

Side effects of hormone therapy in breast cancer

Outline

- ▶ Introduction
- ▶ Most important side effects
- ▶ Treatment : in general
- ▶ Hot flashes
- ▶ Musculoskeletal symptoms
- ▶ Sexual health



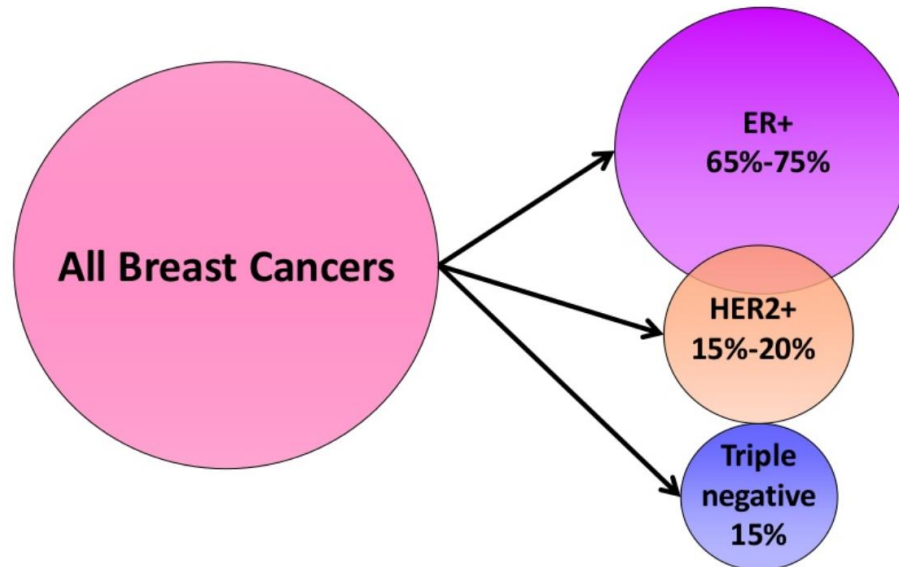
Introduction



Breast cancer: most prevalent cancer in women



Breast cancer subtypes



- ▶ About 70% of breast cancers are ER-positive
- ▶ Cancer cells grow in response to estrogen

Mechanism of action

Estrogen deprivation or estrogen function suppression is the mainstay of treatment in ER+ breast cancer

Selective oestrogen
receptor modulators

Tamoxifen

Selective oestrogen
receptor downregulators

Fulvestrant

Oestrogen synthesis
inhibitors

- Ovarian function suppression
- Aromatase inhibitors

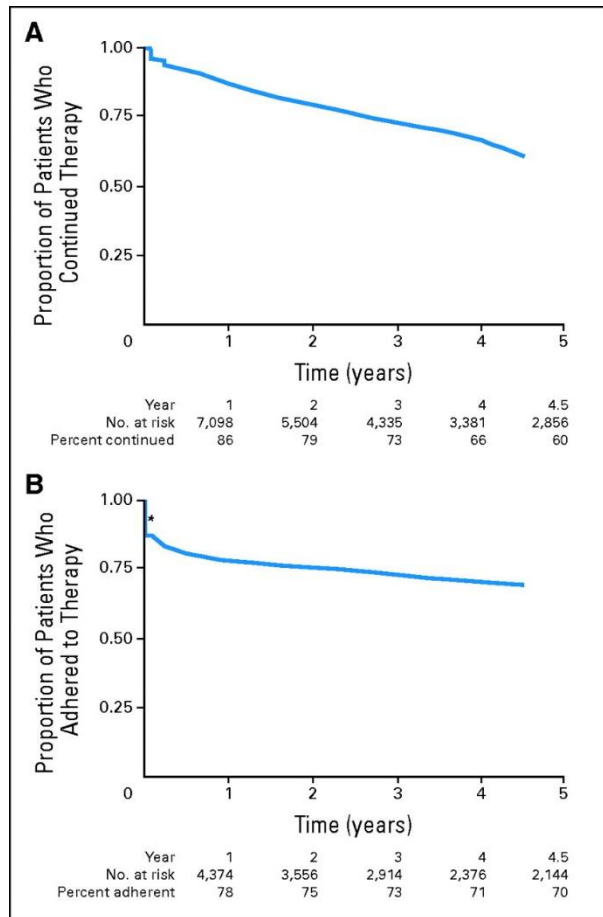
Hormonal therapy in early breast cancer

- ▶ Hormonal therapy is the most effective way to reduce recurrence in hormone sensitive breast cancer (EBCTG)
- ▶ AI's standard of care for postmenopausal women (ATAC)
- ▶ 10 years of therapy > 5 years (MA 17R)
- ▶ AI + ovarian suppression > Tam for high-risk premenopausal women (SOFT / TEXT)

→ **Widely used for a long period of time**

Drugs don't work in people who don't take them!

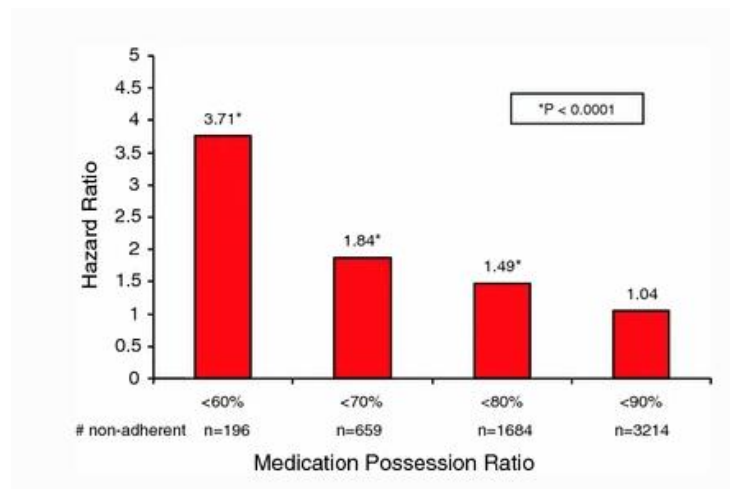
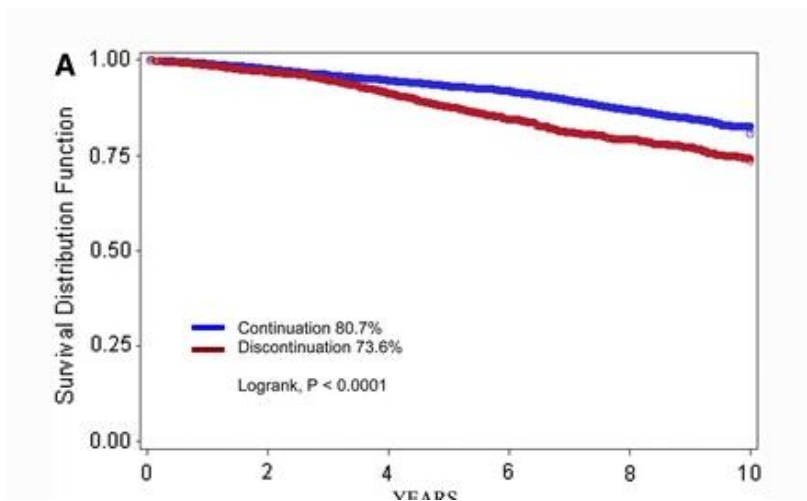
Discontinuation and non-adherence to breast cancer hormonal therapy



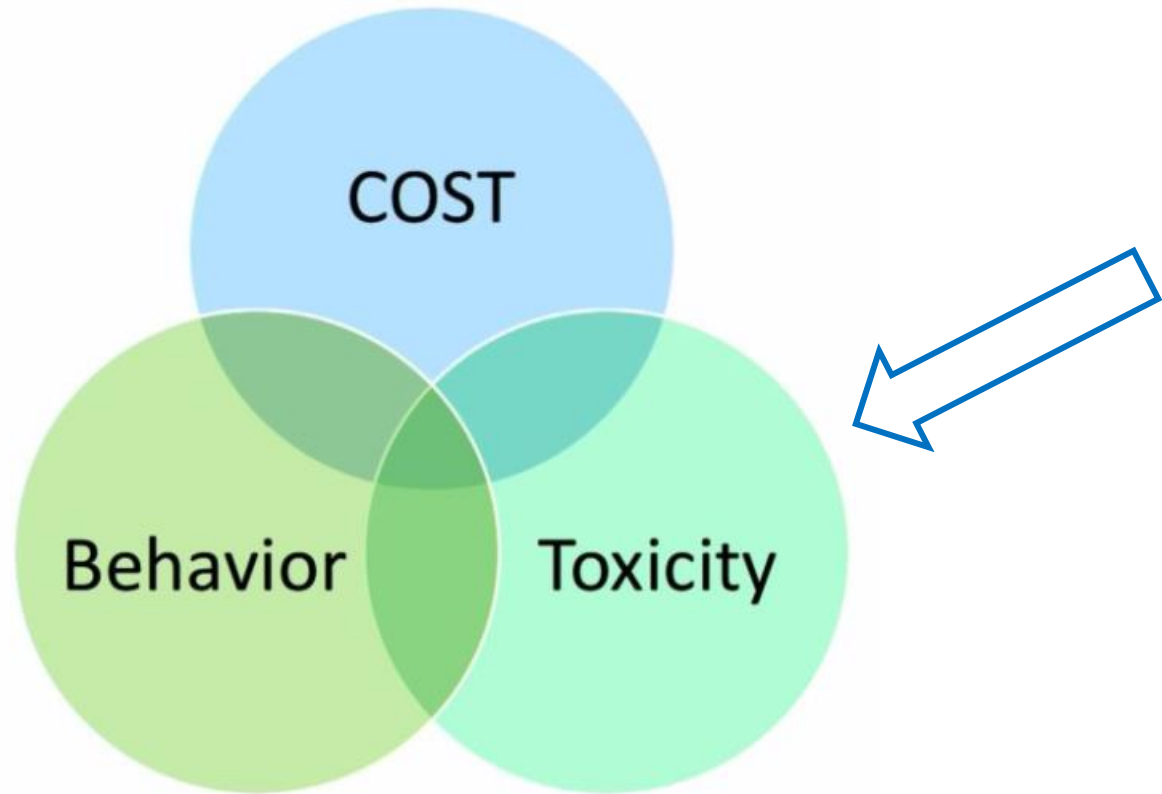
- ▶ \pm 25% of patients stop taking hormonal therapy too early
- ▶ Additionally \pm 25% of patients take their medication intermittently, less than 80% of time

→ Only 49% of patients with BC took adjuvant hormonal therapy for the full duration of time at the optimal schedule!

Does this matter?



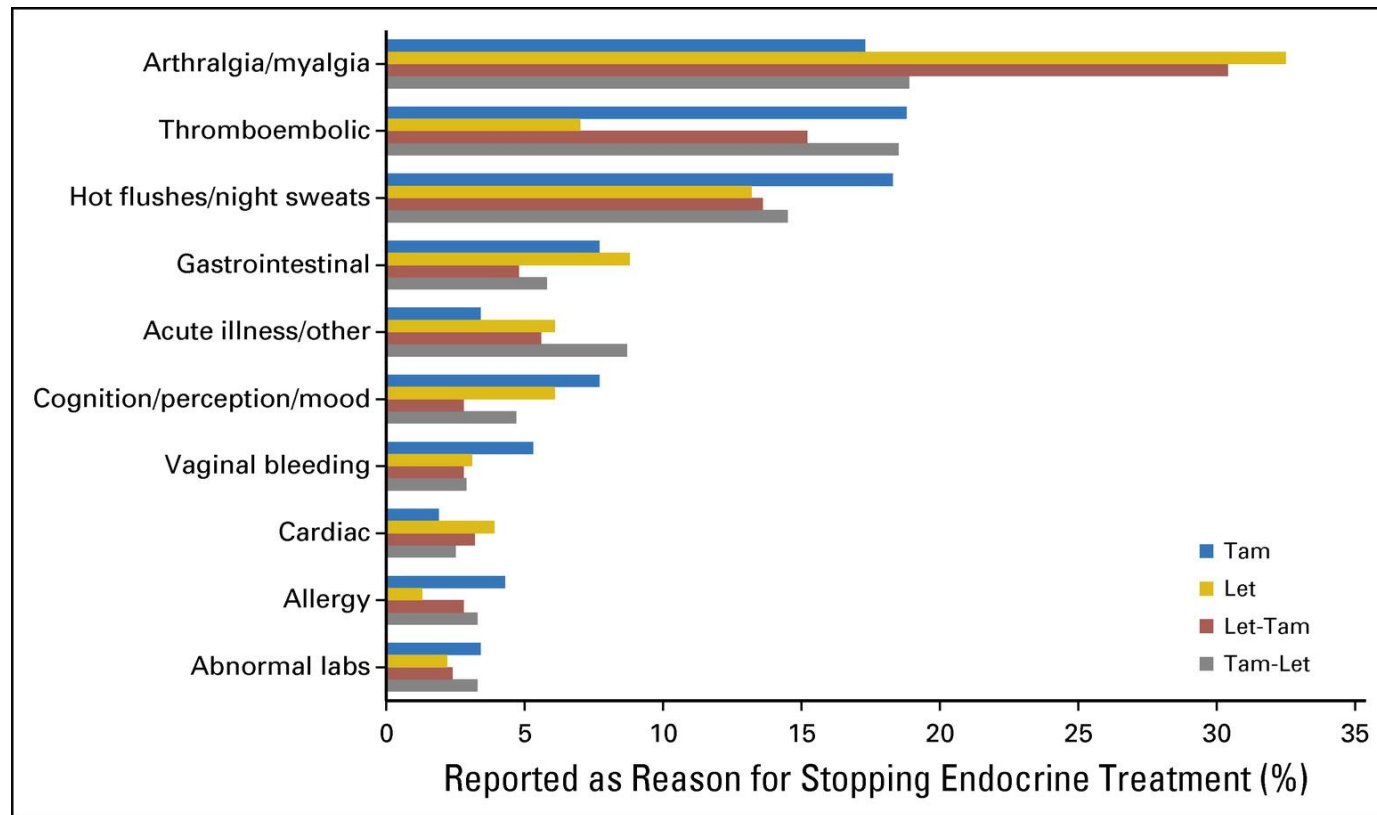
Why are treatment not started of discontinued?





Most important side-effects

Adverse events as a reason for stopping endocrine treatment



Data from SOFT and TEXT

	T (n 1005)	T + OFS (n 1006)	E + OFS (n 1000)
Thrombosis	2,2%	2,2%	0,9%
Hot flashes	7,8%	13,2%	10,7%
Libido decrease	11,5%	15,9%	17,5%
Musculoskeletal symptoms	6,7%	5,9%	12%
Osteoporosis	3,9%	6,1%	11,9%
Depression	4,1%	4,5%	3,9%
Stopped oral endocrine therapy early	22,5%	18,5%	27,8%
Stopped triptorelin early		21,4%	19,6%

Side effects of ET in postmenopausal women (IBIS-II)

Adverse event	Anastrozole (n 1449)	Tamoxifen (n 1489)
Hot flushes	818 (56%)	899 (60%)
Arthralgia	832 (57%)	729 (49%)
Any eye disease	230 (16%)	209 (14%)
Vaginal dryness	189 (13%)	159 (11%)
Fractures	129 (9%)	100 (7%)
Vaginal discharge	30 (2%)	136 (9%)
Hypertension	82 (6%)	73 (5%)
Headache	82 (6%)	61 (4%)
Joint stiffness	74 (5%)	35 (2%)
Vaginal bleeding	35 (2%)	80 (5%)

Conclusion

Endocrine therapy is associated with important symptoms (~ postmenopausal complaints):

- Vasomotor (hot flushes, night sweats)
- Joint pain
- Loss of sexual desire, vaginal dryness/discharge, dyspareunia
- Sleep disturbances, weight gain, cognitive impairment, osteoporosis

- Decrease in functional status
- A lesser quality of life
- More treatment nonadherence

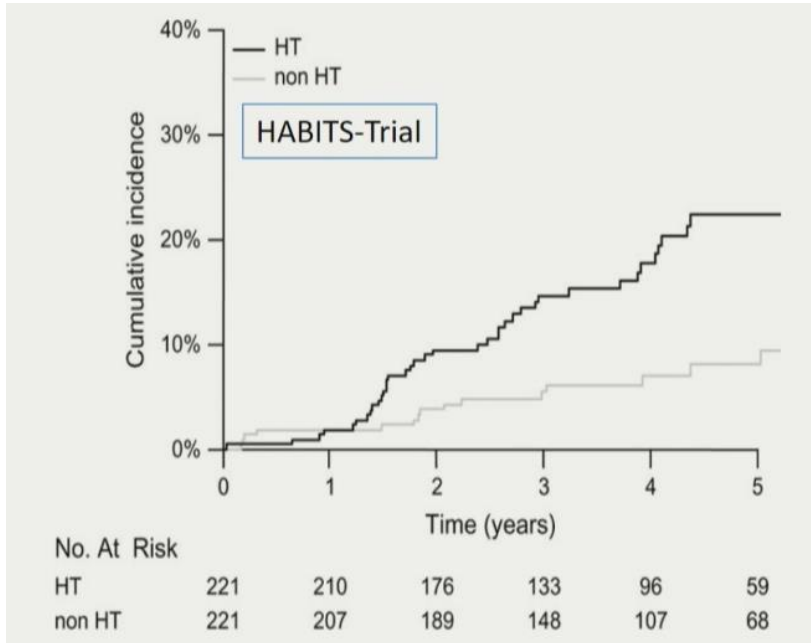


Treatment: in general

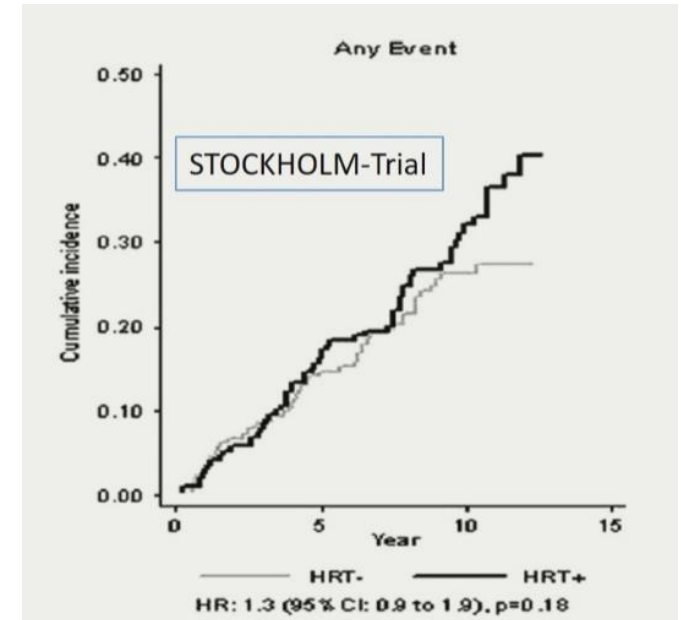
In the general population

- ▶ Hormone-replacement therapy (HRT) is the most effective treatment for postmenopausal symptoms in women with no chronic illnesses

But: in breast cancer survivors – much debate – the score is even



Prematurely stopped after an increase in the risk of breast cancer recurrence was suggested



Risk of breast cancer recurrence was not associated with HRT use

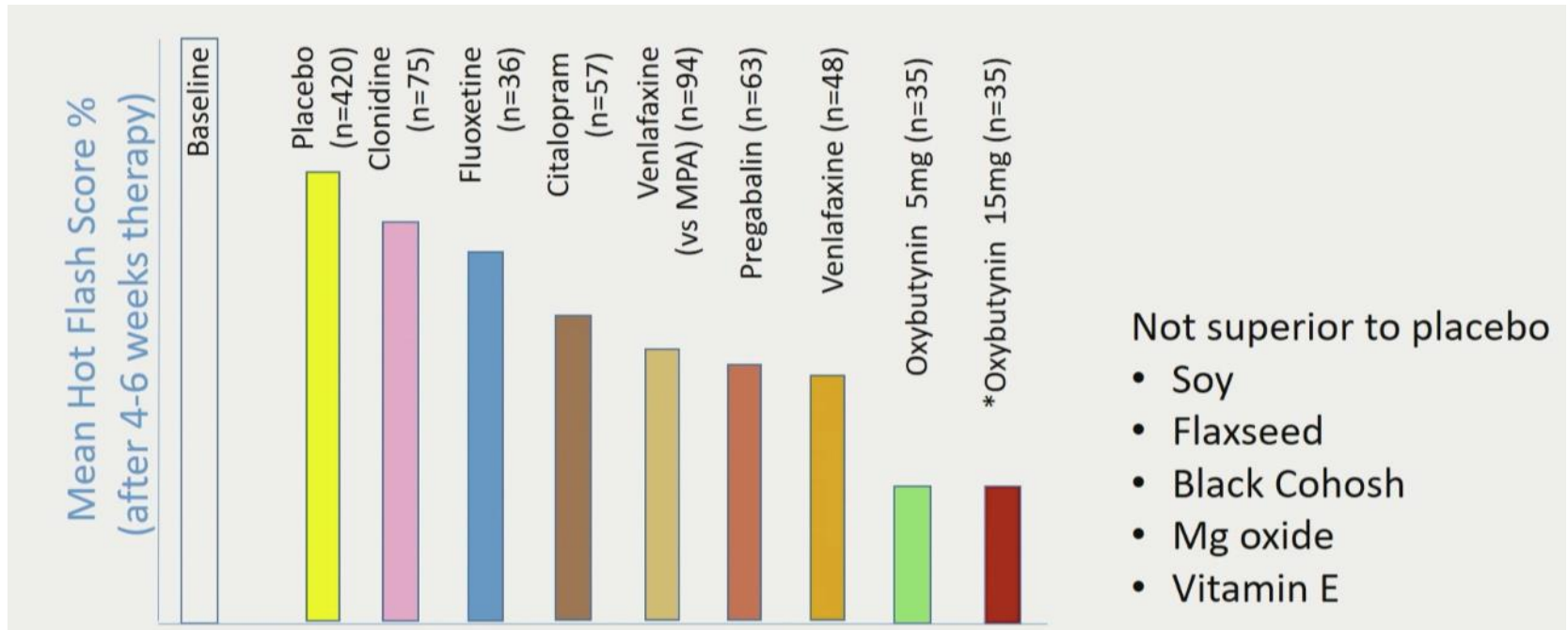
General approaches

- ▶ Physical exercise
- ▶ Mind body medicine (yoga, hypnosis, education, counseling)
- ▶ Cognitive behavioral therapy
- ▶ Acupuncture



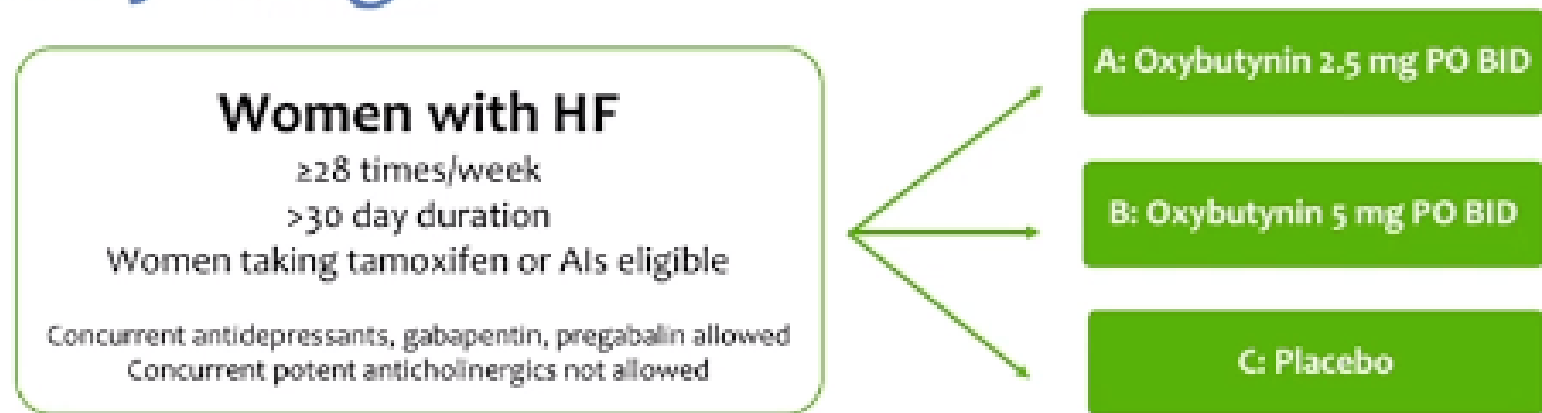
Hot flashes

Effectivity of non-hormonal drugs for reduction of hot flashes (RCT – pos trials)



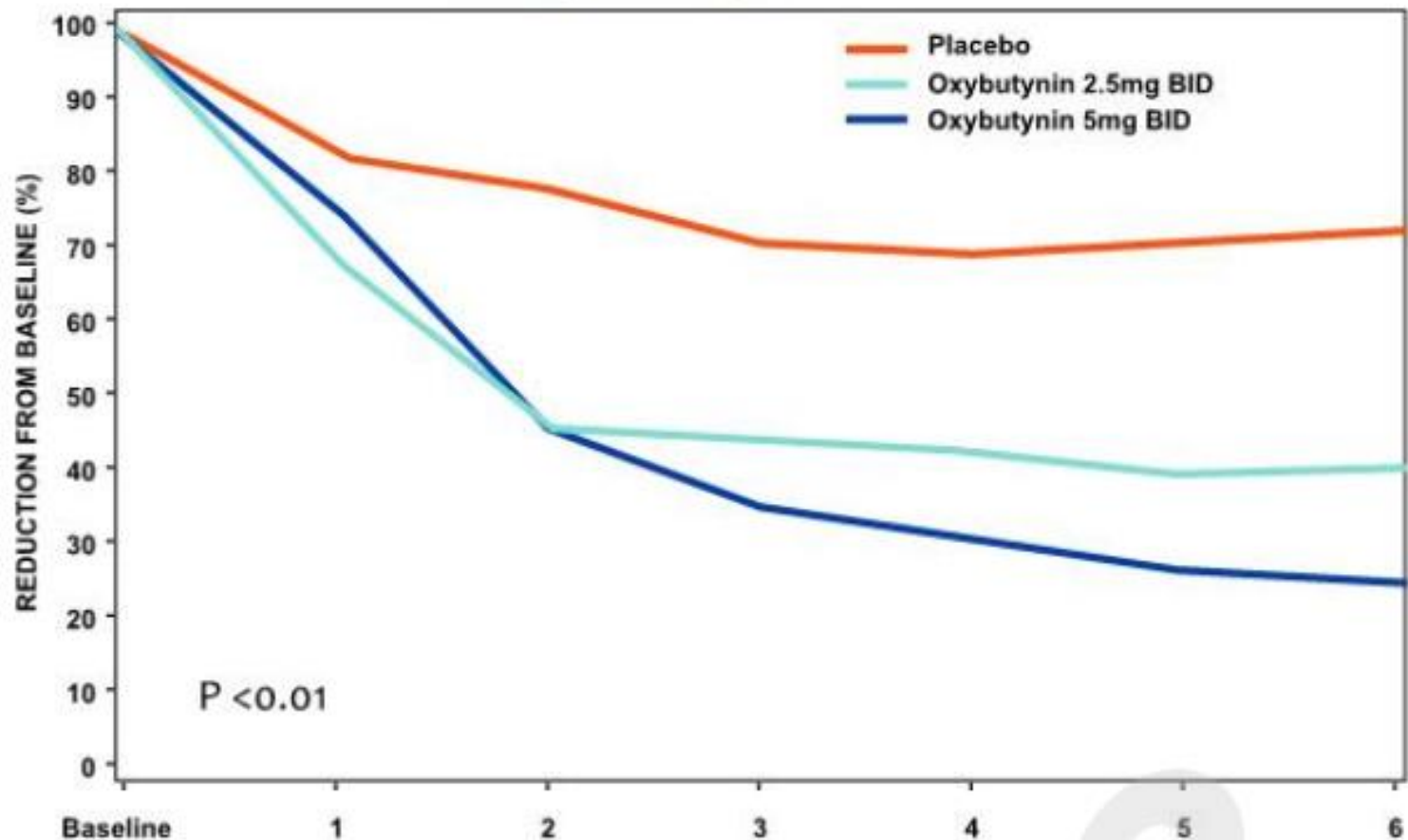
A randomized, double-blind, placebo-controlled trial of oxybutynin for hot flashes.
Leon-Ferre R et al.

Study design



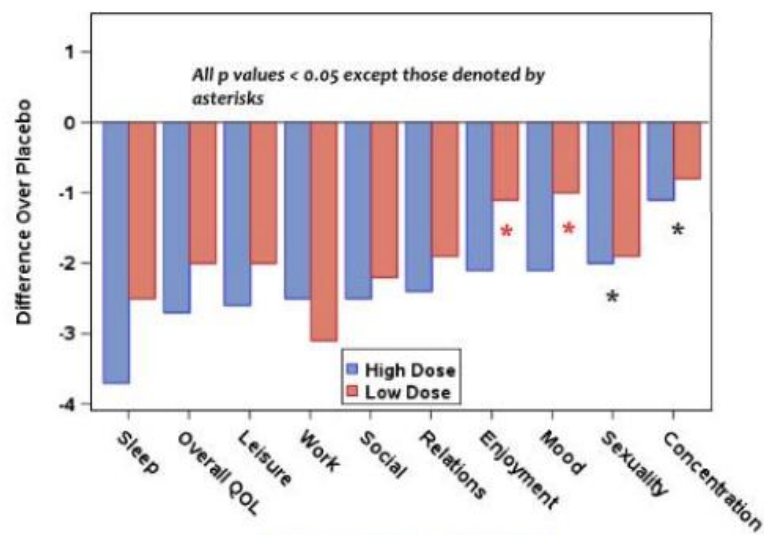
Treatment duration = 6 weeks, after a baseline week without medication (questionnaires)

Results: mean hot flash score (frequency + intensity) reduction from baseline



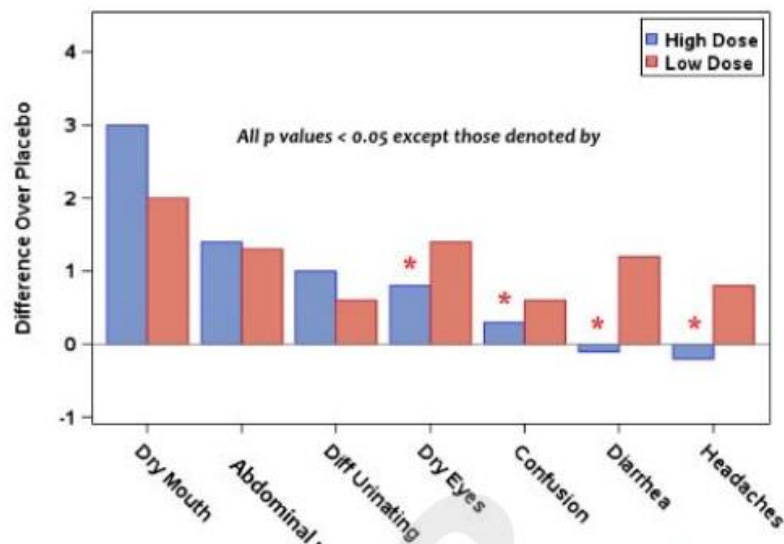
Results: change over placebo

- ▶ Most measures were statistically better with oxybutynin than placebo, except:
- Concentration and sexuality: not improved in either oxybutynin arm
- Mood and life enjoyment: not improved in oxybutynin 2,5 mg BID



Side-effects: change over placebo

- ▶ Both doses were generally well-tolerated
- ▶ Symptoms worsened in both arms: dry mouth, abdominal pain, difficulty urinating
- ▶ Symptoms worsened only with oxybutinin 5 mg BID: dry eyes, episodes of confusion, diarrhea, headaches



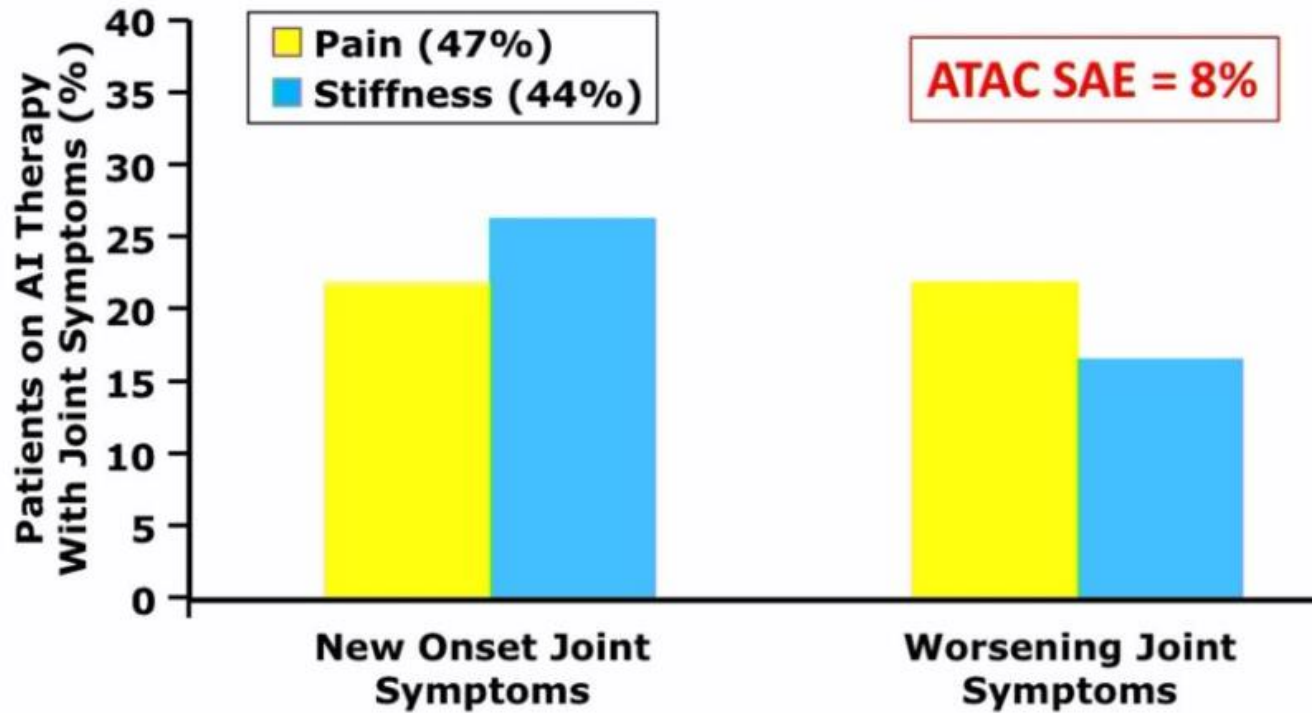
Conclusion of this study

- ▶ Oxybutinin significantly improves hot flashes frequency and severity
- ▶ Use of oxybutynin is associated with positive impact in several quality of life metrics
- ▶ Toxicity was acceptable
- ▶ While the 2 oxybutynin doses were not formally compared patients on 5 mg BID experienced more reduction in hot flashes and improvement in more QoL measures



Musculoskeletal symptoms

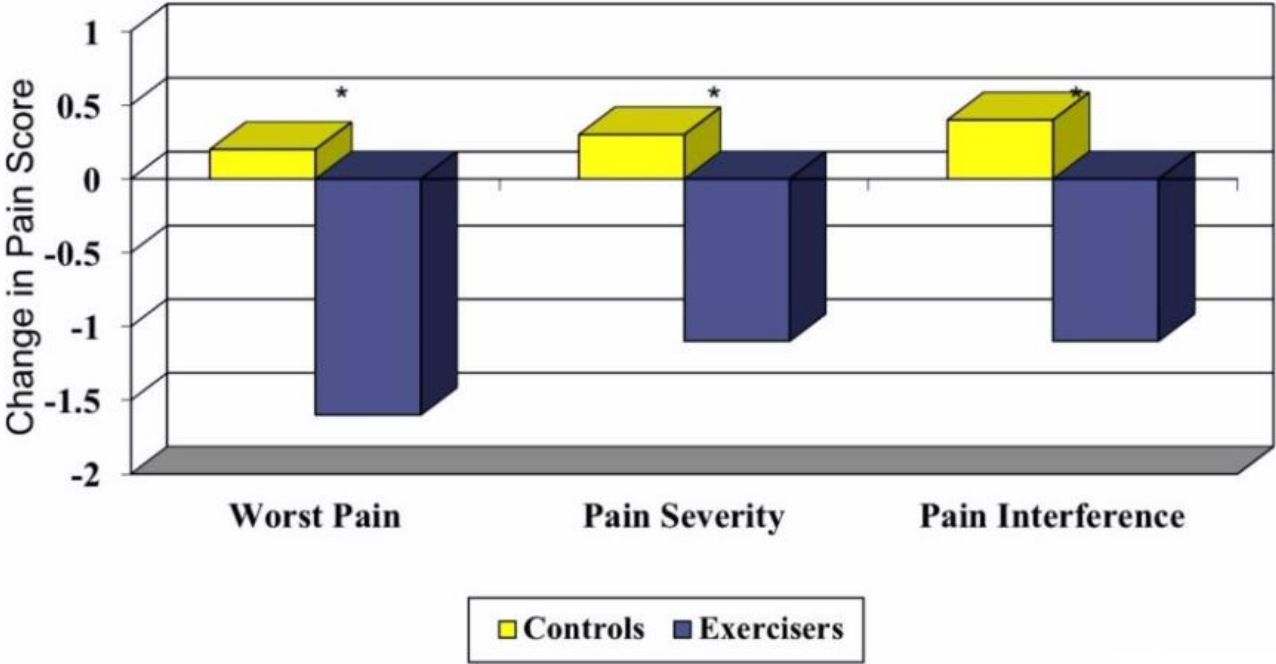
Prevalence of AI-Related Joint Symptoms



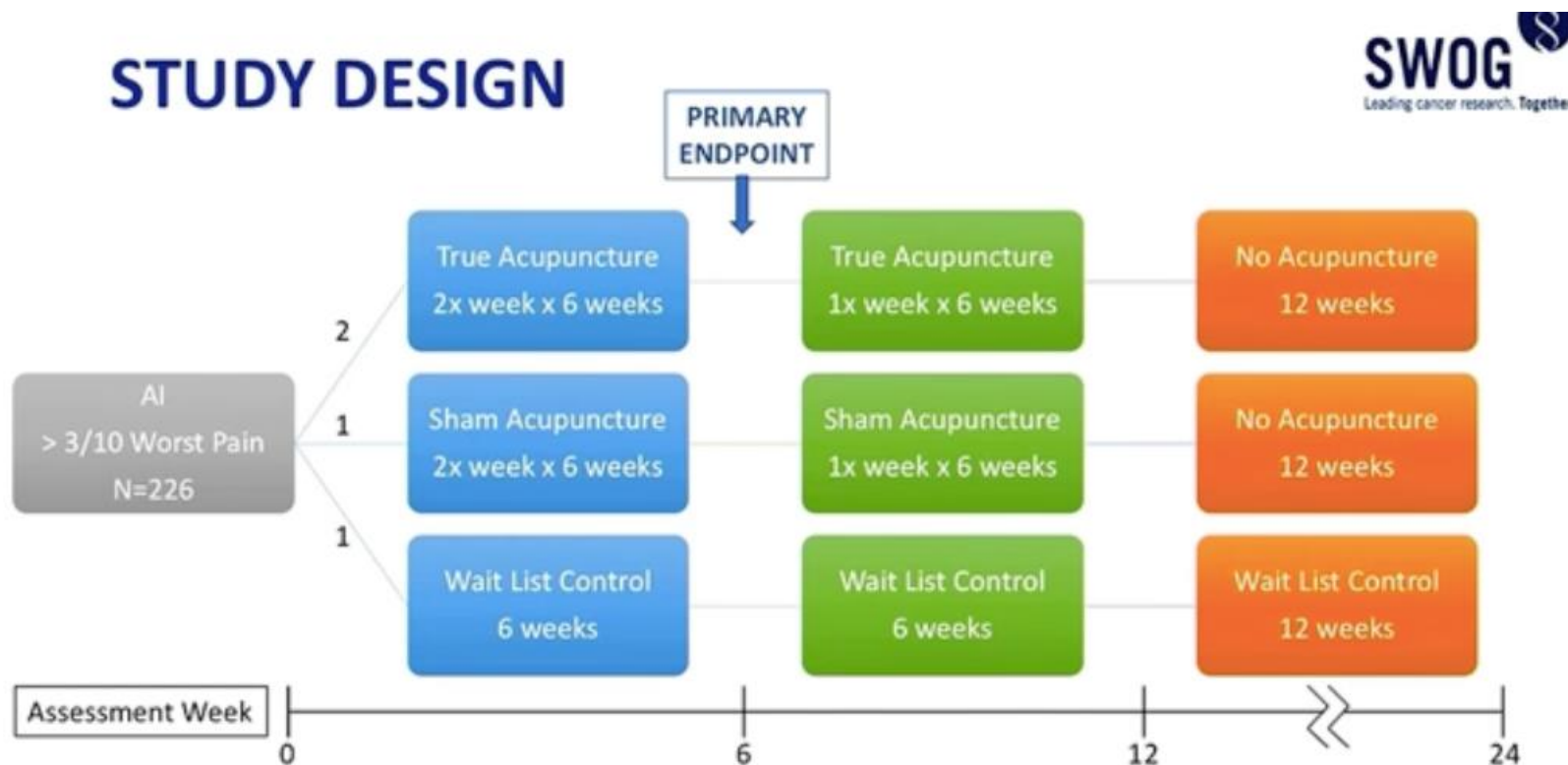
Treatment options

- ▶ Exercise
- ▶ Acupuncture
- ▶ NSAIDs (temporary!)
- ▶ Temporary discontinuation of AI (2–8w), followed by initiation of a different AI
- ▶ Switch to tamoxifen

Randomized exercise trial of aromatase inhibitor-induced arthralgia in breast cancer survivors

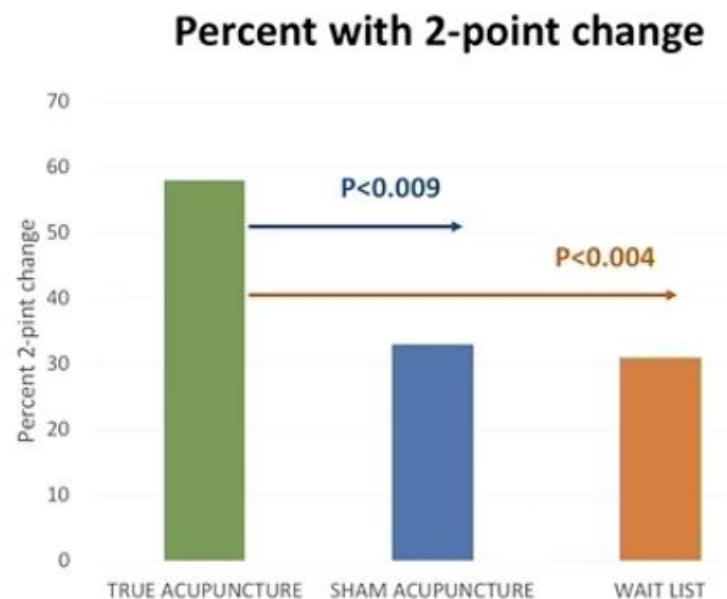


Randomized, blinded, sham-controlled trial of acupuncture for the management of aromatase inhibitor-associated joint symptoms



6-week results – worst pain

WORST PAIN	Fitted Difference*	P-value
True v. Sham	0.92 (0.20-1.65)	.01
True v. Waitlist	0.96 (0.24-1.67)	.01
Sham v. Waitlist	0.05 (-0.81-0.90)	.92



Curcumin?

- ▶ Tam + tumeric: 7,7% decrease in endoxifen AUC
- ▶ Tam + tumeric + piperine: 12,4% decrease in endoxifen AUC
- ▶ Endoxifen levels may drop below the threshold for treatment efficacy
- ▶ Only 16 patients!!



* Supplements

original reports

Dietary Supplement Use During Chemotherapy and Survival Outcomes of Patients With Breast Cancer Enrolled in a Cooperative Group Clinical Trial (SWOG S0221)

Christine B. Ambrosone, PhD¹; Gary R. Zirpoli, PhD²; Alan D. Hutson, PhD¹; William E. McCann¹; Susan E. McCann, PhD, RD¹; William E. Barlow, PhD³; Kara M. Kelly, MD¹; Rikki Cannioto, PhD, EdD¹; Lara E. Sucheston-Campbell, PhD⁴; Dawn L. Hershman, MD⁵; Joseph M. Unger, PhD³; Halle C.F. Moore, MD⁶; James A. Stewart, MD⁷; Claudine Isaacs, MD⁸; Timothy J. Hobday, MD⁹; Muhammad Salim, MD¹⁰; Gabriel N. Hortobagyi, MD¹¹; Julie R. Gralow, MD¹²; George T. Budd, MD⁶; and Kathy S. Albain, MD¹³

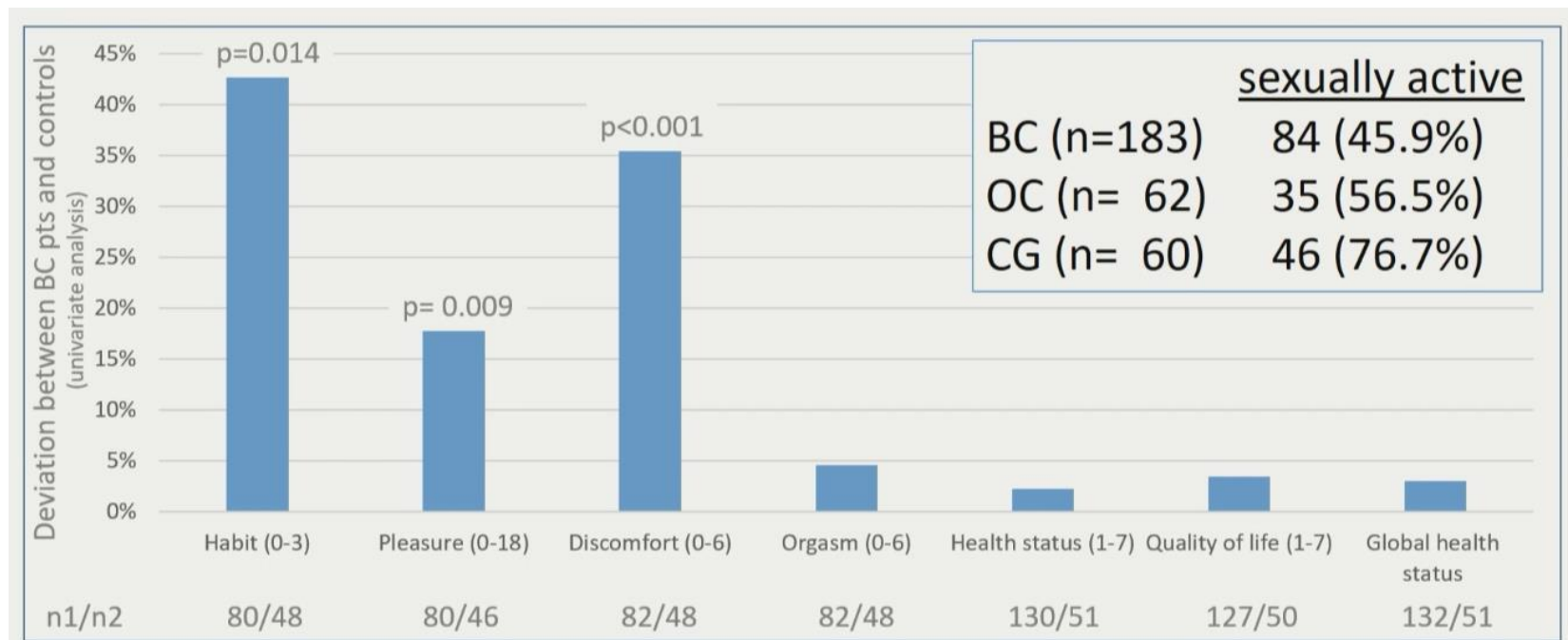
CONCLUSION Associations between survival outcomes and use of antioxidant and other dietary supplements both before and during chemotherapy are consistent with recommendations for caution among patients when considering the use of supplements, other than a multivitamin, during chemotherapy.

J Clin Oncol 37. © 2019 by American Society of Clinical Oncology



Sexual health

Sexual function (SF) and quality of life in patients after treatment for breast (BC) and ovarian cancer (OC)



Patients who received antihormonal therapy at the time of evaluation showed a lower frequency of sexual activity, less satisfaction and more discomfort during sex.

Improving sexual health

▶ Habit

▶ Pleasure

- Partnership
- Experiences (before BC)
- Significance of sex
- Conception of sexual health



Counseling

▶ Discomfort

Vaginal dryness, discharge, discomfort, pain



Drug therapy
(after gynaecol examination)

- ▶ No estrogen → atrophy of the vagina

- ▶ Local treatment of estrogen deprivation
 - Non-hormonal
 - Hormonal

Non-hormonal options for dyspareunia

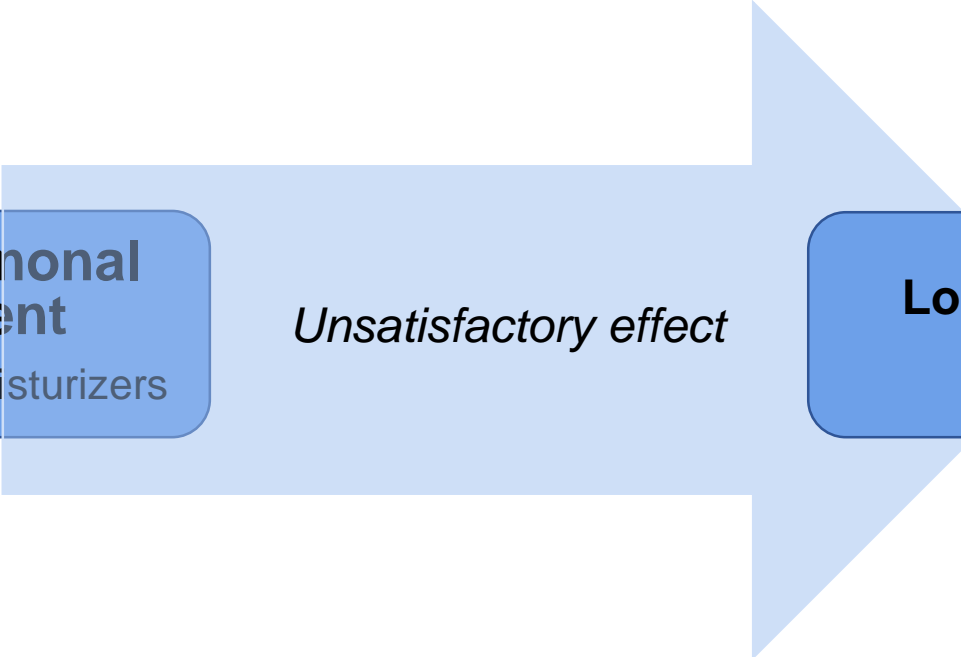
- ▶ Lubricants
- ▶ Moisturizers



Hormonal options for dyspareunia

- ▶ Effect of local HRT on breast cancer recurrence and survival: no increase in risk of recurrence or mortality
- ▶ Local HRT can lead to an increase in the levels of circulating hormones, but the clinical relevance of these augmentations and their effect on recurrence and survival are not clear
- ▶ Increased levels of circulating estradiol are detected only in a minority of patients, mainly in the beginning of treatment
- ▶ Not concomittant with AI? Because the aim of AI is to maximally reduce the serum estrogen level
- ▶ Local HRT clearly improves vaginal atrophy, sexual interest and dysfunction

▶ **Non-hormonal treatment**
▶ Lubricants, moisturizers



Unsatisfactory effect

Local hormonal treatment

Conclusion

- ▶ Hormonal treatment: common and long-term
- ▶ Non adherence is frequent and impacts outcome
- ▶ Toxicity is the most common reason for non-adherence
- ▶ Interventions to reduce symptoms have the potential to improve adherence and breast cancer outcomes



