

BREAST CANCER AND BONE HEALTH

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Conflicts of Interest

None to declare

Objectives

1. To appreciate the impact of breast cancer and its treatment on osteoporosis and fractures
2. To understand the effects of breast cancer therapies on bone
3. To review current recommendations for screening, prevention and management of low bone mass in early stage breast cancer
4. To review the management of bone health in women with metastatic breast cancer

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Breast Cancer - Overview

- Most common cancer in women (excluding non-melanoma skin cancer)
- In 2017 breast cancer accounted for 25% of new cancer diagnoses in women
- Average lifetime risk: 12% (1 in 8)
- Median age at diagnosis: 61
- More than 75% of all breast cancers and 85% of breast cancer deaths occur in postmenopausal women
- 75-80% express hormone receptors (ER &/or PR)

Breast Cancer & Osteoporosis

- Both are common diseases in women
 - At least 1 in 3 women will sustain an osteoporosis-related fracture in their lifetime
- Observational studies suggest an association between higher bone mass breast cancer risk
 - In a meta-analysis, women in the highest BMD category had an increased risk compared to the lowest category
 - 82% for the spine, 62% for the hip
 - For each standard deviation increase in BMD, breast cancer risk increased by
 - 26% for the spine, 20% for the hip

Breast Cancer & Osteoporosis

The role of Estrogen

- Estrogen has been postulated to be the key link in the association between BMD and breast cancer
 - Role in regulation of bone turnover
 - Effect on breast cancer cells
- BMD can be considered a marker of long-term estrogen exposure
- Other factors have also been implicated
 - Growth factors
 - Cytokines

Breast Cancer & Osteoporosis

- Despite the correlation between BMD and breast cancer risk, women with breast cancer are not protected against osteoporosis and fracture
- Post-menopausal survivors of breast cancer are at increased risk for clinical fractures

WHI data

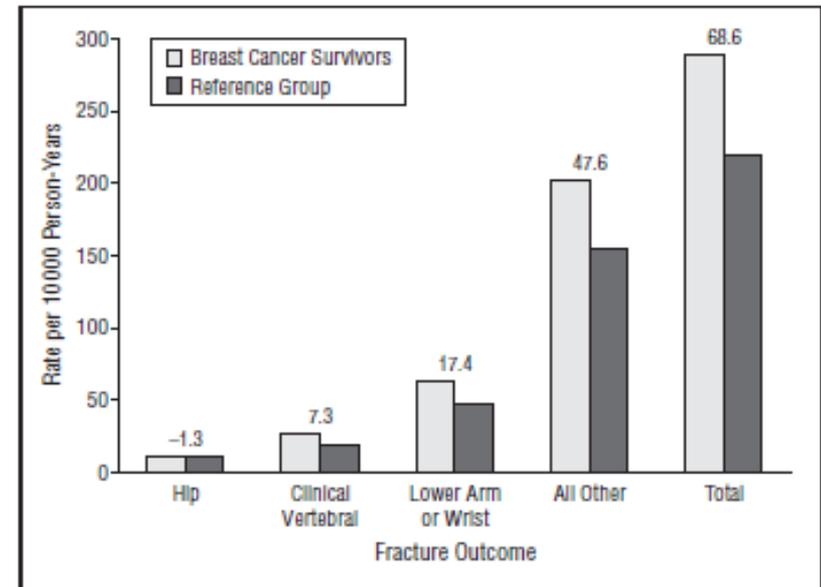


Figure 1. Age-standardized fracture incident rates by survivor status. Standardized rates were calculated using the age distribution of the entire Women's Health Initiative Observational Study cohort. Excess number of fractures per 10 000 person-years are above each set of bars.

Breast Cancer & Osteoporosis

What do we know about fracture risk?

Fracture risk associated with

- age
- non-Hispanic white
- depression indicator
- prior fracture history
- more than 2 falls in the last 12 months
- diabetes
- arthritis
- hip replacement
- emphysema or chronic bronchitis
- osteoporosis

Fracture risk *not* associated with:

- BMI
- years since menopause
- age at diagnosis with breast cancer
- use of HRT

Risk Factors that Increase Fracture Risk in Postmenopausal Women with Breast Cancer

- aromatase inhibitor treatment
- t score < -1.5
- increasing age (>65)
- oral corticosteroid use for more than 6 months
- low BMI (<20 kg/m²)
- family history of hip fracture
- personal history of fragility fracture after age 50
- smoking

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Breast Cancer Therapies that Affect Bone

- Endocrine therapy
 - Tamoxifen
 - Aromatase inhibitors (anastrozole, letrozole, exemestane)
 - GnRH agonists (goserelin, leuprolide)
 - Oophorectomy
- Chemotherapy
- Radiation

Estrogen in Postmenopausal Women

Circulating estrogen is primarily from conversion of adrenal androgens by aromatase

- Low concentrations sufficient to exert biological effects on breast cancer cells that express ER
- Aromatase enzyme highly expressed in breast cancer

Estrogen level can be lowered

- Aromatase inhibitors suppress the already low levels by 80-95%, to virtually undetectable levels
- The interaction of E with the receptor can be targeted using a SERM – competitively binds to the receptor

Choice of Endocrine Therapy

Depends on tumour type and menopausal status

- Tamoxifen:
 - can be used independent of menopausal status
- Aromatase inhibitors:
 - only used in postmenopausal women
 - more effective than tamoxifen in preventing recurrence and are the preferred therapy for postmenopausal women with hormone-sensitive breast cancer
- GnRH analogues:
 - used in premenopausal women in combination with tamoxifen to suppress ovarian function and improve disease-free survival in those at high risk

Adjuvant Therapy in Early Breast Cancer – 1st 5 years

5 years of tamoxifen (standard for premenopausal women)

- Reduces relapse by 41%
- Reduces death by 31%

Aromatase inhibitors are superior to tamoxifen in postmenopausal women

- 2.9% absolute decrease in recurrence - (9.6% vs 12.6%)
- small improvement in overall survival

For premenopausal women who become postmenopausal (naturally or chemotherapy-induced)

- benefit from switching to AI after 2-3 years of tamoxifen

Adjuvant Therapy in Early Breast Cancer – beyond 5 years

There are as many recurrences after 5 years as in the first 5 years of follow-up in early ER + cancers

After 5 years of tamoxifen

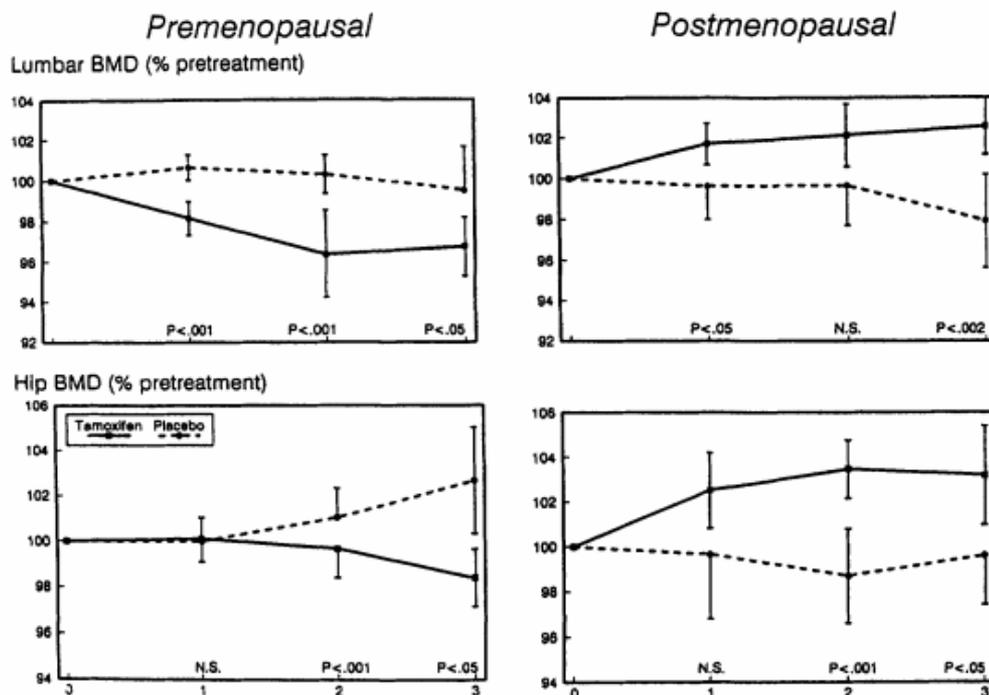
- further reduction in recurrence and mortality with 10 years of therapy for women who remain premenopausal or are unable to tolerate AI therapy
- 42% relative risk reduction with 5 years of letrozole for women who are postmenopausal

Tamoxifen: Effect on BMD

- Most frequently used SERM for adjuvant therapy
 - Antagonistic effects on ER signalling in breast
 - Agonist effects in bone
 - Positive effect on BMD of postmenopausal women recognised since the 1990's

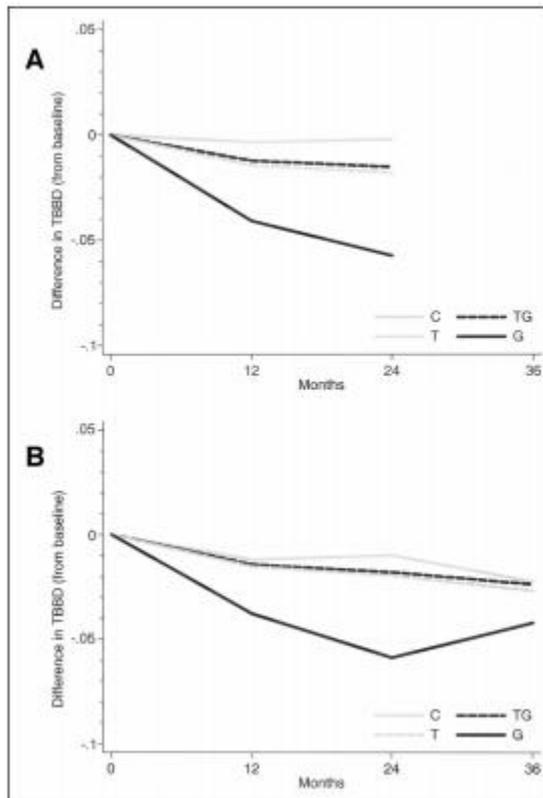
Tamoxifen: Effect on BMD

Agonist effect on bone is not sufficient to prevent bone loss in premenopausal women



GNRH Antagonists and Bone Loss

Effect of adding Tamoxifen



- Estrogen suppression with a GnRH analogue results in significant bone loss
- When combined with the GnRH analogue Goserelin, Tamoxifen significantly reduced bone loss (1.4% vs 5% after 2 years)

Tamoxifen: Fracture Data

After 5 years of tamoxifen therapy (Breast Cancer Prevention Trial)

- 32% reduction in spine, hip, and radius fractures compared with placebo
- Most fractures occurred in women ≥ 50
- Fracture reduction by age of entry into trial
 - ≥ 50 : 29%
 - < 50 : 53%

Aromatase Inhibitor Associated Bone Loss (AIBL)

- Marked increase in bone resorption
- 2-4 fold increased bone loss compared to physiologic menopausal loss
- Most bone loss in the 1st year of therapy
- Partial recovery after discontinuation
- Most trials compared AI to tamoxifen
 - significant reduction in lumbar spine BMD
- Few studies compare effects of different AI therapies
 - All have negative effects on the skeleton
 - 2 RCTs (exemestane vs anastrozole, letrozole vs anastrozole) showed no difference between drugs

Aromatase Inhibitors & Fracture

Compared with Tamoxifen

- RCTs with 5 years of AI therapy suggest an increased absolute fracture risk of about 10%
- Longer duration of use associated with greater risk of fractures
 - OR 1.47 (1.45 adjusting for survival) $p < .0001$
- Fracture incidence
 - 7.5% in the aromatase inhibitor group
 - 5.2% in the tamoxifen group
 - difference in absolute risk 2.2%, NNH 46

Aromatase Inhibitors & Fracture

- However, given the stringent inclusion/exclusion criteria, studies probably underestimate fracture risk
- One RCT estimates the rate at 18-20%
- For 10 years of therapy, risk continues to increase 2-3%/year

What Happens after AI Therapy?

ATAC Trial (Anastrozole & Tamoxifen alone or in combination)

- BMD tends to recover after AI stopped, particularly lumbar spine
- Markers of bone resorption normalise within 3-6 months of withdrawal
- No difference in fracture rate (anastrozole versus tamoxifen) after treatment completed
 - Under-reporting?
 - May be due to bisphosphonate use since this was not controlled after endocrine therapy was stopped

Chemotherapy

- Depresses gonadal function
- High risk of ovarian failure
- Menopause occurs about 10 years earlier in women who receive chemotherapy
- May have some direct effect on bone
- Impact of supportive therapies
 - Glucocorticoids (premedication and anti-emetic)

Radiation

Radiation-induced fractures well documented

- Rib fracture rates reported from 1.8-19%
- Fracture risk increases with
 - Higher radiation dose
 - Pre-existing osteoporosis

Limited data on mechanisms, magnitude and extent of bone loss

- Physiologic changes within the vasculature
- Changes in bone cell number and function
 - Decreased number and activity of osteoblasts
 - Increased number and activity of osteoclasts

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Management of Bone Health in Patients with Breast Cancer

- Except for tamoxifen in postmenopausal women, endocrine therapy has significant negative effects on bone health
- Bone health should be actively monitored and managed in these women
- Several guidelines on bone health in cancer
 - ASCO 2011
 - ESMO 2014
 - Joint position statement on AIBL 2017
 - Use of adjuvant bisphosphonates in breast cancer – ASCO/CCO 2017

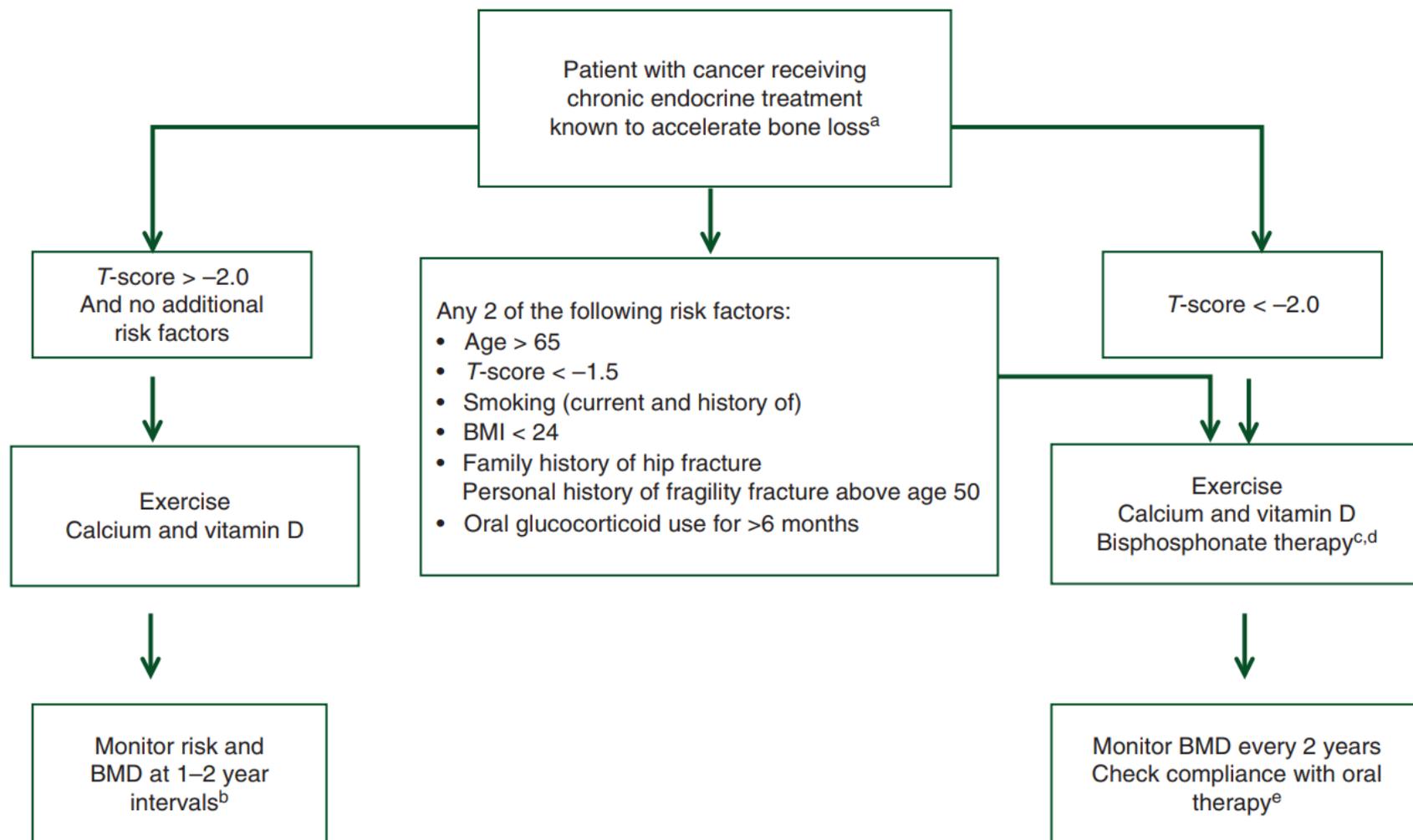
Preventing Bone Loss in Patients on Therapy Known to Increase Fracture Risk

- Baseline fracture risk assessment
- BMD measurement
- Education about risk factors and a healthy lifestyle
 - Physical activity and regular weight-bearing exercise
 - Avoiding tobacco use
 - Limiting alcohol intake
 - Consider supplementation with calcium and Vitamin D
- Antiresorptive therapy in selected cases
 - patients at high risk for bone loss and/or fracture

Assessing Fracture Risk

- Osteoporosis
- High risk for fracture – CAROC or FRAX
 - Recognised to underestimate fracture risk in breast cancer patients on AI therapy
- Fall risk
- Osteopenia/moderate risk plus other risk factors such as AI
- ?Anticancer benefit of therapy

Suggested Algorithm for Managing AIBL



Hadji P, et al. *J Bone Oncol*. 2017;7:1-12.

Coleman R, et al. *Annals of Oncology*. 2014;25(supp 3):124-137.

Treatment Options

- Bisphosphonates
 - Oral and IV
- Denosumab

- SERMS and PTH are not used in breast cancer
 - In patients on AI, SERMS blunt the expected reduction in recurrence
 - Should not use PTH with radiation

Effect of OP Therapy

Data consistently show improved BMD on OP meds

- Studies with bisphosphonates (alendronate, risedronate, zoledronic acid and ibandronate) and denosumab

Less data on fracture

- Benefit shown in postmenopausal but not in premenopausal women

Oral Bisphosphonates in Patients on AI Therapy

- Most trials small
- Underpowered to assess fracture prevention
- Patients often allocated to treatment groups based on BMD
- Positive effect on BMD in patients on AI therapy

IV Bisphosphonates in Patients on AI

- Not designed to show difference in fracture incidence
- Zoledronic acid 4mg every 6 months
- Compared immediate vs delayed therapy
 - Immediate therapy prevented bone loss and BMD improved during therapy
 - Those on delayed therapy lost BMD compared to baseline

Denosumab in Patients on AI

Adjuvant denosumab in breast cancer trial included fracture as a primary endpoint

- > 3400 patients
- Compared with placebo:
 - Bone density improved
 - Fracture risk reduction:
 - Any clinical fracture (50%)
 - Incident morphometric vertebral fractures or worsening prevalent vertebral fractures (46%)
 - Risk reduction independent of age and baseline BMD

What about Premenopausal Women?

- Bone loss in premenopausal women receiving endocrine therapy for early breast cancer is a significant concern because these women typically survive for many years post treatment
- Any premature loss of BMD will disadvantage these women as they age
- Limited data on the extent of recovery after treatment is completed

Effect of Zoledronic Acid on Bone Loss

Anastrozole + GnRH vs
Tamoxifen + GnRH for 36 months

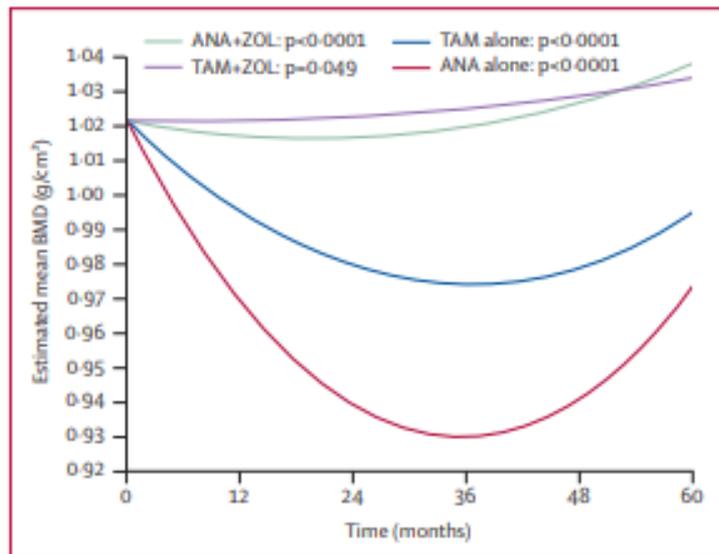


Figure 2: Changes from baseline to 60 months in bone-mineral density (BMD) of lumbar spine

- Both regimens cause bone loss
- Bone loss blunted with tamoxifen
- Partial recovery 2 years after completing therapy
- Zoledronic acid maintained BMD during endocrine therapy and improved BMD at 5 years

Anti-Cancer Effects of Bisphosphonates

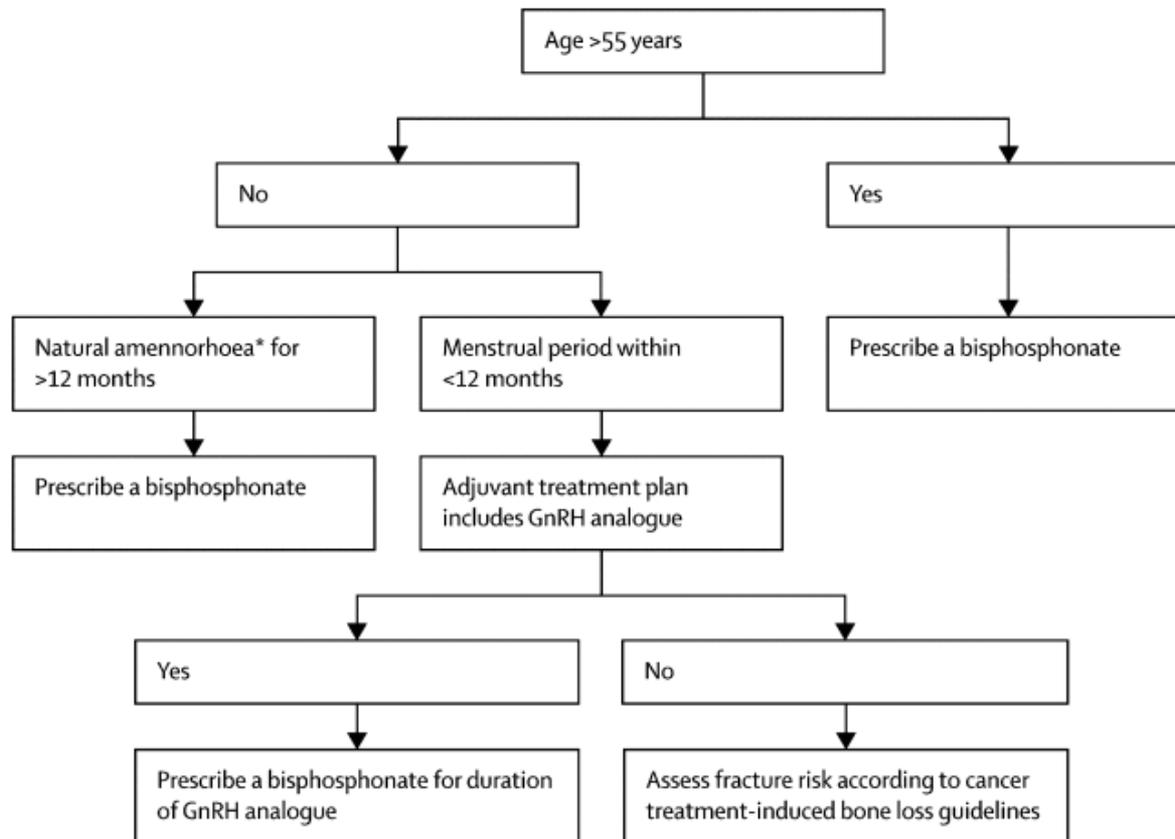
- Population-based case-control studies suggest that oral BP therapy for OP may reduce the incidence of invasive breast cancers
- Phase II studies demonstrated direct anticancer effects of zoledronate on disseminated tumour cells in bone marrow of patients with early breast cancer
 - Reduce residual tumour size
 - Improve response rates compared to chemotherapy alone
- Early trials of adjuvant BPs for the prevention of bone metastases were inconclusive due to their broad inclusion criteria

Anti-Cancer Effects of Bisphosphonates

Meta analysis of adjuvant BP for anti-cancer effects in early breast cancer

- 2-5 years of bisphosphonate therapy
 - No benefit in premenopausal women
 - Significant benefit in postmenopausal women
 - Bone recurrence (34%)
 - Breast cancer mortality (17%)
 - Fractures
- Many groups now recommend adjuvant bisphosphonates to reduce the risk of metastasis in postmenopausal women with early breast cancer

Selection of Patients Suitable for Adjuvant BPs to Prevent Metastases



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Skeletal Related Events

- Bone metastases occur in 60-80% of patients with advanced disease
- Skeletal events include
 - Pain
 - Fractures
 - Are vertebral compression fractures OP or pathologic fracture?
 - Cord compression from extraosseous extension of vertebral metastasis

Skeletal Related Events

Bisphosphonates and denosumab are recognised to reduce skeletal morbidity from metastatic cancer

Agents Used:

- Pamidronate monthly
- Zoledronic acid every 1 or 3 months
- Denosumab 120 mg monthly

Important to consider

- Calcium and vitamin D supplementation (risk of hypocalcemia)
- Oral health – ONJ risk (0.5-1%/year)

What are the Current Guidelines?

- Start zoledronic acid or denosumab in all patients with metastatic breast cancer and bone metastases, whether they are symptomatic or not
- Insufficient evidence to recommend one drug (zoledronic acid, pamidronate, denosumab) over another
 - Denosumab was found to be more effective than zoledronic acid in one RCT of 2000 patients
- Lack of consensus on duration of therapy

In Summary

- In breast cancer patients, in addition to BMD, clinical risk factors influence fracture risk
- Data from the AIBL setting as well as long-term use in the treatment of postmenopausal osteoporosis show that bisphosphonates and denosumab are safe and effective agents for preserving bone health during adjuvant endocrine therapy for breast cancer
- Emerging anticancer benefits provide additional reasons to use antiresorptive agents during adjuvant AI therapy

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If you have questions about Beyond The Break, contact Kevin at

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