

# MANAGING OESTROGEN DEFICIENCY AFTER BREAST CANCER

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Liberate study

# Ovarian failure

**TABLE 3. INCIDENCE OF AMENORRHEA AFTER COMMON ADJUVANT TREATMENTS FOR BREAST CANCER.**

TREATMENT AND DURATION	AGE OF	AGE OF	AGE OF
	<30 YR	30–39 YR	>40 YR
	percent with amenorrhea		
None	0	4–6	20–25
Tamoxifen <sup>42</sup>	0	<5	5–30
Cyclophosphamide, methotrexate, fluorouracil (6 mo) <sup>43</sup>	19	30–40	80–95
Fluorouracil, doxorubicin, cyclophosphamide or fluorouracil, epirubicin, cyclophosphamide (3–6 mo) <sup>38,44</sup>	0	10–25	80–90
Doxorubicin and cyclophosphamide (3 mo) <sup>43,45</sup>	—*	13	57–63

\*No data have been reported on the incidence of amenorrhea among patients younger than 30 years of age who have received doxorubicin and cyclophosphamide.

- develops within one year of therapy in 63%–96% of premenopausal women, receiving chemotherapy
- It is in many cases definitive

# Oestrogen deficiency

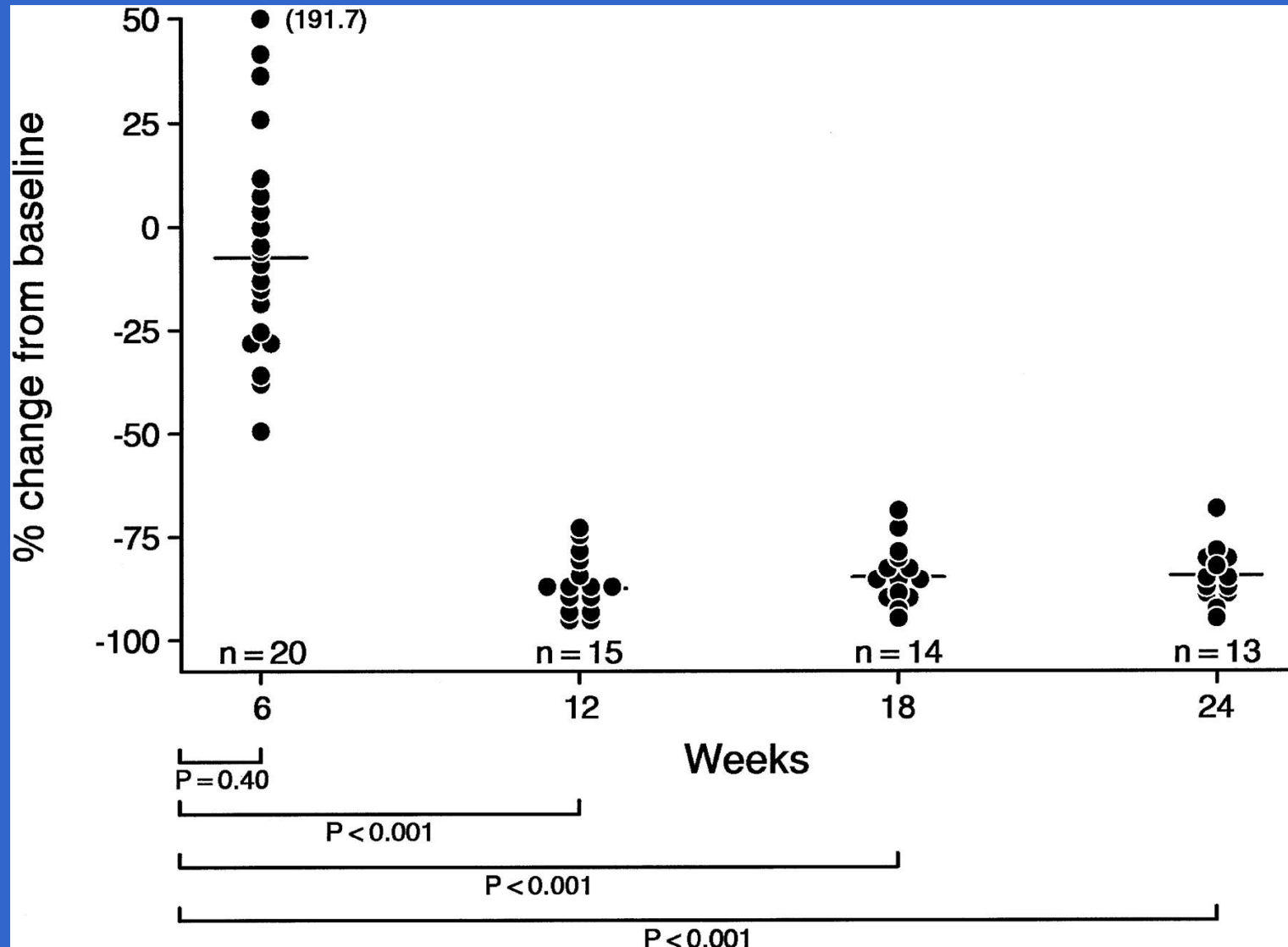
- 70% of the tumours express estrogen receptors
- *Aromatase inhibitors :*
  - More profound E2 deficiency

**TABLE 1.** Effect of aromatase inhibitors on aromatase activity of human breast tumors and human fibroblasts and whole-body aromatization in postmenopausal breast cancer patients

Aromatase inhibitors	<i>In vitro</i> inhibition (IC <sub>50</sub> , nM)		<i>In vivo</i> inhibition of whole-body aromatization	
	Breast tumors	Breast fibroblasts	Oral dose (mg/d)	% Inhibition
First generation				
Aminoglutethimide	20,000	10,000	1,000	90.6
Second generation				
Fadrozole			2	82.4
Formestane	30	30	250	84.8
Third generation				
Letrozole	2	0.8	2.5	98.9
Anastrozole	8	15	1	96.7
Exemestane	15	5	25	97.9

Data are derived from Refs. 134 , 136 , 141 , and 144 145 146 .

% change from baseline (pretreatment) level for E2 at 6, 12, 18, and 24 weeks. TAM started at time 0, and letrozole added after the 6 weeks



# Oestrogen deficiency after Breast Cancer

- Vasomotor symptoms
- Vaginal dryness and sexual problems
- Osteoporosis
- Cognitive function

# Prevalence and Treatment of Menopausal Symptoms Among Breast Cancer Survivors

## Harris et al 2002

	Controls	Breast Cancer Cases						
	<i>n</i> = 73	All cases <i>n</i> = 110	OR <sup>a</sup>	95% CI	No Tamoxifen <i>n</i> = 48	Tamoxifen <i>n</i> = 62	OR <sup>b</sup>	95% CI
Any menopausal symptom	32%	73%	5.3	2.7–10.2	63%	81%	2.6	1.1 –6.25
Under age 55 ( <i>n</i> = 88)	42 ( <i>n</i> = 11)	77 ( <i>n</i> = 48)	17.5	4.0–77	65 ( <i>n</i> = 20)	90 ( <i>n</i> = 28)	6.4	1.4 –29.4
Age 55 and over ( <i>n</i> = 95)	28 ( <i>n</i> = 13)	7 ( <i>n</i> = 32)	6.8	2.5–18.2	9 ( <i>n</i> = 10)	71 ( <i>n</i> = 22)	1.9	0.6 –6.9
Of those with symptoms								
Hot flashes	83%	96	6.0	1.2–33	97	96	0.7	0.1 –8.6
Insomnia	42	38	0.78	0.3–2.0	40	36	0.8	0.3 –2.2
Vaginal dryness	0	6	—	—	7	6	0.9	0.1 –5.6
Mood swings	8	14	1.5	0.3–7.5	27	6	0.18	0.04–0.74
Other (weight gain, fatigue)	0	4	—	—	3	6	2.1	0.20–21

Young women and Tamoxifen users have a 3X higher risk of flushes

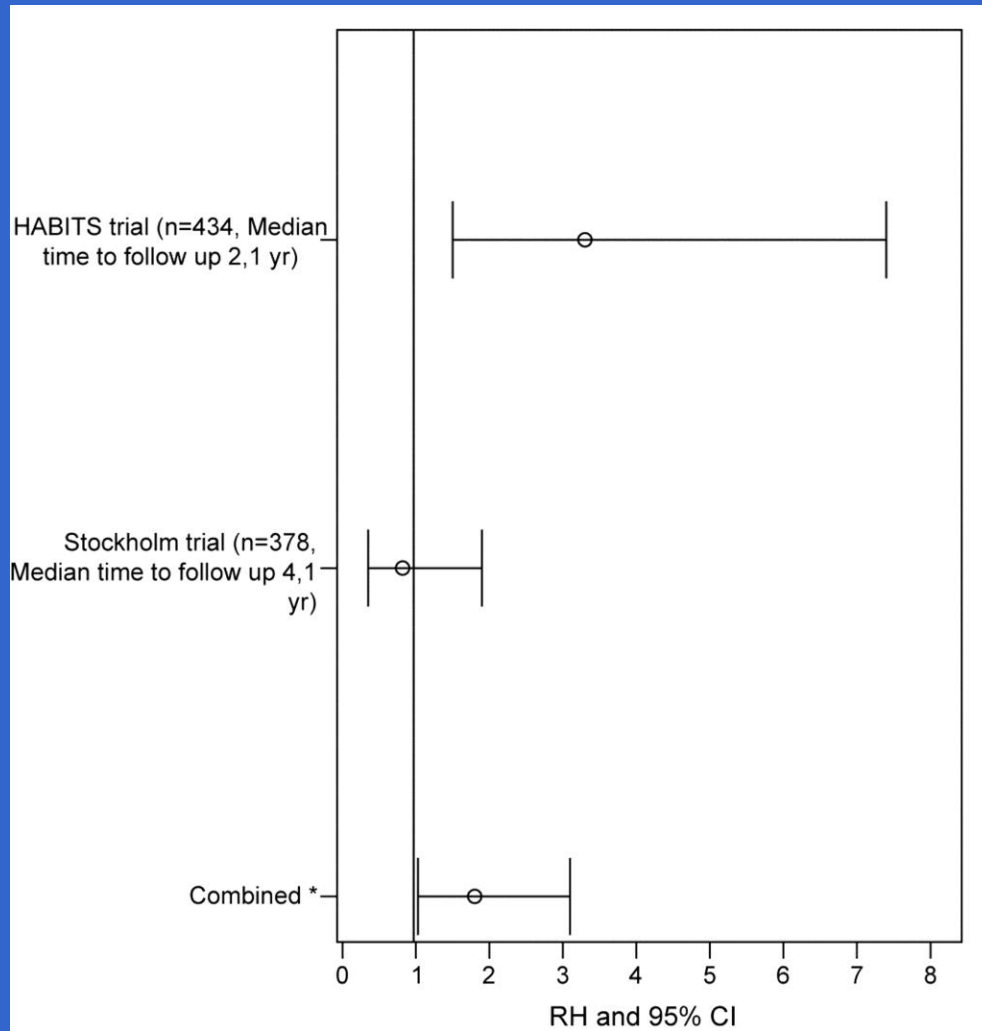
## Survey among breast cancer survivors

- **Younger women** suffered 3 times more frequently from vasomotor symptoms
- But they did not use treatment to relieve their symptoms more often
- Antoine et al Climacteric 2008

Up to 20% of patients with breast cancer consider stopping or actually cease endocrine treatment because of menopausal symptoms

Fellowes et al 2001.

# Summary of the two randomized trials that have been conducted



breast cancer recurrence

RH = 3.3, 95% CI = 1.5 to 7.4

RH = 0.82, 95% CI = 0.35 to 1.9

**RH = 1.8,**  
**95% CI = 1.03 to 3.10**

Test for heterogeneity  
between the two studies  
( $P = .02$ ),

# LIBERATE

- Median follow-up: 3.1 years
- cancer recurrence :15% on tibolone vs. 10% on placebo.
- HR 1.40 [95% CI 1.14-1.70]; p=0.001).
- Kenemans Lancet Oncology 2009

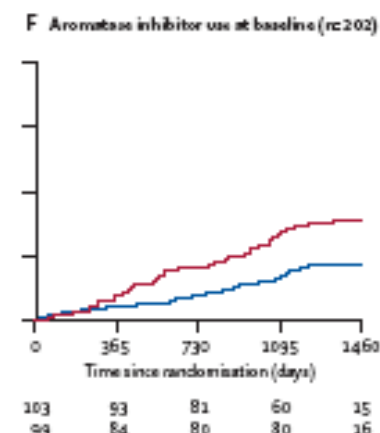
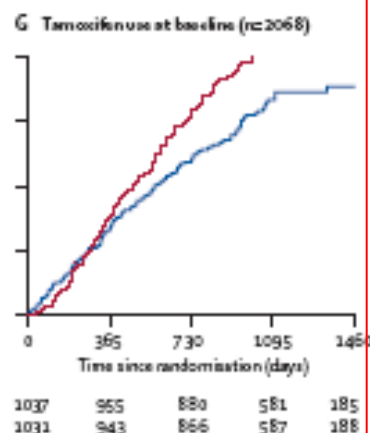
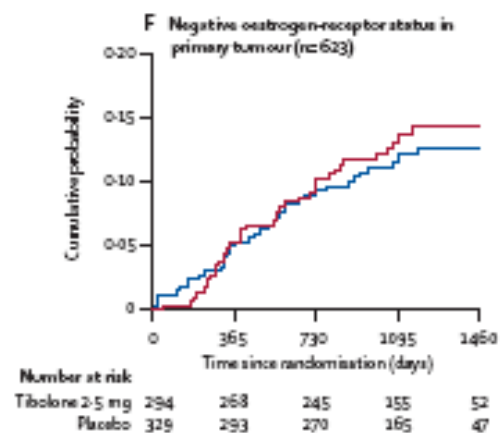
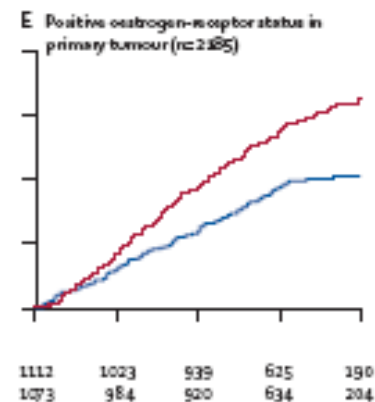
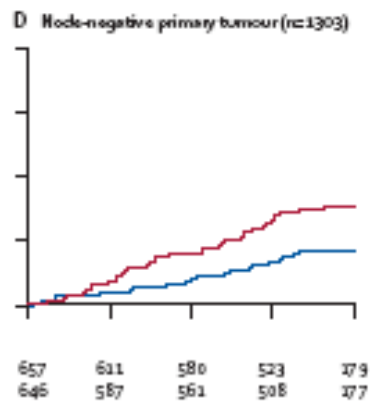
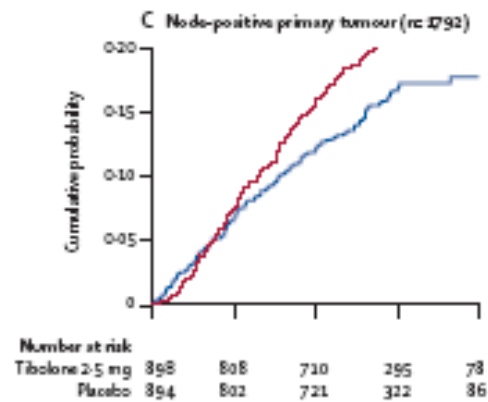
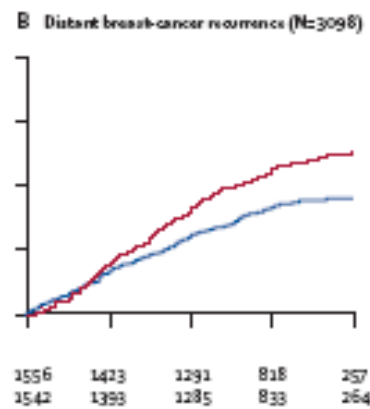
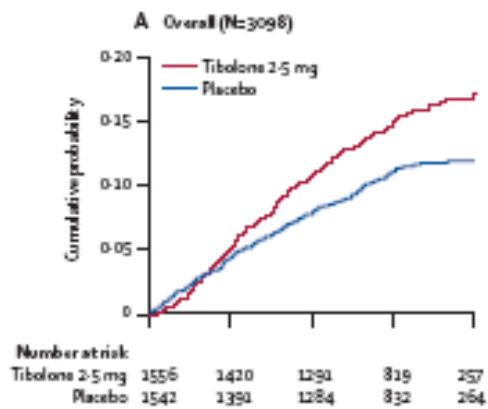


Figure 2: Cumulative probability of breast-cancer recurrence versus time in the ITT population

# Alternatives

Experimental: Animal data or Phase II data

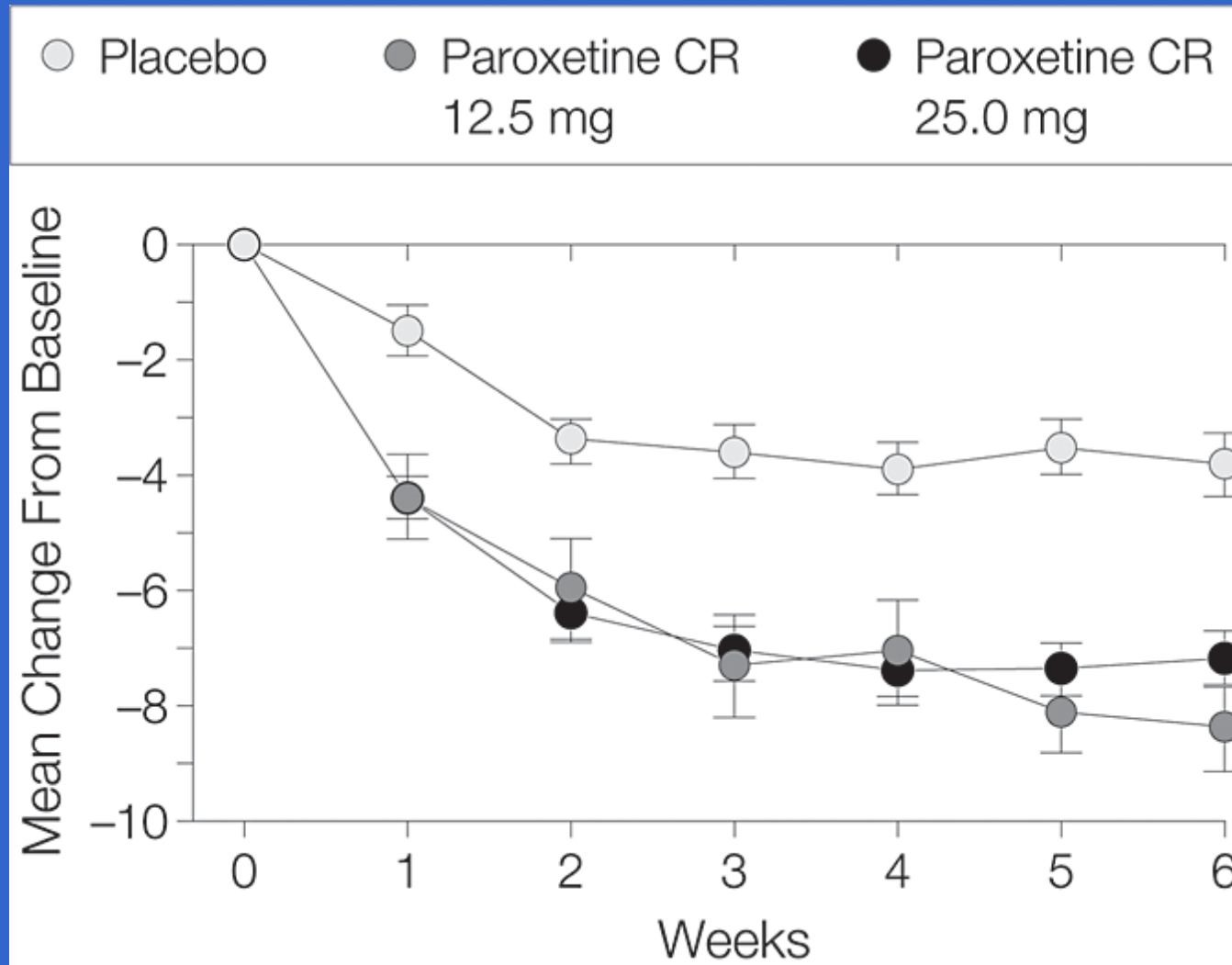
- Tissue-specific hormone replacement therapy (TS-HRT)
- DHEAS
- Estetrol

Berger et al; Visser & Coelingh Bennink The Journal of Steroid Biochemistry and Molecular Biology March 2009

# Oral clonidine in postmenopausal patients with breast cancer experiencing tamoxifen-induced hot flashes:

- Double-blind, placebo-controlled :194 using tamoxifen
- Oral clonidine hydrochloride, 0.1 mg/d/ placebo for 8 weeks.
- Hot flash : -37% clonidine group -20% placebo group
- Clonidine more difficulty sleeping (41% vs 21%; P = 0.02).
- quality-of-life scores (+0.3 points: clonidine vs -0.2 points placebo; P = 0.02) at 8 weeks, although the median difference was 0 in both groups.
- Pandya et al Ann Intern Med. May 2000

# Paroxetine controlled release in the treatment of menopausal hot flashes: randomized controlled trial.



# Antidepressants & P450 enzyme CYP2D6

- Some antidepressants inhibit cytochrome P450 enzyme CYP2D6 which is needed to metabolise tamoxifen to endoxifen.
- Paroxetine, to a lesser extent Fluoxetine Sertraline but not venlafaxine
- *Loprinzi et al Lancet Oncology 2008*

# Gabapentin for hot flashes in 420 women with breast cancer: a randomised double-blind placebo-controlled trial

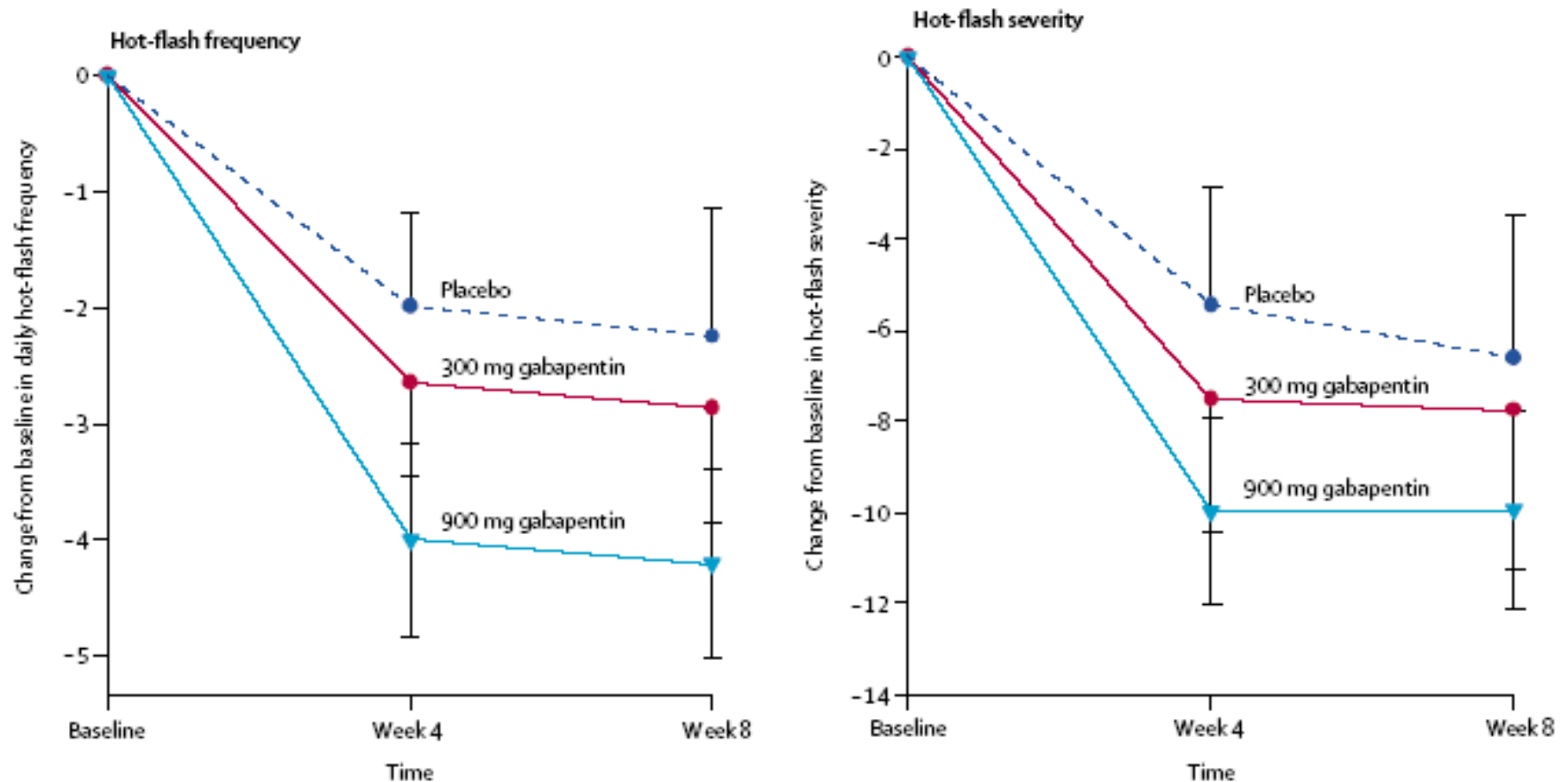
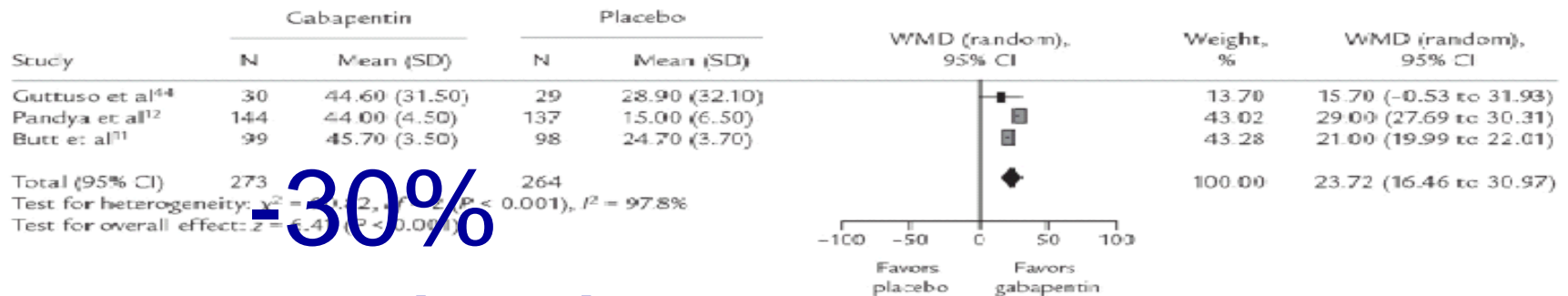


Figure 2: Mean change scores (and 95% CI) for hot-flash frequency and severity

# Systematic review & meta-analysis: Gabapentin for hot flashes in women with natural or tamoxifen-induced menopause:



-30%

reduction  
Flashes  
frequency  
and severity

Figure 1. Percentage reduction in the frequency of hot flashes in women who received gabapentin or placebo.<sup>11,12,44</sup> WMD = weighted mean difference. (The straight line represents the 95% CI of the outcome in each study. The black square represents the mean value; the size of the black square is proportionate to the weight assigned to each study. The diamond [rhombus] represents the pooled estimate of the outcome, and its horizontal dimension represents the CI.)

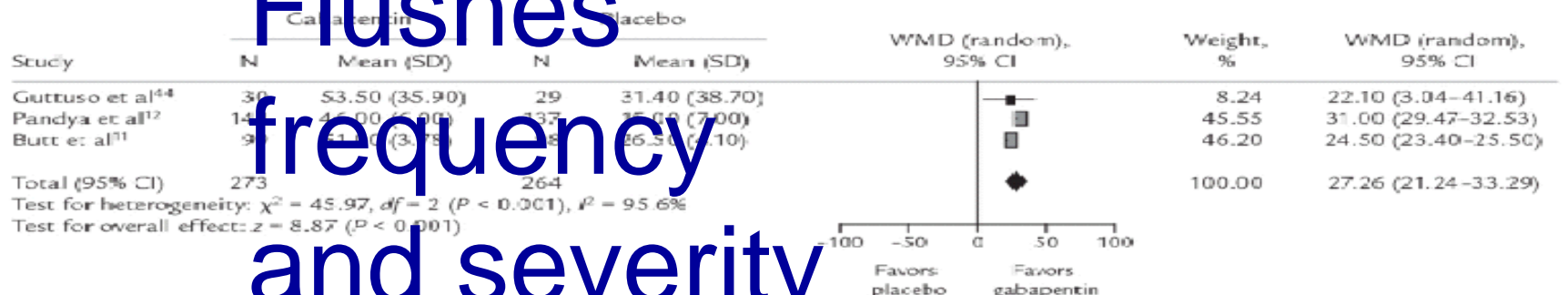
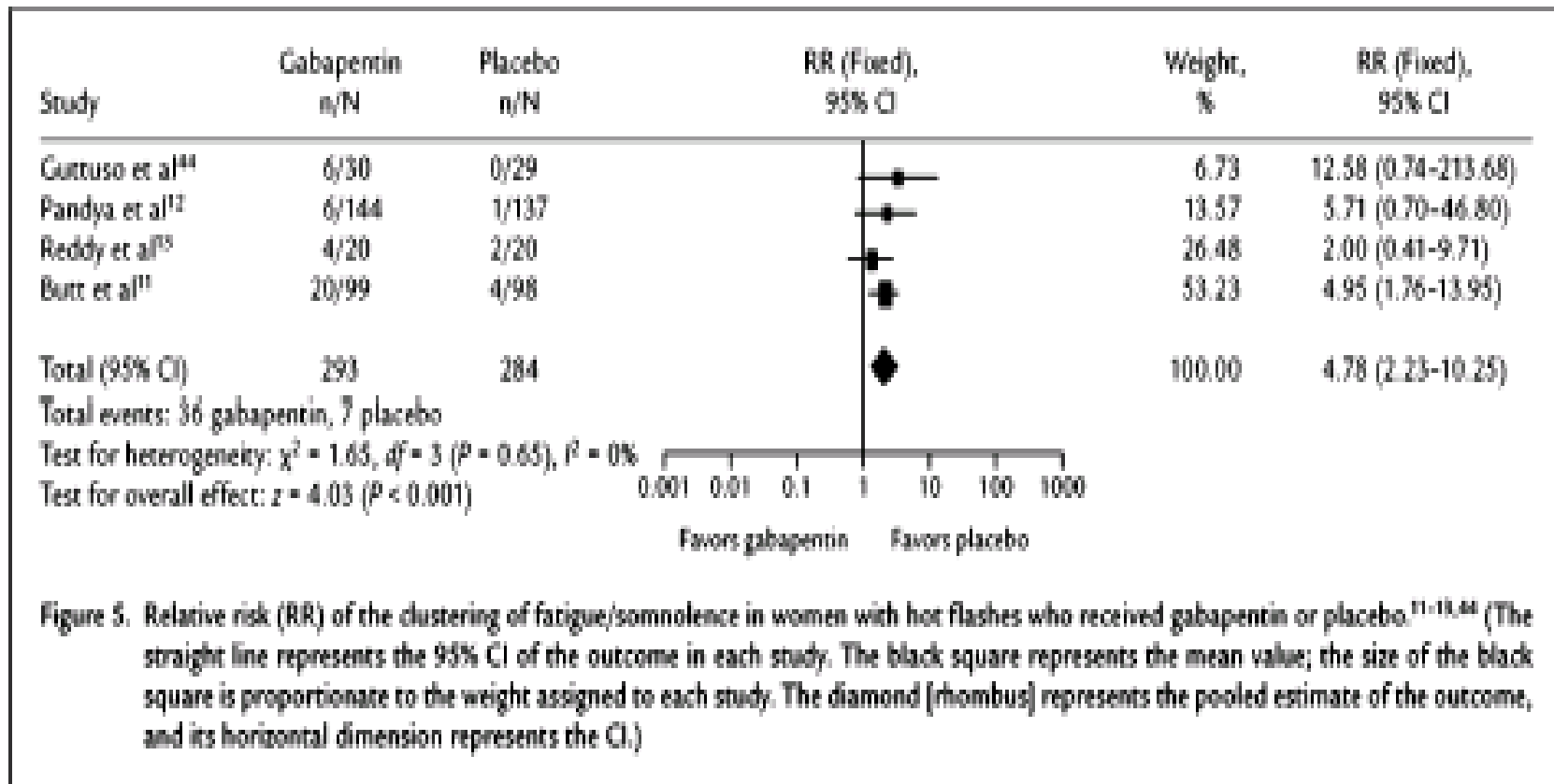
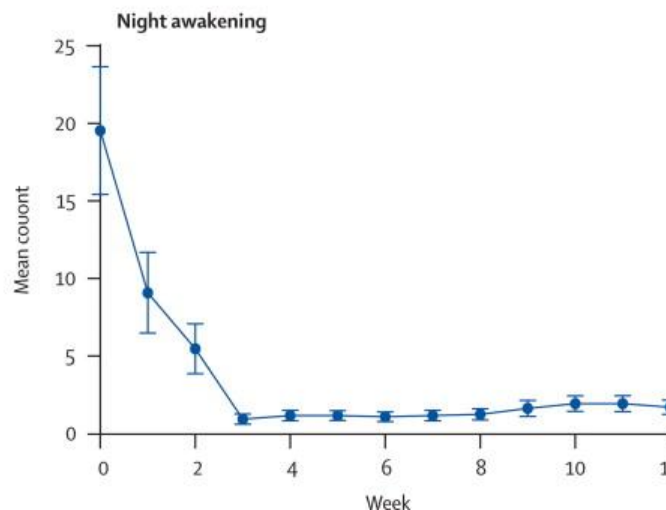
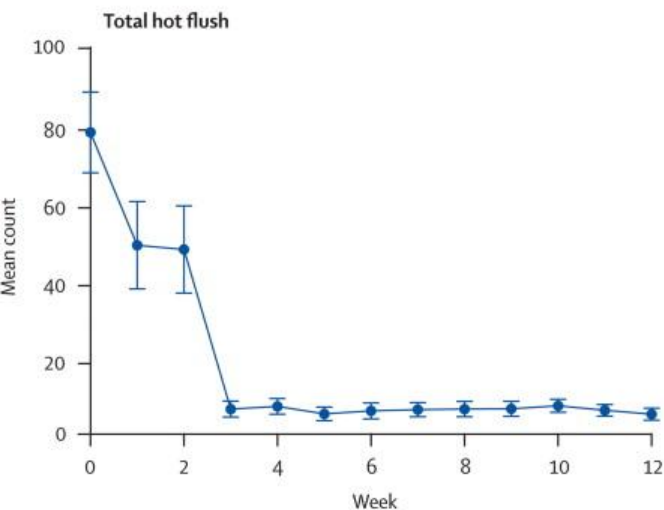
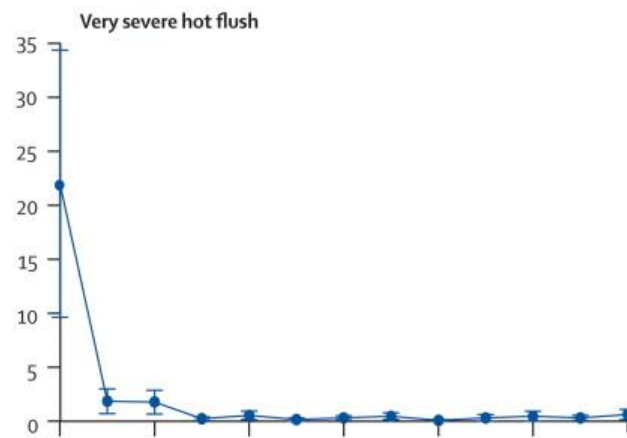
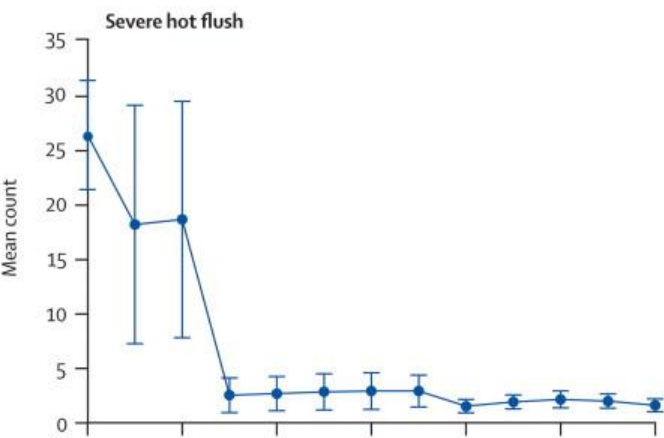
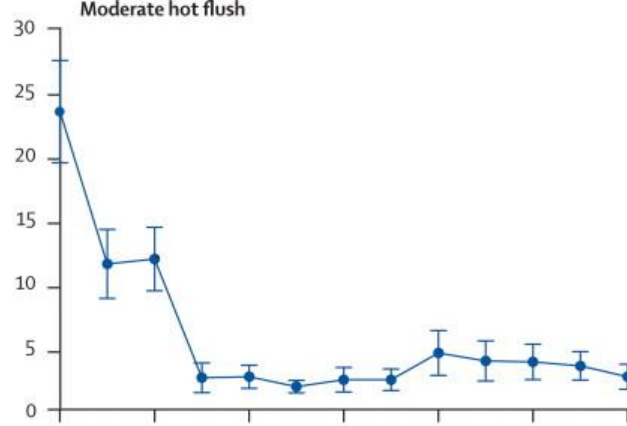
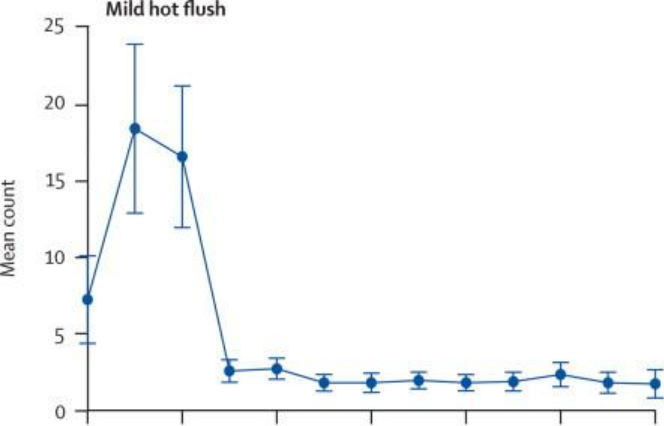


Figure 2. Percentage reduction in the composite score for hot flashes in women who received gabapentin or placebo.<sup>11,12,44</sup> WMD = weighted mean difference. (The straight line represents the 95% CI of the outcome in each study. The black square represents the mean value; the size of the black square is proportionate to the weight assigned to each study. The diamond [rhombus] represents the pooled estimate of the outcome, and its horizontal dimension represents the CI.)

# Systematic review & meta-analysis: Gabapentin for hot flashes in women with natural or tamoxifen-induced menopause:

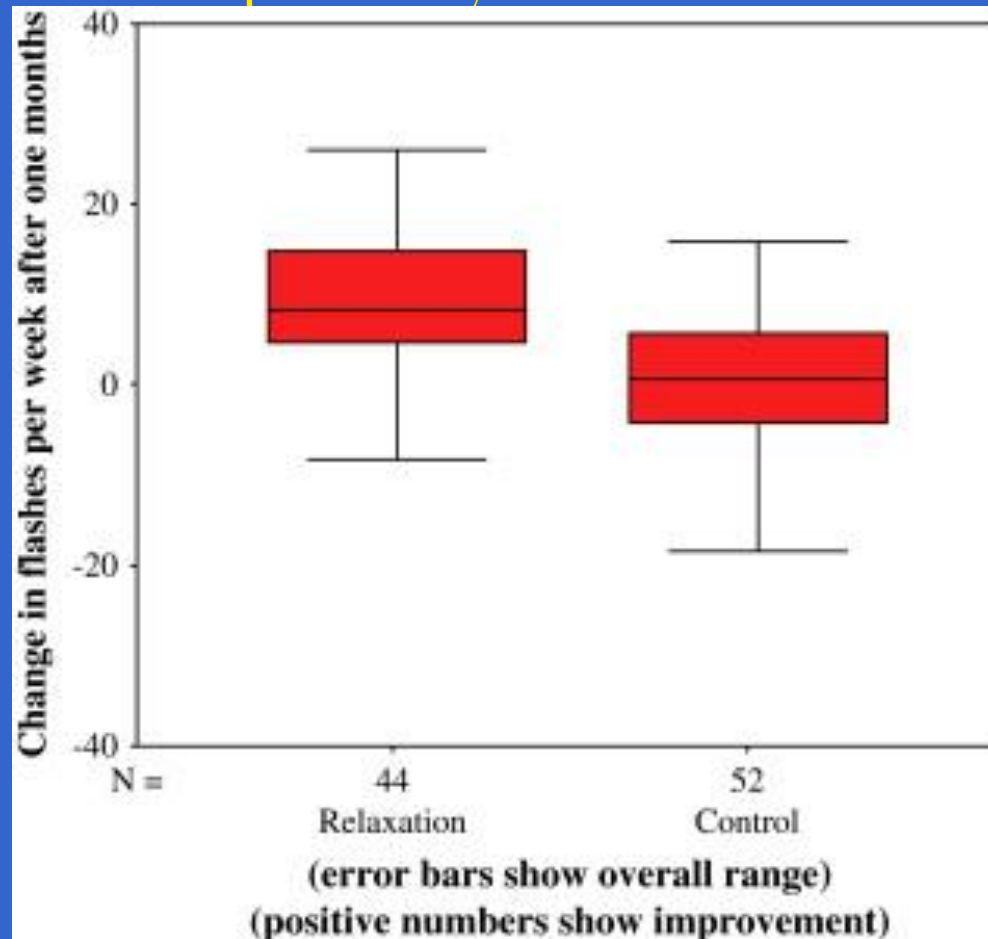




Stellate-ganglion  
block on  
recorded hot  
Flashes, night  
Awakenings,  
severity of hot flushes  
over 12-week  
follow-up period

Lipov et al  
Lancet Oncol. 2008

# A randomized controlled trial of relaxation training to reduce hot flashes in women with primary breast cancer.



Change in number of flashes (median and interquartile range)/week after 1 month

- Fenlon et al J Pain Symptom Manage. 2008

# General recommendations

- Identify triggers hot flashes (eg, alcohol, hot drinks, or spicy food)
- Achieve a normal weight,
- Relaxation
- Try non hormonal therapy (gabapentine, venlafaxine)
- Progestin or HT (informed consent ?)

# Survey among breast cancer survivors

- Current users of **aromatase inhibitors**
  - more sexual disorders (+65%)
  - more unsatisfactory sexual life (50% vs 20%)
  - more vaginal dryness (90% vs 30%)
  - decreased libido (85 % vs 40%)
  
- Antoine et al Climacteric 2008

Caution: Vaginal estradiol appears to be contraindicated in postmenopausal women on adjuvant aromatase inhibitors

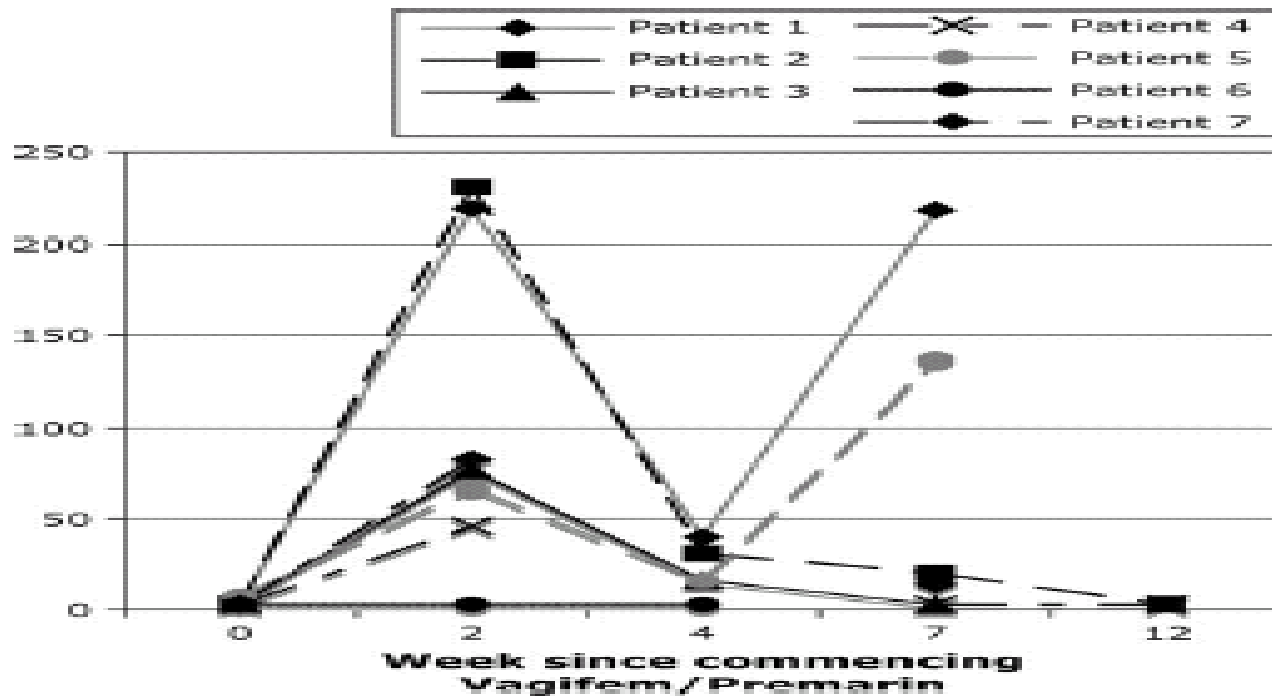


Figure 1. Serum estradiol levels in women receiving concurrent aromatase inhibitors and Vagifem.

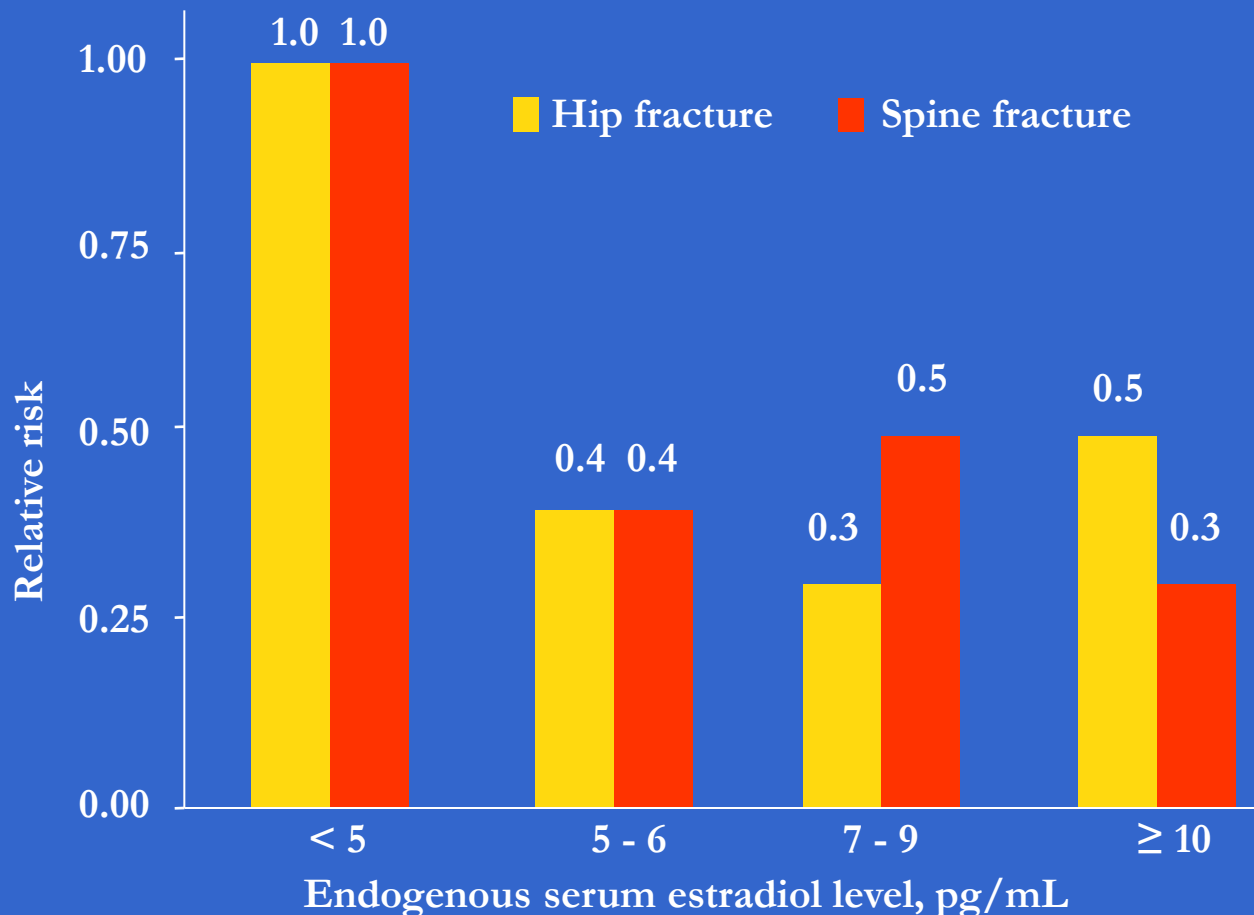
Kendall et al Annals of Oncology 17: 584–587,2006

# Alleviation of symptoms

- Vaginal dryness:
- Oestrogen, given locally are also absorbed.
  - Maybe acceptable in breast cancers who are not using AI
  - Not in AI users
- Preliminary data pilocarpine
- Water-based lubricants (lubex) and polycarbophil moisturisers (Replens)
- Libido decrease
- Probably no place for Testosterone

# Low Estrogen Levels Increase Relative Fracture Risk

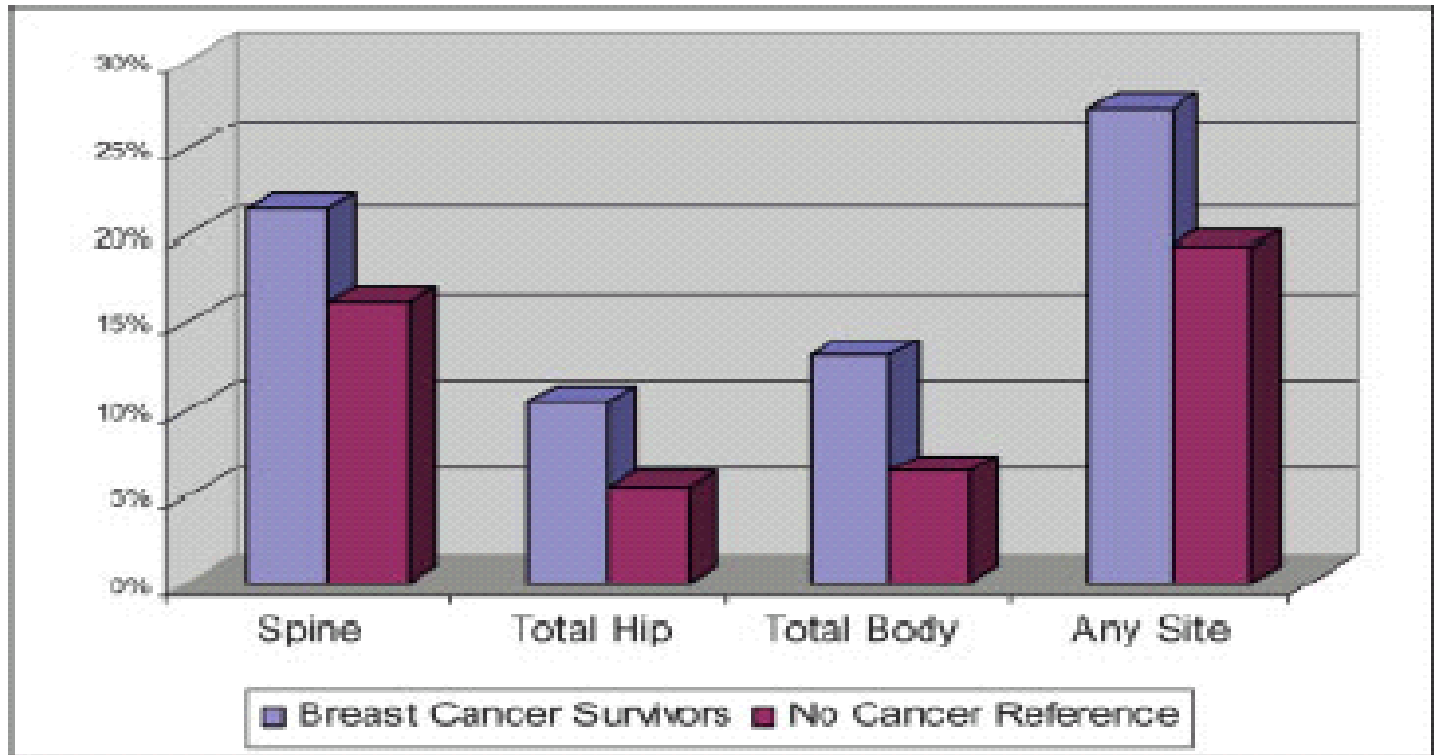
Women  $\geq 65$  years with undetectable estrogen levels ( $< 5$  pg/mL) have a 2.5-fold increased risk for subsequent hip or vertebral fractures\*



\*Compared with women with detectable estrogen levels.

Cummings SR, et al. *N Engl J Med.* 1998

# Osteoporosis is an important disease for BC patients: Rate of bone loss.



Comparison of prevalence of osteoporosis based on DXA measurements  
Chen et al CANCER October 1, 2005 / Volume 104 / Number 7

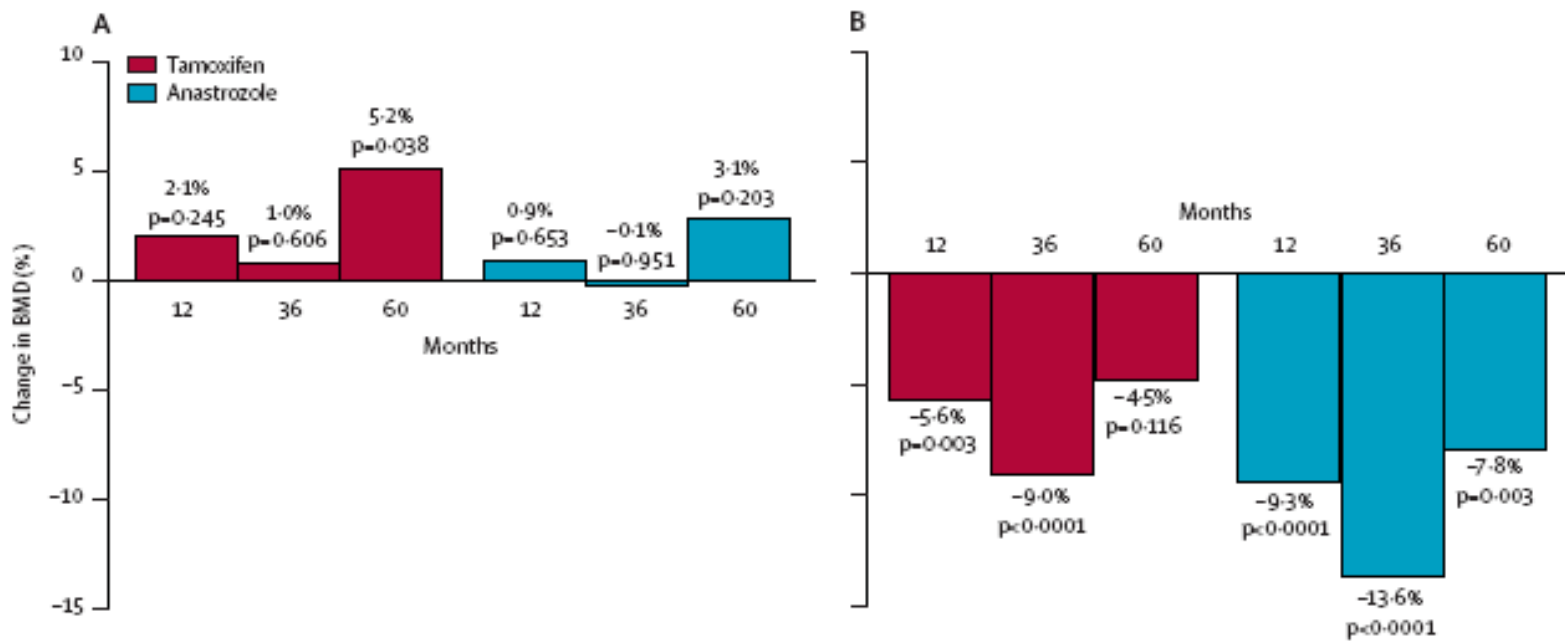
# Prevalence of vertebral fracture in women with non-metastatic BC.



- X 5
- vertebral fracture risk is markedly increased in women with breast cancer.
- Kanis et al Br J
- Cancer. 1999

## ABCSG-12 bone-mineral density substudy.

- Premenopausal women ER+
- Randomised, open-label, 4-arm trial
- TAM (20 mg/day) and goserelin (3.6 mg subcut /28 days)
- vs anastrozole (1 mg/day) and goserelin,
- both with or without zoledronic acid (4 mg IV/every 6 months) for 3 years in.
- BMD at 0, 6, 12, 36, and 60 months.
  - Gnant M et al Lancet Oncol. 2008 Sep;9(9):840-9.



**Figure 3:** Percentage change in lumbar spine bone-mineral density (BMD) from baseline to 12, 36, and 60 months. Patients were randomly assigned to anastrozole or tamoxifen with (A) or without (B) zoledronic acid (4 mg every 6 months) for 36 months and then no treatment from 36 to 60 months. p values were calculated using two-sample t tests for mean differences from baseline.

# Denosumab in Patients Receiving Adjuvant Aromatase Inhibitors

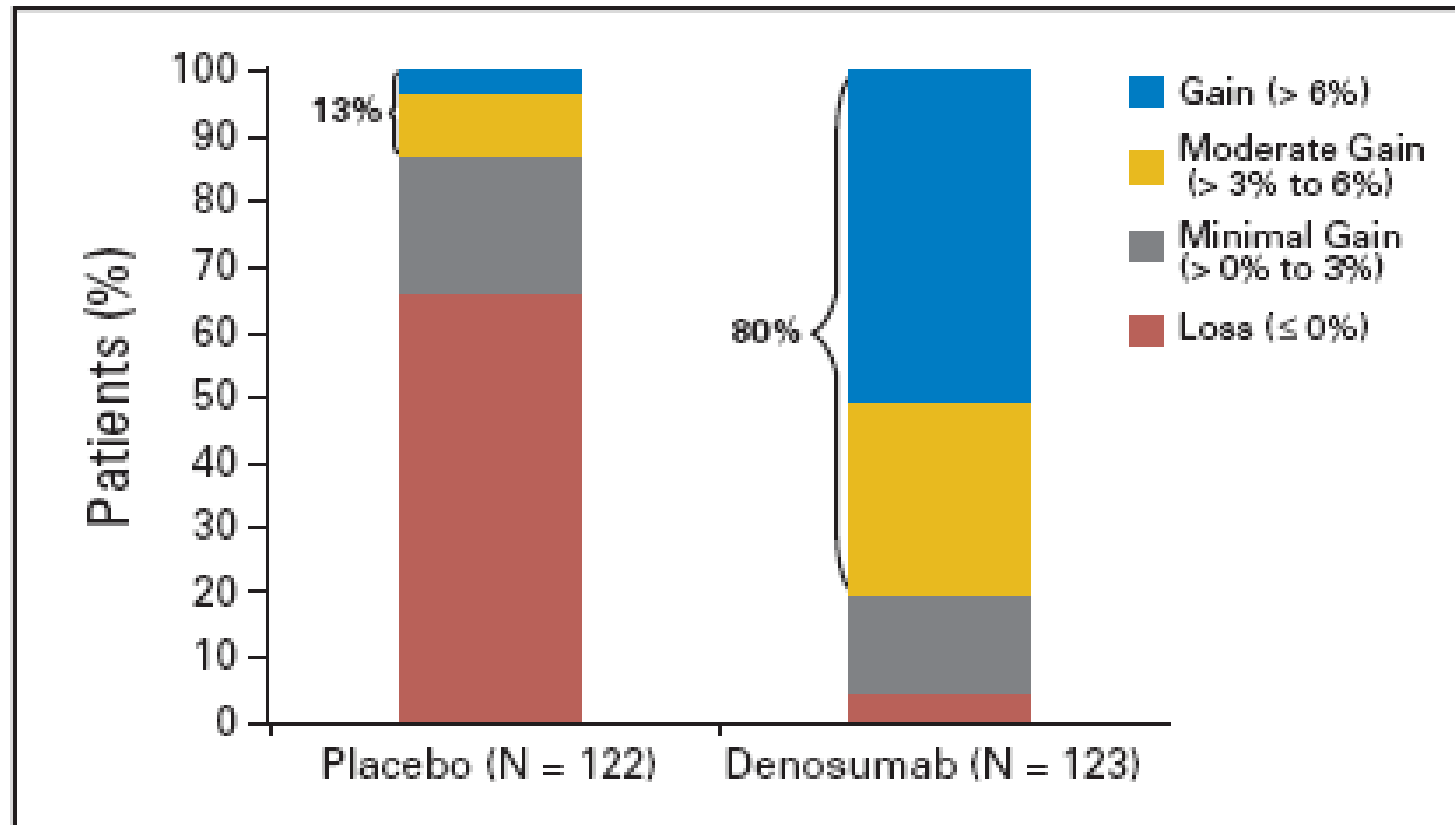
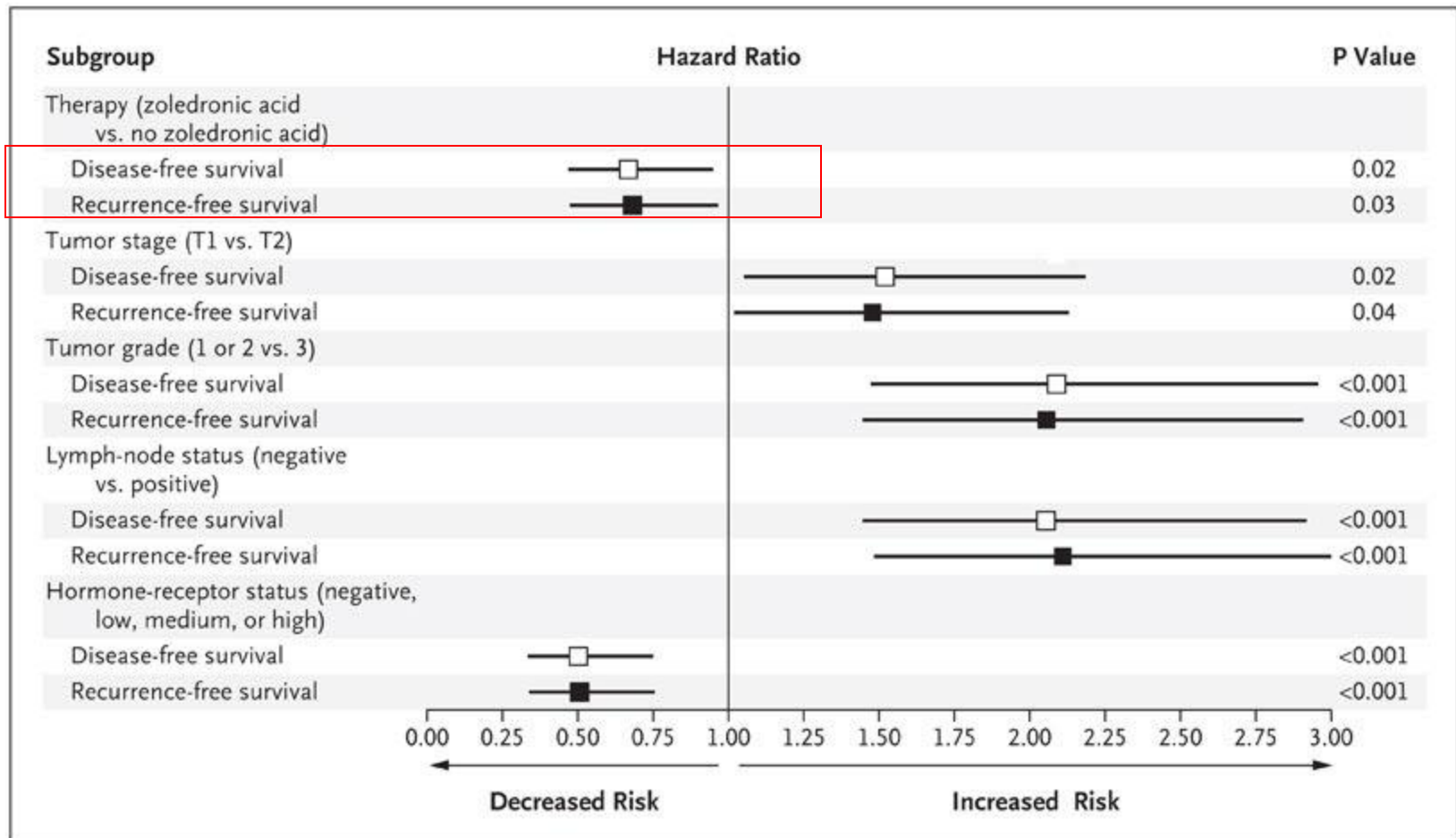


Fig 3. Proportion of patients at 24 months with preservation of lumbar spine bone mineral density (BMD), defined as more than 0% increase from baseline in lumbar spine BMD.

# Additional benefit?



Gnant et al 12.02.09 NEJM Endocrine Therapy plus Zoledronic Acid in Premenopausal Breast Cancer

# Aromatase inhibitor-associated arthralgia syndrome.

- Reason for discontinuation of AI treatment.
- Possible mechanisms: immune cells and cytokines, modulating pain sensitivity.
- Detailed patient symptoms, inflammatory and rheumatologic markers.
- Treatment: non-steroidal anti-inflammatory drugs (limited help).
- Research: high-dose vitamin D and new-targeted therapies to inhibit bone loss.
- [Burstein HJ](#). Breast. 2007

# Effects of anastrozole on cognitive performance in postmenopausal women: a randomised, double-blind chemoprevention trial (IBIS II).

- 111 women to anastrozole, 116 women to placebo.
- At 6 months, ten women in each group excluded, at 24 months, 24 women excluded from the anastrozole group and 32 from the placebo group, leaving 151 of 227 (67%) women.
- No significant differences between the groups for any of the cognitive tasks.
- VA Jenkins et al Lancet Oncology Oct 2008

# Conclusions

- Climacteric symptoms : life style, gabapentin, anti-depressants (*level I*)
- Vaginal dryness AI: moisters, Non AI : local estrogen (estriol) acceptable
- Avoid smoking (*Level I*)
- Regular physical exercise (*Level I*)
- calcium 1500 mg and vitamin D 800 U daily (*level evidence I-III*)
- T-score < 2.5 & between -1.5 and -2.5 in the presence of a fragility fracture or vertebral compression fracture
  - Consider bisphosphonate therapy (*oral level II-III*)  
(*i.v.level I*)