0 and ≥ -2 Severe BMD deficit: Z-score < -2 BMD measurement modality: DXA (unspecified) of Lumbar Spine (vertebrae unspecified), Femoral Neck (FN), Total Hip (TH) Results: **Severe BMD deficit** 18 (16.7%) at any site 14/106 (13.2%) at spine 14/102 (13.7%) at FN 14/101 (13.9%) at TH **Moderate BMD deficit** 39 (36%) at any site 28/106 at spine (26.4%) 26/102 at FN (25.5%) 25/101 at TH (24.8%) **Normal BMD** 64/106 LS (60%) 62/102 FN (61%) 62/101 TH (61%) According to specific diagnosis: **Moderate BMD deficits:** Hematology survivors 40.2% (33/82) Brain/naso group 15.4% (2/13) **Severe BMD deficit**	Strengths: -Reasonable cohort size; -Reasonable duration of f/u; -Korean cohort; -Patients were post pubertal (age >16 and Tanner staging). Limitations: -Minimal information about the DXA in methods; -In discussion authors state: -DXA Z-scores not adjusted for bone size/height or compared to paediatric reference data – the methodology for their DXA data is therefore not clear. The patients with endocrine dysfunction were those with significant OR for moderate or severe BMD deficit, but there are 2 issues: 1. there is no explanation around treatment of endocrine dysfunction 2. The patients with GH deficiency (number not given) had a height SD of < -2 (see comment above about no adjustment of DXA for height).

	(endocrine dysfunction n=8, ovarian tumour n=2, HSCT n=1, surveillance n=5) Total no of participants = **108** <u>Diagnoses</u>: Hematological 82 (75.9%) ALL 41 (38%) AML 7 (6.5%) NHL 26 (24.1%) HL 3 (2.8%) CML 1 (0.9%) LCH 4 (3.7%) Brain/nasopharyngeal 13 (12%) Brain tumour 11 (10.2%) NP carcinoma 2 (1.9%) Sarcoma 5 (4.6%) Other 8 (7.4%) <u>Age at diagnosis:</u> 8.9±4.7 yrs <u>Age at follow-up:</u> 20.3±3.0 yrs <u>Controls:</u> None		Hematology survivors 13.4% (11/82) Brain/naso group 53.8% (7/13) **Univariate analyses:** **Head/neck RT yes vs. no:** FN BMD Z-score–0.93±1.18 vs.–0.46±1.12, P=0.045; TH–1.02±1.16 vs. –0.51±1.12, P=0.026; LS Z-scores (–0.90±1.09 vs. -0.51±1.20; P=0.085). **Survivors >10 years after treatment vs. <10 years** LS: 0.36±1.09 vs. –0.94±1.16; P=0.010; FN: –0.33±1.05 vs. –0.94±1.19, P=0.008; TH: –0.42±1.10 vs. –0.99±1.16, P=0.013; RT, GCs, age at diagnosis, and chemotherapy did not affect LS, FN, or TH BMD Z-scores. **Multivariate analysis:** [Logistic regression Model included sex, age at diagnosis, >10 years from treatment completion to DXA, number of bone densitometry indications, and the presence of endocrine dysfunction as independent variables] **Endocrine dysfunction**** only significant risk factor for moderate or severe BMD deficit: Lumbar spine OR 3.6, 95% CI 1.51–9.60, **p 0.004**; Fem neck OR 2.72, 95% CI 1.15–6.47, **p=0.023**;	**Risk of bias** <u>A. Selection bias:</u> High risk Reason: only 108/315 of eligible cohort had DXA. There were significant differences between the study cohort and non-participants. Also patients were screened for "indications for DXA" therefore an "at risk" population. <u>B. Attrition bias:</u> Low risk Reason: cross-sectional study and >75% of study group had the DXA at all three sites. <u>C. Detection bias:</u> Low risk Reason: blinding not mentioned in the protocol but low BMD by DXA not subjective <u>D. Confounding:</u> High risk Reason: height, weight, BMI not taken into account. Participants were >16 yrs and had Tanner staging (although this not recorded in results). Sex and Age were used in multivariable analysis.

			Total Hip OR 4.2, 95% CI (1.69–10.52, **p=0.002** (**described as Growth Hormone dysfunction CTCAE grade 2/higher + height SD <-2/ Sex hormone dysfunction CTCAE grade 2/higher (gonadotropin abnormality, irregular menstruation, premature menopause, oligospermia, or azoospermia) and Thyroid hormone dysfunction CTCAE grade 2 or higher hypothyroidism or hyperthyroidism)	

Abbreviations: ALL=acute lymphoblastic leukemia; AML= acute myeloid leukemia; BMD=bone mineral density; BMI=body mass index; CI=confidence interval; CML=chronic myeloid leukemia; CTCAE=common terminology criteria for adverse events; DXA=dual-energy X-ray absorptiometry; FN=femoral neck; FU=follow-up; GCs=glucocorticoids; HL=Hodgkin lymphoma; LCH=Langerhans cell histiocytosis; LS=lumbar spine; NHL=non-Hodgkin lymphoma; NR=not reported; OR=odds ratio; RT=radiotherapy; SCT=stem cell transplantation; TH=total hip.

Who needs BMD surveillance?				
Zürcher et al. High impact physical activity and bone health of lower extremities in childhood cancer survivors: A cross-sectional study of SURfit International. Int J Cancer. 2020 Oct 1;147(7):1845-1854.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Cross-sectional single center trial Treatment era: Sept 2015 to Febr 2018 Follow-up: Median 22.2 years since diagnosis (IQR 16.0; 29.1)	Type and number of non-participants: not described; Rueeg et al. BMC Cancer 2017 may include more information. Type and number of participants: N=150 CCS Eligible: CCS identified in the Swiss Childhood Cancer Registry who were treated at a Swiss Pediatric Oncology clinic, aged ≥16 years at study, <16 years at diagnosis and ≥ 5 years since the last cancer diagnosis, baseline assessments and valid bone measurement Of 161 eligible CCS, 11 participants with <4 days of valid accelerometer measurements and one participant who was a wheelchair user were excluded. Diagnoses: I Leukemia: n=57 (35%) II Lymphoma: n=34 (21%) III Central nervous system tumor: n=18 (11%) IV–XIII Other tumors: n=52 (32%) Age at diagnosis: Median 6.7 years (IQR 3.2; 11.7) Age at follow-up: Median 28.5 years (IQR 23.4; 36.6)	Chemotherapy: Cumulative anthracycline dose (mg/m2): n=91 (57%) Median: 180 (IQR 120; 250) Cumulative steroid dose (mg/m2): n=82 (61%) Median: 3,410 (IQR 2,063; 4,227) Radiotherapy: Received cranial radiation therapy: n=28 (17%) Cranial radiation dose ≥24 Gy: n= 21 (13%) SCT: NR Limb amputation: NR Other: NR	Outcome definitions: Total and trabecular volumetric bone mineral density (mg/cm3) [total and trab vBMD] at 4% of tibia length (Z-scores) Cortical volumetric bone mineral density (mg/cm3) [cort vBMD], Total cortical cross-sectional area (mm2) [total CSA] Strain strength index (mm3) [SSI] at 66% tibia length. Bone mineral Density assessed by DXA: Femoral neck (FN) Total hip (TH) Lumbar spine (LS) areal BMD expressed in g/cm2 and by age and gender-matched z-scores Low bone health was defined as BMD Z-score < -1 BMD measurement modality: Densitometric and microstructural bone health was measured by pQCT (XCT 2000; Stratec Medical, Pforzheim, Germany) and DXA (Discovery A densitometer; Hologic, Bedford, MA). Results: Low bone health (BMD Z-score <-1) at any site measured by pQCT or DXA: females: 56%, males: 70%	Strengths: -Both possible determinants (physical activity) and outcome were validly assessed Limitations: -The multivariable analyses were adjusted for muscle mass which is a possible mediator, and therefore analyses may be overadjusted. -Only low BMD and not very low BMD (Z-score <-2) was described. -For the risk factor analyses, only bone health with continuous measures were presented. **Risk of bias** A. Selection bias: Unclear Reason: There is no description of the selection bias at baseline; no comparison of respondents and non-respondents. The respondents had a mean level of moderate to vigorous physical activity (MVPA) of 39 min per day (IQR; 26–53) (active group). The respondents agreed to participate in a trial for weight bearing PA. B. Attrition bias: Low risk Reason: the outcome was assessed for almost all included participants

	Controls: NA		Low lumbar spine BMD Z-score: females: 30%, males: 50% Low bone health in both pQCT and DXA: females: 19% ; males: 34% Low pQCT Z-scores (tibia 4%): Total vBMD: females 23/70 (32.9%) males 49/88 (55.7%) Trabecular vBMD: females 16/70 (20.5%) males 18/88 (20.5%) Any pQCT site: females 24/70 (34.3%) males 49/88 (55.7%) Low DXA Z-scores: Femoral neck: females 19/72 (26.4%) males 20/84 (23.8%) Total hip: females 12/72 (16.7%) males 15/84 (17.9%) Lumbar spine: females 20/70 (28.6%) males 37/85 (43.5%) Any DXA site: females 30/72 (41.7%) males 43/86 (50.0%) Relation between physical activity tertile groups according to impact peak duration (IPD) and bone health. Multivariable model: Total vBMD: IPD mid vs. low, beta 6.6 (95%CI -8,64 to 21,84), p=0.40; high vs. low beta 11.62 (95%CI -4,16 to 27,40), p=0.15 Trabecular vBMD: IPD mid vs. low, beta 6,16 (95%CI -7,59 to 19,91), p=0.38; high vs. low beta 14.43 (95%CI -0,19 to 28,67), **p=0.049** Cortical vBMD: IPD mid vs. low, beta -11,51 (95%CI -19,94 to -3,07), p=0.008; high vs. low beta -8.77 (95%CI -17,48 to -0,07),	C. Detection bias: Low risk Reason: low BMD by DXA is a hard end-point, not susceptible to subjectivity of the assessor D. Confounding: Low risk Reason: important confounders were taken into account into multivariable models. Over adjustment may have occurred, because of including muscle mass into the model (probably a mediator).

			p=0.050 (**N.B: association in the opposite direction**) FN BMD Z-score: IPD mid vs. low, beta 0.2 (95%CI -0,2 to 0,5), p=0.36; high vs. low beta 0.4 (95%CI 0 to 0.8), **p=0.044** TH BMD Z-score: IPD mid vs. low, beta 0.1 (95%CI -0,2 to 0,4), p=0.47; high vs. low beta 0.4 (95%CI 0.06 to 0.7), **p=0.022** LS BMD Z-score: IPD mid vs. low, beta 0.08 (95%CI -0,4 to 0,5), p=0.73; high vs. low beta 0.14 (95%CI -0.3 to 0.6), p=0.54 (N.B. risk estimates of confounders not described) Impact peak number (IPN) not significant for all outcomes. Differences in densitometric and microstructural measures between three tertile groups of impact loading duration (ILD) physical activity ranged from 3 to 13% (adjusted for all covariates) with tendency to better bone health in high ILD group.	

Abbreviations: BMD=bone mineral density; CCS=childhood cancer survivors; DXA=dual-energy X-ray absorptiometry; IQR=inter quartile range; NA=not applicable; NR=not reported; pQCT=peripheral quantitative computed tomography; SCT=stem cell transplantation.

What surveillance modality should be used?

What surveillance modality should be used?				
Azcona et al. Reduced Bone Mineralization in Adolescent Survivors of Malignant Bone Tumors: Comparison of Quantitative Ultrasound and Dual-Energy X-Ray Absorptiometry. J Pediatr Hematol Oncol. 2003;25(4):297-302.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Diagnostic test**	**Main outcomes**	**Additional remarks**
Study design: Cross-sectional study Treatment era: 1984-2000 Follow-up: Mean disease-free survival 4.97 years (range 3.6-6.3)	Type and number of non-participants: Eligible cohort 75 white patients who completed treatment of a bone tumor at the University hospital of Pamplona, Spain from 1984 to 2000, who were in remission. 39 non-participants. Type and number of participants: 36 adolescent survivors (21 boys and 15 girls) of malignant bone tumor Controls: NA Diagnoses: Osteosarcoma 23/36 (63.9%) Ewing sarcoma 13/36 (36.1%) Age at diagnosis: Mean 14.3 years (range 12.7-15.9) Age at follow-up: Mean 19.4 years (range 17.8-21.0) All patients with Ewing sarcoma received local radical radiotherapy 15 patients with osteosarcoma received local intraoperative radiotherapy.	Diagnostic test(s): -Quantitative ultrasound of the distal metaphysis of the proximal phalanxes of the last four fingers of the nondominant hand (DBM Sonic 1200 ultrasound densitometer) -DXA of the lumbar spine (L1-L4) (Hologic QDR-4500 W) Outcome definitions: Osteopenia: Z-score ≤-1 using previously published reference values. QUS sensitivity, specificity, positive and negative predictive values and diagnostic accuracy for detecting osteopenia	Prevalence/risk of late effect: LS BMD SDS: whole group: -0.58 (range -0.92 to -0.24; p=0.008) OS: -0.59 (-1.08 to -0.11) and ES: -0.57 (-1.07 to -0.08) QUS (Ad-SoS) SDS: OS: -0.26 (0.83 to 0.32) and ES: -0.48 (-1.60 to 0.64) The differences between OS and ES were not significant. For QUS, differences in SDS were significant between women and men: -0.90 vs 0.06 (p=0.03) Diagnostic outcomes (sensitivity, specificity, PPV, NPV, ROC): QUS sensitivity 36.4% (range 12.8%-66.4%), specificity 80.0% (range 61.1-92.3%), PPV 44.4% (range 20.9%-70.8%), NPV 74.1% (range 63.7%-82.3%) QUS diagnostic accuracy 66.7% (range 50.2%-80.5%) Correlation QUS (Ad-SoS; m/s) and DXA (g/cm^2): r =0.44, p= 0.008	Strengths: -BMD was assessed by both QUS and DXA in all survivors -Diagnostic values were calculated Limitations: -Small sample size of one tumor type -QUS was assessed at the phalanxes whereas BMD was assessed at the lumbar spine (different locations) -no description of the non-participants **Risk of bias** A. Selection bias: Unclear Reason: the study group consisted of less than 75% of the original cohort, and the article provides no flowchart or comparison between participant and non-participant characteristics. B. Index test bias: Unclear Reason: not described whether the index test results were interpreted without knowledge of the results of the reference standard in all patients.

	Methotrexate: Total cumulative dose (g/m^2) OS 65.6 (37.1; 84.5), ES 0.2 (0.2; 0.3) Cyclophosphamide: Total cumulative dose (g/m^2) OS 4.3 (2.0; 6.0), ES 17.7 (13.8; 21.8) Ifosfamide: Total cumulative dose (g/m^2) OS 17.9 (10.9; 32.0), ES 35.0 (6.8; 52.5) Doxorubicin: Total cumulative dose (mg/m2) OS 428.5 (121.6), ES 470.4 (178.4) Actinomicin D: Total cumulative dose (mg/m2) OS 4.3 (3.3; 6.5), ES 9.7 (3.7) Bleomycin: Total cumulative dose (mg/m2) OS 95.9 (44.6), ES 170.8 (63.2) Vincristine: Total cumulative dose (mg/m2) OS 6.3 (3.9; 9.3), ES 24.1 (17.9; 35.8) Cisplatin: Total cumulative dose (mg/m2) OS 466.0 (146.1), ES 0.0			C. Reference test bias: Unclear Reason: not described whether reference test results were interpreted without knowledge of the results of the index test in all patients. D. Verification bias: Unclear Reason: the interval between the index test(s) and reference standard was not described. E. Attrition bias: Low risk Reason: all participants received the same reference standard and index test.

Abbreviations: Ad-SoS=amplitude dependent speed of sound; BMD=bone mineral density; DXA=dual-energy X-ray absorptiometry; ES=Ewing sarcoma; LS=lumbar spine; NPV=negative predictive value; OS=osteosarcoma; PPV=positive predictive value; QUS=quantitative ultrasound; ROC=receiver operating characteristic; SDS=standard deviation score.

What surveillance modality should be used?				
Brennan et al. Reduced bone mineral density in young adults following cure of acute lymphoblastic leukaemia in childhood. British J Cancer (1999) 79 (11/12), 1859-1883.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Diagnostic test**	**Main outcomes**	**Additional remarks**
Study design: Single-center cross-sectional study Treatment era: During UKALL I-VIII, X or Memphis V Follow-up: Participants were at least 2 years from completion of cancer therapy. 6.8 till 28.6 years after cranial radiation (median 17.8 years)	Type and number of non-participants: NR Type and number of participants: -31 young adult survivors (16 male) of ALL, median age 17.8 years (range, 6.8 – 28.6 y) after cranial RT -All in first remission -All had achieved final height; progressed spontaneously through puberty -All had normal estradiol, testosterone, gonadotrophins -None had fractures -None received GH therapy Diagnoses: Acute lymphoblastic leukemia Age at diagnosis: Median age 6.9 years (range, 1.6 – 16 y) Age at follow-up: Median age 23 years (range, 18.8 – 33 y) Controls: 35 age and BMI matched healthy medical students (18 male) Median age 21.6 years (range, 21 – 25 y) None had received any chronic medication within the last 3 years	Diagnostic test(s): *BMD measurement modality:* BMD was assessed in the patients (survivors) only: ***QCT:*** T12 to L3 using single energy QCT on a GE 9800 general purpose scanner with low dose scanning technique and liquid K2HPO4 calibration phantom 28 patients QCT performed using Philips SR 4000 CT with solid calcium hydroxyapatite reference phantom Mean trabecular BMD measured in mg cc mineral equivalents of either K2HPO4 in water (n = 4) or calcium hydroxyapatite (n = 28). Precision (CV%) of technique in the department = 1% in normal subjects and 2.5% in osteoporotic patients *Reference ranges* GE scanner: Block et al 1989 for men; Genant et al 1983 for women *Reference ranges* Phillips scanner: Image Analysis, Inc. ***DXA***: Integral (mixed cortical and trabecular) bone of L2 to L4 and right femoral neck using Lunar DPX-L scanner. Mean BMD measured in g cm^{-2}.	Prevalence/risk of late effect: NR In survivors, significantly lower vertebral trabecular BMD (QCT: median Z-score -1.25 ($p<0.001$), in integral bone of the lumbar spine (DXA median Z-score: -0.74; $p=0.001$, in cortical bone of the forearm (SXA: median Z-score: -1.35; $p<0.001$) and integral bone of the femoral neck (DXA median Z-score -0.43; $p=0.03$) Results: Correlations between the modalities: No significant correlation between QCT and SXA: 0.07; $p=0.73$ No significant correlation between QCT and DXA spine: 0.33; $p=0.08$ **Significant correlation between QCT and DXA femoral neck: 0.53; p=0.004** **Significant correlation between DXA spine and SXA: 0.45; p=0.02** **Significant correlation between DXA spine and DXA femoral neck: 0.41; p=0.03** No significant correlation between DXA femoral neck and SXA: r=0.14; p=0.45 8 patients classified as severe	Strengths: -Controls which were comparable to survivors by age and BMI. The controls were well assessed for not having chronic health problems. -GHD was well assessed Limitations: -Small study sample -selection of the sample was not described (reasons for non participation; it is not known whether the sample is representative for young adult survivors of ALL). -Controls were medical students which may be a relatively healthy group. -Only correlations were calculated to examine potential risk factors **Risk of bias** A. Selection bias: Unclear Reason: cohort selection not reported. B. Index test bias: Low risk Reason: all measures were objectively assessed by valid apparatus. The index test results were interpreted without knowledge of the results of the reference standard in all patients.

	and all underwent physical examination to exclude any undetected pathology Only labs: osteocalcin and ICTP <u>Cancer treatment</u> *Chemotherapy:* Over 2–3 years with either UKALL protocols I, II, III, IV, V, VI, VII, VIII, X or Memphis V. UKALL protocols I, II, III, V and VII, were standard regimens of vincristine, prednisolone (total dose 5–5.9 gm m2), L-asparaginase, methotrexate (total dose 1.7–1.92 gm m2) and 6-mercaptopurine. UKALL IV, VI and Memphis V contained same drugs but administered in a pulsed manner. UKALL VIII included the same drugs but were administered in a sustained manner UKALL X was similar to the standard regimes but with addition of intensification blocks in some, but not all, patients. *Radiotherapy:* All received between 18 and 25 Gy cranial RT (11 received 18 Gy) Four subjects also received 24 Gy spinal irradiation.	Precision of the measurement in the department = 0.5% in spine and 2.5% in femoral neck. *Reference ranges:* Provided by manufacturer Lunar. Weight corrected Z-scores. ***SXA***: In distal nondominant forearm using an Osteometer DTX-100 scanner measuring predominantly cortical bone. BMD measured in g cm2. Precision of measurement = 1%. *Reference ranges*: manufacturer <u>Outcome definitions:</u> Correlations between QCT, DXA and SXA Patient cohort classified into three GH status groups: Group 1 – GH-deficient, peak GH response to both tests of less than 9 mU ml; Group 2–GH insufficient, peak GH response to both tests less than 20 mU ml but one or both responses greater than 9 mU ml; Group 3–GH normal, peak GH response to one or both tests greater than 20 mU ml Bone markers Type I collagen cross-linked C-teleopeptide (ICTP) Osteocalcin	GH-deficient (group 1) 12 patients GH insufficient (group 2) 11 patients normal (group 3) No difference in GH status groups for BMD measurements, QCT spine, DXA spine or DXA femoral neck (P = 0.8, P = 0.96 and P = 0.4, respectively) No correlation between BMD measurements at any of the four sites with time of since or age at diagnosis. No difference in markers of bone turnover between patients and controls; median (range) serum osteocalcin 13.3 (1.8–40.7) and 12.0 (2.9–43.6) ng ml (P = 0.7), respectively, ICTP 5.0 (2.7–8.8) and 4.9 (3.5–8.3) mg L (P = 0.67) respectively Final height SDS of whole cohort significantly reduced but reduction in stature only noted in the subset with severe GH-deficient (group 1); not in GH status groups 2 or 3. But no difference in BMD measurements between the three GH status groups.	<u>C. Reference test bias</u> Low risk Reason: All measures were objectively assessed by an apparatus. (see B) <u>D. Verification bias:</u> Unclear Reason: Likely, all tests were done on the same day, but this was not described. <u>E. Attrition bias</u>: Unclear Reason: it was not described how many patients got each of the different tests.

Abbreviations: BMD=bone mineral density; BMI=body mass index; GH=growth hormone; ICTP=type I collagen cross-linked C-teleopeptide; NR=not reported; RT=radiotherapy; QCT=quantitative computed tomography; SDS=standard deviation score; SXA=single X-ray absorptiometry.

What surveillance modality should be used?				
Kaste et al. QCT versus DXA in 320 survivors of childhood cancer: association of BMD with fracture history. Pediatr Blood Cancer 2006; 47:936-943.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Diagnostic test**	**Main outcomes**	**Additional remarks**
Study design: Retrospective study Treatment era: Not specified; probably end 1980-1990 (age at examination was 16.4 years and the study was published in 2006) Follow-up: NR	Type and number of non-participants: none It was a retrospective study of medical records Type and number of participants: 320 pediatric cancer patients at least 5 years of age. "Survivors", but time since stop therapy not specified. Controls: None Age at diagnosis: NR Age at examination: 16.4 (range: 5.1-36 yrs) Diagnosis Brain tumor (n=142) Leukemia/lymphoma (n=146) Solid tumor (n=32) Cancer treatment: NR	Diagnostic test(s): -Quantitative computed tomography by Siemens Somatom-Plus spiral CT scanner (Siemens, Iselin, NY) and Mindways QCT Calibration Phantoms and software (Mindways Software, Inc., South San Francisco, CA) at lumbar spine. -DXA Hologic 4500 QDR-A fan beam system (Hologic, Inc., Bedford, MA) at lumbar spine in anterior projections of L1 – L4 and lateral projections of L2 – L4. LS BMD and BMAD Z-scores were calculated. Normative values in the manufacturer´s reference database were used to calculate Z-scores. Outcome definitions: -Diminished BMD was defined as a Z-score at least two standard deviations below the reference mean values. -Questionnaire about the patient's fracture history before the DXA examination was available for only half of the study cohort.	Prevalence/risk of late effect: QCT Z-score: <-2: n=96 (30%) QCT Z-score median: -1.43 range: -5.96 to 3.2) DXA Z-score <-2: n=89 (27.8%) DXA Z-score median: -1.30 (-5.5 t0 2.8) Diagnostic outcomes (sensitivity, specificity, PPV, NPV, ROC): Significant linear relationship between average BMD of the L1–L2 as measured by DXA and QCT (Pearson correlation coefficient 0.52, P < 0.0001). Correlation between DXA-derived BMAD and QCT BMD (Pearson correlation coefficient 0.60, P<0.0001). Significant linear relationship between DXA and QCT Z-scores (Pearson correlation coefficient 0.64, P < 0.0001) Agreement of QCT and DXA with diagnosis of Z-score <-2 was fair K=0.32 Risk factors Higher age and non-white race were associated with higher BMD in L1 and L2. Non-whites has also higher QCT BMD values.	Strengths: -Large study sample -Statistical analyses were well-performed -QCT and DXA were performed at the same location (L1 and L2) Limitations: -Type of tumors and type of treatment not specified. -Retrospective study, information may have been lacking or wrongly interpreted from the medical records. -Lots of information was not described, e.g. time since completion of treatment. Diagnostic values were not calculated **Risk of bias** A. Selection bias: Unclear Reason: not specified whether all children who were treated in a certain period for cancer were included or not (probably not). Also the follow-up period and treatment period were not specified. B. Index test bias: Unclear Reason: as the data came from the medical records, it is not known whether the medical doctor interpreted the DXA and QCT

				without knowledge of the results of the reference standard in all patients The evaluation of fractures were performed only on the basis of patient self-report. <u>C. Reference test bias:</u> Unclear Reason: not clearly specified the reference standard in all patients <u>D. Verification bias:</u> Low risk Reason: both DXA and QCT should have been performed within same 24-hour period. <u>E. Attrition bias:</u> Low risk Reason: all participants received the same reference standard and index test.

Abbreviations: BMD=bone mineral density; DXA=dual-energy X-ray absorptiometry; NPV=negative predictive value; NR=not reported; PPV=positive predictive value; QCT=quantitative computed tomography; ROC=receiver operating characteristic.

When should surveillance be initiated and at what frequency should it be performed?

When should surveillance be initiated and at what frequency should it be performed?				
Demirkaya et al. Time-dependent alterations in growth and bone health parameters evaluated at different posttreatment periods in pediatric oncology patients. Ped Hematol and Oncol 2011;28:588-599.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Prospective study Treatment era: 1997-2005 Follow-up: First evaluation: mean 2.62 ± 1.44 years Second evaluation: mean 6.55 ± 1.71 years after the completion of treatment	Type and number of non-participants: Eligible cohort: 72 children who were treated with chemotherapy and/or RT and completely recovered at least 6 months before the enrollment. Six patients were excluded (3 were not reached; 2 died; 1 experienced cancer recurrence) Type and number of participants: 66 children treated for lymphoma or solid tumors Diagnoses: Non-Hodgkin lymphoma: 18 (27.3%) Hodgkin lymphoma: 9 (13.6%) Wilms tumor: 14 (21.2 %) Soft tissue sarcoma: 8 (12.1%) Neuroblastoma: 5 (7.6%) Retinoblastoma: 4 (6.1%) Bone tumor: 3 (4.5%) CNS tumor: 3 (4.5%) Nasopharynx carcinoma: 1 (1.5%) Germ cell tumor: 1 (1.5%) Age at diagnosis: Mean 6.55 ± 4.77 years (2 months to 17.7 years) Age at follow-up: not specified Controls: not provided	Chemotherapy: 66 (100%) Radiotherapy: 21 (31.8%) SCT: 0 Limb amputation: 0 Other: 0 Treatment modalities Chemotherapy, n (%) 66 (100) Corticosteroid, n (%) 19 (28.8) Dose (mg/m2), mean ± SD (range) Dexamethasone (n = 15) 513.05 ± 159.70 (245–780) Prednisolone (n = 1) 1900.0 ± 0.0 (1900–1900) Methotrexate, n (%) 20(30.3) Dose (g/m2), mean ± SD (range) 35.07 ± 37.49 (20–144) Cyclophosphamide, n (%) 37 (56.1) Dose (g/m2), mean ± SD (range) 6.98 ± 5.96 (1.20–22.20) Ifosfamide, n (%) 17 (25.8) Dose (g/m2), mean ± SD (range) 14.47 ± 15.0(6.0–54.0) Vinca alkaloid, n (%) 62 (93.9) Anticancer antibiotics, n (%) 45 (68.2) Platin group, n (%) 14 (21.2) Etoposide, n (%) 20 (30.3)	Outcome definitions: Normal: BMD Z-score ≥ -1 Osteopenia: BMD Z-score ranging from -1 and -2 Osteoporosis: BMD Z-score ≤ -2 BMD measurement modality: Dual-energy X-ray absorptiometry (DXA) method using a Hologic (Bedford, MA) QDR Delphi W (S/N 70232) computerized densitometry device at L2-L4 lumbar vertebrae Results: First evaluation: -normal (n=23) -osteopenia (n=26, 39.4%) -osteoporosis (n=17, 25.8%) Second evaluation: -normal (n=46, 69.6%) -osteopenia (n=13, 19.7%) -osteoporosis (n=7, 10.6%) Mean BMD Z-score: At first evaluation: -1.26 ± 1.12 (range -4.3 to 2.0) at second evaluation: -0.48 ± 1.25 (range -3.30 to 3.40) Significant recovery was observed in BMD at second evaluation.	Strengths: -Longitudinal design Limitations: -Short period of follow-up -No specified other risks factors for low BMD -No control group **Risk of bias** A. Selection bias: Unclear Reason: no comparison in baseline characteristics between participants and non-participants. It is not known whether those who had two DXA assessments were a selective sample of all eligible patients. B. Attrition bias: Low risk Reason: the outcome was assessed for all subjects enrolled in the study C. Detection bias: Low risk Reason: low BMD detection by DXA

		Intrathecal therapy, n (%) 19 (28.8) Radiotherapy, n (%) 21 (31.8) Cranium/craniospinal, n (%) 7 (33.3) Neck/mantle region, n (%) 7 (33.3) Other regions, n (%) 7 (33.3) Primary region RT dose (cGy), mean ± SD (range) 3561 ± 1367 (1560–5400)	No significant correlation was detected between follow-up duration and BMD Z-score. No osteoporosis after 8 years. <u>Risk factors for low BMD:</u> Radiotherapy: BMD *z*-score 1st evaluation (−1.64) ± 1.19 [(−4.3)−0.8]* 2nd evaluation (−1.10) ± 1.12 [(−3.3)−0.7]** No Radiotherapy: (−1.05) ± 1.04 [(−2.6)−2.0] * (−0.19) ± 1.21 [(−2.1)−3.4] ** *p= .049 **p= .013 No difference between patients with and without chemo (yes/no and dose)	

Abbreviations: BMD=bone mineral density; CNS=central nervous system; DXA=dual-energy X-ray absorptiometry; RT=radiotherapy; SCT=stem cell transplantation; SD=standard deviation.

When should surveillance be initiated and at what frequency should it be performed?				
Gurney et al. Bone Mineral Density Among Long-Term Survivors of Childhood Acute Lymphoblastic Leukemia: Results From the St. Jude Lifetime Cohort Study. Pediatr Blood Cancer. 2014 Jul;61(7):1270-6.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Retrospective single-center cohort study with cross-sectional and prospective data, St Jude Life Cohort Treatment era: Not specified Follow-up: Not specified, had to be at least 10 years post-diagnosis to be included	Type and number of non-participants: NR Type and number of participants: Group 1: Patients with ALL, >18 years + ≥ 10 years from their original cancer diagnosis Group 2=After Completion of Therapy (ACT) clinic: Patients > 2 years after treatment + > 5 years from diagnosis until they are age 18 years or older and at least 10 years post-diagnosis. Group 1: Of the 883 active participants, 845 had BMD test (61% of the 1,383 eligible cohort) Group 2: Of those, 400 had a prior BMD test conducted in the ACT clinic for analysis of BMD change over time Diagnoses: ALL (100%) Age at diagnosis: Median 5.02 (range: 3.07–9.33) Age at follow-up: Median 31.3 (range: 25.6–37.4) Controls: NR	Chemotherapy: Prednisone equivalent dose 9,520 (1,120–10,400) mg/m² (1 mg prednisone=0.15 mg dexamethasone) Etoposide 0.0 (0.0–9,208) Teniposide 0.0 (0.0–3,241) Methotrexate 5,426 (2,596–18,332) Cyclophosphamide 3,490 (0.0–9,556) Anthracycline 46 (0.0–88) Vincristine 41 (6.3–57) Radiotherapy: Spinal radiation: 15 Gy and almost every patient who received spinal radiation also received at least 24 Gy cranial radiation. 18 cranial RT <18 Gy, 185 18 to 24 Gy, 237 ≥24 Gy SCT: 21 (20 allogeneic HSCT for high risk or relapsed ALL or secondary AML + 1 autologous HSCT for a 2nd brain tumor) Limb amputation: NA Other: Ethnicity	Outcome definitions: -BMD and its Z-score via QCT -Change in BMD over a median of 8.5 years BMD measurement modality: BMD from the direct axial images quantitative computed tomography of the midvertebral bodies L1 and L2. BMD was defined as the average of values obtained from L1 and L2 and Z-score was calculated Results: **Prevalence** BMD Z-score of <-2 : 5.7% Z-score -1 to -2 : 23.8% 70.5% BMD Z-score in the normal range (>-1). At age 40 years, BMD Z-score of <-1 was 37.9% (95% CI 33.3–42.5%) overall, 46.2% (95%CI 39.9–52.4%) for males and 28.3% (95% CI 21.9–34.9%) for females. **Analysis over time** Initial test, BMD Z-score of <-2; 15.2% At the subsequent test: 7.0% 91.8% either improved their BMD Z-score category or remained in the same category over the follow-up period 67% of those who previously had a BMD Z-score of <-2 improved by	Strengths: -Large study sample -Use of QCT Limitations: -Age at time of treatment was not included in multivariable analysis. -Craniospinal RT is significant, particularly for women – but we don't know if there is a difference of cranio-spinal RT between men and women (for example age at this time) -It is unclear how the cumulative dose of anthracycline and glucocorticoids was calculated **Risk of bias** A. Selection bias: Unclear Reason: no data about non-participants B. Attrition bias: Low risk Reason: outcome for all the study particpants C. Detection bias: Low risk Reason: low BMD by DXA is a hard end-point, not susceptible to subjectivity of the assessor

			1 or more categories a median of 8.5 years later – due to recommendations for calcium and vitamin D supplementation and/or lifestyle counseling to optimize bone health (bisphosphonates were not prescribed)	

Abbreviations: ACT=after completion of therapy; ALL=acute lymphoblastic leukemia; AML=acute myeloid leukemia; BMD=bone mineral density; CI=confidence interval; IQR=interquartile range; NR=not reported; QCT=quantitative computed tomography; RT=radiotherapy; SCT=stem cell transplantation.

Who needs BMD surveillance?				
Latoch et al. A long-term trajectory of bone mineral density in childhood cancer survivors after discontinuation of treatment: retrospective cohort study. Arch Osteoporos. 2021 Feb 26;16(1):45.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Retrospective cohort study Treatment era: 1987 to 2015 Follow-up: Median (range) 6.12 (4.0-22.0) years since end of treatment	Type and number of non-participants: Of the 773 childhood cancer survivors who visited oncology outpatient's clinic between 1990 and 2016 for late effects, 326 (42%) had at least one DXA scan after cessation of treatment Type and number of participants: N=326 childhood cancer survivors diagnosed with cancer under 18 years of age with a DXA scan available after cessation of treatment, who had no history of conditions which may have affected bone mineral density and content (i.e., apparent endocrine or renal disorders). Patients with relapse were excluded from the analysis. N=123 survivors had multiple DXA measurements Diagnoses: Multiple types of childhood cancer (excluding brain and bone tumor survivors) Acute lymphoblastic leukemia (ALL) n=138 (42.3%) Acute myeloblastic leukemia (AML) n=12 (3.7%) Chronic myeloblastic leukemia (CML) n=3 (0.9%) Hodgkin lymphoma n=48 (14.7%)	Chemotherapy: Corticosteroids: n=232 (71.2%) Median (IQR) prednisone equivalent dose: 2081 (1600-3081) mg/m2; mean (SD): 3126 ± 2000 mg/m2 MTX: n=166 (50.9%) Median (IQR) MTX dose: 2 (1-5) g/m2; mean (SD): 3.057 ± 1.89 g/m2 Radiotherapy: CRT: n=83 (25.5%) Median (IQR) CRT dose: 18 (12-18) Gy TBI: n=13 (4.0%) Abdominal: n=54 (16.7%) SCT: N=23 (7%) Limb amputation: NR Other:	Outcome definitions: Low BMD: Z-score ≤ − 1.0, Very low BMD: Z-score ≤ − 2.0 BMD measurement modality: DXA of the lumbar spine (L1-L4) and total body (DPX-L, GE-Healthcare Lunar, Madison, WI) Results: **Prevalence** Low BMD TB: 24% Low BMD LS: 20% Very low BMD LS and/or TB: 8% **Multivariable model** Low TB BMD: Age at diagnosis (increase per 1 year): OR=0.97, 95%CI 0.91–1.04, p=0.439 Age at DXA scan (increase per 1 year): OR=0.95, 95%CI 0.87–1.03, p=0.215 BMI at DXA scan (underweight n = 17 vs. normal n = 246) OR=3.16, 95%CI 1.1–9.07, p=0.032 Radiotherapy to the head and neck (yes n = 165 vs. no n = 161): OR=1.74, 95%CI 0.92–3.32, p=0.089 Stem cell transplantation (yes n = 23 vs. n = 303, majority had TBI): OR=3.13, 95%CI 1.02–9.63, p=0.046 Low LS BMD:	Strengths: -Longitudinal DXA measurements Limitations: -Very selective cohort -Possible selection of the survivors with two DXA measurements. Only 123 of 326 (38%) participants had two assessments. It is unknown whether this is a selective cohort or not. **Risk of bias** A. Selection bias: High risk Reason: Only 42% of the survivors seen at the late effects clinic had a DXA scan B. Attrition bias: Low risk Reason: all included survivors had a DXA scan and were included in the analysis High risk for the longitudinal analysis Reason: Only 38% of the included survivors had longitudinal DXA measurements C. Detection bias: Low risk Reason: low BMD by DXA is a hard end-point, not susceptible to subjectivity of the assessors

	Non-Hodgkin lymphoma n=28 (8.6%) Wilms tumor n=39 (12.0%) Soft tissue sarcoma n=19 (5.8%) Neuroblastoma n=13 (4.0%) Germ cell tumor n=13 (4.0%) Langerhans cell histiocytosis n=7 (2.1%) Hepatoblastoma n=3 (0.9%) Melanoma n=2 (0.6%) Retinoblastoma n=1 (0.3%) <u>Age at diagnosis:</u> Median (IQR) 7.27 (4.41–10.06) years <u>Age at follow-up:</u> Median (IQR) 16.0 (12.92-19.0) years <u>Controls:</u> Normative values from the DXA manufacturer		Sex (male n = 179 vs. female n = 147): OR=1.84, 95%CI 1.00–3.41, p=0.050 Age at diagnosis (increase per one year): OR=0.94, 95%CI 0.88–1.01, p=0.175 BMI at DXA scan (underweight n = 17 vs. normal n = 246): OR=3.57, 95%CI 1.24–10.23, p=0.004 Radiotherapy to the head and neck (yes n = 165 vs. no n = 161): OR=2.54, 95%CI 1.32–4.90, p=0.016 **Longitudinal BMD course** Mean time between the second (DXA2) and first (DXA1) densitometry was 5.54 years (mean age, 17.11 ± 3.67 vs. 11.57 ± 4.03 years Mean Z-scores between DXA1 and DXA2: TB: −0.176 vs. −0.262, p=0.293 LS: −0.277 vs. −0.180, p=0.842 Number of patients with TB BMD Z-score <−2 was 18 vs. 6, and that with Z-score <−1 and ≥ −2 was 23 vs. 19; LS BMD Z-score <−2 was 9 vs. 6 and Z-score <−1 but > − 2 was 28 vs. 14 patients	<u>D. Confounding:</u> Low risk Reason: the analyses were adjusted for all possible confounders

Abbreviations: BMD=bone mineral density; BMI=body mass index; CI=confidence interval; CRT=cranial irradiation; DXA=dual-energy X-ray absorptiometry; IQR=interquartile range; LS=lumbar spine; MTX=methotrexate; NR=not reported; RT=radiotherapy; SCT=stem cell transplantation; TB=total body; TBI=total body irradiation

When should surveillance be initiated and at what frequency should it be performed?				
Marinovic et al. Improvement in bone mineral density and body composition in survivors of childhood acute lymphoblastic leukemia: a 1-year prospective study. Pediatrics Vol 116 No1 July 2005 e102-108.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Prospective cohort Treatment era: 1995-1999 Follow-up: 1 year (0 to 3 years after cessation of ALL therapy)	Eligible: (1) 3 to 21 years of age; (2) white origin; (3) 0 to 3 years after cessation of ALL therapy; and (4) no relapse, second neoplasm, or bone marrow transplant. Exclusion criteria were (1) cranial irradiation, (2) pregnancy, and (3) chronic diseases or any treatment associated with altered bone metabolism. Type and number of non-participants: N=19 declined to participate of n=56 potential study subjects. No difference was found between participating and nonparticipating subjects with respect to age, gender, or length of time since the completion of treatment. Type and number of participants: 37 patients (17 girls, 20 boys) at baseline and 34 at second measurement one year later Control subjects: n=74, matched by age, sex and pubertal stage were randomly identified for each patient from a large, healthy group of white children (*n*=266) who were longitudinally investigated for BMD	Chemotherapy: Predniso(lo)ne, vincristine, daunorubicin, L-asparaginase, 6-mercaptopurine, cytarabine, cyclophosphamide, intrathecal MTX; IV MTX in n=4 Radiotherapy: None SCT: None Limb amputation: None Other: *Biochemical Parameters*: Calcium, Phosphorus, magnesium, alkaline phosphatase, 25-hydroxyvitamin D, 1.25-dihydroxyvitamin D, parathyroid hormone, osteocalcin, bone alkaline phosphatase and CrossLaps.	Outcome definitions: BMD longitudinal changes BMD measurement modality: BM(A)D LS and TB using DXA of the lumbar spine (L2-L4) (Lunar DPXL, Madison, WI) Results: The median BMDTB in ALL patients at baseline: slightly non-significantly reduced (*P*=.06) At 1 year follow-up: no difference from control subjects was found (*P*=0.23). Median areal BMDLS at baseline: significantly lower in patients than controls at baseline (*P*=.04) At 1 year follow-up: not significantly slightly reduced (*P=0* .06) None of the subjects had a BMD Z-score <-2 or TB BMD Z-score <-1 All biochemical bone parameters were within the normal range. Longitudinal assessment Both groups showed an annual increment in their BMD measurements. TB BMD (but not LS BMD) demonstrated a significantly higher increase	Strengths: -Homogenous study population -Matched controls -Longitudinal study -Few attrition between baseline and follow-up Limitations: -Small sample size **Risk of bias** A. Selection bias: Low risk Reason: Only 66% of original population participated, but no differences between age, gender or length of time since completion of treatment between those who did and did not participate. B. Attrition bias: Low risk Reason: very few loss to follow-up C. Detection bias: Low risk Reason: low BMD LS and TB by DXA is a hard end-point, not susceptible to subjectivity of the assessor

	Diagnoses: ALL (100%) Age at diagnosis: Median age 3.3 years (range 1.1-16.6 years) Age at baseline: Median age 7.9 years (25th and 75th percentile 6.2; 9.8) Age at follow-up: Median age 8.9 years (25th and 75th percentile 7.3; 11.0) Time since completion of therapy: Median period of 2.2 years (range: 0.1–3.1 years) Control group: Age at baseline median 7.9 years (25th and 75th percentile 6.5; 10.2) Age at follow-up median 9.1 years (25th and 75th percentile 7.6; 11.7)		(*P*=.01) in ALL patients as compared with control subjects BMD TB: Patients baseline 0.843 (0.803; 0.917) follow up 0.886 (0.827; 0.962) change: 0.034 (0023; 0044) p=0.005 Control subjects baseline 0.872 (0.838; 0.956); follow up: 0.901 (0.858; 0.983); change: 0.025 (0014; 0031) p=.003 BMD LS: Patients baseline 0.682 (0.629; 0.758) follow-up: 0.732 (0.671; 0.847); change: 0.039 (0022; 0074), p= .0003 Control subjects baseline: 0.720 (0.656; 0.817); follow up: 0.773 (0.685; 0.876) change: 0.034 (0006; 0053) p<0.001 BMAD LS: Patients baseline: 0.146 (0.131; 0.166); follow up: 0.149 (0.137; 0.169) change: 0.004 (0.002; 0.008); p=0.19 Control subjects baseline 0.152 (0.137; 0.164); follow up: 0.153 (0.139; 0.168); change: 0.002 (_0004; 0008); p=.04	

Abbreviations: ALL=acute lymphoblastic leukemia; BMD=bone mineral density; LS=lumbar spine; MTX=methotrexate; TB=total body.

When should surveillance be initiated and at what frequency should it be performed?				
Muszynska-Roslan et al. Is the Treatment for Childhood Solid Tumors Associated with Lower Bone Mass than that for Leukemia and Hodgkin Disease? Pediatric Hematology and Oncology, 26:1, 36-47, 2009.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Longitudinal study Treatment era: Not reported Follow-up: Two assessment time points: Time from end of therapy to 1st assessment (which was reported by diagnosis category): -ALL: 2.4 ± 1.9 years -Hodgkin lymphoma: 2.8 ± 2.1 years -Solid tumor: 3.7 ± 4.6 years Time from end of therapy to 2nd Assessment: -ALL: 5.8 ± 3.4 years -Hodgkin lymphoma: 6.3 ± 2.9 years -Solid tumor: 6.9 ± 4.6 years	Type and number of non-participants: NR Type and number of participants: 114 CCS treated for ALL, Hodgkin lymphoma, and solid tumors. Diagnoses: ALL: 43 (37.7%) Hodgkin lymphoma (HL): 35 (30.7%) Solid Tumor: 36 (31.6%) Age at diagnosis: Median age at diagnosis 8.4 years (range 1.4-17 years) Age at follow-up: Two assessment time points: Median age 12.8 years (range 5.1–23.5) at 1st assessment and 16.4 years (range 7.3–27.2) at 2nd assessment Controls: Reference data from 473 age and sex-matched healthy controls.	Chemotherapy: Corticosteroid: -Overall: 78/114 (68.4%) -ALL: 43/43 (100%); median cumulative dose 2950mg prednisone/m2 (range 1680-5540mg/m2) -Hodgkin lymphoma: 35/35 (100%); median cumulative dose 1200mg prednisone/m2 (range 800-1600mg/m2) -Solid tumor: 0/36 (0%) Methotrexate: -Overall: 43/114 (37.7%) (100% of ALL patients, no HL or ST patients) Radiotherapy: -Cranial radiation: 28/114 (24.6% of full cohort, 65.1% of ALL cohort); (1200Gy) -Mediastinal RT: 32/114 (28.1% of full cohort, 91.4% HL cohort); (20Gy) -Abdominal RT: 41 (36%) -Extra-abdominal local radiation: 4/114 (3.5%) SCT: NR Limb amputation: NR	Outcome definitions: Low BMD Z-score <-2 BMD measurement modality: DXA (lunar) of total body and lumbar spine (L2-L4) Low BMD: (1st; 2nd assessment): ALL: 10.5%; 8.7% HL: 6.9%; 6.9% Solid Tumor: 30.5%; 16.6% Median TB BMD Z-score* (1st, 2nd assessment): ALL: 0.26 ± 1.7; 0.12± 1.5 HL: 0.11±0.9; -0.09±1.2 Solid Tumor: -1.14±1.2**; -0.40±0.6 (** p=0.00001, difference between examined and reference group) Median Spine BMD Z-score* (1st, 2nd assessment): ALL: 0.23 ± 1.3; 0.15± 1.6 HL: 0.23±1.1; -0.09±0.8 Solid Tumor: -1.13±1.1**; ? ±0.8 (** p=0.00002, difference between examined and reference group) *Age and sex-adjusted Z-score, 21 patients with height Z-score <-1 assess according to bone age Multiple regression analyses:	Strengths: -Highlights potential risk for low BMD in those treated for Solid Tumors -Large reference group Limitations: -Relatively small study sample -Fracture not reported **Risk of bias** A. Selection bias: High risk Reason: information on non-participants not reported, and mean age at diagnosis rather old for these tumor types. B. Attrition bias: Low risk Reason: outcomes appear to have been assessed in full study group (although not definitively stated) C. Detection bias: Low risk Reason: low BMD by DXA hard end-point (not subjective assessments)

			"Increasing age and male sex were independently associated with higher *Z*-scores of total BMD (p = .054 and p = .021, respectively) and spine BMD (p <.0001 and p = .03)." (no additional details reported)	

Abbreviations: ALL=acute lymphoblastic leukemia; BMD=bone mineral density; DXA=dual-energy X-ray absorptiometry; HL= Hodgkin lymphoma; NR=not reported; RT=radiotherapy; SCT=stem cell transplantation.

When should surveillance be initiated and at what frequency should it be performed?				
Pluijm et al. Catch-up Bone Mineral Density Among Long-term Survivors of Childhood Cancer? Letter to the Editor: Response to the Article of Gurney et al. 2014. Pediatr Blood Cancer. 2015;62:369-370.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Retrospective single center observational study with two consecutive DXA assessments Treatment era: 1965-2004 Follow-up: Median period between DXA scans was 3.2 years (range 0.9-10.9 years)	Type and number of non-participants: NR Type and number of participants: 188 adult childhood cancer survivors Diagnoses: ALL survivors and most other disease subtypes Age at diagnosis: NR Age at follow-up: Median age 24.5 years Controls: NR	Chemotherapy: NR Radiotherapy: NR SCT: NR Limb amputation: NR Other: NR	Outcome definitions: NR BMD measurement modality: BMD_{TB} and BMD_{LS} assessed with DXA (Lunar device) Results: BMD_{TB} at DXA2 was mean 0.08 SDS ($P > 0.01$) and BMD_{LS} was 0.06 SDS ($P = 0.03$) higher than at DXA1. BMD_{TB} increased significantly over time in AML, NHL and renal tumor survivors, and BMD_{LS} in AML, but not in ALL survivors. Analyzed by gender, BMD_{TB} and BMD_{LS} improved significantly only in males. PBM for BMD_{LS} seemed to be reached at about 23; BMD_{TB} tended to increase till age 26/27.	Strengths: -Two consecutive DXA measurements -Analyses were performed in different patient subgroups Limitations: -This is letter to the editor and therefore, did not include lot of data -Not reported whether the sample is representative -Changes over time could not be adjusted for possible confounders -Possible confounders were not assessed (e.g. vitamin D) -Patients got a DXA based on doctors indication and therefore selection bias may have occurred resulting in overestimating of people with low BMD **Risk of bias** A. Selection bias: High risk Reason: the patients got a DXA scan on indication of their MD. Therefore this sample may be a selection of a group to be suspected to have a high risk of low BMD. B. Attrition bias: High risk

				Reason: only in 40-50% of the sample two DXA scans were performed. <u>C. Detection bias:</u> Low risk Reason: DXA is a hard endpoint.

Abbreviations: ALL=acute lymphoblastic leukemia; AML=acute myeloid leukemia; NR=not reported; BMD=bone mineral density; BMDTB= total body bone mineral density; BMDLS=lumbar spine bone mineral density; DXA=dual-energy X-ray absorptiometry; NHL=non-Hodgkin lymphoma; NR=not reported; PBM=peak bone mass; SCT=stem cell transplantation; SDS=standard deviation score.

When should surveillance be initiated and at what frequency should it be performed?				
Pluskiewicz et al. Skeletal status in survivors of acute lymphoblastic leukemia assessed by quantitative ultrasound at the hand phalanges: a longitudinal study. Ultrasound in Med & Biol, vol30 No 7, pp 893-898, 2004.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Longitudinal, observational study Treatment era: NR. All patients treated according to BFM-95 and New York Program Follow-up: 5.7 ± 2.9 years after completion of therapy and 2 years earlier	Eligible 54 survivors of childhood ALL from a single center in Poland Type and number of non-participants: 16 of the 54 eligible participants Type and number of participants: 38 (21 male) survivors of ALL = 70% of eligible participants Controls: 1402 (774 male) randomly selected students from same region in Poland Age at diagnosis: NR Age at baseline study: 11.9 ± 3.8 y Age at second DXA: 13.9 ± 3.8 y Time from completion of chemotherapy 5.7 ± 2.9 y after completing therapy 11 ± 14.4y after diagnosis	Chemotherapy: Daunorubidomycine, endoxan, vincristine, PEG-asparaginase, prednisone, methotrexate, 6-thioguanine (doses not provided) Radiotherapy: 18 – 24 Gy in 15 participants	Outcome definitions: - Calculation of means, SDs and correlation analyses - Significant level established with *p* value below 0.05 -Least Significant Change (LSC) calculated for Ad-SoS by CV% X 2 X 1.41, representing a statistical difference at the 95% confidence level Diagnostic test(s): -Quantitative ultrasound of the distal metaphysis of the proximal phalanxes of the last four fingers of the nondominant hand (DBM Sonic 1200 ultrasound device) which measures amplitude dependent speed of sound (Ad-SoS) (m/s) -DXA-L (Lunar) lumbar spine performed in 5 patients with low baseline Ad-SoS values Results: At baseline, mean Ad-SoS values in the whole group and in boys did not differ from controls and, in girls, was significantly higher. At second measurement, Ad-SoS in patients was significantly higher than in controls. The same trends were observed in both genders, but without	Strengths: -Standardized imaging by single operator -Control group was similar to participants in regard to age, weight and height -No loss to follow up -Longitudinal study Limitations: -Small to modest sized cohort -Lack of measurements at diagnosis of ALL, during treatment, in the first years after completion of therapy -Lack of BMD measurements in the whole group -Lack of precision of spine BMD measurements for children -Only short-term precison was used - Nonweight-bearing hand phalanges may not entirely express skeletal changes in weight-bearing skeleton -No laboratory data collected -Tanner stage assessed only in patients -Longitudinal measurements not performed in controls -Two separate control groups used -Short follow-up time -Only correlations were calculated for the examination of the potential risk factors, no multivariable analyses.

			significance. Ad-SoS values Survivors baseline: 1990±76 Controls baseline: 1973± (63 Survivors Second measure-all 2045±86 Controls Second measure-all 2016± 86 Longitudinal change -In survivors: mean Ad-SoS in whole group (*n* =38) and both genders increased (p <0.000001 boys; p<0.00001 girls) compared with baseline. In 37 survivors, the Ad-SOS increased and in 31 of them Ad-SoS increase > LSC. In patients, mean baseline Ad-SoS values was 1990+76 m/s and at 2nd measurement2045+86 m/s. In controls, mean baseline Ad-SoS values was 1973+64 m/s and at 2nd measurement 2016+86 m/s. -One male patient, Ad-SoS decreased by 29 m/s. - At baseline, mean Ad-SoS values in whole group and boys did not differ from controls; was significantly higher (P<0.01) in girls -At second measurement, Ad-SoS in patients significantly higher than controls.(p<0.05) -No effect with cranial RT -Correlation between Ad-SoS and: -age $p < 0.0001$ -period after diagnosis NS -period after completion of the therapy: $p < 0.01$ -body size p < 0.0001	**Risk of bias** A. Selection bias: High risk Reason: study group represents less than 75% of eligible population; no flowchart or comparison between participant and non-participant characteristics is included B. Attrition bias: High risk Reason: only 70% of the survivors who had a second measurement were included in this study. The controls were measured only once, so attrition bias is not an issue. C. Detection bias: Unclear Reason: not described whether the outcome assessors were blinded for important determinants related to the outcome

			-Tanner stage at baseline (range, 0.58-0.74, *p* 0.006 - 0.00001) -Tanner stage at follow-up (range, 0.75-0.79; *p* 0.0001 - 0.0000001)	

Abbreviations: Ad-SoS=amplitude dependent speed of sound; ALL=acute lymphoblastic leukemia; BMD=bone mineral density; DXA=dual-energy X-ray absorptiometry; NR=not reported; NS=not significant; RT=radiotherapy.

When should surveillance be initiated and at what frequency should it be performed?				
Tabone et al. Bone Mineral Density Evolution and Its Determinants in Long-term Survivors of Childhood Acute Leukemia. Hemasphere. 2021 Jan 12;5(2):e518.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Longitudinal cohort study Treatment era: Later than 1980 Follow-up: Mean (±SD) 13.8 ± 4.9 years since diagnosis	Type and number of non-participants: 4123 surivors included in the French LEA cohort. 113 (3%) survivors had a DXA scan before the age of 18 years and a follow-up scan after the age of 18 24 of these 113 survivors were excluded because of insufficient or low quality data Type and number of participants: 89 leukemia survivors with a DXA scan before the age of 18 years and a follow-up scan after the age of 18 Diagnoses: ALL: n=68 (76.4%) AML: n=21 (23.6%) Age at diagnosis: Mean (±SD) 8.5 ± 5.1 years Age at follow-up: NR Controls:	Chemotherapy: Corticosteroids: n=66 (74%) Mean (±SD) prednisone equivalent dose: 6118.2 ± 3197.9 mg/m2 Radiotherapy: CRT: n=12 (13.6%) TBI: n=37 (42%) SCT: N=44 (49.4%) Limb amputation: NA Other: GHD Treated: 5 (6%) Untreated: 0 Hyopgonadism Treated: 26 (29.5%) Untreated: 4 (4.5%)	Outcome definitions: Low BMD: Z-score ≤-2 BMD measurement modality: DXA of the lumbar spine, femoral neck, total hip, and total body was performed using Hologic (Hologic Inc, Bedford, Massachusetts) and GE-Lunar (Madison, Wisconsin) scanners Results: Mean (± SD) interval from diagnosis to first scan 7.0 ± 4.7 yrs Mean (± SD) interval from diagnosis to second scan 11.7 ± 5.2 yrs Mean (± SD) interval between both scans 4.8 ± 2.6 yrs Median (minimum–maximum) 3.8 (1.30–12.75) yrs **Longitudinal BMD course** Mean difference in BMD Z-score between the first and second scan: LS: +0.11, 95%CI −0.05 to 0.28, p=0.170 FN: +0.21, 95%CI 0.02–0.40, p=0.033 TH: +0.19, 95%CI 0.01-0.38, p=0.036 TB: +0.03, 95%CI −0.19 to 0.25, p=0.815 Difference in the proportion of survivors with a BMD Z-score ≤-2	Strengths: -Longitudinal BMD measurements Limitations: -Selective cohort, very low response rate (3%) -two different DXA apparatus were used **Risk of bias** A. Selection bias: High risk Reason: The vast majority of the LEA cohort did not have multiple DXA scans (only 3%). It is unclear on what basis multiple scans were performed, but this was likely on clinical indication and therefore a selective cohort B. Attrition bias: Low risk Reason: all included patients had a DXA scan C. Detection bias: Low risk Reason: low BMD by DXA is a hard end-point, not susceptible to subjectivity of the assessor D. Confounding: NA Reason: risk factor analysis for BMD Z-score change was univariable and therefore not included

			between the first and second scan: LS: 1st 15.7%, 2nd 14.6%, p=0.834 FN: 1st 14.5%, 2nd 4.3%, p=0.04 TH: 1st 14.5%, 2nd 7.2%, p=0.171 TB: 1st 7%, 2nd 9,3%, p=1 *N.B. risk factor analysis for BMD Z-score change was univariable and therefore not included*	

Abbreviations: ALL=acute lymphoblastic leukemia; AML=acute myeloid leukemia; BMD=bone mineral density; CRT=cranial irradiation; DXA=dual-energy X-ray absorptiometry; FN=femoral neck; GHD=growth hormone deficiency; LEA=French acronym for “leukemia in children and adolescents”; LS=lumbar spine; NA=not applicable; NR=not reported; TB=total body; TH=total hip; SCT=stem cell transplantation; SD=standard deviation

What should be done when abnormalities are identified?

What should be done when abnormalities are identified?				
Cohen LE et al. Bone Density in Post-Pubertal Adolescent Survivors of Childhood Brain Tumor. Pediatric Blood Cancer 2012; 58:959-963.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Intervention**	**Main outcomes**	**Additional remarks**
Study design: Observational study: Retrospective and prospective review of medical records Treatment era: July 2003 and May 2008 Follow-up: Mean (SD) 8.5 ± 3.6 years	Type and number of non-participants: 237 were included in the database Type and number of participants: Subsample of 36 patients less than 20 yrs of age Brain tumor (medulloblastoma, astrocytoma/glioma or craniopharyngioma) at risk of pituitary hormone deficiencies Endocrinology Program at Chidren's Hospital Boston (CHB) Post pubertal Bone age > 14 years in girls and > 16 years in boys Referred for a DXA as part of clinical care N=13 of these patients had follow up DXA Intervention group: Not an intervention study. The study cohort consisted of brain tumor survivors of medulloblastoma, astrocytoma/glioma or craniopharyngioma Control group: Age-matched normative data expressed as Z-score for 413 healthy Americans aged 9-25 years Age at diagnosis: Mean (SD) 8.4 ± 3.9 years	BMD treatment: Not an intervention study (survivors with GHD treated with rhGH) Treatment controls: Not applicable to study design (survivors with untreated GHD) Outcome definitions: BMD in post-pubertal adolescent survivors of childhood brain tumor to determine if they had adequate BMD as they approached time of peak bone mass accrual. The study examined risk factors for impaired BMD (age at diagnosis, time from diagnosis, tumor treatment, endocrinopathies from treatment. BMD measurement modality: Hologic DXA for BMD (g/m2) measurements of total hip, femoral neck, and L1-L4 spine	Prevalence/risk of late effect: Study Analysis: BMD Z-scores and crude BMD of the total hip, femoral neck, lumbar spine (L1-L4) compared to age-matched, normative data (Z-scores) Results: Femoral neck BMD Z-score: Mean (SD) -0.83 (1.2); median: -0.95; Z-score < -2: 22% Femoral neck BMAD: Mean (SD) -0.38 (1.1); median: -0.23; Z-score < -2: 6% LS BMD: Mean (SD) -0.91 (1.4); median: -0.90: Z-score < -2: 25% Femoral neck BMAD: Mean (SD) -0.43 (1.3); median: -0.45; 11% Hip BMD: Mean (SD) -0.91 (1.3); median: -1.20; 17% BMD was significantly lower in patients closer to diagnosis (r=0.37), Patients diagnosed at younger age had higher spinal BMD Z-scores (r=-0.41) Patients with history of one or more fractures had lower BMD Z-scores of femoral neck, hip, and spine and lower absolute BMD at hip and lower absolute BMAD at femoral neck and spine.	Strengths: -Only study focused on cohort of childhood survivors of brain tumor who are of similar age and pubertal age -Different locations of DXA scans (hip and lumbar spine) BMD and BMAD were assessed Limitations: -DXA performed as part of routine clinical assessment and not part of research study -Use of DXA 2D assessment of bone -No collected data on Vitamin D and calcium intake or type of fracture (trauma vs. fragility) -Very small sample size -Retrospective chart review of collected clinical data -No information on physical activity -Lack of bone biomarkers -For the risk factors: only correlations were calculated and no multivariable analyses have been performed **Risk of bias** A. Selection bias: High risk Reason: retrospective chart review at one institution. DXA scans were performed as part of routine care. Possibly, the patients with a high

	Age at follow-up: Mean (SD) 16.9 ± 1.9 years Cancer treatment: -Chemotherapy: not provided directly but consistent with chemotherapy used for brain tumor treatment. -Radiotherapy: cranial RT in 30 of 36. N=14 of the 30 had also spinal RT -SCT: not applicable -Limb amputation: not applicable -Other: none		Patients treated for hypothyroidism had higher spine BMD than those without. **Among patients with GHD (n=29), those treated (n=20) with rhGH for >1 year had higher BMD and BMAD of the hip, spine and femoral neck compared to those untreated (n=9).** No difference in BMD with respect to spinal and / or cranial RT, chemotherapy or treated hypogonadism, regularity of menarche Higher lumbar spine BMD Z-scores among the GH treated patients than among those not receiving therapy No difference in BMD or BMAD among those who had a follow-up DXA scans about 2 years after the first one. Effect of intervention: No intervention evaluated. Assessment of risk factors on BMD summarized above.	risk of low BMD got a DXA (of whom the MD expected that they had a low BMD) B. Attrition bias: High risk. Reason: only information collected clinically for 13 of 30 patients was available for longitudinal assessment. Convenience sample. C. Detection bias: High risk Reason: high risk as data collected for chart review and not blinded. D. Performance bias: High risk Reason: data reported were collected for clinical care and no intervention offered.

Abbreviations: BMD=bone mineral density; DXA=dual-energy X-ray absorptiometry; GHD=growth hormone deficiency; rhGH=recombinant human growth hormone; RT=radiotherapy; SCT=stem cell transplant.

What should be done when abnormalities are identified?				
Dubnov-Raz et al. Changes in fitness are associated with changes in body composition and bone health in children after cancer. Acta Pediatrica 2015;104:1055-61.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Intervention**	**Main outcomes**	**Additional remarks**
Study design: Quasi-experimental Non-randomized single arm intervention Exercise program versus no exercise program Controls were recruited to participate – agreed to baseline and follow-up testing but declined the intervention Treatment era: Not reported Follow-up: 6 months	Eligible participants intervention group: -Children aged 7-14 years -Who had received cancer treatment or bone marrow transplantation -Who had completed all treatment at least 6 months before the study began follow-up clinics of Edmond and Lily Safra Children's hospital in Israel -Who were interested in performing the exercise program Exclusion criteria: -Presence of any chronic disease -Current treatment with any type of chronic medication -Self-reported fatigue -Hospital admission in the past three months -Known cardiac dysfunction] -Low hemoglobin or neutrophil count Eligible controls: -Participants who were not currently active in organized sports, did not wish to participate in the exercise program or had no accessible exercise groups near their home Type and number of (non)-participants: n=85 were invited of which 24 agreed to participate: Of the 12 children in the intervention group, 2 did not participate in the intervention due to medical reasons Of the 12 children in the control group, 1 was lost to follow-up	BMD treatment: Intervention group: commercially "Go active" gym chain in Israel similar in all branches provided a three time supervised group-based exercise session per week during six months that included 15 minutes of aerobic warm-up, 30 minutes of strengthening/cardiac conditioning activities using bands, balls, games, free weights, and 10-15 minutes of active cool down with walking and stretching. Specific exercise dose and intensity not reported. Treatment controls: None – agreed to maintain current lifestyle Outcome definitions: BMD lumbar Z-score; Continuous BMD values lumbar, femur, total body BMD measurement modality: Dual-energy X-ray absorptiometry (Lunar Prodigy; General Electric Healthcare, Madison Wisconsin, Lunar DPX software version 3.6)	Prevalence/risk of late effect: BMD lumbar spine Z-scores, by sex, age, weight, ethnicity, and femoral neck (g/cm2) and total body BMC (g and g/cm2) assessed with DXA scan Baseline lumbar Z-scores were within normal limits Effect of intervention: No effect **Results of the between groups**: Lumber BMD Z-score: p=0.90 Lumber BMD g/cm2: p=0.13 Total body BMC (g) p=0.70 Total body BMD (g/cm^2) p=0.39 Femoral head BMD (g/cm^2) p=0.18 Within group effects: Intervention group baseline median (range): BMD LS Z-score: baseline -0.10 (-0.75till -0.80) BMD LS Z-score: fup: -0.10 (-0.85 till -1.05) p=0.44 BMD LS baseline: (g/cm^2) 0.84 (0.78-0.92) BMD LS fup: (g/cm^2) 0.88 (0.79-0.97) p=0.02 TB BMC (g) baseline: 1435 (1117-2051) TB BMC (g) fup: 1631 (1076-1993) P=0.07	Strengths: -Measurement techniques were well described and are valid -Intervention was well structured, designed and described in a SOP. -Two groups comparable at baseline despite self-selection into intervention or not Limitations: -Bias by intention (self-selection) -No intention to treat analysis -Poorly described intervention – likely not bone specific -No data provided on non-participants (target population difficult to identify) -Participants not selected because of low BMD -No compliance data -Small sample size: statistical tests to compare baseline characteristics were performed unless power was too low **Risk of bias** A. Selection bias: High risk Reason: those who refused intervention were the comparison group; target population not described B. Attrition bias: Unclear Reason: more than 75% of those who enrolled completed the intervention although adherence data were not provided

	Type and number of participants: 21 Intervention group: 10 (6 females age 7.8-13.8, median 11.1 y) Time since cancer treatment end (0.9-5.5, median 3.0 y) Control group: 12 (with 1 lost-to-fup) (6 females age 9.0-12.8, median 11.8 y) Time since cancer treatment end (1.5-4.2, median 2.6 y), 2 were diagnosed with another disease than cancer (aplastic anaemia, Wiskott-Aldrich syndrome) Age at diagnosis: Not reported Age at follow-up: Not reported although 6 months after start of intervention Cancer treatment: -Chemotherapy: all 21 participants exposed to chemotherapy and/or "Steroids", specific agents and doses not reported -Radiotherapy: 9 exposed – type, region, dose not reported -SCT: 6 exposed – details not reported Limb amputation: not reported		TB BMD baseline (g/cm^2) 0.95 (0.87-1.01) TB BMD fup (g/cm^2) 0.97 (0.86-1.03) P=0.01 Femoral head BMD (g/cm^2) baseline: 0.85 (0.75—0.89) Femoral head BMD (g/cm^2) fup: 0.89 (0.82—0.95) Control group median (range): Lumber BMD baseline Z-score -0.90 (-1.32-0.00) Lumber BMD fup Z-score -0.80 (-1.10-[-0.10) p=0.09 Lumber BMD baseline g/cm2 -0.75 (0.63-0.82) Lumber BMD fup Z-score 0.79 (0.69-0.85) p=0.008 Total body BMC (g) baseline 1293 (1124-2069) Total body BMC (g) fup 1445 (1222-2139) Total body BMD (g/cm^2) baseline 0.90 (0.87-0.99) Total body BMD (g/cm^2) fup 0.91 (0.90-1.03) Femoral head BMD (g/cm^2) baseline: 0.82 (0.70—0.97) Femoral head BMD (g/cm^2) fup: 0.86 (0.72—0.97) p=0.24	C. Detection bias: High risk Reason: no blinding D. Performance bias: High risk Reason: No blinding (Contamination of the control group: Low risk Reason: control group was not motivated to participate in exercise)

Abbreviations: BMC=bone mineral content; BMD=bone mineral density; fup=follow-up; LS=lumbar spine; TB=total body; SCT=stem cell transplantation.

What should be done when abnormalities are identified?				
Follin et al. Bone loss after childhood acute lymphoblastic leukaemia: an observational study with and without GH therapy. Eur J of Endocrinology 2011; 164 695-703.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Intervention**	**Main outcomes**	**Additional remarks**
Study design: Observational prospective study (quasi experimental) Treatment era: 1971 - 1992 Follow-up: years since CRT GH group: 21 (8-27) No GH group: 19 (9-27)	Eligible participants -Treated for ALL with chemotherapy and CRT -During 1971 and 1992 -Children's hospital Lund Sweden -18 years of age -GHD Type and number of non-participants: Of the 58 eligible survivors, 14 were excluded (7 declined participation, and 7 had other reasons). Of the 44 who were included, 13 were excluded due pregnancy, not GHD, declined GHD, declined participation). Of the 81 eligible controls, 37 were first excluded, and 13 after inclusion. Type and number of participants: GH treatment (n=18), and no GH treatment (n=13) and matched population controls (n=28) 18 were offered GH therapy of which 15 completed the 5 year study. N=13 was not offered GH therapy but had regular contact with a MD/nurse during 8 years of follow-up. Controls:	BMD treatment: GH treatment: 0.5 mg/day for women and men (Humantrope Eli Lilly). Treatment controls: Untreated GH deficient ALL group, who had regular contact with a doctor or nurse. Population controls: No information Outcome definitions: Changes in areal and volumetric BMD and markers of bone turnover from baseline to 12 Month BMD measurement modality: Areal BMD was measured with dual X-ray absorptiometry (DXA, 4500QDR-A/Discovery fanbeam; Hologic). QCT (Lightspeed Ultra 8-detector; GE Healthcare) of the lumbar spine L1- L2, Tibial cortical and trabecular bone content were also assessed with QCT	Baseline BMD At baseline, no significant differences in BMD between the groups GH group: BMD Femoral Neck Z-score: -0.2 (-1.6 to 1.5) BMD Z-score lumbar spine: -0.4 (-1.6 to 1.5) No GH group BMD Femoral Neck Z-score: 0 (-1.5 to 1.3) BMD Z-score lumbar spine: -0.2 (-1.4 to 2.1) Controls BMD Femoral Neck Z-score: 0.3 (-0.9 to 2) BMD Z-score lumbar spine: -0.1 (-1.5 to 2.1) Effect of GH treatment No significant difference in BMD, BMAD after 5 years, at any site . between those treated with GH and no GH and controls. The median net difference for the GH-treated versus non-GH-treated group for femoral Z-scores and for Z-scores at L2–L4 levels were -0.20 vs -0.25 and -0.10 vs -0.25 respectively. No GH versus controls	Strengths: -Longitudinal study with long follow-up -Matched control group -Three groups were comparable for baseline characteristics. -Detailed description of reasons for inclusion and exclusion and analyses Limitations: -Many eligible patients were excluded at baseline and after inclusion -No randomization of the GH therapy -Only correlations were calculated for examination of potential risk factors **Risk of bias** A. Selection bias: High risk Reason: no randomization, many people were excluded, not blind. B. Attrition bias: Low risk Reason: although the follow-up was very long, few participants and controls were lost to follow-up. More than 80% completed it. C. Detection bias: Unclear Reason: not stated whether the outcome assessors were blinded.

	N=28 reference controls (n=13 during 8 years of follow-up and n=15 for 5 years of follow-up <u>Age at diagnosis:</u> In years, mean (SD) GH therapy: 3.9 (1-17) No GH therapy: 4.2 (2-9) <u>Age at follow-up:</u> In years, mean (SD) GH therapy: 25 (22-32) No GH therapy: 25 (19-32) <u>Cancer treatment:</u> -Glucocorticoids: GH therapy: dose 2508 (1600-6682) No GH therapy: dose 2410 (1540-6573) -Anthracyclines GH therapy: dose 120 (80-540) No GH therapy: dose 120 (40-540) -High dose methotrexate i.t. GH therapy: dose 60 (12-144) No GH therapy: dose 72 (12-204) -High dose methotrexate i.v. GH therapy: dose 3000 (3000-4000) No GH therapy: dose 1763 (30-4000) -High dose methotrexate p.o. GH therapy: dose 2672 (533-4200) No GH therapy: dose 2723 (1097-3900) -Decadron dose (mg/m2) GH therapy: dose 370 (296-390) No GH therapy: dose 325 (200-400) *Radiotherapy*: n/target dose -Spinal radiation GH therapy:2/23 No GH therapy: 2/23		After 8 years of follow-up, No GH: Z-scores at FN decreased significantly compared with baseline (0 to -0.5; p<0.003) and were significantly lower than in controls. <u>Risk factors:</u> MTX (higher dose) was negatively correlated with Lumbar spine BMD: r=-0.31 Corticosteroids, level of IGF1, GH response to GHRH arginine, dose of CRT and time since diagnosis were not correlated to BMD LS or FN.	<u>D. Performance bias:</u> High risk Reason: the participants and personnel assessors were not blinded from knowledge of which intervention was received.

	-Testes radiation GH therapy:4/24 No GH therapy: 5/24 -SCT: NR -Limb amputation: NR			

Abbreviations: ALL=acute lymphoblastic leukemia; BMD=bone mineral density; CRT=cranial radiotherapy; DXA=dual energy X-ray asorptiometry; FN=femoral neck; GH=growth hormone; GHD=growth hormone deficiency; LS=lumbar spine; NR=not reported; QCT=quantitative computed tomography; SCT=stem cell transplantation; SD=standard deviation.

What should be done when abnormalities are identified?				
Kaste et al. Calcium and cholecalciferol supplementation provides no added benefit to nutritional counseling to improve bone mineral density in survivors of childhood acute lymphoblastic leukemia (ALL). Pediatr Blood Cancer. 2014;61(5):885-93.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Intervention**	**Main outcomes**	**Additional remarks**
Study design: Double-blind, placebo controlled randomized controlled trial Treatment era: 1984-1997 Follow-up: Median time since treatment 8.4 yrs (range 4.6-19.1)	Type and number of non-participants: Eligible cohort 772 survivors of ALL. Type and number of participants: 424 survivors of childhood ALL ≥5 yrs in remission. Eligible for intervention (Z score BMD<0): n=279; 4 elected not to participate. Total that remained: n=275 Intervention group: 141 survivors of childhood ALL with a LS BMD Z-score < 0 Control group: 134 survivors of childhood ALL with a LS BMD Z-score > 0 Completed trial: n=188 Age at diagnosis: Median 4.6 yrs (range 0.2-18.8) Age at follow-up: Median 17.0 yrs (range 9.0-36.1) Cancer treatment: -Glucocorticoids: 424/424 (100%); Dose <5,000 mg 85/424 (20%), ≥5,000 mg 339/424 (80%) -Cyclophosphamide: 424/424 (100%); Dose <7,500 mg/m^2	BMD treatment: Nutritional counseling to encourage recommended daily intake of calcium and cholecalciferol Once daily calcium carbonate (1,000 mg) and cholecalciferol (800 International Units) during 24 months Treatment controls: Nutritional counseling to encourage recommended daily intake of calcium and cholecalciferol during 24 months Placebo Outcome definitions: LS BMD change between the supplement and the placebo group at 24 months follow-up Low BMD was defined as Z-score <-1 Very low BMD was defined as Z-score <-2 BMD measurement modality: QCT of the lumbar spine (L1-L2)	Prevalence/risk of late effect at baseline: N=424 Median Z-score LS BMD: Females: -0.3 (-3.7 to 3.2) Males: -0.6 (-3.9 to 5.1) Low BMD (Z-score <-1): 102/424 (24.1%) Very low BMD (Z-score <-2): 29/424 (6.8%) vitamin D levels N=387 <30 ng/ml: n=291 (69%) <=20 ng/ml: n=114 (27%) <=10 ng/ml: n=20 (5%) Endocrinopathy:11.6% Factors associated with **HIGHER** LS BMD Z-scores at baseline (n=484) Survival time (yrs), β 0.01, 95%CI -0.05-0.06, p=0.84; Age at study entry (yrs), β 0.01, 95%CI -0.01-0.04, p=0.37; **Gender** (female vs. male), β 0.38, 95%CI 0.15-0.6, **p=0.001**; **Race (non-White vs. White)**, β 0.58. 95%CI 0.28-0.89, **p<0.0001**; **BMI (kg/m^2),** β 0.05, 95%CI 0.03-0.07, **p<0.001**; Tanner stage (cont.), β -0.05, 95%CI -0.17-0.07, p=0.43; Smoking (no vs. yes), β 0.23, 95%CI -0.08-0.54, p=0.15;	Strengths: -RCT -Intervention and control group did not differ on baseline characteristics -Large and well-characterized cohort -Study conducted conform previously published methods paper Limitations: -About ¾ medication compliance -Vitamin D supplementation was also given to vitamin D replete survivors, in whom you would not expect an effect -Loss to follow up was high (32%) -No intention to treat analysis -Contamination of control group: median vitamin D and calcium intake in intervention and control group increased for vit D with median of 147 and 185 IU per day, and for calcium with 907 and 840 mg/day. **Risk of bias** A. Selection bias: High risk Reason: although there was random sequence allocation and allocation concealment, only 54,9% of the initial cohort was analyzed (424 pts out of 772)

	196/424 (46.2%), ≥7,500 mg/m^2 228/424 (53.8%) -Methotrexate: 424/424 (100%); Dose <10,000 mg/m^2 150/424 (35.4%), 10,000–19,999 mg/m^2 89/424 (21.0%), ≥20,000 mg/m^2 185/424 (43.6%) -Cranial radiotherapy: 153/424 (36.1%); RT dose: 1-23 Gy 118/424 (27.8%), ≥24 Gy 35/424 (8.3%) -SCT: 0/424 (0%)		Moderate/vigorous physical activity (minutes/week), β 0.0007, 95%CI -0.0001-0.0015, p=0.11; **Lower dose of Cyclophosphamide** (<7,500mg/m^2 vs. ≥7,500mg/m^2), β -0.29, 95%CI -0.55- -0.05, **p=0.02**; **Higher dose of Glucocorticoid** (<5,000mg/m^2 vs. ≥5,000mg/m^2), β 0.72, 95%CI 0.29-1.14, **p=0.001**; Methotrexate dose (<10,000 mg/m^2 vs. 10,000-19,999 mg/m^2), β -0.08, 95%CI -0.57-0.4; (≥20,000 mg/m^2 vs. 10,000-19,999 mg/m^2), β -0.29, 95%CI -0.69, 0.11, p=0.33 No association between levels of vitamin D and BMD <u>Multivariable linear regression (n=188)</u> <u>Effect of intervention:</u> After adjusting for baseline LS-BMD Z-score, age, sex, race, radiation dose, and chemotherapy, there were no differences in mean LS-BMD values or mean LS-BMD Z-scores between supplement and placebo groups. <u>Linear regression LS BMD Z-score change</u>: **Intervention vs control:** Supplement group, β 0.03, 95%CI -0.13-0.19, p=0.70; Survival time (yrs), β 0.0.0045, 95%CI -0.04-0.05, p=0.83 **Age at study entry** 9-12 vs. 22-35 yrs, β 0.15, 95%CI -0.2-0.49; 13-17 vs. 22-35 yrs, β -0.23, 95%CI -0.49-0.03; 18-21 vs. 22-35 yrs, β -0.25, 95%CI (-0.52-0.03), **p=0.01**	<u>B. Attrition bias:</u> High risk Reason: the outcome was assessed for only 68.4% of the study group, but survivors not completing were equally distributed among the supplement and placebo group, and did not differ from those who completed by gender, age at diagnosis, treatment protocol, or baseline LS-BMD Z-score. However, non-completing participants were slightly older. <u>C. Detection bias:</u> Low risk Reason: the outcome assessors were blinded for important determinants related to the outcome <u>D. Performance bias:</u> Low risk Reason: the participants and personnel assessors were blinded from knowledge of which intervention was received N.B.: contamination of control group. Increase in ca and vitamin D levels was similar in both intervention and control group. In addition, in both groups, BMD Z scores seem to increase.

			Gender (female vs. male), β 0.14, 95%CI -0.02-0.31, p=0.09; Race (non-White vs. White), β 0.15. 95%CI -0.12-0.43, p=0.28; Tanner stage (cont.), β 0.04, 95%CI -0.05-0.13, p=0.36; Moderate/vigorous physical activity (minutes/week), β -0.0003, 95%CI -0.0011-0.0004, p=0.42; Cranial radiation exposure (<24Gy vs. ≥24Gy), β 0.04, 95%CI -0.24-0.31, p=0.79; Cyclophosphamide dose (<7,500mg/m^2 vs. ≥7,500mg/m^2), β 0.0014, 95%CI -0.18-0.18, p=0.99; Glucocorticoid dose (<5,000mg/m^2 vs. ≥5,000mg/m^2), β -0.30, 95%CI -0.66-0.05, p=0.10; Methotrexate dose (<10,000 mg/m^2 vs. 10,000-19,999 mg/m^2), β -0.37, 95%CI -0.75-0; (≥20,000 mg/m^2 vs. 10,000-19,999 mg/m^2), β -0.20, 95%CI -0.51, 0.11, p=0.16	

Abbreviations: ALL=acute lymphoblastic leukemia; BMD=bone mineral density; BMI=body mass index; CI=confidence interval; LS=lumbar spine; QCT=quantitative computed tomography; RCT=randomized controlled trial; RT=radiotherapy; SCT=stem cell transplantation.

What should be done when abnormalities are identified?				
Mogil et al. Effect of Low-Magnitude, High-Frequency Mechanical Stimulation on BMD Among Young Childhood Cancer Survivors A Randomized Clinical Trial. 2016; JAMA Oncology. Volume 2: pages 908 – 914.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Intervention**	**Main outcomes**	**Additional remarks**
Study design: Double-blind, placebo controlled randomized controlled trial performed at St Jude Children's hospital, USA Treatment era: End nineties-Early 2000-s Follow-up: >5 years from cancer diagnosis	Eligible: -Childhood cancer survivors aged 7 till 17 years treated at St Jude. -In remission, at least 5 years from diagnosis -Whole body or LS BMD Z-scores < -1. Not eligible -Children requiring oral glucocorticoid therapy -Pharmacologic agents for impaired BMD other than Ca or Vit D -Bracing -Pregnancy Type and number of non-participants: 69 of 149 presumed eligible declined participation Type and number of participants: 65 CCS, 7 to 17 years of age, 5 or more years from diagnosis, and not currently receiving treatment for cancer, with age- and sex-specific lumbar or whole-body BMD z scores of less than −1.0 Intervention group: 32 CCS mean age (SD) 13.6 (3.7) years, 18 male, 27 white 10 participants did not complete study Median adherence: 70.1%	BMD treatment: Low-magnitude (<1.0g), high frequency mechanical stimulation (LMS) device used at home. The mechanical signal (0.3 g at 32-37 Hz) produced a subtle, sinusoidal, vertical translation less than 100 µm via a linear electromagnetic actuator. Participants were instructed to stand on a platform for 10 minutes twice daily for 1 year. Calcium (800-1200mg/d) and vitamin D supplements (cholecalciferol, 400 IU/d) Treatment controls: The placebo group stood on a device identical in appearance to the active platform. The placebo device emitted a 500-Hz audible hum but did not deliver the signal. Calcium (800-1200mg/d) and vitamin D supplements (cholecalciferol, 400 IU/d) Outcome definitions: Changes in areal and volumetric BMD and markers of bone turnover from baseline to 12 Month BMD measurement modality: Areal BMD was measured with dual x-ray absorptiometry	Prevalence/risk of late effect: Z-scores less than −1.0 Effect of intervention: Total-body BMD z mean (SD) scores (intention to treat analysis) improved by 0.25 (0.78) (95% CI -0.09 to 0.59) in the intervention (n=22) and decreased by –0.19 (0.79) (95% CI -0.51 – 0-12) in the placebo group (n=26) (P=0.05). L1, L2 BMD Z-score (intention to treat analysis) improved by 0.08 (0.51) (95% CI -0.13 to 0.30) in the intervention (n=22) and by 0.14 (0.51) (95% CI -0.06 to 0.35) in the placebo group (n=26) (P=0.68). Other operationalizations of LS BMD were not significantly different between intervention and control group. Tibial trabecular bone among participants completing 70% or more of the prescribed sessions increased by a mean of 11.2% (95%CI, 5.2 to 17.2%) compared with those completing less than 70% who decreased by a mean of −1.3%(95%CI, −7.3 to 4.7%; P=0.02).	Strengths: -Study design RCT -Adherence was closely monitored -Statistics: intention to treat analysis and per protocol (for those with good compliance/adherence) -Control group had a similar device (device was blind for the patients) No femoral neck or Total hip BMD assessment, whereas primary effects can be expected in these regions) Limitations: -26% of participants did not complete study. -Moderate power -Low compliance in interventional group (only half of participants completed 70% or more sessions). -No longitudinal (only at baseline and follow-up) measurements of biomarkers. No conclusions may be drawn from the biomarkers part of the study. **Risk of bias** A. Selection bias: Low risk Reason: randomization, the groups were comparable in baseline characteristics Differences in characteristics between those who and who did not participate was not clear.

	Control group: 33 CCS mean age (sd): 13.6 (2.9) yrs; 17 male, 26 were white 7 participants did not complete study. Median adherence: 63.7% Age at diagnosis: In years, mean (SD) For intervention group 3,3(2,5) For placebo group 4,2 (2,4) Age at follow-up: In years, mean (SD) For intervention group 13,6 (3,1) For placebo group 13,6 (2,9) Cancer treatment: -Glucocorticoids: 36 (55%) dose g/m^2 (SD) 10,5 (4,4) for intervention group, 11,0 (4,0) for placebo group -Anthracyclines: 40 (62%) dose mg/m^2 (SD) 143,2 (80.5) for intervention group, 144,8 (91,5) for placebo group -High dose metothrexate: 34 (52%) dose g/m^2 (SD) 17,3 (7,9) for intervention group, 14,7 (4.0) for placebo group -Alkylating agents: 43 (66%) dose g/m^2 (SD) 6,2 (8,6) for intervention group, 5,3 (9,4) for placebo group -Cranial radiotherapy: 18 (28%) -Abdominal/pelvic radiation: 5 (7%) -Spinal radiation: 2 (3%) -SCT: Unknown -Limb amputation: None	(DXA,4500QDR-A/Discovery fanbeam ;Hologic). QCT (Lightspeed Ultra 8-detector; GE Healthcare) of the lumbar spine L1- L2, Tibial cortical and trabecular bone content were also assessed with QCT	Circulating osteocalcin at 12 months correlated with change in total body BMD (r = 0.35, P=0.02). Change in circulating receptor activator of nuclear factor κ-B ligand was higher in the intervention than in the placebo group (0.06 [0.16] vs −0.04 [0.17] pmol/L) (P=0.04).	B. Attrition bias: High risk Reason: outcome was assessed in 74% of enrolled patients. Compliance was low. The selection bias in non-complained patients is unclear C. Detection bias: Low risk Reason: the outcome assessors were blinded for important determinants related to the outcome. D. Performance bias: Low risk Reason: the participants and personnel assessors were blinded from knowledge of which intervention was received.

Abbreviations: BMD=bone mineral density; DXA=dual-energy X-ray absorptiometry; CCS=childhood cancer survivors; CI=confidence interval; LS=lumbar spine; QCT=quantitative computed tomogrpahy; RCT=radomized controlled trial; SD=standard deviation.

What should be done when abnormalities are identified?				
Van den Heijkant et al. Effects of growth hormone therapy on bone mass, metabolic balance, and well-being in young adult survivors of childhood acute lymphoblastic leukemia. J Pediatr Hematol Oncol 2011;33:e231-8.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Intervention**	**Main outcomes**	**Additional remarks**
Study design: Open label, longitudinal uncontrolled single arm trial Treatment era: Between 1972 and 1990 Follow-up: Mean time since CRT 20.7±3.2 years	Eligible participants -Low BMD (<-1 SD) at the LS or femoral sites and / or low IGF-1 (<-1 SD) -Not treated with GH -Treated for ALL at the paediatric department of the VUMC or AMC, Amsterdam -Aged above 20 years Type and number of non-participants: Of the 45 young adult survivors of childhood ALL 34 were eligible and included. Of these, 13 refused to participate (mainly because they did not have physical complaints) and 1 had multiple handicaps. Type and number of participants: 20 young adult survivors of childhood ALL with low BMD (<-1 SD) at lumbar spine (LS) or femoral sites and/or low IGF-1 (SD score ≤-1). 17 started with GH therapy and 14 completed the 2 year study period Intervention group: Same as above Control group: No control group Age at diagnosis:	BMD treatment: Human Growth hormone (Eli Lilly penfill system) given subcutaneously for 2 years. The initial dose was 0.1 mg/m^2 of body surface. The dose was increased every 2 weeks by 0.1 mg/m^2 until IGF-1 rose above the mean of a reference group. Treatment controls: IGF-1 serum concentration Outcome definitions: LS, femoral neck (FN), femoral trochanter (FT), and total body BMD measured after 24 months of treatment. BMD measurement modality: LS, femoral neck (FN), femoral trochanter (FT), and total body BMD and BMC measured by DXA (Hologic QDR-2000).	Prevalence/risk of late effect: LS BMD Z-score at baseline was -0.92±1.14, and at end of intervention -0.89±0.88. FN BMD Z-score at baseline was -0.82±1.22, and at end of intervention -0.56±1.13. FT BMD Z-score at baseline was -0.73±0.93, and at end of intervention -0.57±0.86. Total body values (Z-scores) are not given. Effect of intervention: A significant increase in crude total body BMD measurements (g/cm2) was observed after 24 months of GH treatment (p=0.005),but not at the other skeletal sites or total body BMC (KG). A significant increase in FN BMD Z-score was also observed (P=0.02). The increases were attributable to the subset of GH-deficient patients. The increase in total body BMD was higher in the group GHD patients as compared to those without GHD (p=0.004)	Strengths: -None identified Limitations: -No control group -No randomisation -The number of subjects was very limited -The ranges of measurements were quite high to support firm conclusions -Subgroup analyses were performed with very small numbers **Risk of bias** A. Selection bias: High risk Reason: the number of subjects with GHD and those with no GHD were not balanced. Of the 34 persons who were included, 13 refused to participate mainly because they did not have physical complaints. People with complaints may have participated. B. Attrition bias: High risk Reason: of the 20 persons who started, 14 completed the 2 year study. Those who stopped had anorexia, side effects etc. C. Detection bias: High risk

	Mean age 6.8±3.8 years <u>Age at follow-up:</u> Mean age 23.9±3.0 years <u>Cancer treatment:</u> -Chemotherapy: 20 patients (100%) received chemotherapy, which included corticosteroids, vincristine, methotrexate,6-mercaptopurine. No dose specification is given. -Radiotherapy: 17 patients (85%) received cranial irradiation in doses varying from 2000 to 2500 Gy. -High dose MTX and intrathecal chemotherapy (MTX, cytosine-arabinoside and prednisone): N=3 -SCT: 0 (0%) -Limb amputation:0 (0%) -Other: 0 (0%)			Reason: the assessors were not blinded for important determinants related to the outcome. <u>D. Performance bias:</u> High risk Reason: the participants and assessors were not blinded from knowledge of which intervention was received.

Abbreviations: ALL=acute lymphoblastic leukemia; BMC=bone mineral content; BMD=bone mineral density; CRT=cranial radiotherapy; DXA=dual-energy X-ray absorptiometry; FN=femoral neck; FT=femoral trochanter; GH=growth hormone; GHD=growth hormone deficiency; LS=lumbar spine; MTX=methotrexate; SCT=stem cell transplantation; SD=standard deviation