Dealing with menopausal symptoms in breast cancer patients

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Disclosure

- Gideon Richter: Speaker at sponsored symposia, consultant
- MSD (previously Organon): Advisory board, consultant, speaker at sponsored symposia
- Actavis: Speaker at sponsored symposia, consultant
- Bayer/Schering: Speaker at sponsored symposia
- Pfizer: Speaker at sponsored symposia
- Exeltis: Consultant, speaker at sponsored symposia
- Lenus Pharma: Speaker at sponsored symposia
- Apomedica: Speaker at sponsored symposia
- Mylan: Speaker at sponsored symposia

The New York Times

Hormone Studies: What Went Wrong?

By GINA KOLATA

For nearly nine months, doctors and researchers have been struggling with an intractable problem: how could two large high-quality studies come to diametrically different conclusions about menopause, hormone therapy and heart disease?

The question arose in July, when scientists saw data from a large federal study called the Women's Health Initiative, which was ended early when it became clear that a widely used hormone-replacement drug, Prempro, had risks, including heart attacks, that exceeded its benefits.

That finding directly contradicted previous studies showing that the hormones reduced heart disease risk — in particular, the Nurses' Health Study, a large research effort that has been going on for years.

The question is why.

To answer it, researchers are reviewing the data, scrutinizing the design of each study and examining other research that may help reconcile the disparate findings.

PERSONAL HEALTH: PROTECTING BONES

Even without hormone therapy, women can take steps to prevent osteoporosis. Page 6.

But so far, as they noted at a recent symposium at the Harvard School of Public Health, they have had no luck. As one explanation after another fails to hold up, the mystery deepens.

The effort is crucial because the contradiction has vast implications, not just for women's health but for medical research in general.

This does not mean that doctors are changing their new advice on hormone therapy. In the wake of the Women's Health Initiative, even many who once advocated the drugs after menopause now say women should use them only to relieve unbearable symptoms, like severe hot flashes, and should take them for the shortest possible time.

Even if it turns out that the drugs do protect some women against heart disease — that the Women's Health Initiative did not tell the whole story — there are better ways of doing it, medical experts say, than taking drugs that also confer other risks.

But as their efforts to reconcile the two studies continue to fall short, the experts

Continued on Page 6

Two Studies, One Big Disagreement

Experts are mystified about why two well-designed studies of hormone therapy for women produced strikingly similar results, with one exception.

WOMEN'S HEALTH INITIATIVE

OBSERVATIONAL STUDIES, INCL. NURSES' HEALTH STUDY

Figures show the percentage difference in risk to those women taking hormone therapy over those not taking it.

THE DISCREPANCY: HEART DISEASE RISK

29% increase

61% decrease

WHAT THE STUDIES AGREE ON: DECREASED RISKS

COLORECTAL CANCER 63% 66%

HIP FRACTURE 66% 75%

BREAST CANCER 26% overall; 15% in less than 5 years; 53% 5 years or more

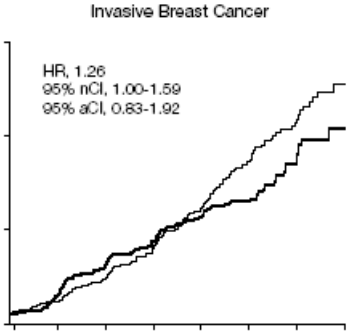
STROKE 41% 45%

PULMONARY EMBOLISM 113% 110%

THE NEW YORK TIMES, TUESDAY, APRIL 22, 2003

Cumulative Hazards Breast Cancer

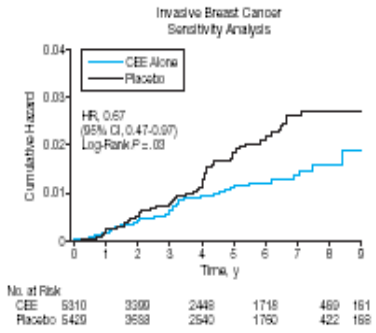
WHI: CE + MPA

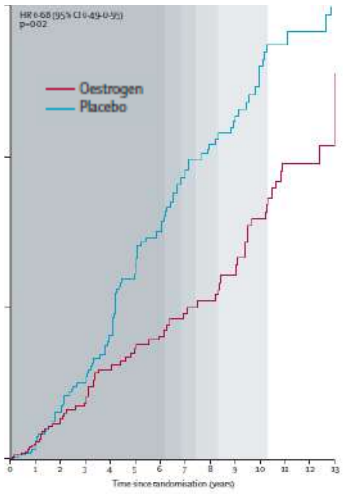


WHI JAMA 2002

Cumulative Hazards Breast Cancer

WHI: Estrogen only

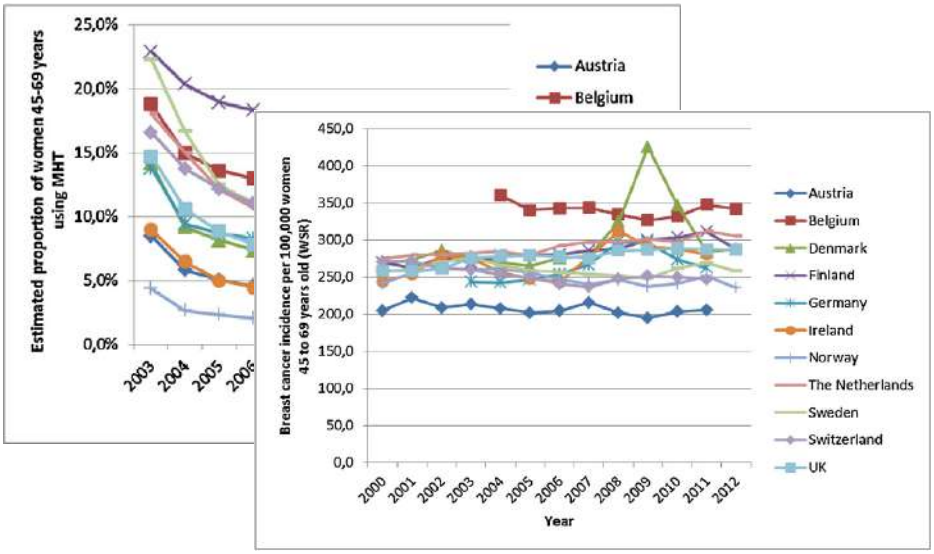




Stefanick ML, et al. JAMA 2006
Anderson GL. et al. Lancet Oncol 2012

HRT and Breast Cancer

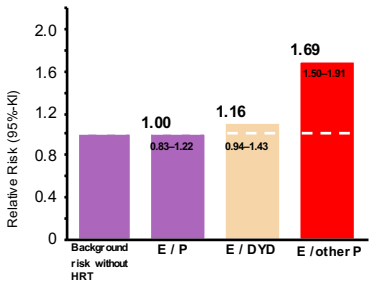
11 European Countries



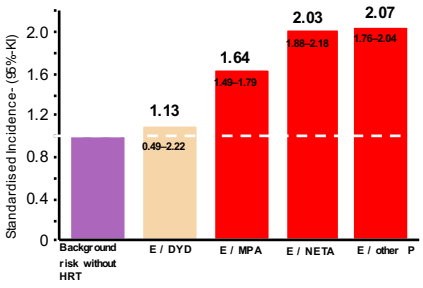
Antoine C. et al. Maturitas 2016

Association of HRT and Breast Cancer
Type of Progestogen

French Cohort Study E3N (n = 80,377)
Duration of observation: mean 8.1 years
Age: 40-65 years (mean 53.1 ± 4.5)



Finnish Cohort Study (n = 221,551)
Duration of observation: max. 11 years
Age: > 50 years (62.5% between 50 – 54a)

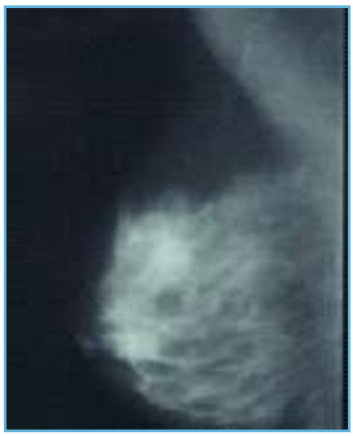


■ Significant difference to risk without HRT

E: Estrogen
P: Progesterone
DYD: Dydrogesterone
P: Progestogens

Fournier A. et al. Breast Cancer Res Treat 2008
Lyytinen H. et al. Obst Gyn 2009

Risk Situation after Diagnosis of Breast Cancer



Prevalence and Intensity of Menopausal Symptoms

Natural vs. Chemotherapy-induced Menopause

	Patient (n = 41)	Control (n = 57)	P value
Age in years, median (interquartile range)	48 (45–52)	54 (53–55)	<0.0001
Months since last period at initial assessment, median (interquartile range)	15.6 (13.3–17.8)	15.9 (11.0–21.7)	0.75
Chemotherapy drugs received			
CEF	27	NA	
CMF	5		
AC	5		
Others	4		

	Patient	Control	P value
Assessment 0			
Median FACT-ES score (interquartile range)	58 (50.5–61.5)	NA	
Assessment 1			
Median FACT-ES score (interquartile range)	58 (54–62)	62 (56–65)	0.05
% with moderate/severe hot flashes	51.4 ↑	19.3	0.003
Assessment 2			
Median FACT-ES score (interquartile range)	61 (51–62)	62 (57–67)	0.04
% with moderate/severe hot flashes	27.3 ↑	10.4	0.002

	Assessment 1	Assessment 2
Hot flashes	0.003	0.002
Cold sweats	NS	NS
Night sweats	NS	NS
Vaginal discharge	0.005	0.02
Vaginal itching/irritation	NS	NS
Vaginal bleeding/spotting	NS	NS
Vaginal dryness	NS	NS
Pain on intercourse	NS	NS
Lost interest in sex	0.03	0.003
Weight gain	NS	0.005
Lightheaded/dizzy	0.03	NS
Vomiting	NS	NS
Diarrhea	NS	NS
Headaches	0.09	0.07
Feeling bloated	0.05	NS
Breast tenderness	0.06	0.01
Mood swings	0.05	NS
Irritable	NS	0.07
Total FACT-ES score	0.05	0.04

Functional Assessment of Cancer Therapy Endocrine symptoms (FACT-ES)

Mar Fan HG. Et al, Annals Oncol 2010

Tamoxifen induced side effects by lenghth of treatment

Side effects from tamoxifen [a]	Number of participants taking tamoxifen (N = 241)			
	Length of tamoxifen treatment (number of months)			
	≤ 12 months N = 110 (46%)	13 – 24 months N = 39 (16%)	25 – 36 months N = 32 (13%)	> 36 months N = 57 (24%)
No side effects	19 (29)	12 (18)	16 (24)	19 (29)
Hot flashes (yes)	78 (50)	24 (16)	14 (9)	36 (23)
Severe hot flashes [b]	14 (46)	4 (13)	2 (6)	9 (29)
Vaginal dryness (yes)	37 (44)	21 (25)	9 (11)	16 (19)
Severe vaginal dryness [b]	5 (27)	5 (27)	1 (6)	6 (34)
Sleep problems (yes)	49 (56)	18 (21)	2 (2)	16 (19)
Severe sleep problems [b]	11 (52)	5 (24)	0	5 (24)
Other side effects:				
Weight gain	1 (7)	2 (14)	4 (29)	7 (50)
Irritability and mood swings	2 (22)	2 (22)	1 (11)	3 (34)
Depression	0	3 (60)	0	2 (40)
Any side effect	91 (52)	27 (15)	16 (9)	38 (22)
At least one severe side effect	25 (49)	7 (14)	2 (4)	15 (29)

Lorizio W. et al, Breast Cancer Res Treat 2012

Mortality in Breast Cancer Patients

Prediagnosis HRT

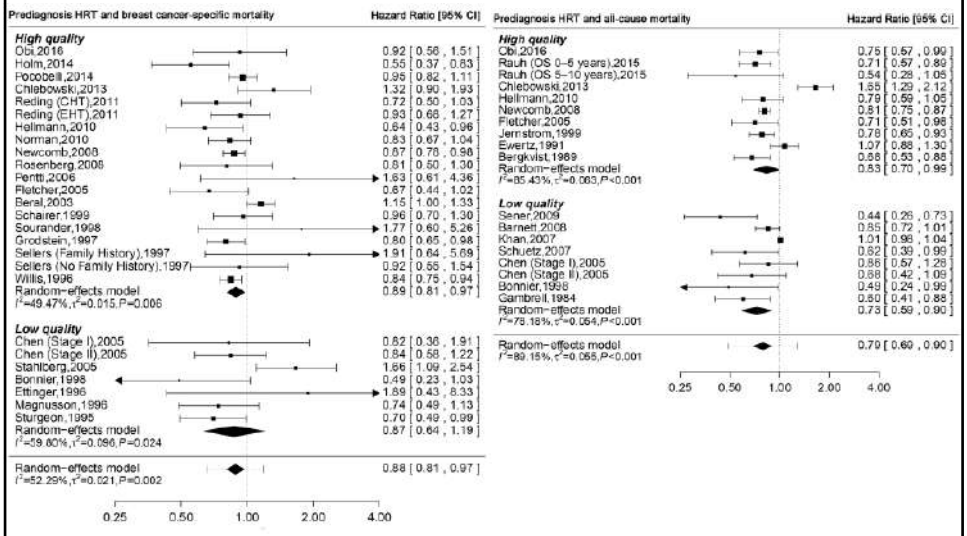
		BC mortality	Overall mortality
		N = 3,135, 291 events	N = 3,135, 399 events
Type of MHT	N	HR fully adj. 95% CI	HR fully adj. 95% CI
Never use (reference)	1,081	1	1
Past use	610	1.19 (0.87, 1.62)	0.87 (0.66, 1.15)
Current use (types combined)	1,444	0.72 (0.53, 0.97)	0.66 (0.52, 0.86)
Monoestrogen	330	0.84 (0.53, 1.34)	0.72 (0.49, 1.07)
Comb. E/P	994	0.66 (0.46, 0.99)	0.63 (0.47, 0.84)

MARIEplus Study, Follow-up 6.1 a

Obi N. et al. Int J Cancer 2016

Mortality in Breast Cancer Patients

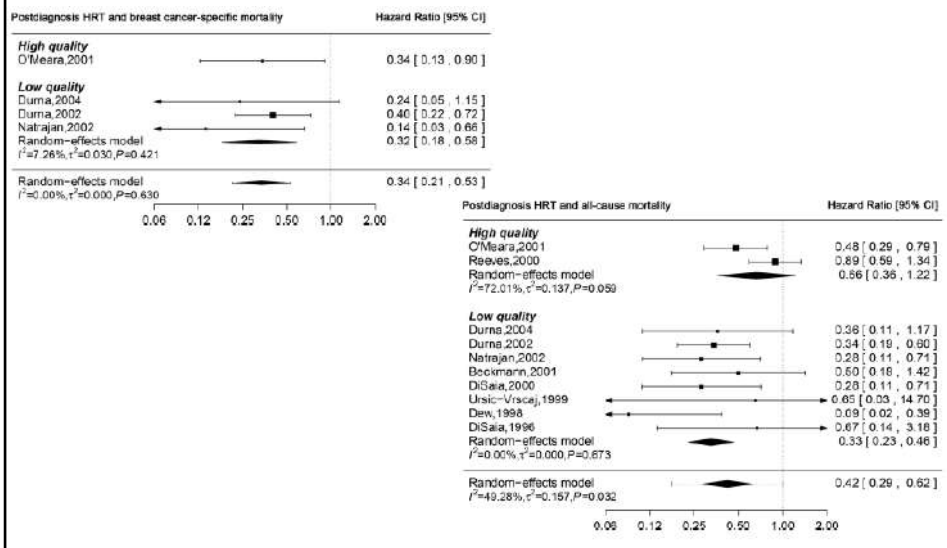
Pre-diagnosis HRT



Yu X. et al. Breast Cancer 2017

Mortality in Breast Cancer Patients

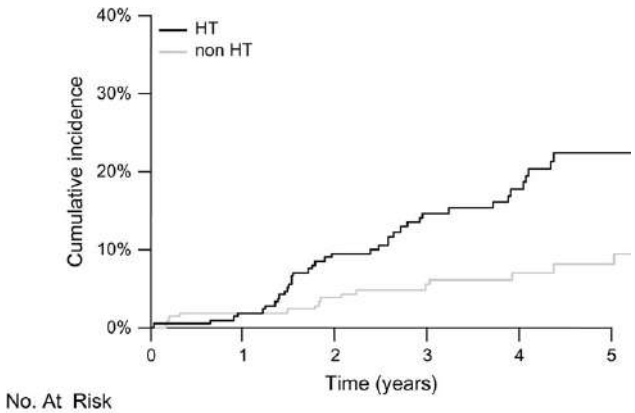
Post-diagnosis HRT



Yu X. et al. Breast Cancer 2017

Mortality in Breast Cancer Patients

Post-diagnosis HRT



No. At Risk

HT	221	210	176	133	96	59
non HT	221	207	189	148	107	68

HABITS Study

Holmberg L. et al. J Natl Cancer 2008

Pathophysiology of Hot Flushes

Antihypertensive drugs
(Clonidine)

- Peripheral (cutaneous) vasodilatation due to small increases in basal temperature

- Decrease in Estrogen → Phyto-Estrogens
  - Accelerated response of thermoregulatory system
  - Sympathetic activation of central α2-receptors that are involved with temperature regulation

Selective *Serotonin*
Re-uptake Inhibitors (SSRIs)

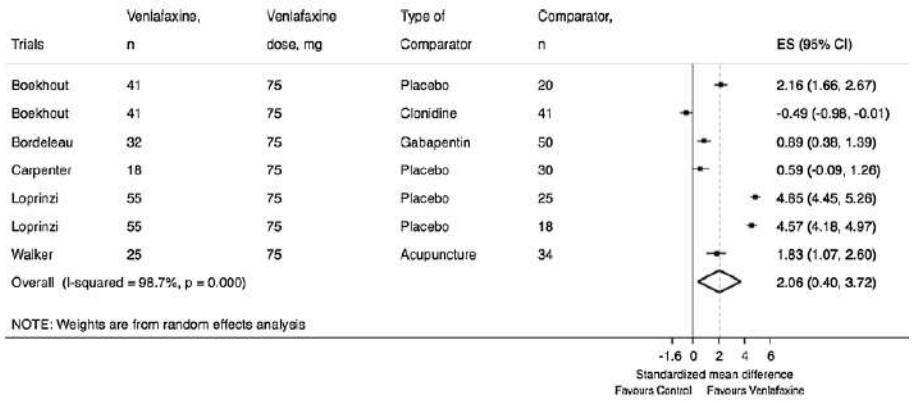
Serotonin *Noradrenaline*
Re-uptake Inhibitors (SNRIs)

- Symptomatic women: tight thermoregulatory margin → small changes of body temperature lead to hot flushes and chills

Other psychotropic substances → Anticonvulsant drugs
Unknown mode of action

SNRIs

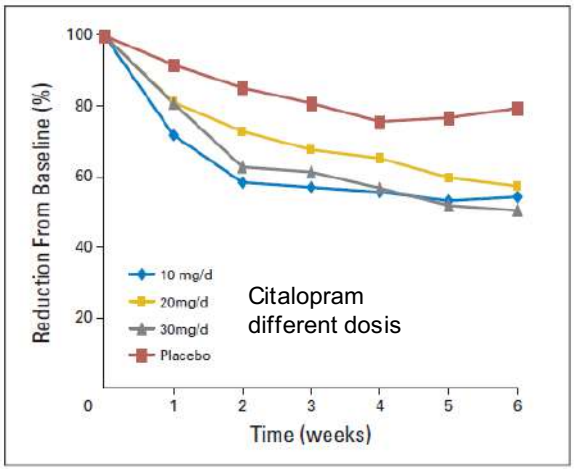
Efficacy in hot flushes



Ramaswami R. et al Breast Cancer Res Treat 2015

SSRIs

Efficacy in hot flushes



Barton DL. et al J Clin Oncol 2010

SSRI/SNRI

Safety, Efficacy, and Cost for Treatment

Generic (Brand Name) Recommended First Line Medications for Hot Flashes	Daily Doses	Appropriate for Tamoxifen users	Approximate cost of 30 day supply
Selective Serotonin Reuptake Inhibitors (SSRIs)			
1. Paroxetine (Paxil)			
Paroxetine salt (Brisdelle®) (FDA approved for hot flashes)	7.5mg	No	$150-$200+
Paroxetine (Paxil)	10mg 20mg	No No	$5.00+ $5.00+
Paroxetine ER (Paxil CR)	12.5mg 25mg	No No	$40-$250 $40-$250
2. Citalopram (Celexa)	20mg	No	$4.00-$12.00
3. Escitalopram (Lexapro)	10mg	No	$8.00-$10.00
Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)			
1. Venlafaxine (Effexor XR)	37.5mg	Yes	$6.00-$12.00+
2. Desvenlafaxine ER (Pristiq)	50mg	Yes	$140-$240+

Stubbs C. et al J Okla State Med Assoc. 2017

Phyto-Estrogens

- **Black Cohosh**
  - Clinical data: +++
  - Results: contradictory
  - Hot flushes ↓ ?

- **Red Clover**
  - Clinical data: ++
  - Results: only 1/6 RCTs demonstrated efficacy
  - Hot flushes ↓ ?

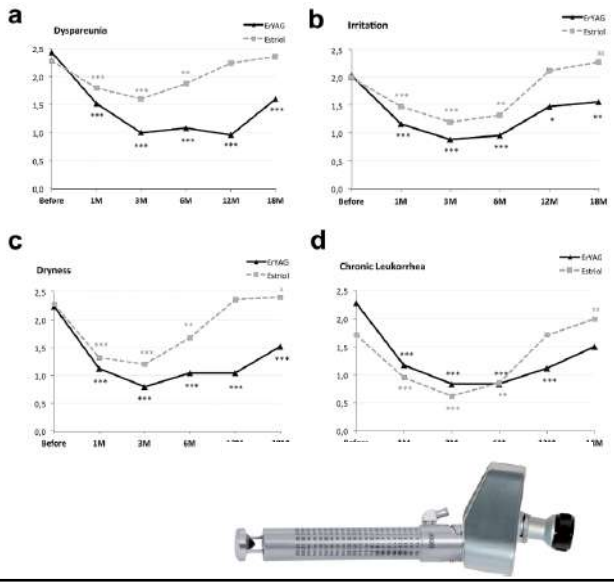
- **St. John's Wort**
  - Clinical data: +
  - Hot flushes ↓ ?

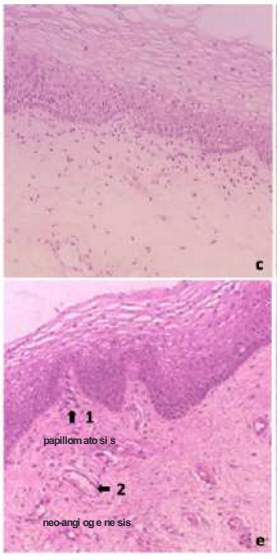
Missing data concerning long-term safety

Hall et al 2011

Erbium:YAG Laser versus topical Estriol

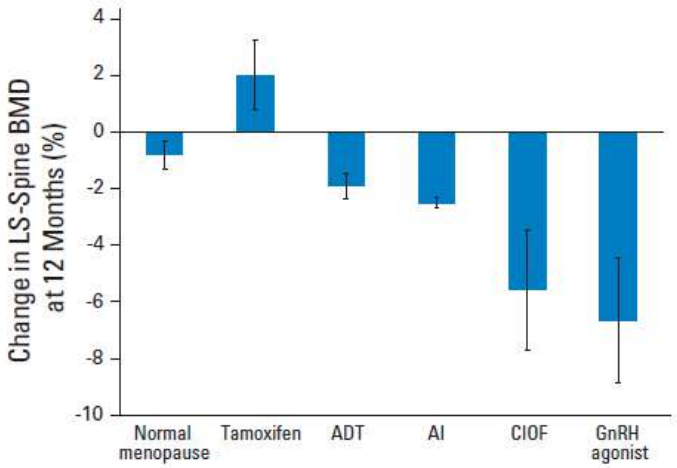
VVA





Gaspar A et al, Lasers Surg Med 2017

Change in bone mineral density (BMD)



Lustberg M. et al. J Clin Oncol 2012

Treatment of Postmenopausal Osteoporosis

Treatment	Study	Fracture incidence (%)	
		placebo	treatment
Alendronate	FIT 1[36]	15.0	8.0
Risedronate	VERT-NA[38]	16.3	11.3
Risedronate	VERT-MN[39]	29.0	18.1
Ibandronate	BONE[37]	9.6	4.7
Zoledronic acid	HORIZON[40]	10.9	3.3
Denosumab	FREEDOM[26]	7.2	2.3
Raloxifene	MORE[41]	21.2	14.7
Lasofoxifene[a]	PEARL[42]	9.5	5.7
Bazedoxifene	No acronym[43]	4.1	2.3
Teriparatide[b]	FPT[29]	14.0	5.0
Strontium ranelate	SOTI[44]	32.8	20.9

Reginster JY et al, Drugs 2011

Conclusion

- Breast cancer risk probably lower (or absent) with bioidentical hormones (Progesterone, Dydrogesterone)
- Breast cancer-specific and overall mortality unrelated to prediagnosis HRT
- Climacteric symptoms in breast cancer patients ↑
- Medical treatment of hot flushes: SSRI or SNRI
- HRT or Phyto-Estrogens ??
- Prophylaxis of osteoporosis (AI): Bisphosphonate or Denosumab