

Fractures in Cancer

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MASCC/ISOO

Annual Meeting on Supportive Care in Cancer • June 21-23, 2019



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Conflicts of Interest

- No conflicts of interest



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Objectives

- To increase awareness of skeletal toxicity of cancer therapy
- To gain understanding of the prevalence of skeletal toxicity
- To review RCTs of antiresorptive therapy on skeletal health
- To review international guidelines of management of skeletal (bone) health



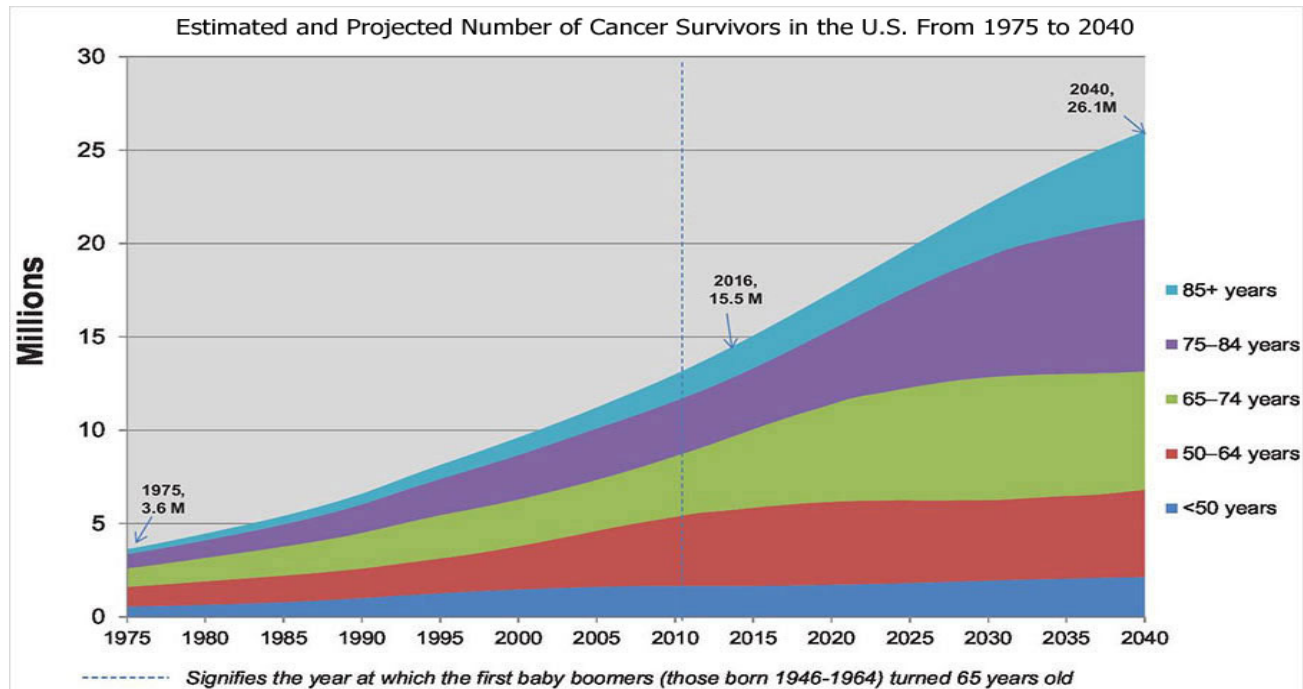
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Cancer survivorship is rising



Adults aged 65 years of age and older are a significant proportion of cancer survivors, comprising 60% in 2018 and projected to rise to 73% by 2040

BluethmanSM. Am Assoc Cancer Res 2016
NCI Surveillance Research 2016-2019



Bone health issues rise with advancing age

- Osteoporosis and low bone mass (osteopenia) affect 54% of individuals 50 years of age and older *Wright JBMR 2016*
- By the age of 65 years, 16.2% and 48.3% have osteoporosis and low bone mass, altogether 64.5% of older adults have bone health issues.

Looker, CDC 2015



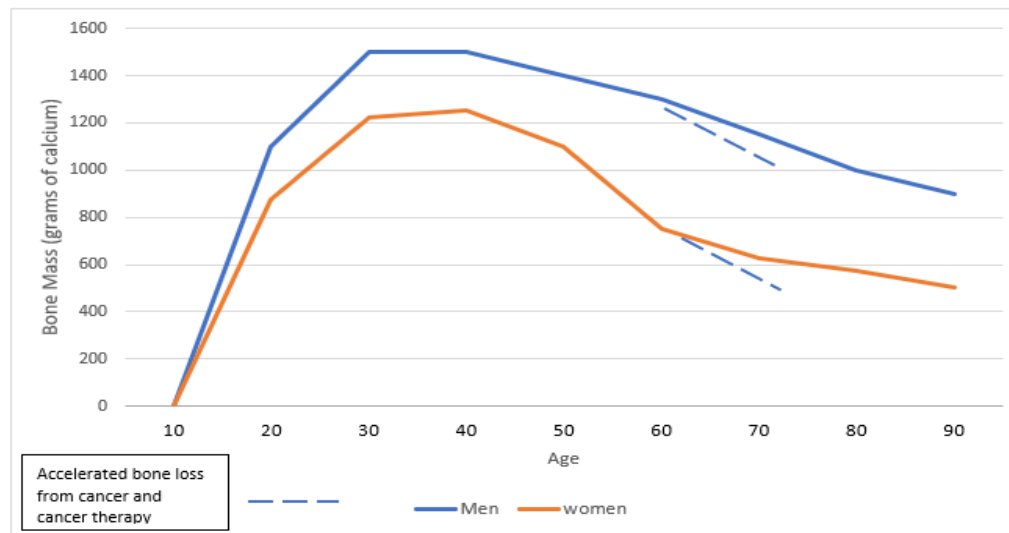
Aging and Bone Mass



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By the time individuals are diagnosed with cancer, they have already suffered considerable bone loss. Cancer and Cancer Rx accelerate this bone loss



Childhood Cancer Survivors



- In childhood cancer (ALL) up to 39% sustain fractures (*Arikoski JBMR 1999*)
- In 186 patients with ALL 16% had morphometric fractures at diagnosis (*Halton, JBMR 2009*)
- Fracture rate is 6-fold higher than expected (*van der Sluis, J Pediatrics 2002*)
- Some controversy regarding long term survivors. Childhood Cancer Survivor Study 7400 patients, no increased risk (22 years) (*Wilson, Cancer 2012*)



Breast Cancer

- Premenopausal women suffer Chemotherapy induced ovarian failure (*Shapiro, JCO 2001*)
- Premenopausal women suffer bone loss with tamoxifen. 75% higher risk of fractures than for healthy controls (*Kyvermitakis Osteop Int 2018*)
- Ovarian function suppression and aromatase inhibitors indicated in HR+BC-fractures 7.7% in combined group, tamoxifen 6% and tamoxifen alone 5.5% (*Burstein JCO 2016*)
- Postmenopausal women AI lose most BMD first 5 years, effect disappears after meds are stopped Forbes JF. (*Lancet Oncol 2008*)
- All AIs result in an increase of fracture risk 33-45% (*Coleman Lancet Onc 2007, Rabaglio Annals Onc 2009, Forbes Lancet Onc 2008*)
- Vertebral fractures are common in women with BC (*Kanis Br J Cancer 1999*)
- Older cancer survivors had a fracture risk 2.8 times higher than NHANES III (*Edwards SCC 2018*)



Prostate Cancer & Non Hodgkins Lymphoma



- In a RCT with denosumab, of PC on ADT, the control group had a fracture rate of 3.9% at 36 months (*Smith NEJM 2009*)
- 5 years after starting ADT 19% of men on ADT had a fracture v. 12.6% of those who did not receive ADT (*Shanian NEJM 2008*)
- Mortality was two fold higher in men PC who fracture v. those who are fracture free (*Beebe Dimmer Pharmacoepidemiol 2012*)
- **NHL:** Patients who received chemotherapy had OR of 2.44 of having a fracture, and OR 1.27 of having osteoporosis compared to those who did not receive chemotherapy (11 yr fu) (*Cabanillas Leuk lymphoma 2007*)
- **Stem cell transplantation (HSCT).** Fracture incidence is 8% (*Pundole JCO 2015*)
- 8-fold higher risk of fracture as compared to NHANES III (*Pundole JCO 2015*)



Plasma Cell Disorders

- Plasma Cell Disorders: fracture rates a 17-fold higher than normal population (*McIlroy Br J Hem 2017*)
- Poorer survival in those who fracture 20% higher mortality (*McIlroy Br J Hem 2017*)
- Incidence of fractures 19/1000 person-years (*Gregersen Br J Hem 2006*)
- Colorectal, endometrial, melanoma and NHL. Fracture risk was higher in the cancer group 14.6% (*Chen Osteo Int 2009*)
- Hip fracture risk RR 2.09 in women with such diagnoses (*Chen Osteo Int 2009*)



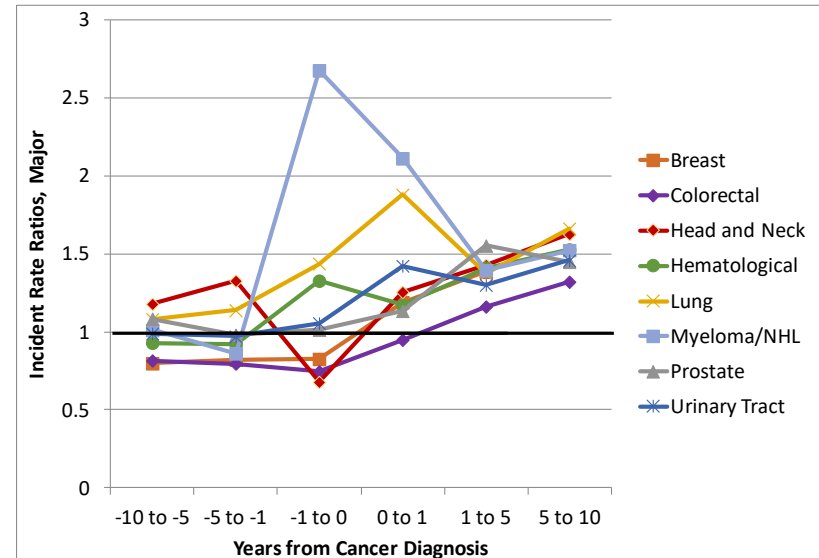
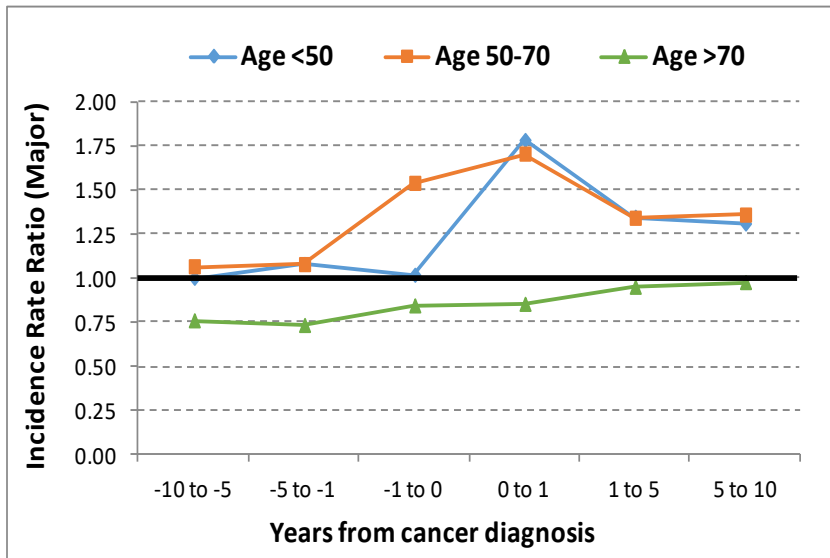
Fractures have been reported in multiple cancers



- **Gynecologic Cancers:** Women with cervical cancer s/p XRT suffered more pelvic fractures (*Baxter JAMA 2005*)
- **Thyroid cancer:** 128 women on TSH suppressive therapy were assessed. VFs were found in 28.5% of patients, with a higher prevalence in those with the lowest TSH levels. In the whole population, VFs were significantly and independently associated with TSH level <1.0 mU/L, osteoporosis, advanced age, and duration of L-T4 therapy. *Mazzioti JCEM 2018*
- In Sweden an increased risk of fractures, within the first year after diagnosis was seen in patients with primary bone cancer OR=3.51 (95% CI: 1.54-8.01), multiple myeloma OR 5.21 (95% CI: 2.96-9.19), metastases to the bone OR 5.28 (95% CI: 3.58-7.79), metastases to other organs than bone OR 1.85 (95% CI: 1.50-2.29), lung cancer OR 1.90 (95% CI: 1.51-2.38), and cancer of the liver, gall bladder and pancreas OR 2.14 (95% CI: 1.39-3.31). *Vestergard Acta Oncologica 2009*



Manitoba Study



Singh JBMR 2017



Causative Factors for the Rise in Fractures



- Aging and high prevalence of bone health issues, 64% of adults 65 yrs + have bone health issues. *Looker CDC 2015*
- Inflammation which accelerates bone loss. *Straub Semin Arth Rheum 2015*
- Endocrine Factors *Bokemeyer JCO 1996*
- Direct Effect of Chemotherapy *Fam JBMR 2016*
- Hormonal therapy *(Coleman Lancet Onc 2007, Rabaglio Annals Onc 2009, Forbes Lancet Onc 2008)*
- Disuse bone loss *(Alexandre Joint, bone, spine : revue du rhumatisme. 2011)*
- Malnutrition, Sarcopenia *(Ryan, Proceedings of the Nutrition Society. 2016)*
- Opioids *(Edwards, Bone. 2015)*
- Vitamin D deficiency *(Blutt, Endocrinology 1997)*
- Corticosteroids *(Liu, Clinical Inter aging 2015)*



Direct Effect of Chemotherapy on Bone



Agent	Effects on Bone
Lenalidomide	None reported
Thalidomide	None reported
Cyclophosphamide ¹	Inhibition of bone formation
CEF regimen ²	Reduction of trabecular volume, bone loss
Doxorubicin ³	Negatively affects bone geometry, trabecular microarchitecture, and femur mechanical properties in growing Wistar rats
Abiraterone ⁴	Results in anabolic and anti-resorptive actions on bone.
Taxanes ⁵	Myelosuppression results in bone loss by increasing resorption
Imatinib ⁶	Increases bone resorption, hyperphosphaturia
Methotrexate ⁷	Increases apoptosis of osteocytes 4-fold, increases osteoclast 1.8-fold
Cisplatin ⁸	Negatively affects bone repair

Katikaneni R, Nichols T, et al. Prevention of chemotherapy-induced osteoporosis by cyclophosphamide with a long-acting form of parathyroid hormone. *Journal of endocrinological investigation*. 2011;34(11):e392-397.

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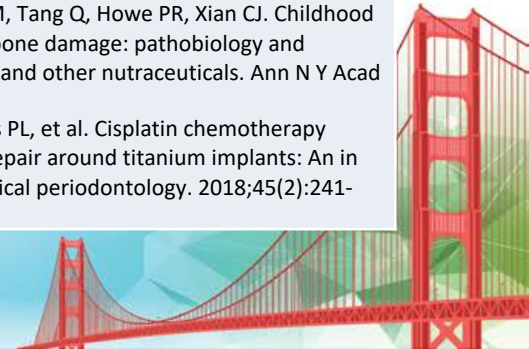
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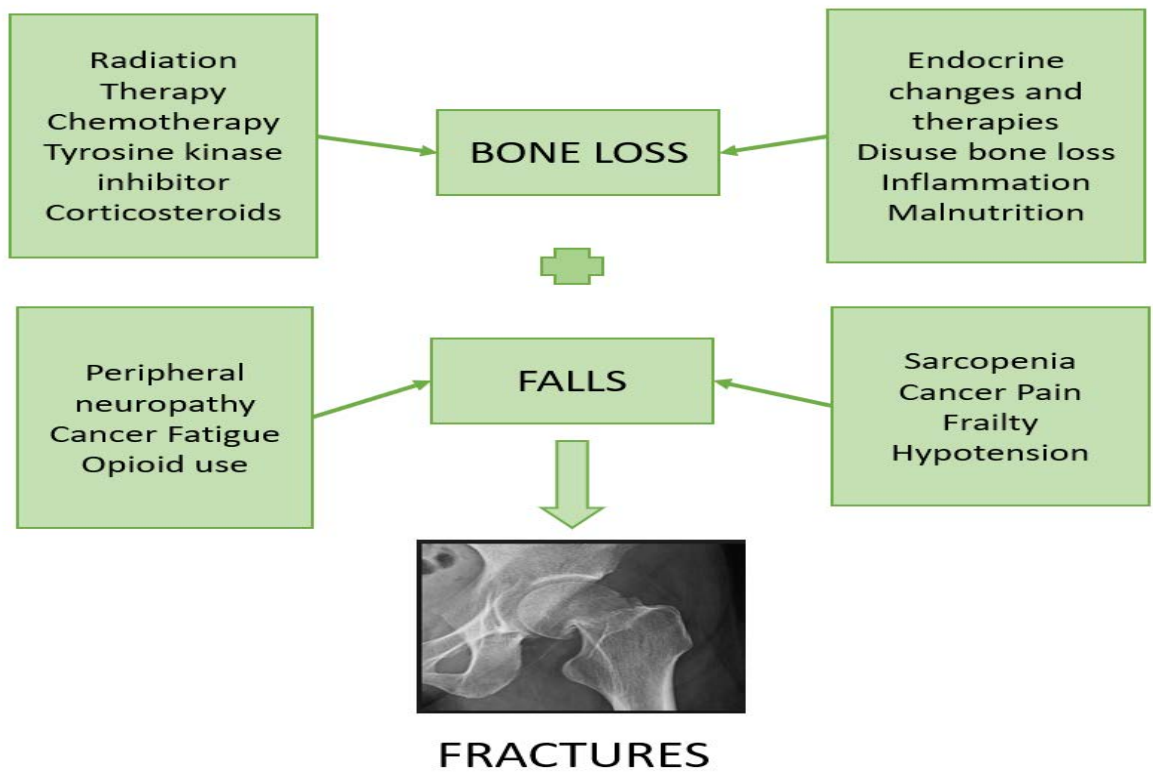


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Mechanisms for Fracture Occurrence



Other Agents

- Tyrosine kinase inhibitors:
 - deceleration in growth,
 - promotes osteoclast differentiation and osteoblast apoptosis
 - RCT decline in BMD. Imatinib & Dasatinib *(Berman, Leukemia res 2013)*

mTOR inhibitors:

Everolimus reduced bone turnover and reversed the increase in bone resorption associated with both progressive disease in bone and effects of exemestane on normal bone turnover.

Adding everolimus to exemestane therapy also reduced the incidence of breast cancer progression in bone *(Hadji, Critical Rev Hem Onc, 2013)*



Radiation Therapy and Bone

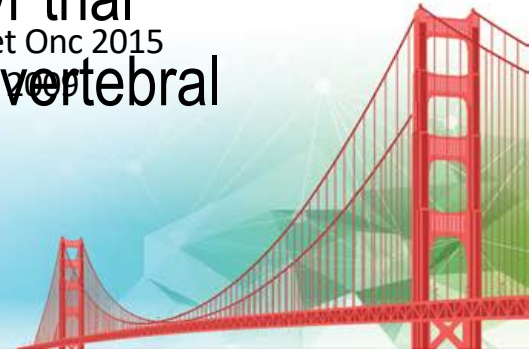


- Radiation induced rib fracture (LC) 37% at 3 year
- Sacral insufficiency fractures (anal/rectal CA and Gyn CA) 2-34%
- WHI, risk of pelvic fracture varied from HR 3.16 (anal CA),
- HR 1.66 (cervical CA) and HR 1.65 (rectal CA)
- Bone atrophy, loss of osteoblasts, vascular changes
- Insufficiency fracture have a high rate of delayed and non union
Cannon, J Am Acad Orthop Surg 2008
Abe AJR 1992
Herman Int J Rad Onc 2009
Denham BJ Int J Radiat Oncol 2009
- ZOL can reduce bone loss associated with XRT



Randomized clinical trials

- Preserve bone mass
- Patients on AIs:
 - Coral ALN-Leuprolide
 - BATMAN- ALN-Anastrozole
 - SABRE- RIS-Anastrozole
 - ARIBON- IBN-Anastrozole
 - Z-FAST, Zo-FAST- ZOL-Anastrozole
 - Clodronate
- Prevent Fractures
- ABCSG 18-Dmab-anastrozole 3 year study. Reduced vertebral fractures by 50%, in women with osteopenia or even normal BMD
- Prostate cancer- PC Dmab on ADT 3 yr trial
Grant Lancet Onc 2015
62% reduction in vertebral fractures



Clinical Guidelines

- Childrens' Oncology Group
- National Comprehensive Cancer Network 2009, 2013
- European Society for Medical Oncology 2014
- International Society for Geriatric Oncology 2016
- European Medicine agency 2017
- Cancer Care Ontario 2017
- IOF, CABS, ECTS, IEG, ESCEO, IMS, SIOGA
- ASCO 2019 in process



American Society of Clinical Oncology



- USPSTF served as background
- Oncology studies reviewed
- Focused on fracture prevention
- Emphasis placed on the “Graying of America” a growing number of older adults in the cancer population.
- Aging associated with age-related bone loss, therefore advanced is an important risk factor for fractures
- Cancer and Cancer treatment are conducive to accelerated bone loss
- Traditional risk factors
- Recommend risk stratification in those who have risk factors
- Recommend utilizing FRAX or BMD testing
- Guidelines focus on the general cancer population



Conclusions

- A rising number of cancer survivors
- Late-term toxicity of cancer care seen in multiple cancers
- Multifactorial origin to bone loss
- Bisphosphonates and RANKL binding agents effective
- Greater awareness is necessary
- Prevention of fractures is necessary for Quality of Life in cancer survivors



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