

General recommendation

CAYA cancer survivors and their healthcare providers should be aware of the risk of low (Z-score ≤ -1 and > -2) and very low (Z-score ≤ -2) bone mineral density, and pay specific attention to possible consequences (e.g. acute and chronic back pain, vertebral and non-vertebral low-trauma fractures, and loss of height due to vertebral fractures) after treatment with:

- Cranial or craniospinal radiotherapy (high-quality evidence for very low BMD)
- Total body irradiation (high-quality evidence for low BMD, unknown effect for very low BMD)
- Corticosteroids as anti-cancer treatment (moderate-quality evidence for low BMD, no significant effect for very low BMD)

Other risk factors for low and very low bone mineral density in CAYA cancer survivors include¹:

- Hypogonadism (moderate-quality evidence for very low BMD; BMD assessment is recommended according to standard endocrine care, which is best done by a medical bone health specialist²)
- Growth hormone deficiency (moderate-quality evidence for low BMD; BMD assessment is recommended according to standard endocrine care, which is best done by a medical bone health specialist²)
- Low BMI or underweight (high-quality evidence for very low BMD)
- Male sex (moderate-quality evidence for very low BMD)
- White race (moderate-quality evidence for low BMD)
- Lack of physical activity³ (moderate-quality evidence for low BMD)
- Current or prior smoking (moderate-quality evidence for low BMD)

Who needs bone mineral density surveillance?

Bone mineral density surveillance is recommended for CAYA cancer survivors treated with cranial or craniospinal radiotherapy (high-quality evidence for very low BMD).

Bone mineral density surveillance is reasonable for CAYA cancer survivors treated with TBI (high-quality evidence for low BMD).

Due to insufficient evidence⁴, no recommendation can be formulated for or against BMD surveillance for CAYA cancer survivors treated with corticosteroids as anti-cancer treatment. The surveillance decision should be made by the CAYA cancer survivor and healthcare provider together, after careful consideration of the potential harms and benefits (see Survivor Information Brochure) and additional risk factors.

What surveillance modality should be used?

A DXA scan of the lumbar spine (posterior-anterior L1-L4), total body less head (in children and adolescents), and total hip (in adolescents and adults) are recommended for surveillance of bone mineral density (evidence-based guidelines).

QCT is not recommended for surveillance of bone mineral density (evidence-based guidelines and expert opinion).

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

BMD surveillance is recommended at entry into LTFU (between two to five years following completion of therapy), and if normal (Z-score > -1), it is recommended to repeat surveillance at 25 years of age when peak bone mass should be achieved. Between these two measurements and thereafter, BMD surveillance should be performed as clinically indicated based on BMD and ongoing risk assessment (expert opinion).

What should be done when abnormalities are identified?

In CAYA cancer survivors with a BMD Z-score ≤ -2 , referral to (or consultation of) a medical bone health specialist² is recommended for further (endocrine) evaluation, interpretation of BMD findings, treatment, and follow-up (expert opinion).

In CAYA cancer survivors with a BMD Z-score ≤ -1 and > -2 , it is recommended to:

- Evaluate for the presence of endocrine defects (hypogonadism, GHD etc.), and consult a medical bone health specialist² for further evaluation and interpretation of BMD findings as clinically

indicated (very low-quality evidence and evidence-based guidelines)

- Repeat DXA after 2 years, and thereafter as clinically indicated based on BMD change (i.e. in case of BMD decline more than the DXA machine's least significant change) and ongoing risk assessment (expert opinion)

In all at-risk CAYA cancer survivors⁵, regardless of their BMD Z-score, it is recommended to counsel about lifestyle habits that are important to maintain or improve bone health:

- Engage in regular physical activity³, especially weight-bearing and fall prevention activities (evidence-based guidelines and expert opinion)
- Abstain from smoking (moderate-quality evidence for low BMD and evidence-based guidelines)
- Limit or avoid alcohol intake (evidence-based guidelines)
- Consume adequate dietary vitamin D (at least 400 IU/day) and calcium (at least 500 mg/day) irrespective of vitamin D status, and advise vitamin D supplementation in survivors with 25OHD levels <20 ng/ml⁶ (plus calcium if the recommended amount of dietary calcium is not met) as per local or national guidelines (evidence-based guidelines and expert opinion)
- Advise nutritional supplementation for CAYA cancer survivors with low BMI or underweight (expert opinion)

It is reasonable to refer at-risk CAYA cancer survivors⁵ with a history of low-trauma vertebral and non-vertebral fractures (from entry into LTFU onwards) to a medical bone health specialist² for further evaluation and treatment (expert opinion).

Abbreviations: BMD=bone mineral density; BMI=body mass index; CAYA=childhood, adolescent and young adult; DXA=dual energy X-ray absorptiometry; LTFU=long-term follow-up; PBM=peak bone mass; TBI=total body irradiation.

¹As in the general population (except for sex; female sex in the general population); ²A medical bone health specialist is defined as any specialist who is caring for BMD deficits in CAYA cancer survivors, such as an endocrinologist (most settings), internist, pediatrician, rheumatologist, family physician, or general practitioner, depending on country and setting; ³The WHO global recommendation on physical activity for health for adults is 150 minutes of moderate-intensity activity (or equivalent) per week, measured as a composite of physical activity undertaken across multiple domains: for work (paid and unpaid, including domestic work); for travel (walking and cycling); and for recreation (including sports). For adolescents, the recommendation is 60 minutes of moderate- to vigorous-intensity activity daily; ⁴Insufficient evidence to determine if early detection of low BMD after treatment with corticosteroids reduces morbidity in CAYA cancer survivors, and whether the risk of very low BMD is increased in the long-term; ⁵Survivors treated with C(S)RT (high-quality evidence), TBI (high-quality evidence), or corticosteroids (moderate-quality evidence); ⁶Target 25OHD levels should be >20 ng/ml.

Green representing a strong recommendation to do with a low degree of uncertainty; Yellow representing a moderate recommendation to do with a higher degree of uncertainty; Red representing a recommendation not to do.

Publication

van Atteveld JE, Mulder RL, van den Heuvel-Eibrink MM, Hudson MM, Kremer LCM, Skinner R, Wallace WH, Constine LS, Higham CE, Kaste SC, Niinimäki R, Mostoufi-Moab S, Alos N, Fintini D, Templeton KJ, Ward LM, Frey E, Franceschi R, Pavasovic V, Karol SE, Amin NL, Vrooman LM, Harila-Saari A, Demoor-Goldschmidt C, Murray RD, Bardi E, Lequin MH, Faienza MF, Zaikova O, Berger C, Mora S, Ness KK, Neggessers SJCMM, Pluijm SMF, Simmons JH, Di Iorgi N. Bone mineral density surveillance for childhood, adolescent, and young adult cancer survivors: evidence-based recommendations from the International Late Effects of Childhood Cancer Guideline Harmonization Group. *Lancet Diabetes Endocrinol* 2021;9:622-637.