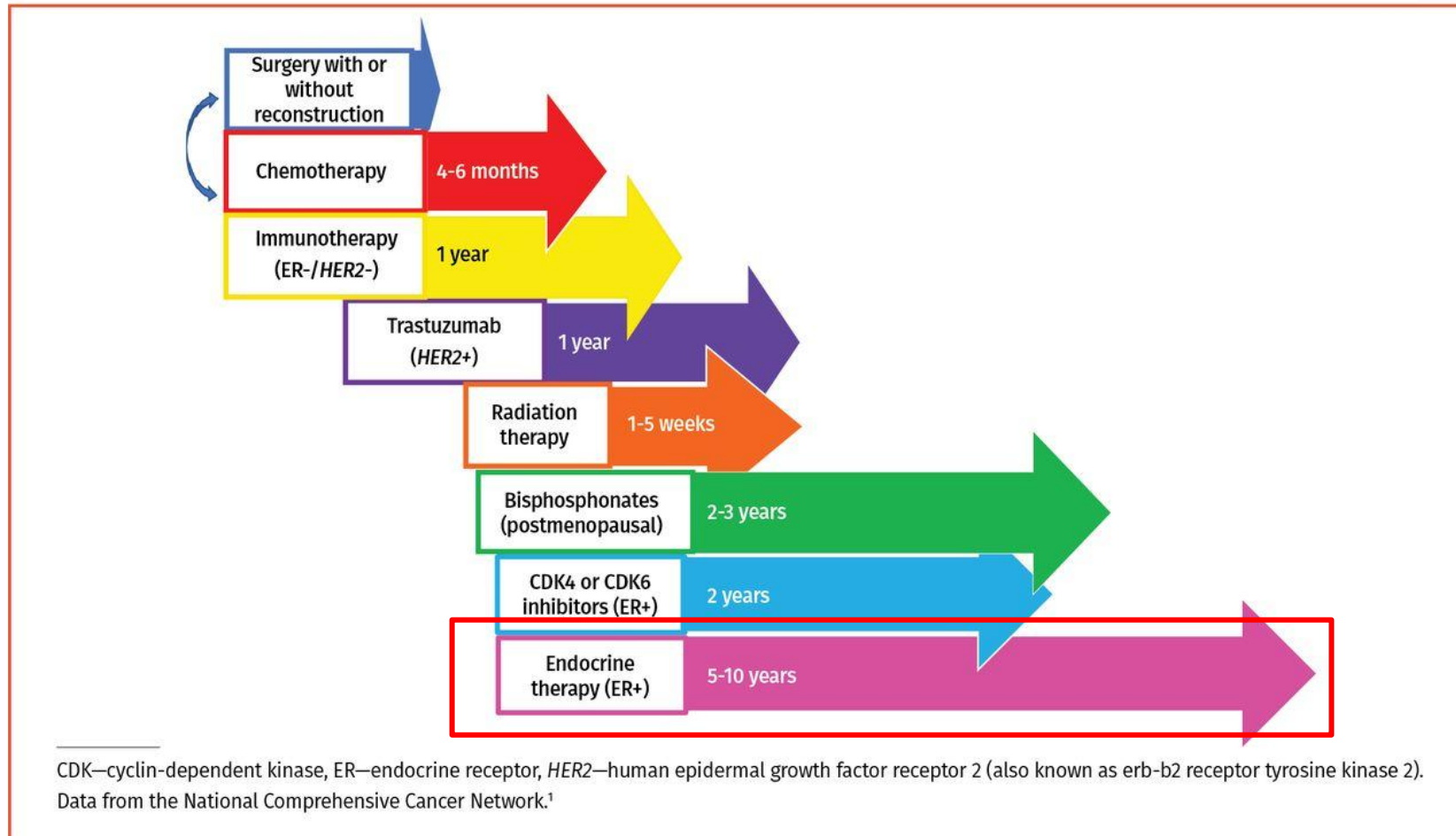# Bone Heath in Breast Cancer Survivors

Marilyn L. Kwan, PhD

Senior Research Scientist

Pathways Community Forum

March 6, 2025

Overview of Breast Cancer Therapies

Surgery with or without reconstruction

Chemotherapy — 4-6 months

Immunotherapy (ER-/HER2-) — 1 year

Trastuzumab (HER2+) — 1 year

Radiation therapy — 1-5 weeks

Bisphosphonates (postmenopausal) — 2-3 years

CDK4 or CDK6 inhibitors (ER+) — 2 years

Endocrine therapy (ER+) — 5-10 years

CDK—cyclin-dependent kinase, ER—endocrine receptor, HER2—human epidermal growth factor receptor 2 (also known as erb-b2 receptor tyrosine kinase 2). Data from the National Comprehensive Cancer Network.[1]

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Hormonal Therapy (Endocrine Therapy) to Treat Breast Cancer

- Hormonal therapy for breast cancer works in 2 ways:
  - <u>Blocking</u> the hormones from attaching to their receptors on the cancer cells and preventing their growth
  - <u>Decreasing</u> the production of specific hormones in the body
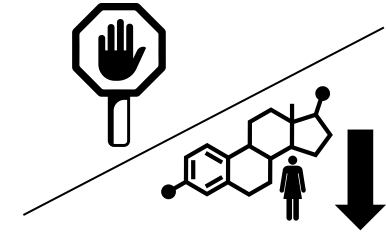
- Hormonal therapy for breast cancer is effective only if it has receptors for 2 important hormones, estrogen or progesterone (ER+ or PR+)

ER+ or PR+

- Lowering the production or preventing the attachment of estrogen on breast cancer cells can help treat breast cancer
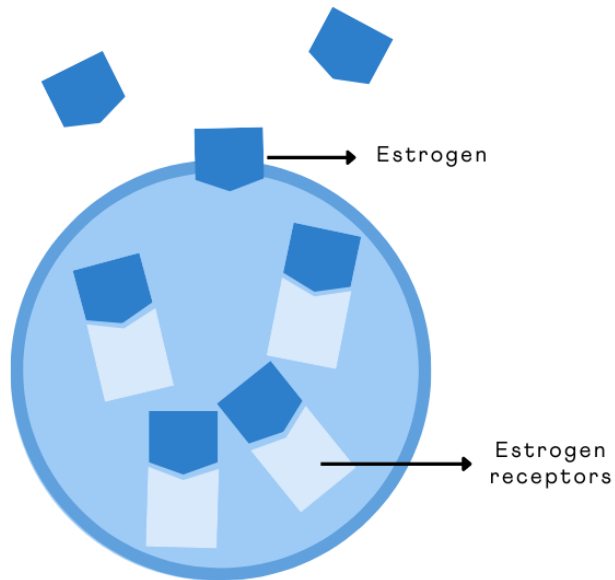
- Two types of hormonal therapy:
  - Selective Estrogen Receptor Modulators (Tamoxifen, Toremifene)
  - Aromatase Inhibitors (Anastrozole, Exemestane, Letrozole)

SERMs and AIs

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Selective Estrogen Receptor Modulators (SERMs, Tamoxifen)

SERMS (TAMOXIFEN) – HOW THEY WORK

Estrogen
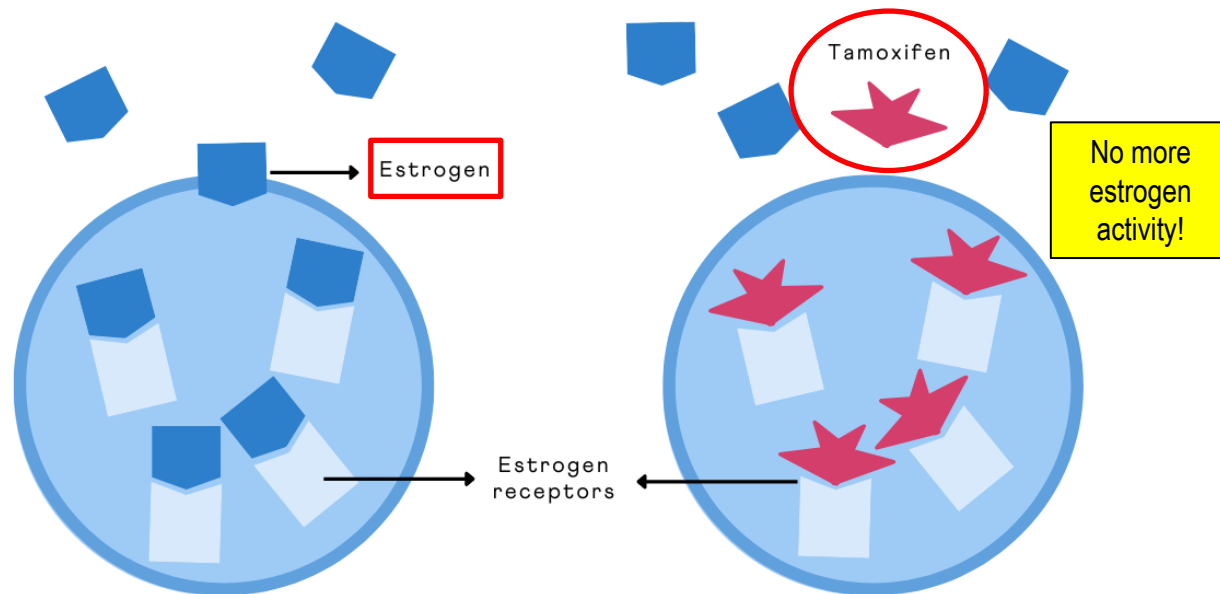
Estrogen receptors

Breast Cancer Cell

Selective Estrogen Receptor Modulators (SERMs, Tamoxifen)

SERMS (TAMOXIFEN) - HOW THEY WORK

Estrogen

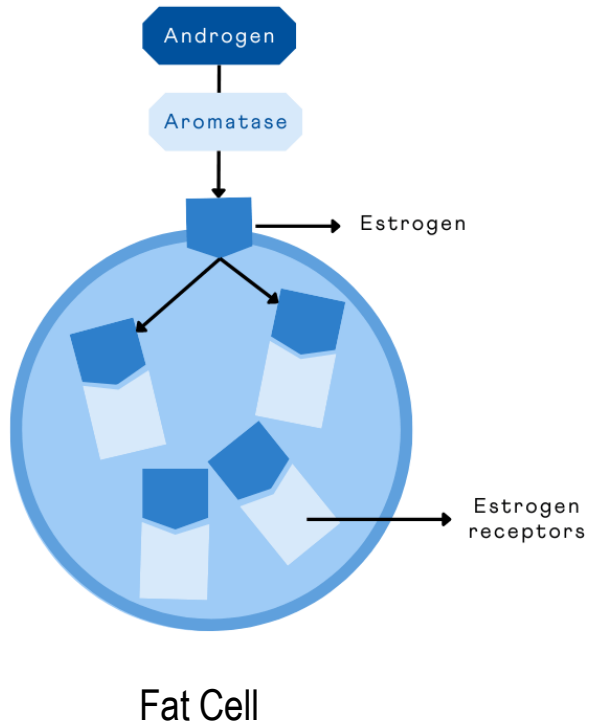No more estrogen activity!

Tamoxifen

Estrogen receptors

Breast Cancer Cell

- <u>Block</u> estrogen activity in the breast
- Bind to estrogen receptors on cancer cells, thereby hindering their growth
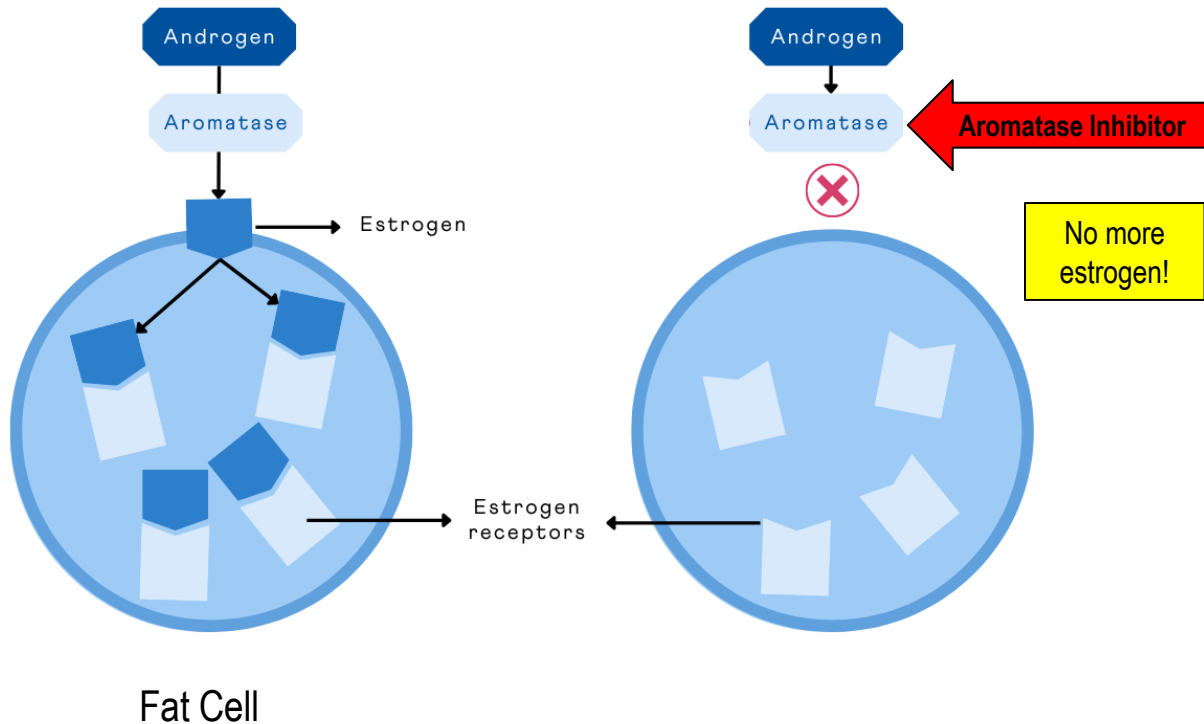- Used in pre-menopausal and post-menopausal women

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Aromatase Inhibitors (Anastrozole, Exemestane, Letrozole)

AROMATASE INHIBITORS – HOW THEY WORK

Androgen → Aromatase → Estrogen

Estrogen receptors

Fat Cell

Aromatase Inhibitors (AIs)

AROMATASE INHIBITORS – HOW THEY WORK

Androgen → Aromatase → Estrogen → Estrogen receptors

Fat Cell

Androgen → Aromatase ← Aromatase Inhibitor ✗

No more estrogen!

- <u>Lower</u> estrogen levels in the body
- Stop aromatase (enzyme in fat tissue) from changing androgen into estrogen
- Used mainly in post-menopausal women

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Women with breast cancer on AIs have an increased risk for osteoporosis and fractures

Benefits

- **AIs** are effective hormonal therapy for postmenopausal women with hormone receptor-positive, early-stage breast cancer

Possible Side Effects of AIs

- Muscle pain (myalgia)
- Joint pain
- Hot flashes
- Vaginal dryness
- Cardiovascular disease
- Osteoporosis and bone fractures

AI-related bone loss is more rapid than bone loss associated with menopause, and severity increases with duration of treatment

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Pathways Bone Health Study – Specific Aims

1. Examine incidence of osteoporosis and fracture in women on AIs for their primary breast cancer

2. Investigate how lifestyle, molecular, and genetic factors influence risk of osteoporosis and fracture
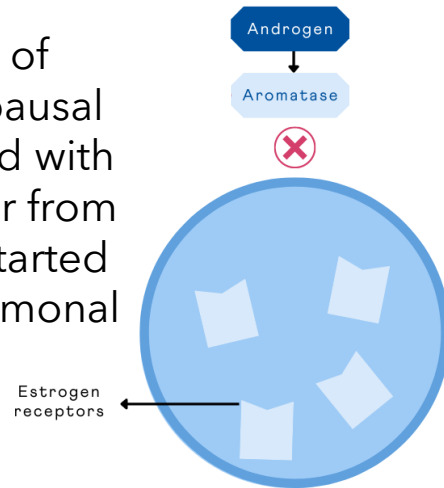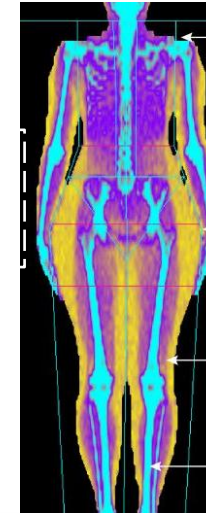
Pathways Bone Health Study – Study Design

Prospective study of 2,152 postmenopausal women diagnosed with HR+ breast cancer from 2005-2013 who started an AI for their hormonal therapy

Bone mineral density (BMD) measurements were collected from DXA scan reports
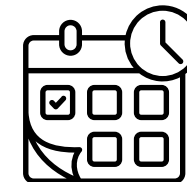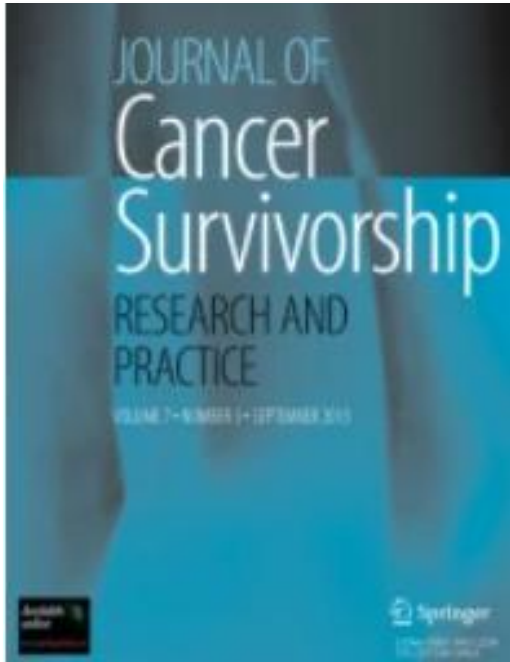
- femoral neck, total hip, and lumbar spine

All incident (new) major fractures were confirmed in the electronic health record by the study endocrinologist

- humerus, wrist, hip, or spine

Median follow-up of 6.1 years (range 0.2–9.8) from breast cancer diagnosis

A prospective study of lifestyle factors and bone health in breast cancer patients who received aromatase inhibitors in an integrated healthcare setting

Marilyn L. Kwan[1] · Joan C. Lo[1] · Cecile A. Laurent[1] · Janise M. Roh[1] · Li Tang[2] · Christine B. Ambrosone[2] · Lawrence H. Kushi[1] · Charles P. Quesenberry Jr[1] · Song Yao[2]
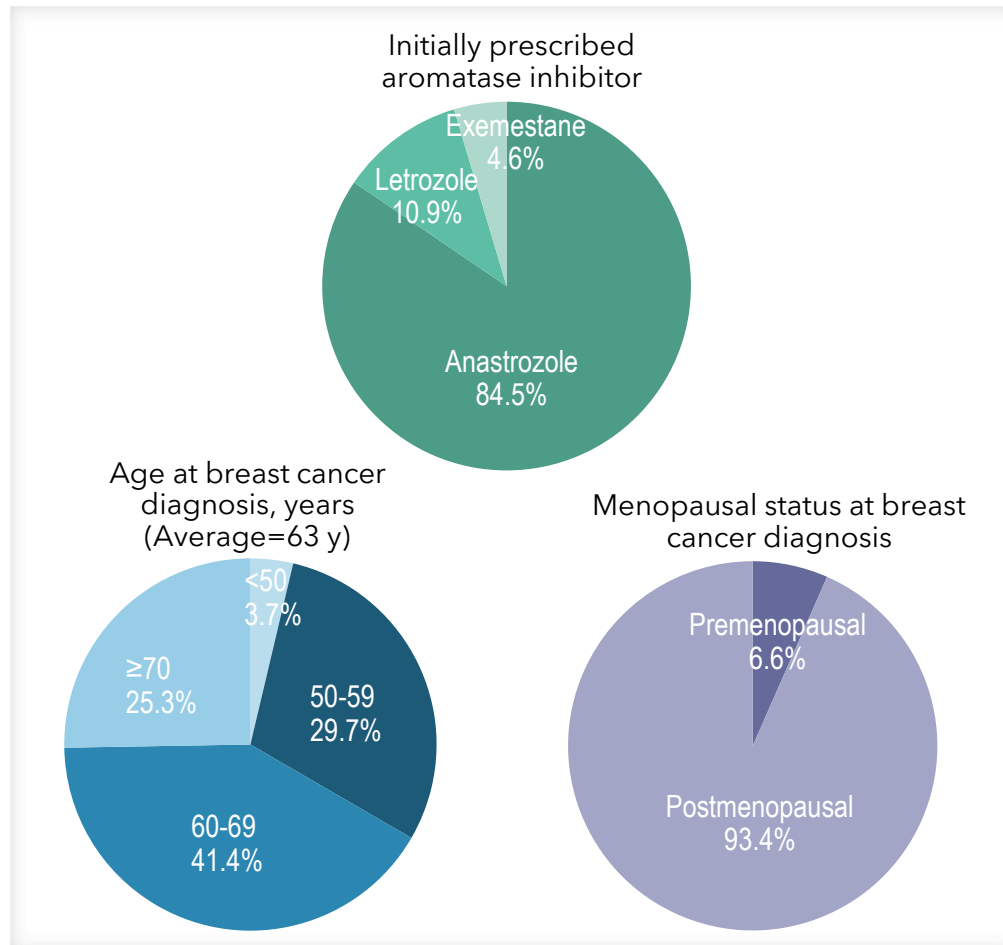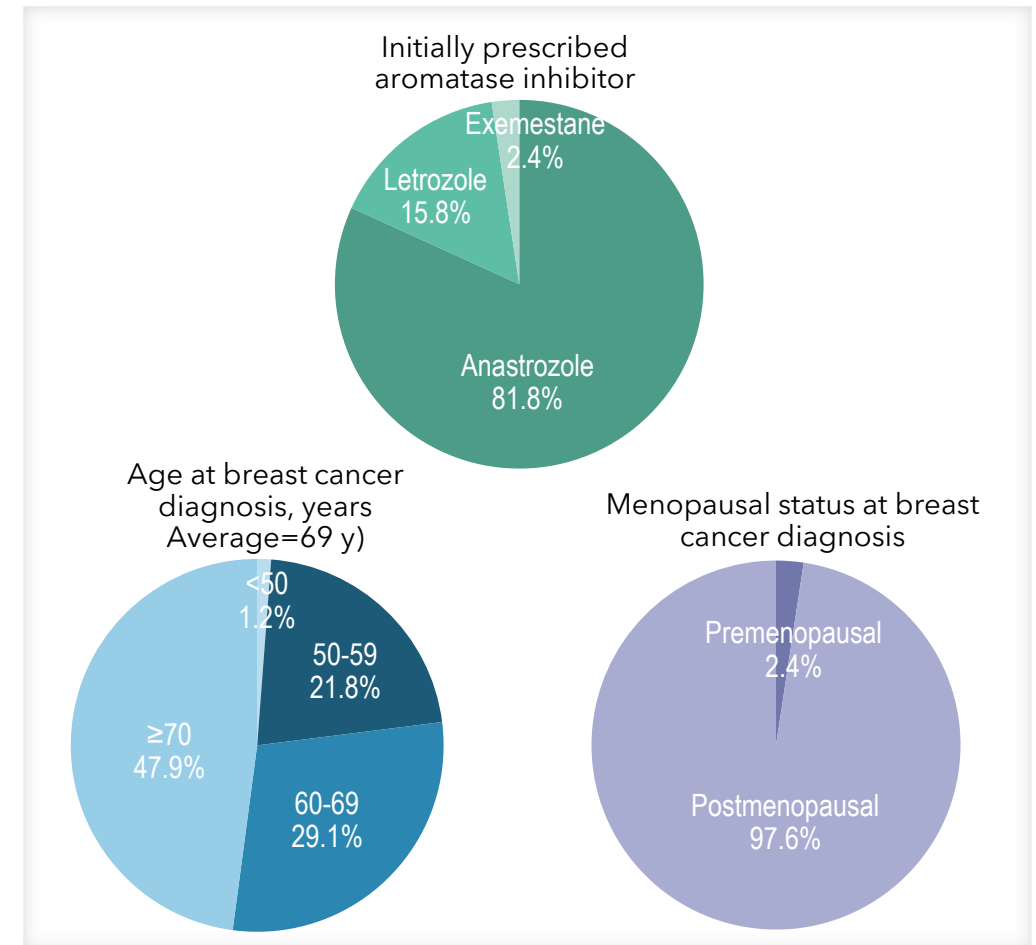
Characteristics of Pathways Bone Health Cohort

Pathways Study participants treated with aromatase inhibitors (n=2152)

Participants treated with aromatase inhibitors n=2,152

Initially prescribed aromatase inhibitor
- Exemestane 4.6%
- Letrozole 10.9%
- Anastrozole 84.5%

Age at breast cancer diagnosis, years (Average=63 y)
- <50 3.7%
- 50-59 29.7%
- 60-69 41.4%
- ≥70 25.3%

Menopausal status at breast cancer diagnosis
- Premenopausal 6.6%
- Postmenopausal 93.4%

Fracture after aromatase inhibitor initiation n=165

Initially prescribed aromatase inhibitor
- Exemestane 2.4%
- Letrozole 15.8%
- Anastrozole 81.8%

Age at breast cancer diagnosis, years Average=69 y)
- <50 1.2%
- 50-59 21.8%
- 60-69 29.1%
- ≥70 47.9%

Menopausal status at breast cancer diagnosis
- Premenopausal 2.4%
- Postmenopausal 97.6%

Less Physical Activity Associated with Higher Risk of Fracture

- **Research Question:** How do modifiable lifestyle factors like physical activity impact fracture risk in 2,152 BC patients on AIs?

- **Important findings:**
  - Women engaging in <u>less aerobic exercise</u> (<150 minutes per week) during the 6 months after diagnosis had <u>more than twice the risk</u> of having a fracture over the next 6 years (HR=2.4; 95% CI: 1.3, 4.4)

  - Women who had none or infrequent moderate-vigorous physical activity during the 6 months before diagnosis had <u>nearly twice the risk</u> of osteoporosis (HR=1.9; 95% CI: 1.1; 3.4).

- **What does this mean?:** Physical activity can be recommended to prevent osteoporosis and fracture in women on AI therapy

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Publications to Date

Journal of Cancer Survivorship
https://doi.org/10.1007/s11764-021-00993-0

A prospective study of lifestyle factors and bone health in breast cancer patients who received aromatase inhibitors in an integrated healthcare setting

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Bone Health History in Breast Cancer Patients on Aromatase Inhibitors

Marilyn L. Kwan[1]*, Joan C. Lo[1], Li Tang[2], Cecile A. Laurent[1], Janise M. Roh[1], Malini Chandra[1], Theresa E. Hahn[2], Chi-Chen Hong[2], Lara Sucheston-Campbell[2], Dawn L. Hershman[3], Charles P. Quesenberry Jr.[1], Christine B. Ambrosone[2], Lawrence H. Kushi[1], Song Yao[2]

Breast Cancer Research and Treatment (2020) 180:187–195
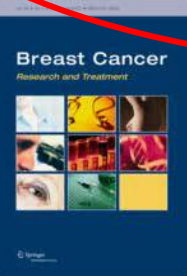https://doi.org/10.1007/s10549-019-05518-z

EPIDEMIOLOGY

Serum bone markers and risk of osteoporosis and fragility fractures in women who received endocrine therapy for breast cancer: a prospective study

Song Yao[1] · Cecile A. Laurent[2] · Janise M. Roh[2] · Joan Lo[2] · Li Tang[1] · Theresa Hahn[3] · Christine B. Ambrosone[1] · Lawrence H. Kushi[2] · Marilyn L. Kwan[2]

Breast Cancer Res Treat
DOI 10.1007/s10549-016-4068-5

EPIDEMIOLOGY

Bone remodeling and regulating biomarkers in women at the time of breast cancer diagnosis

Song Yao[1] · Yali Zhang[1,2] · Li Tang[1] · Janise M. Roh[3] · Cecile A. Laurent[3] · Chi-Chen Hong[1] · Theresa Hahn[2] · Joan C. Lo[3] · Christine B. Ambrosone[1] · Lawrence H. Kushi[3] · Marilyn L. Kwan[3]

Cancer Causes Control
DOI 10.1007/s10552-017-0888-9

BRIEF REPORT

Patterns and reasons for switching classes of hormonal therapy among women with early-stage breast cancer

Marilyn L. Kwan[1] · Janise M. Roh[1] · Cecile A. Laurent[1] · Jean Lee[1] · Li Tang[2] · Dawn Hershman[3] · Lawrence H. Kushi[1] · Song Yao[2]

Breast Cancer Research and Treatment
https://doi.org/10.1007/s10549-017-4626-5

EPIDEMIOLOGY

Changes in bone mineral density in women with breast cancer receiving aromatase inhibitor therapy

Marilyn L. Kwan[1] · Song Yao[2] · Cecile A. Laurent[1] · Janise M. Roh[1] · Charles P. Quesenberry Jr.[1] · Lawrence H. Kushi[1] · Joan C. Lo[1]

JAMA Network Open

Research Letter | Oncology

Description of Major Osteoporotic Fractures in Women with Invasive Breast Cancer Who Received Endocrine Therapy

Joan C. Lo, MD; Cecile A. Laurent, MS; Janise M. Roh, MSW, MPH; Jean Lee; Malini Chandra, MS, MBA; Song Yao, PhD; Marilyn L. Kwan, PhD

ARTICLE   OPEN

A polygenic score associated with fracture risk in breast cancer patients treated with aromatase inhibitors

Christine Hook[1], Udit Chatterjee[2], Haiyang Sheng[2,3], Qianqian Zhu[4], Timothy Robinson[5], Janise M. Roh[6], Cecile A. Laurent[6], Catherine Lee[6], Jennifer Delmerico[6], Joan C. Lo[6], Christine B. Ambrosone[6], Lawrence H. Kushi[6], Marilyn L. Kwan[6] and Song Yao[1,2]

npj Breast Cancer (2024)10:9 ; https://doi.org/10.1038/s41523-024-00615-9

Future Work: Develop Fracture Risk Prediction Model

- Develop a fracture risk prediction model for breast cancer patients who are eligible to receive an AI to treat their breast cancer

  - Model will include patient demographics, clinical characteristics, genetics, circulating biomarkers, and bone density results

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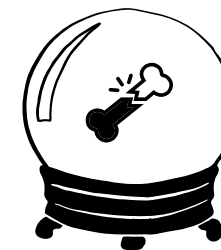
FRAX (Fracture Risk Assessment Tool) to calculate the 10-year probability of fracture in healthy patients

"BC-FRAX" to calculate the 5-year probability of fracture for breast cancer patients eligible for AI

1. Age
2. Weight (kg)
3. Height (m)
4. Femoral Neck BMD
5. Bone biomarker level
6. Polygenic risk score
7. Physical activity level

Example

	T1		T2		T3
	T1		T2		T3
	T1		T2		T3

Clear   Calculate

The 5 year probability of Fracture: (X.X%)

Major osteoporotic: XX
Hip Fracture: XX

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Thank You!