Living with and beyond cancer
Clinical impact: focus on long-term health

Osteoporosis

EMAS
European Menopause and Andropause Society

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Gynecological cancer

Treatment (oophorectomy, chemotherapy, radiation therapy)

Premature ovarian insufficiency / early menopause

- **Menopausal symptoms**
- **Genitourinary symptoms**
- **Anxiety / depression**
- **Sexual dysfunction**

- **Long – term implications on the incidence of chronic conditions**

Long-term health consequences of premature or early menopause and considerations for management.

- **Women with early menopause (<45 y) or premature ovarian insufficiency (<40 y) are at increased risk for:**
  - **Osteoporotic fractures**
  - **Cardiovascular disease**
  - **Cognitive decline**
  - **Depression**
  - **Early death**

Faubion S et al. Climacteric. 2015;18(4):483-91.

Long-term health consequences of premature or early menopause

Table III Associations (odds ratios [OR] and 95% CI) of age at natural menopause with the prevalence (baseline, 2010) and incidence (follow-up, 2010–2016) of multimorbidity in postmenopausal women ($n = 5107$), Australian Longitudinal Study on Women's Health (ALSWH).

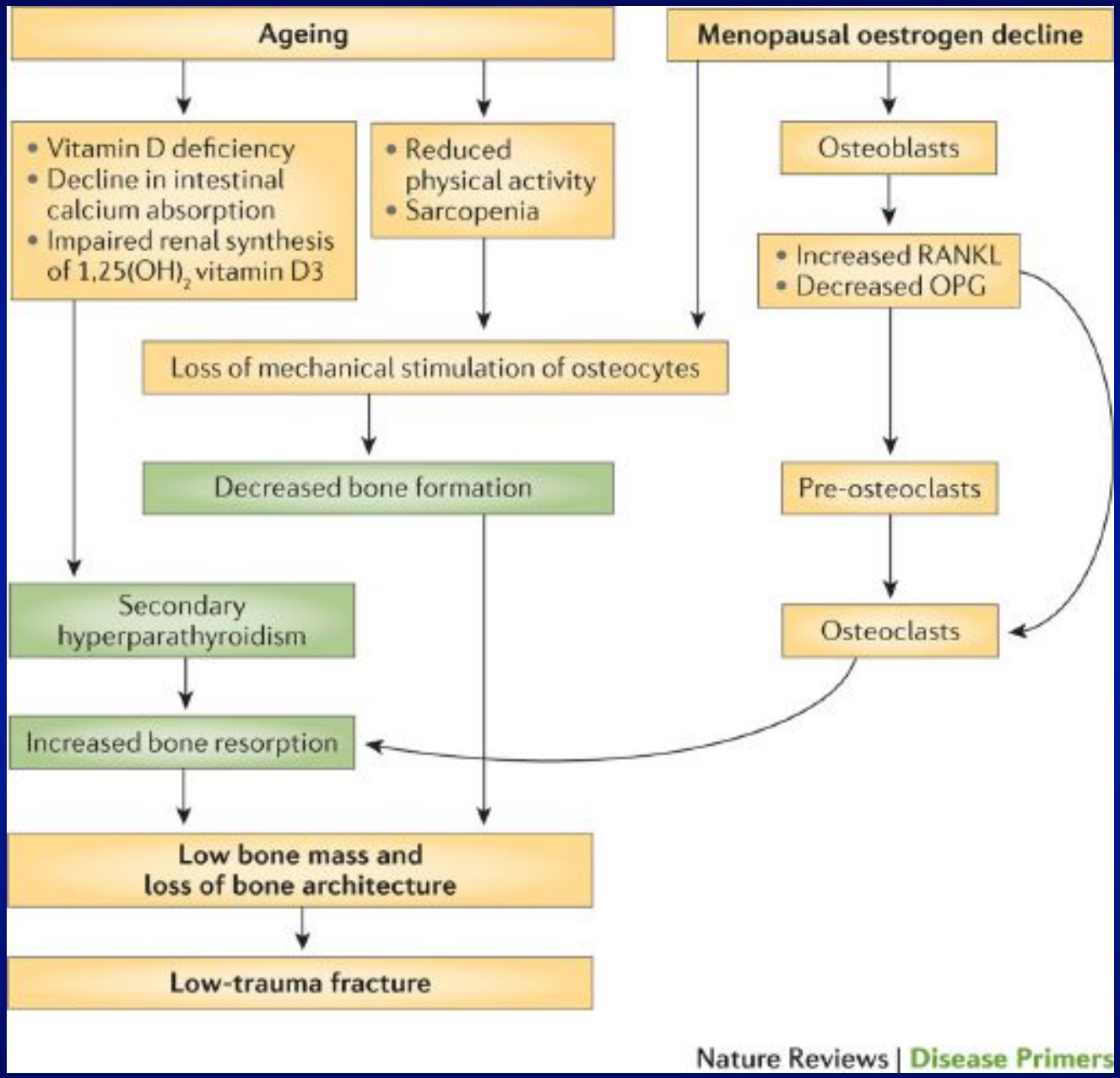
	Age at natural menopause						
	≤40 ($n = 119$)	41–45 ($n = 456$)	46–49 ($n = 740$)	50–51 ($n = 1207$)	52–53 ($n = 1009$)	≥54 ($n = 1576$)	$P_{quadratic}$ [a]
Baseline (2010)							
No. and % of cases	84 (70.6)	266 (58.3)	427 (57.7)	662 (54.9)	526 (52.1)	849 (53.9)	
Crude model[b]	3.57 (1.39, 9.19)	1.77 (0.85, 3.71)	0.80 (0.36, 1.79)	Ref	0.72 (0.34, 1.53)	0.84 (0.44, 1.59)	0.0127
Fully adjusted model[c]	1.98 (1.31, 2.98)	1.15 (0.92, 1.42)	1.11 (0.92, 1.34)	Ref	0.89 (0.75, 1.05)	0.95 (0.82, 1.11)	
Follow-up (2010–2016)							
No. and % of cases	53 (44.5)	187 (41.0)	323 (43.6)	487 (40.4)	392 (38.9)	631 (40.0)	
Crude model[d]	3.15 (1.82, 5.45)	1.02 (0.66, 1.59)	1.51 (1.07, 2.11)	Ref	1.13 (0.81, 1.57)	1.15 (0.86, 1.55)	0.0360
Fully adjusted model[e]	3.03 (1.62, 5.64)	0.96 (0.58, 1.58)	1.35 (0.93, 1.98)	Ref	1.20 (0.84, 1.73)	1.23 (0.89, 1.71)	

[a] $P_{quadratic}$: a quadratic term of the age at natural menopause (continuously) was added in the age-period adjusted model to test whether a nonlinear association was present.
[b] Adjusted for age at S6 (2010).
[c] Adjusted for age at S6 (2010), parity, ever menopausal hormone (MHT) users, education, country of birth, body mass index, physical activity and smoking status.
[d] Adjusted for age at S6 (2010), survey years (S7–8) and number of chronic conditions at S6 (2010).
[e] Adjusted for age at S6 (2010), survey years (S7–8) and number of chronic conditions at S6 (2010), parity, ever MHT users, education, country of birth, body mass index, physical activity and smoking status.

- **Women with age at menopause<40 years had 3 times higher incidence of 2 or more chronic diseases during 6 years follow-up**

Xu X, Jones M, Mishra GD. Age at natural menopause and development of chronic conditions and multimorbidity: results from an Australian prospective cohort. Hum Reprod 2020;35(1):203-211.

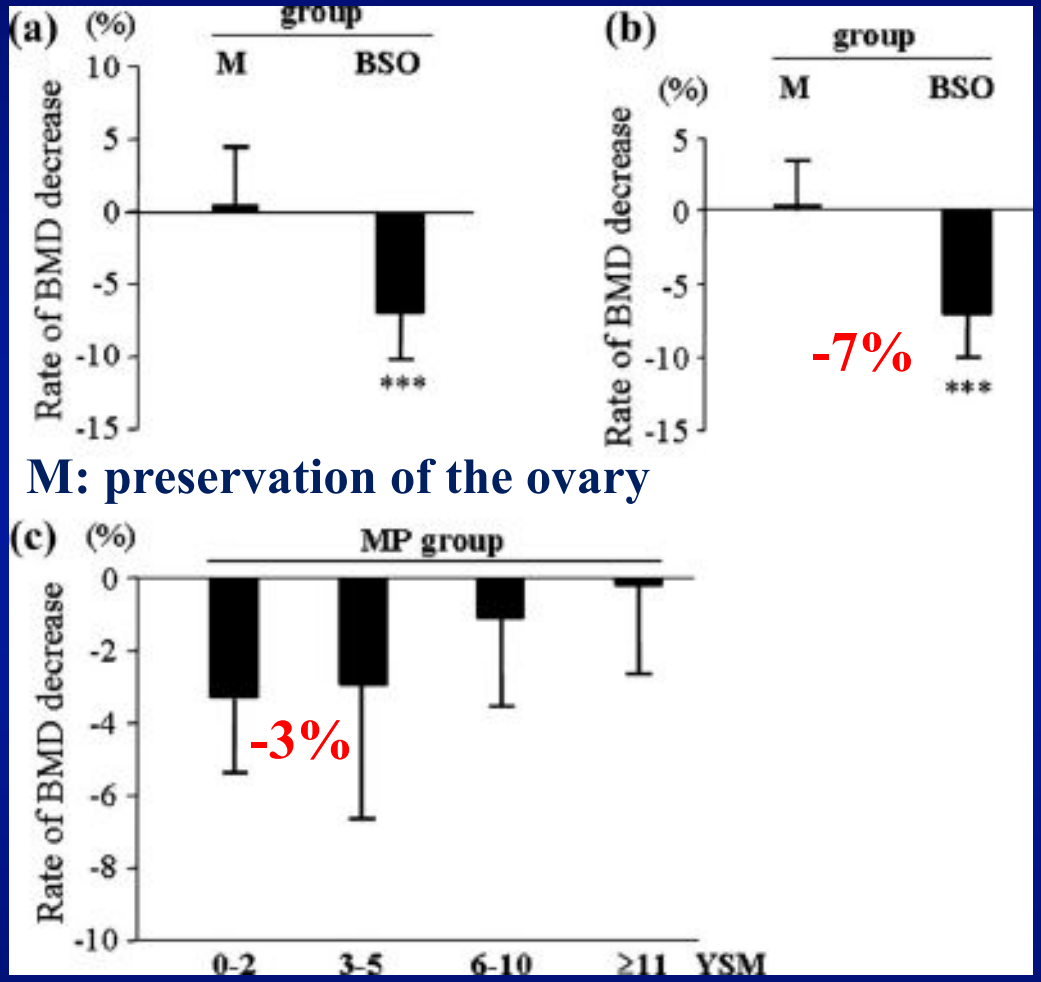
Pathogenesis of postmenopausal osteoporosis



Davis, S. R. Lambrinoudaki I *et al.* (2015) Menopause
Nat. Rev. Dis. Primers doi:10.1038/nrdp.2015.4

Effect of bilateral oophorectomy on BMD annual change in premenopausal women

All women



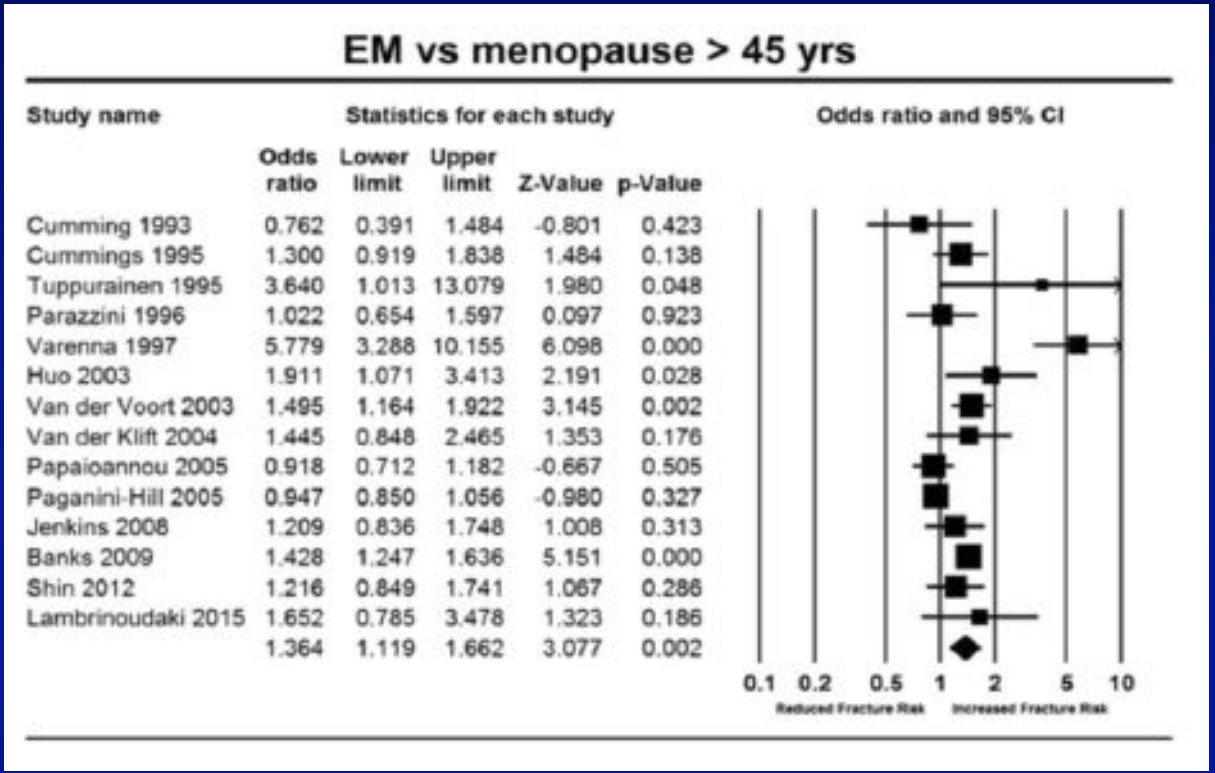
Women in their 40s

Postmenopausal women

Yoshida T, et al Climacteric 2011;14:445–52

Effect of early menopause on fracture risk

- ✓ 462.393 women
- ✓ 12.130 fractures



- ➢ Women with early menopause (< 45 years) have 36% higher risk of sustaining an osteoporotic fracture compared to women with menopause > 45 years
- ➢ The risk was independent of fracture site.

Anagnostis P et al, Endocrine 2018

Breast cancer - Causes of Bone Loss

1. *GnRH analogues:* medically induced menopause.

2. *Aromatase Inhibitors (AIs)* reduce the peripheral conversion of androgens to estrogens: both steroidal (exemestane) and non-steroidal AIs (letrozole and anastrazole) lead to bone loss.

3. *Chemotherapy:* > medically induced menopause. Possible direct skeletal toxicity (data from postmenopausal women).

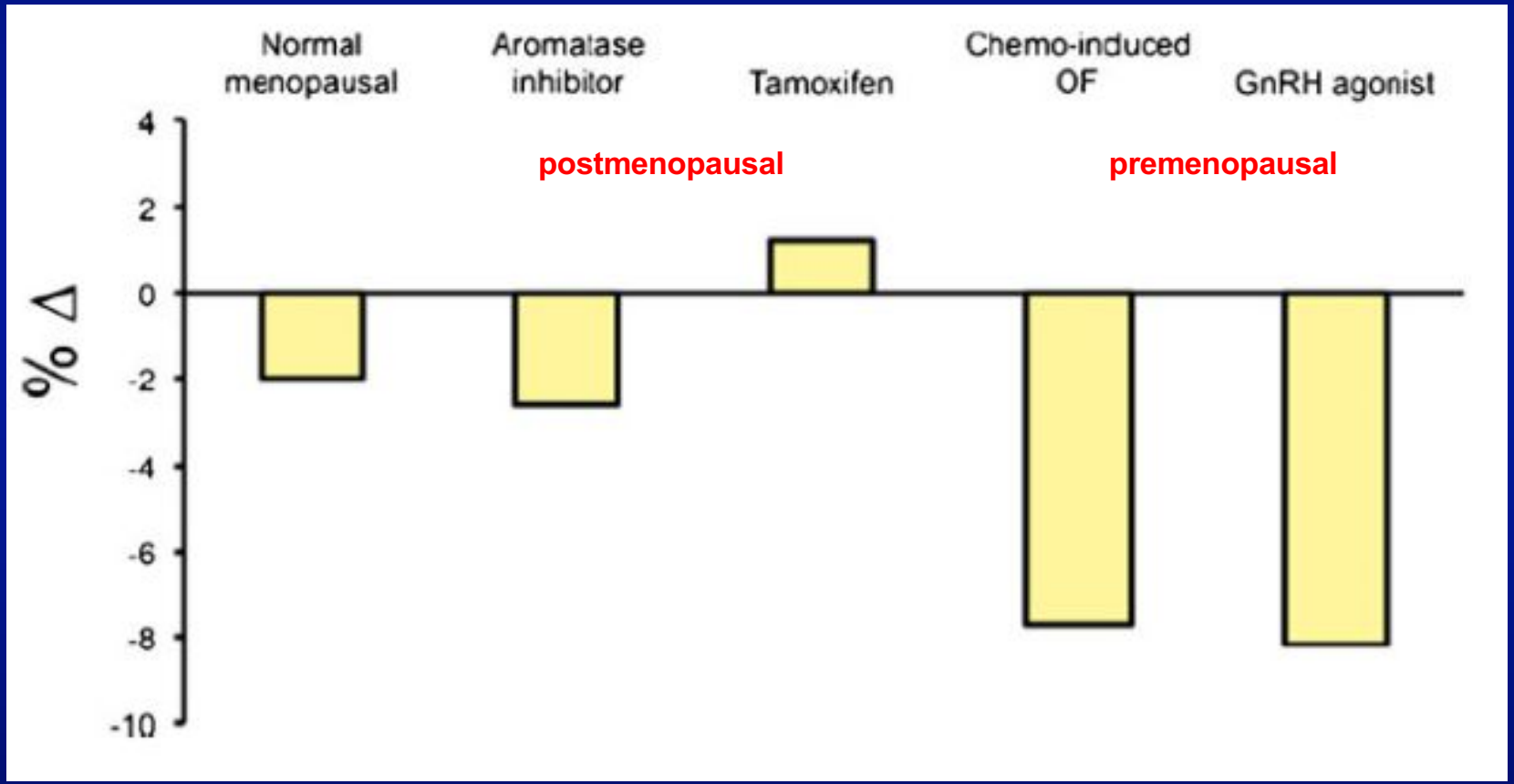
4. *Tamoxifen* is a selective estrogen receptor modulator: estrogen agonist effect in bone may counteract bone loss in postmenopausal women. **In premenopausal women Tmx increases bone loss.**

Review article **2017**

Osteoporosis management in patients with breast cancer: EMAS position statement

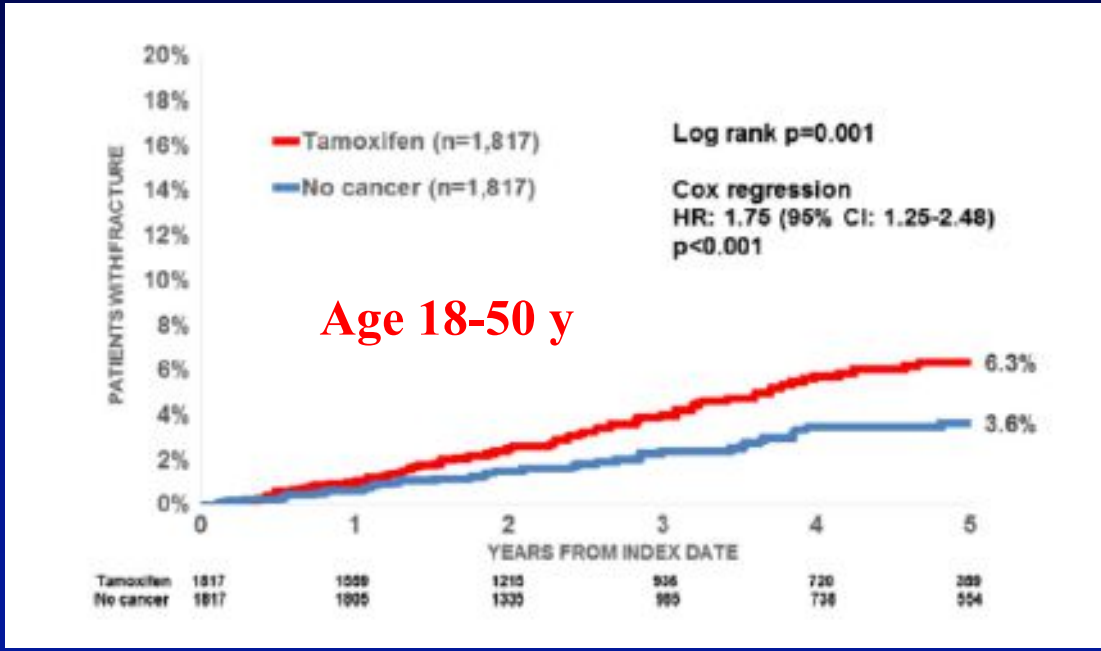
Florence A. Trémollieres[a,*], Iuliana Ceausu[b], Herman Depypere[c], Irene Lambrinoudaki[d], Alfred Mueck[e], Faustino R. Pérez-López[f], Yvonne T. van der Schouw[g], Levent M. Senturk[h], Tommaso Simoncini[i], John C. Stevenson[j], Petra Stute[k], Margaret Rees[l]

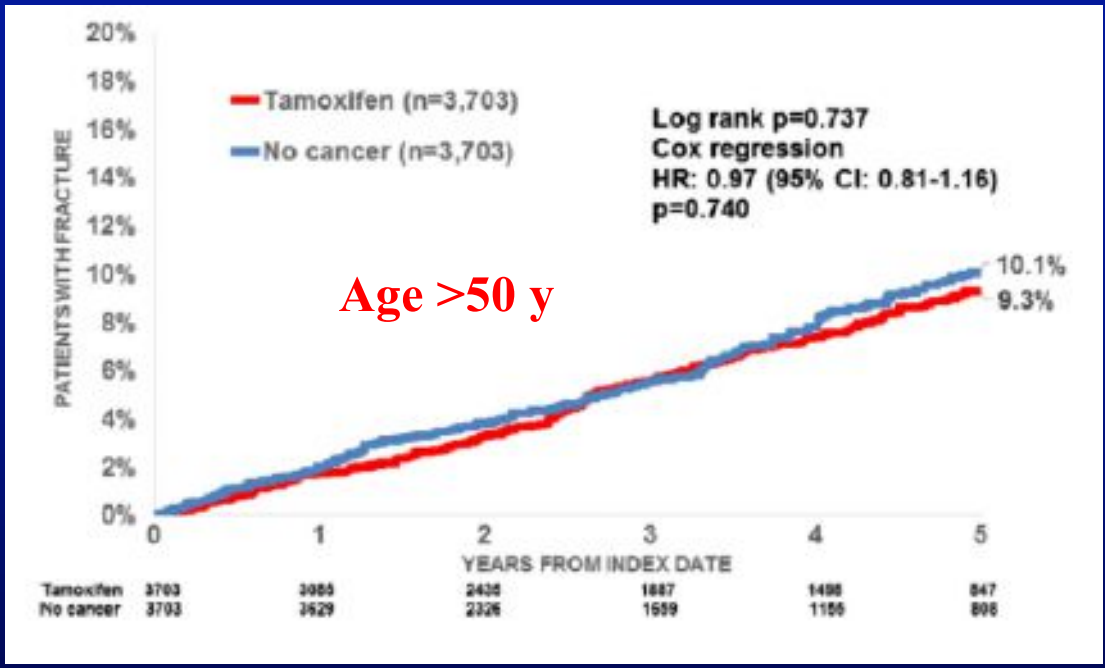
Annual BMD change in women with breast cancer



Loomee Doo · Charles L. Shapiro

Curr Osteoporos Rep (2013) 11:311–318





The tamoxifen paradox—influence of adjuvant tamoxifen on fracture risk in pre- and postmenopausal women with breast cancer

I. Kyvernitakis[1,2,3] · K. Kostev[4] · P. Hadji[1,3]

Osteoporosis International (2018) 29:2557–2564

- **5520 women with breast cancer receiving adjuvant tamoxifen**
- **5520 healthy controls matched for age and BMI**
- **Primary outcome: incident fractures**

Osteoporotic fractures in patients with breast cancer treated with aromatase inhibitors

Table 1
Rate of osteoporotic fractures in aromatase inhibitors phase III trials.

Trials	Number of fractures/total population number	Aromatase inhibitor	Control	p
Anastrozole				
-ATAC	356/5 216	5.9%	3.7% (1)	<0.0001
-ABCSG 8/ARNO 95	50/3 224	2.0%	1.0% (1)	0.015
-ITA	4/448	1.0%	1.3% (1)	0.6
Letrozole				
-MA.17	140/5 187	3.6%	2.9% (2)	0.24
-BIG 1-98	388/4 895	9.3%	6.5% (1)	<0.001
Exemestane				
-I.E.S.	125/4 742	3.1%	2.3% (1)	0.08

Control group: (1) vs tamoxifene; (2) vs placebo.

BMD and fracture rate in postmenopausal women with breast cancer: Aromatase inhibitors VS tamoxifen

	Drugs	N	Duration (months)	BMD change in lumber spine	Fracture	p value (relative risk, 95% CI)
ATAC*[33]	Anastrozole vs tamoxifen	197	60	−6·1% vs +2·8%	NA	p<0·001
ATAC[34]	Anastrozole vs tamoxifen	6186	60	NA	11·0% vs 7·7%	p<0·0001 (1·49, 1·25–1·77)
TEAM-GER[35]	Exemestane vs tamoxifen	200	12	−2·8% vs +0·5%	NA	p=0·0008
BIG 1–98[36]	Letrozole vs tamoxifen	4895	60	NA	9·3% vs 6·5%	p<0·001 (1·38, 1·13–1·69)
IES[37]	Exemestane* vs tamoxifen	206	60	−1·0% at year 2	7·0% vs 5·0%	p=0·003 (1·45, 1·13–1·87)

BMD=bone mineral density. NA=not applicable. *Initial therapy of tamoxifen for 2–3 years, then either tamoxifen or exemestane for a total of 5 years of therapy.

Table 2: Effects of aromatase inhibitors on bone loss and fracture risk in postmenopausal women

Rachner TD et al. Lancet Diabetes Endocrinol. 2018 Mar 2018.

Breast cancer and fracture risk

- The 3 year fracture risk is 5 times higher in newly diagnosed patients with breast cancer than in general population.

- Even in women with normal BMD, the fracture risk is high: placebo arm (no osteoporosis treatment) of *ABCSG-18 Study* 10% (normal BMD) vs 11% (low BMD) fracture rate.

Gnant M et al, Lancet 2015
Coleman R et al, Ann Oncol 2014

Cancer treatment and osteoporosis

Conclusions

- Gonadotoxic effect of the primary cancer treatment (surgery / radiotherapy / chemotherapy)
- Long-term medical therapy after primary treatment
    - Gonadal suppression
    - Anti-estrogen therapy
- The younger the age of the patient, the more pronounced the effect on the skeleton