CHILDHOOD CANCER SURVIVOR STUDY
Analysis Concept Proposal

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Title: Fracture risk among long-term survivors of childhood cancer

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Background and Rationale:
Survivors of childhood cancer are at risk of developing bone-related sequelae as a result of disturbances in normal bone metabolism during childhood or adolescence which can compromise attainment of normal peak bone mass[1]. These disturbances may develop as a consequence of the debilitating effects of the cancer experience, such as nutritional deficiencies and reduced exercise capacity,[2,3] or because normal bone mineral accretion and skeletal development are affected by corticosteroids and chemotherapeutic agents given to treat cancer[3-7]. Bone mineral density (BMD) can be adversely affected as a result of gonadal failure following exposure to radiation and/or certain chemotherapeutic agents (eg, aklyating agents), or as a consequence of hypothalamic pituitary endocrinopathies following irradiation to the central nervous system[8,9]. Moreover, direct radiation to bone can have a cytotoxic effect on the epiphyseal chondrocytes[10], increase hypervascularity, and have long-term deleterious effect on bone strength[11,12].

In the general population, low BMD has been associated with a loss of height, stooped posture, severe pain, increased bone fragility and susceptibility to fracture. Although previous studies have shown that survivors are at increased risk of low BMD[13-18], the occurrence of fracture among long-term survivors is largely uncharacterized. To date, most studies that have examined fracture risk among childhood cancer survivors have considered only those fractures occurring on treatment or within the first five years of completing therapy.[19,20] It is not clear whether alterations to bone metabolism during therapy impact post-therapy risk of fractures. In addition, most studies of fracture risk among individuals treated for childhood cancer have been restricted to survivors previously treated for acute lymphoblastic leukemia or malignancies of the central nervous system[7,19-21]. Small sample sizes have limited the consideration of additional factors, such as demographic and lifestyle factors and gonadotoxic therapy, on fracture risk.

The purpose of this study is to characterize the risk of fractures among individuals participating in the Childhood Cancer Survivor Study (CCSS) and identify treatment and host related risk factors that predispose survivors to an increased risk of fracture. The CCSS, which holds accurate detailed information on treatment, health-related behaviors and socioeconomic status, will provide the opportunity to examine the risk of fracture among long-term cancer survivors in a large, well characterized population, and facilitate the identification of

additional factors, such as physical activity levels, body mass index (BMI) and balance and movement disorders, which may predispose survivors to an increased risk of fracture as they age.

Specific aims:

1. Describe the prevalence of fracture among adult survivors of childhood cancer as a function of age, sex and time since diagnosis.
2. Compare the prevalence of fracture among adult survivors of childhood cancer to siblings.
3. Identify disease, treatment, and individual risk factors that increase the risk of fracture among survivors of childhood cancer.

Hypotheses:

1. Survivors of childhood cancer are at an increased risk of fracture compared to sibling controls
2. Survivors of childhood cancer with the highest risk of fracture will have the following characteristics
    a) History of corticosteroid use, especially dexamethasone vs. prednisone
    b) History of systemic methotrexate use
    c) History of alkylating agent use
    d) Increasing dose of cranial radiation
    e) Increasing dose of radiation to the ovaries or testes
    f) Younger age at diagnosis
    g) Low physical activity levels
    h) A limitation affecting mobility (such as surgical amputation of lower limb)
    i) A medical condition affecting balance and/or coordination
    j) Increasing doses of radiation to the long bone

Study population

CCSS participants who completed the 2007 follow-up questionnaire and consented to abstraction of their medical record will be included in these analyses. A comparison group of siblings who completed the 2007 follow-up questionnaire will also be included.

Outcome of interest:

The primary outcome of interest in these analyses is the occurrence of fractures among cancer survivors and their siblings as reported in the 2007 Follow-up Questionnaire (question F11). In this question, participants are asked if they have ever broken a bone. If the participant's response is yes, they are then asked to provide a description of all incidents in which they have fractured a bone. We will analyze fractures, overall, as the main outcome of interest. We will also do a sub-analysis of low impact fractures. In our sub-analyses, fractures will be divided into two types; firstly, those fractures associated with a traumatic incident such as vehicular accident or a fall from considerable height; or secondly, as a low impact fracture, where the individual falls from a height not expected to result in a fracture, such as standing height, or identified by imaging, such as a compression fracture of the vertebral body. We will distinguish between fractures occurring pre-diagnosis, around diagnosis and post therapy based on self-reported age at fracture.

Independent variables

1. Date of birth
2. Date of questionnaire completion
3. Sex
4. Cancer diagnosis
5. Date of cancer diagnosis
6. Race/ethnicity (Race 5 code)
7. Dexamethasone (yes/no)
8. Prednisone (yes/no)
9. Alkylating agents (yes/no, alkylating agent score, alkylating agent dose)
10. Cyclophosphamide (yes/no, cumulative dose)
11. Busulfan (yes/ no cumulative dose)
12. CCNU (yes/no, cumulative dose)
13. Chlorambucil (yes/no, cumulative dose)

14. Nitrogen mustard (yes/no, cumulative dose)
15. Procarbazine (yes/no, cumulative dose)
16. Thio-TEPA (yes/no, cumulative dose)
17. Methotrexate (yes/no cumulative dose)
18. Anthracycline agents (yes/no, anthracycline score)
19. Platinum agents (yes/no, platinum score)
20. Vincristine (yes/no)
21. Radiation doses (maximum) to the pituitary, thyroid, ovary, and testes, as well as focal radiation to the long bones of the limbs*
22. Surgery (amputation of lower limb/limb sparing surgery of a lower limb/bilateral oophorectomy/bilateral orchidectomy/other surgery/none)
23. Hematopoeitic stem cell transplant (allogenic, autologous)
24. BMI (calculated from A1-2 FU2007)
25. Smoking status (current/ever/never - N7-N14 FU2007)
26. Physical activity (included as a binary variable classifying the participant as either meeting or not meeting the Centers for Disease Control and Prevention guidelines for physical activity using data collected in questions N15-N22 FU2007)
27. Self-report of growth hormone deficiency (F8 FU2007). This variable will be used for descriptive purposes only†
28. History of a surgical procedure to treat scoliosis
29. Conditions affecting nervous system, balance and equilibrium (D4-5, K2, K5, K8, K11-14 FU2007)
30. Hearing loss (D1-3 FU2007)
31. Menopausal status (F13 – 16 FU2007 questionnaire). This variable used for descriptive purposes only. †
32. Blindness in one or both eyes (D8 - 9 FU2007 questionnaire)
33. Medical screening to assess bone strength or bone mineral density (C2 FU2007 questionnaire)

*Cut off points for radiation categories will be selected on the basis of both biologic plausibility and statistical separation of groups.

†Previous studies have shown that endocrinopathies such as ovarian dysfunction, androgen and growth hormone deficiency may increase the risk of low BMD among survivors of childhood cancer. However, due to the inherent difficulties of measuring these endocrinopathies using self-report questionnaire, treatment exposures associated with the development of these endocrinopathies will be used in place of these outcomes in statistical models.

Statistical analyses

1. Risk for overall fractures (occurring five years after diagnosis) and for traumatic and low impact fractures will be compared between survivors and siblings in age and gender adjusted models using generalized linear models. (Prior to beginning analyses, Drs Dilley and Green will review patient responses describing the occurrence of fractures, to determine if traumatic and low impact fractures can be distinguished with confidence. All discrepancies in calls will be refereed by Dr Kaste).
2. Associations between survivor characteristics (diagnosis, treatment, specific late effects, and lifestyle) and fracture rates will also be evaluated in generalized linear models.
3. Descriptive statistics will be used to evaluate the association between self-reported osteoporosis and fracture outcomes.
4. Summary statistics will be used to describe the prevalence of fractures among survivors of childhood cancer as a function of elapsed time since diagnosis.

Table 1: Characteristics of survivors and siblings reporting the occurrence of one or more fractures

	Survivors		Siblings		
	No.	Proportion with fractures (%)	No.	Proportion with fractures (%)	P
Age at follow-up, years					
18-29					
30-39					
40-49					
50+					
Sex					
Male					
Female					
Race					
White					
Non-white					
Smoking status					
Yes					
No					
BMI					
Underweight					
Normal					
Overweight					
Obese					
Not determined					
Meets the guidelines for physical activity					
Yes					
No					
Not indicated					

Table 2: Traumatic and low impact fractures among survivors of childhood cancer by treatment characteristics

	No. of survivors with a traumatic fracture (%)	No. of survivors with a low impact fracture (%)	No. of survivors with multiple low impact fractures (%)
Sex			
Male			
Female			
Age at fracture, years			
<18			
18-29			
30-39			
40-49			
50+			
Diagnosis[1]			
Leukemia			
Hodgkin's lymphoma			
Non-Hodgkin's lymphoma			
Kidney cancer			
Neuroblastoma			
Soft tissue sarcoma			
Bone tumor			
CNS tumor			
Age diagnosis			
0-4			
5-9			
10-14			
15-19			
Glucocortcoid history			
Dexamethasone +/- prednisone			
Prednisone only			
None			
Alkylating agent score			
0			
1			
2			
3			
Methotrexate			
Yes			
No			
Radiation to the pituitary[2]			
none			
≤20Gy			
21 – 24Gy			
25 – 29Gy			
≥30Gy			
Radiation to the testes[2]			
none			
≤14Gy			
15 – 19Gy			
20 – 24Gy			
≥25Gy			
Radiation to ovaries[2]			
none			
≤1Gy			
1 – 9Gy			
10 – 19Gy			
≥20Gy			
Surgery			
Lower limb amputation			
Bilateral oophorectomy			
Bilateral orchiectomy			
No surgery			
HSCT[1]			
Yes			
No			

1 Excluded from multivariable analyses due to colinearity with other variables

2 Cut off points for radiation categories will be selected on the basis of both biologic plausibility and statistical separation of groups

Table 3: Characteristics of survivors and siblings reporting the occurrence of one or more fractures

Characteristic	No.	%	PR	95%CI	P
Age at follow-up, years					
18-29					
30-39					
40-49					
50+					
Sex					
Male					
Female					
Race					
White					
Non-white					
Smoking status					
Yes					
No					
BMI					
Underweight					
Normal					
Overweight					
Obese					
Not determined					
Meets the guidelines for physical activity					
Yes					
No					
Not indicated					

Table 4: Determinants of fracture among survivors of childhood cancer

Factor		N	%	Univariate analysis PR	95% CI	p	Multivariate analysis PR	95% CI	p
Sex	Male								
	Female								
Diagnosis[1]	leukemia						-----	-----	-----
	Hodgkin's lymphoma						-----	-----	-----
	Non-Hodgkin's lymphoma						-----	-----	-----
	Kidney cancer						-----	-----	-----
	Neuroblastoma						-----	-----	-----
	Soft tissue sarcoma						-----	-----	-----
	Bone tumor						-----	-----	-----
	CNS tumor						-----	-----	-----
Race	White								
	Non-white								
Age diagnosis	0-4								
	5-9								
	10-14								
	15-19								
Length of follow-up	5-14								
	15-24								
	25-34								
	35+								
BMI	≥25								
	<25								
Glucocortcoid history	Dexamethasone +/- prednisone								
	Prednisone only								
	None								
Alkylator history	0								
	1								
	2								
	3								
Methotrexate	Yes								
	No								
Radiation to HP axis[2]	none								
	≤20Gy								
	21 – 24Gy								
	25 – 29Gy								
	≥30Gy								
Radiation to testes[2]	none								
	≤14Gy								
	15 – 19Gy								
	20 – 24Gy								
	≥25Gy								
Radiation to ovaries[2]	none								
	≤1Gy								
	1 – 9Gy								
	10 – 19Gy								
	≥20Gy								
Surgery	Lower limb amputation								
	Bilateral oophorectomy								
	Bilateral orchiectomy								
	No surgery								
HSCT[1]	Yes						-----	-----	-----
	No						-----	-----	-----
Condition effecting balance/coordination[3]	Yes								
	No								
Menopausal status[1]	Not menopausal						-----	-----	-----
	Perimenopausal or postmenopausal						-----	-----	-----
Radiation to the long bones	No								
	Yes								

1 Excluded from multivariable analyses due to colinearity with other variables
2 Cut off points for radiation categories will be selected on the basis of both biologic plausibility and statistical separation of groups
3 Will be evaluated for colinearity with cranial irradiation before including in multivariate models

Table 5: Determinants of low impact fracture among survivors of childhood cancer

				Univariate analysis			Multivariate analysis		
Factor		**N**	**%**	**PR**	**95% CI**	**p**	**PR**	**95% CI**	**p**
Sex	Male								
	Female								
Diagnosis[1]	leukemia						-----	-----	-----
	Hodgkin's lymphoma						-----	-----	-----
	Non-Hodgkin's lymphoma						-----	-----	-----
	Kidney cancer						-----	-----	-----
	Neuroblastoma						-----	-----	-----
	Soft tissue sarcoma						-----	-----	-----
	Bone tumor						-----	-----	-----
	CNS tumor						-----	-----	-----
Race	White								
	Non-white								
Age diagnosis	0-4								
	5-9								
	10-14								
	15-19								
Length of follow-up	5-14								
	15-24								
	25-34								
	35+								
BMI	≥25								
	<25								
Glucocortcoid history	Dexamethasone +/- prednisone								
	Prednisone only								
	None								
Alkylator history	0								
	1								
	2								
	3								
Methotrexate	Yes								
	No								
Radiation to HP axis[2]	none								
	≤20Gy								
	21 – 24Gy								
	25 – 29Gy								
	≥30Gy								
Radiation to testes[2]	none								
	≤14Gy								
	15 – 19Gy								
	20 – 24Gy								
	≥25Gy								
Radiation to ovaries[2]	none								
	≤1Gy								
	1 – 9Gy								
	10 – 19Gy								
	≥20Gy								
Surgery	Lower limb amputation								
	Bilateral oophorectomy								
	Bilateral orchiectomy								
	No surgery								
HSCT[1]	Yes						-----	-----	-----
	No						-----	-----	-----
Condition effecting balance/coordination[3]	Yes								
	No								
Menopausal status[1]	Not menopausal						-----	-----	-----
	Perimenopausal or postmenopausal						-----	-----	-----
Radiation to the long bones	No								
	Yes								

1 Excluded from multivariable analyses due to colinearity with other variables
2 Cut off points for radiation categories will be selected on the basis of both biologic plausibility and statistical separation of groups
3 Will be evaluated for colinearity with cranial irradiation before including in multivariate models

References

1 Nysom, K., Holm, K., Michaelsen, K. F., Hertz, H., Muller, J. & Molgaard, C. Bone mass after treatment for acute lymphoblastic leukemia in childhood. *J Clin Oncol* **16**, 3752-3760 (1998).

2 Atkinson, S. A., Halton, J. M., Bradley, C., Wu, B. & Barr, R. D. Bone and mineral abnormalities in childhood acute lymphoblastic leukemia: influence of disease, drugs and nutrition. *Int J Cancer Suppl* **11**, 35-39 (1998).

3 Warner, J. T., Evans, W. D., Webb, D. K., Bell, W. & Gregory, J. W. Relative osteopenia after treatment for acute lymphoblastic leukemia. *Pediatr Res* **45**, 544-551 (1999).

4 Abramson, E. C., Chang, J., Mayer, M., Kukla, L. J., Shevrin, D. H., Lad, T. E., Buschman, R. & Kukreja, S. C. Effects of cisplatin on parathyroid hormone- and human lung tumor-induced bone resorption. *J Bone Miner Res* **3**, 541-546 (1988).

5 Gnudi, S., Butturini, L., Ripamonti, C., Avella, M. & Bacci, G. The effects of methotrexate (MTX) on bone. A densitometric study conducted on 59 patients with MTX administered at different doses. *Ital J Orthop Traumatol* **14**, 227-231 (1988).

6 Meister, B., Gassner, I., Streif, W., Dengg, K. & Fink, F. M. Methotrexate osteopathy in infants with tumors of the central nervous system. *Med Pediatr Oncol* **23**, 493-496 (1994).

7 van Beek, R. D., de Muinck Keizer-Schrama, S. M., Hakvoort-Cammel, F. G., van der Sluis, I. M., Krenning, E. P., Pieters, R. & van den Heuvel-Eibrink, M. M. 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* **46**, 88-93 (2006).

8 Henderson, R. C., Madsen, C. D., Davis, C. & Gold, S. H. Bone density in survivors of childhood malignancies. *J Pediatr Hematol Oncol* **18**, 367-371 (1996).

9 Hesseling, P. B., Hough, S. F., Nel, E. D., van Riet, F. A., Beneke, T. & Wessels, G. Bone mineral density in long-term survivors of childhood cancer. *Int J Cancer Suppl* **11**, 44-47 (1998).

10 Markbreiter, L. A., Pelker, R. R., Friedlaender, G. E., Peschel, R. & Panjabi, M. M. The effect of radiation on the fracture repair process. A biomechanical evaluation of a closed fracture in a rat model. *J Orthop Res* **7**, 178-183 (1989).

11 Nyaruba, M. M., Yamamoto, I., Kimura, H. & Morita, R. Bone fragility induced by X-ray irradiation in relation to cortical bone-mineral content. *Acta Radiol* **39**, 43-46 (1998).

12 Wagner, L. M., Neel, M. D., Pappo, A. S., Merchant, T. E., Poquette, C. A., Rao, B. N. & Rodriguez-Galindo, C. Fractures in pediatric Ewing sarcoma. *J Pediatr Hematol Oncol* **23**, 568-571 (2001).

13 Halton, J. M., Atkinson, S. A., Fraher, L., Webber, C. E., Cockshott, W. P., Tam, C. & Barr, R. D. Mineral homeostasis and bone mass at diagnosis in children with acute lymphoblastic leukemia. *J Pediatr* **126**, 557-564 (1995).

14 Arikoski, P., Komulainen, J., Riikonen, P., Jurvelin, J. S., Voutilainen, R. & Kroger, H. Reduced bone density at completion of chemotherapy for a malignancy. *Arch Dis Child* **80**, 143-148 (1999).

15 Brennan, B. M., Rahim, A., Adams, J. A., Eden, O. B. & Shalet, S. M. Reduced bone mineral density in young adults following cure of acute lymphoblastic leukaemia in childhood. *Br J Cancer* **79**, 1859-1863 (1999).

16 Kaste, S. C., Rai, S. N., Fleming, K., McCammon, E. A., Tylavsky, F. A., Danish, R. K., Rose, S. R., Sitter, C. D., Pui, C. H. & Hudson, M. M. Changes in bone mineral density in survivors of childhood acute lymphoblastic leukemia. *Pediatr Blood Cancer* **46**, 77-87 (2006).

17 Holzer, G., Krepler, P., Koschat, M. A., Grampp, S., Dominkus, M. & Kotz, R. Bone mineral density in long-term survivors of highly malignant osteosarcoma. *J Bone Joint Surg Br* **85**, 231-237 (2003).

18 Barr, R. D., Simpson, T., Webber, C. E., Gill, G. J., Hay, J., Eves, M. & Whitton, A. C. Osteopenia in children surviving brain tumours. *Eur J Cancer* **34**, 873-877 (1998).

19 van der Sluis, I. M., van den Heuvel-Eibrink, M. M., Hahlen, K., Krenning, E. P. & de Muinck Keizer-Schrama, S. M. Altered bone mineral density and body composition, and increased fracture risk in childhood acute lymphoblastic leukemia. *J Pediatr* **141**, 204-210 (2002).

20 Halton, J. M., Atkinson, S. A., Fraher, L., Webber, C., Gill, G. J., Dawson, S. & Barr, R. D. Altered mineral metabolism and bone mass in children during treatment for acute lymphoblastic leukemia. *J Bone Miner Res* **11**, 1774-1783 (1996).

21 van der Sluis, I. M., van den Heuvel-Eibrink, M. M., Hahlen, K., Krenning, E. P. & de Muinck Keizer-Schrama, S. M. Bone mineral density, body composition, and height in long-term survivors of acute lymphoblastic leukemia in childhood. *Med Pediatr Oncol* **35**, 415-420 (2000).