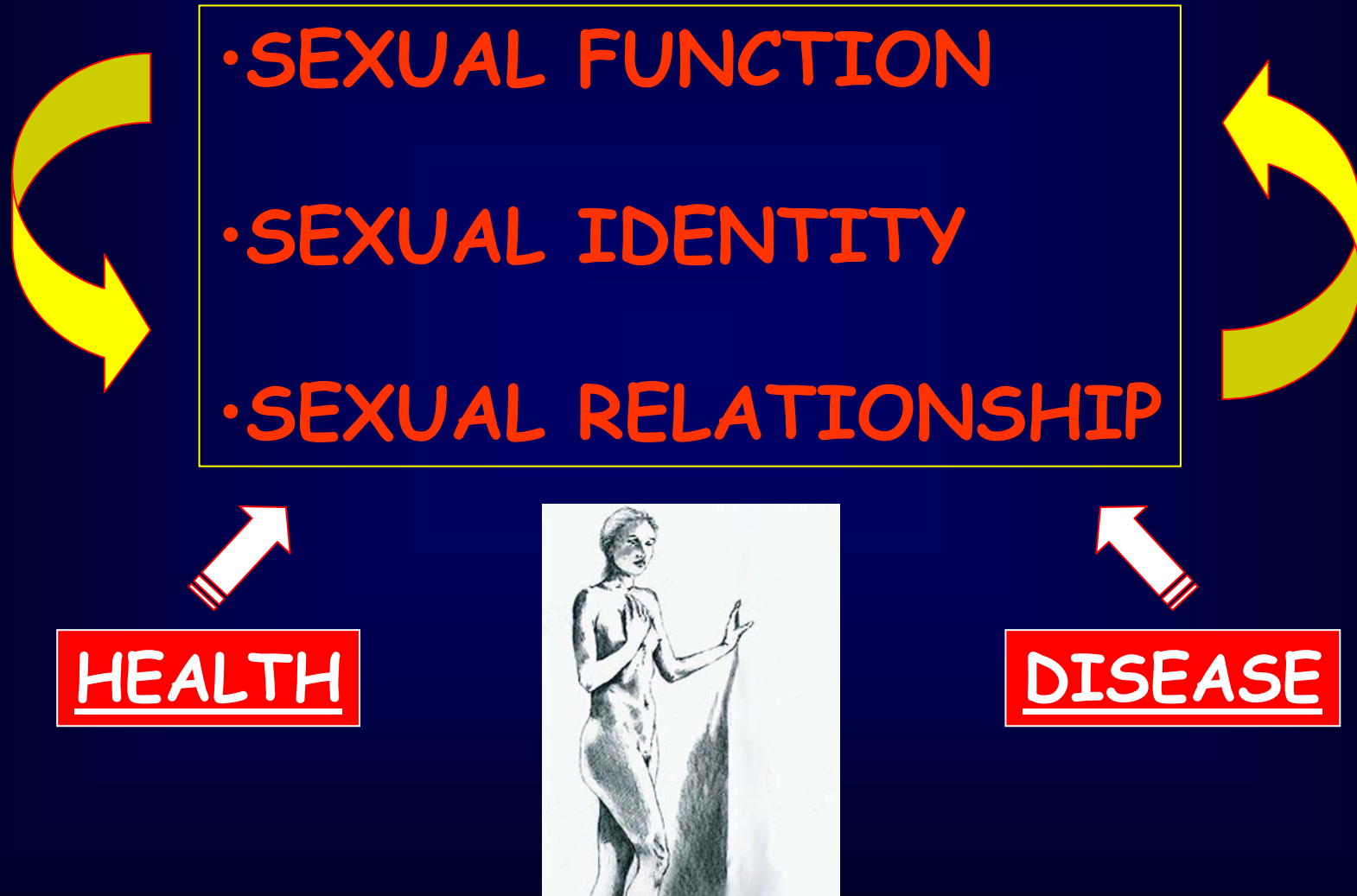


Hormone replacement therapy for pre-menopausal women with breast and gynecological cancer: impact on mood and sexual desire.

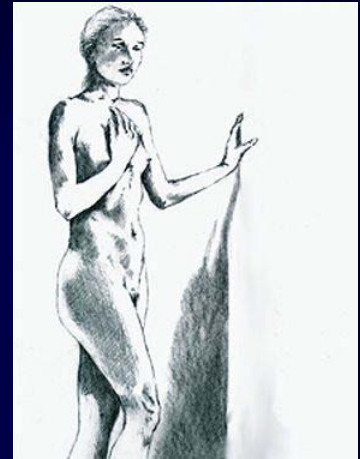
Rosella Nappi
University Padova
Johannes Bitzer
University Basel

WOMEN'S SEXUALITY



IMPACT OF DISEASES ON SEXUAL WELL-BEING

- PRIMARY
Diagnosis (acute/chronic)
- SECONDARY
(side-effects, surgery, drugs...)
- TERTIARY
(self-image, self-esteem, depression,
social and relationship issue...)
- PERSONAL HISTORY
(education, experiences, partner...)



BREAST CANCER IN YOUNG WOMEN

Table I Incidence of breast cancer by age

Age	Annual incidence/100 000 women
<20	0.1
20–24	1.4
25–29	8.1
30–34	24.8
35–39	58.4
40–44	116.1
45–49	198.5

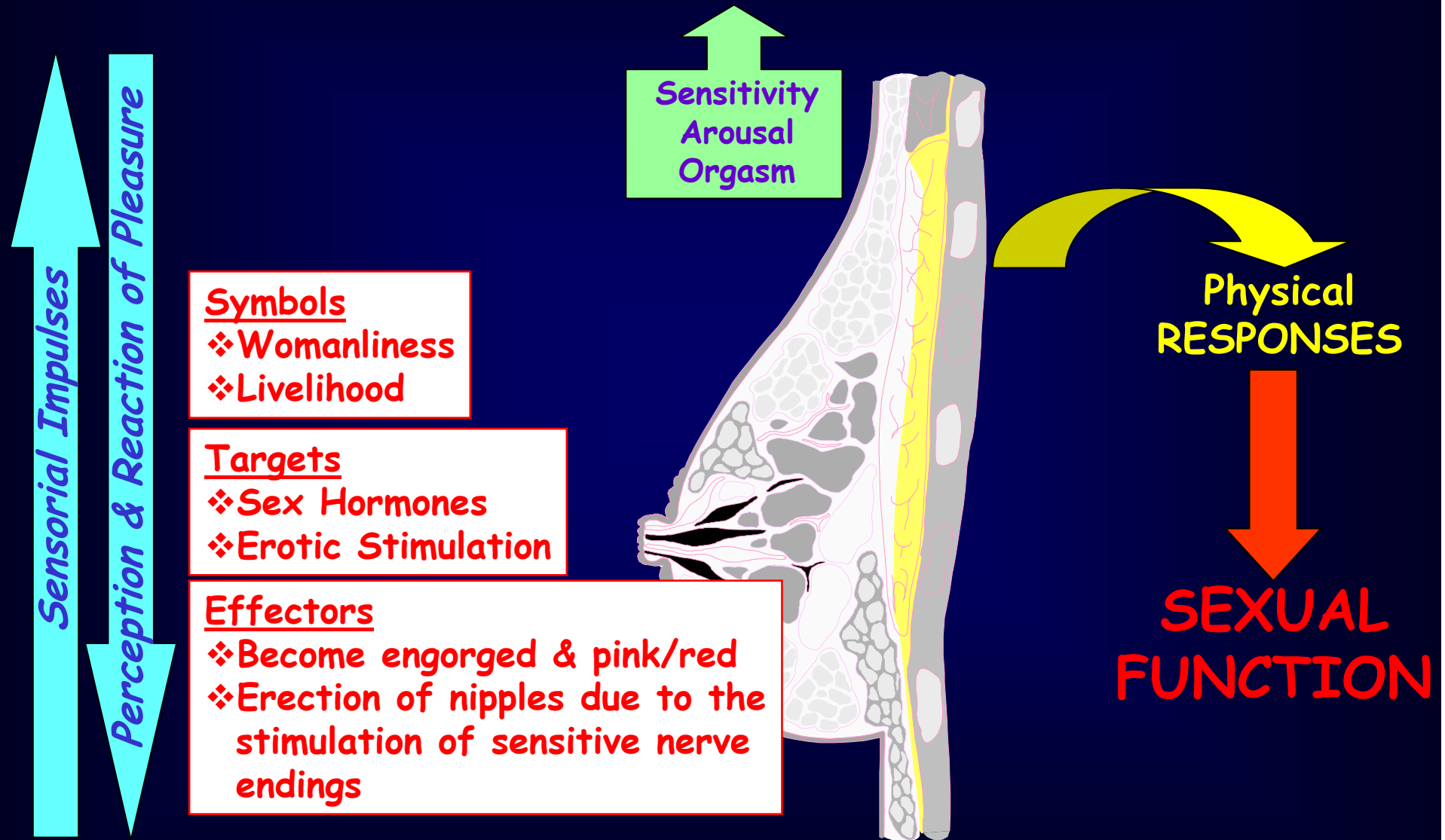
91.3

Reproduced from *Future Oncol* 2007;3(5):569–574 with permission of Future Medicine Ltd. and the authors Pagani and Goldhirsch (2006).

- *2.7% of BC between 25–35 yrs (Axelrod et al, 2008)*

KEY SEXUAL ORGANS IN WOMEN:

3) THE BREASTS



KEY SEXUAL ORGANS IN WOMEN:

2) THE GENITALS

Vulva

- ❖ Sensitive to touch & pressure
- ❖ Rich of small vessels & sensory nerve endings

Clitoris

- ❖ Erectile organ highly vascularized & innervated
- ❖ Comprises glans, body & crura & consists of 2 paired corpora cavernosa with vestibular bulbs surrounding the urethra
- ❖ Is devoted to pleasure

Vagina

- ❖ Interface of the coitus
- ❖ Produces neurogenic transudate to guarantee lubrication
- ❖ In the anterior fornix is located the controversial G-spot (glandular & vascular tissues)

Arousal
Engorgement
Lubrication

Physical
RESPONSES

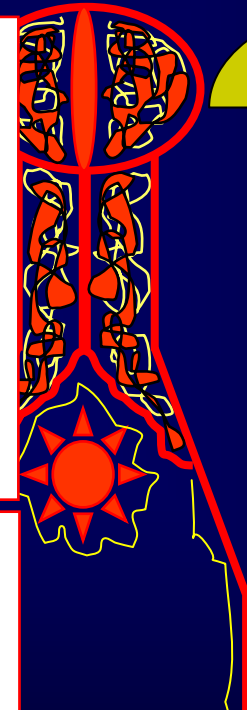
SEXUAL
FUNCTION

Uterus

- ❖ Changes position during coitus
- ❖ Contracts during orgasm

RE Nappi, 2003

Sensorial Impulses
Perception & Reaction of Pleasure



NERVE SPARING SURGICAL TECHNIQUES FOR GYNECOLOGICAL MALIGNANCIES

- Autonomous pelvic nerves are essential for bladder and rectum function as well as **sexuality**.
- These nerves are usually permanently damaged during radical oncological surgery and this results in urological, **sexual** and proctological morbidity.
- Japanese surgeons have paved the way for surgical approaches to dissect these nerves during surgery and **leave them intact**.
- Significant progress has been made in understanding the **neuroanatomy** and the neurophysiology of autonomic pelvic plexus.
- There is **not yet a consensus** concerning to which part of uterine support ligaments a NS approach should be directed.

The female inferior hypogastric (= pelvic) plexus: anatomical and radiological description of the plexus and its afferences-applications to pelvic surgery

- ❖ Useful landmarks for a safe surgical approach during pelvic surgery;
- ❖ The new concept of NSRH has to be considered in order to reduce morbidity without compromising the oncological disease control.

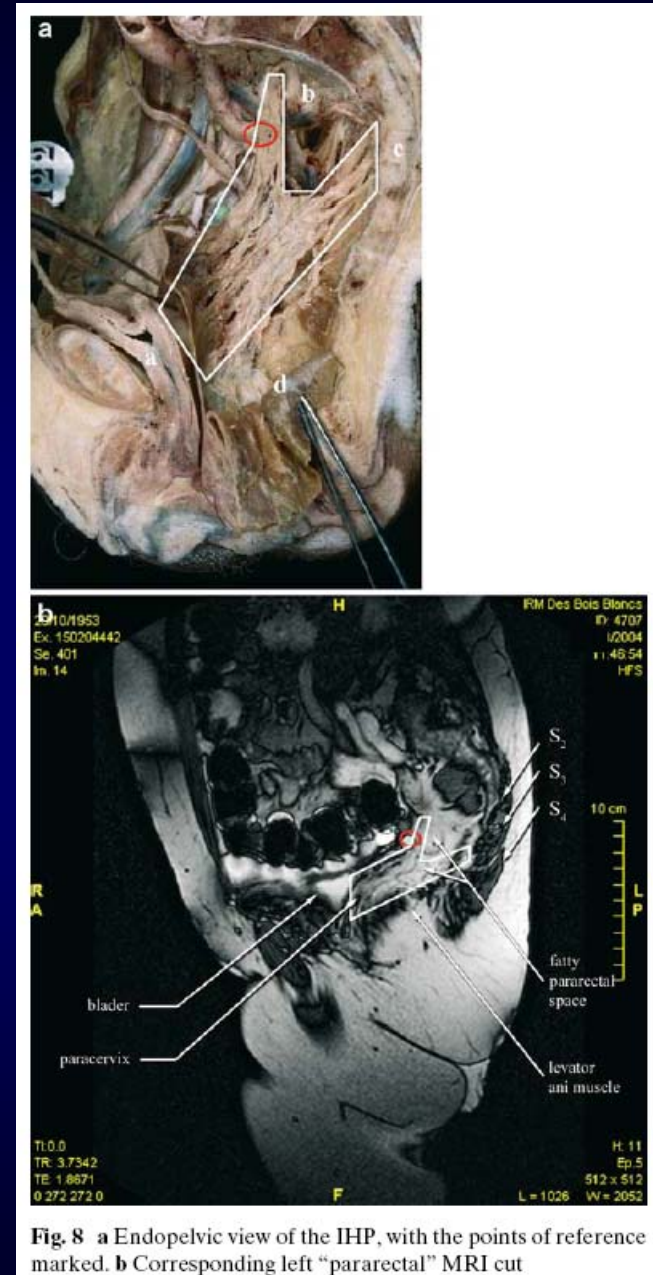


Fig. 8 a Endopelvic view of the IHP, with the points of reference marked. b Corresponding left "pararectal" MRI cut

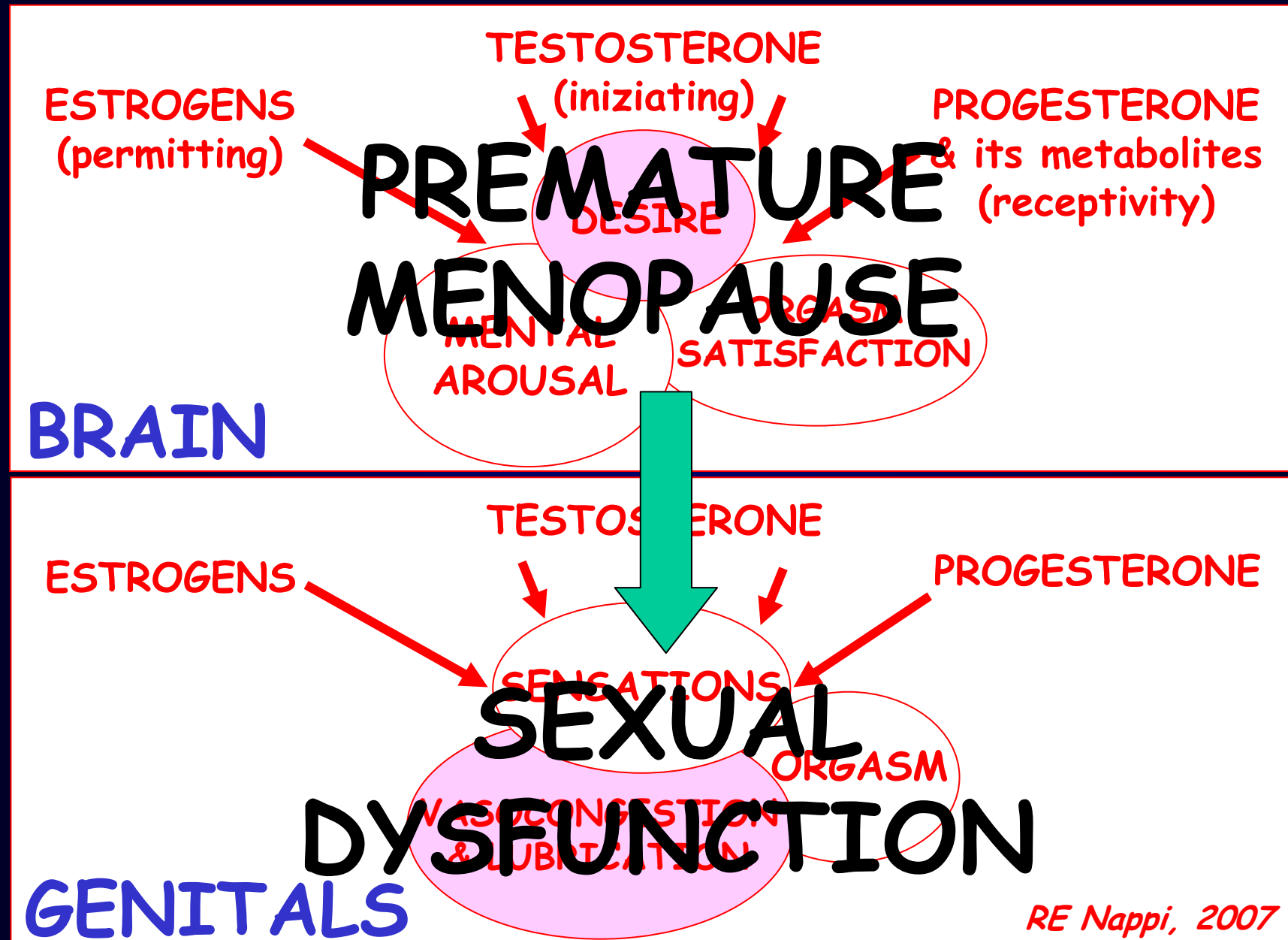
PREMATURE MENOPAUSE

- Spontaneous ovarian failure affects, on average, 1% of women younger than 40 years
- Iatrogenic menopause for benign and malignant conditions affects 3.4-4.5%
- Abrupt sex-steroid withdrawal in surgical menopause vs variable lag time between medical treatments and onset of premature menopause
- Approximately 25% of breast cancer patients are premenopausal at diagnosis
- In premenopausal women chemotherapy combined with endocrine treatments causes premature menopause in over 80% of patients during the 1^o year after diagnosis.

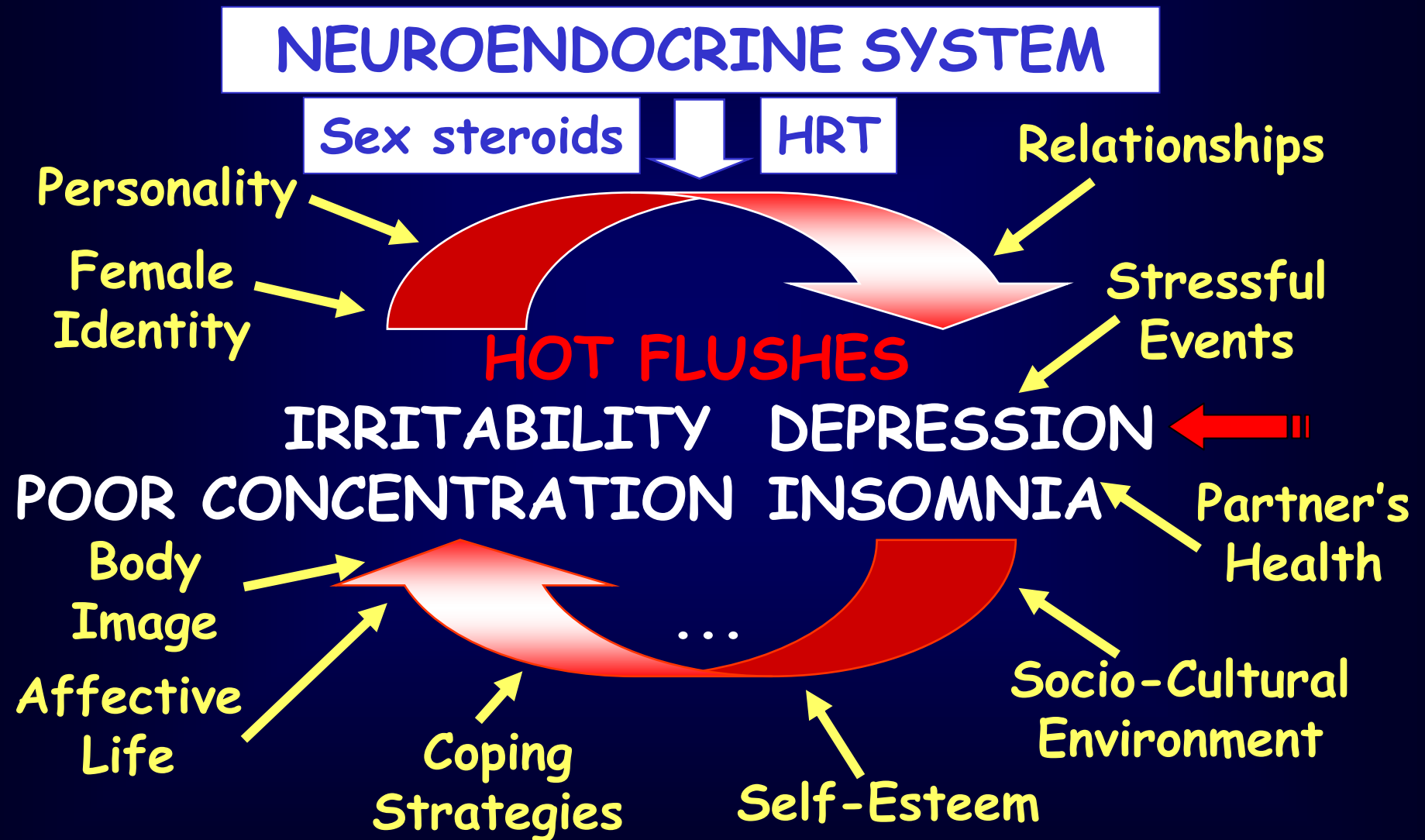
IATROGENIC PREMATURE MENOPAUSE IN MALIGNANCIES

- Type of Cancer
- Stage
- Prognosis
- Age at Diagnosis
- Surgical Approach
- Conservative vs Radical Treatment
- Adjuvant Chemotherapy and/or Radiotherapy
- Associated Side-Effects
- Severity of Recurrence

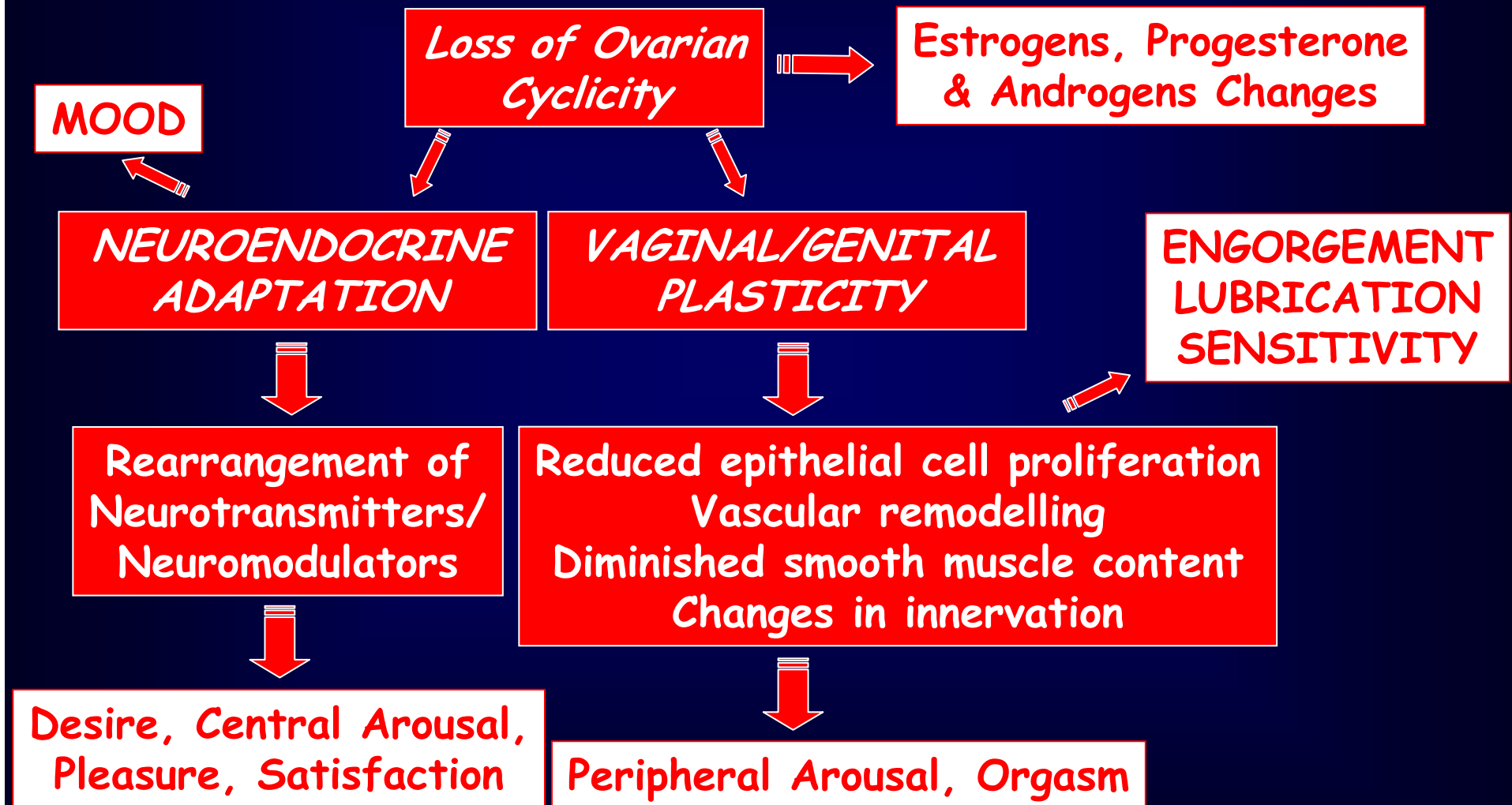
SEX HORMONES & SEXUAL FUNCTION



"DOMINO" EFFECT OF MENOPAUSAL SYNDROME



SEX HORMONES-DEPENDENT SEXUAL CIRCUITRIES AT MENOPAUSE



MENOPAUSE AFTER BREAST CANCER: A SURVEY ON BCS

- A questionnaire-based survey on 250 breast cancer patients (144 in postmenopause and 106 in premenopause at time of diagnosis) to determine the prevalence of menopausal symptoms and attitudes towards HRT and other treatments.
- Adjuvant therapy with **tamoxifen or tamoxifen plus chemotherapy** is associated with a significant **worsening** of menopause-related symptoms of postmenopausal women.
- The incidence of vasomotor and dystrophic symptoms is significantly **higher in premenopausal women treated with chemotherapy and/or hormonotherapy as compared with postmenopausal women** ($P < 0.000$ and $P = 0.02$, respectively).
- **Premenopausal women** are more concerned about risk of breast cancer recurrence than older women and at the same time **are significantly more worried about the impairment of the quality of life** due to adjuvant therapy ($P = 0.005$). Younger women are more prone to consider HRT than postmenopausal women ($P = 0.05$).

ASSOCIATION OF BREAST CANCER & ITS THERAPY WITH MENOPAUSAL SYMPTOMS

- Data from the Cancer and Menopause Study (CAMS), a tumor-registry-based cohort of breast cancer survivors (BCS) diagnosed before age 50.
- Mean age of the participants was 50 years. The prevalence of symptoms was **high**.
- Hot flashes occurred in
17% PREMENOPAUSAL
51% PERIMENOPAUSAL
71% POSTMENOPAUSAL
- Hot flashes, **vaginal dryness**, and **pain with intercourse** were more severe in postmenopausal compared with perimenopausal BCS. **Having had a transition during breast cancer treatment was associated with worse hot flash severity, independent of current menopause status.**

HRT: AN EVOLVING CONCEPT FOR THE INDIVIDUALIZED CARE

STANDARD

OTHER TREATMENTS:
Tibolone, Androgens,
SERMs, local therapies...

LOW

ULTRA-LOW

New trends in HRT favor the lowest effective doses for symptoms relief and bone loss prevention in healthy recently menopausal women.

SYSTEMIC DOSE

HRT IN WOMEN WITH AN HISTORY OF BREAST CANCER

- The HABITS trial was one of several trials begun in the 1990s to evaluate the potential risk of recurrent breast cancer in women using HRT. Although it was designed to enroll at least 1300 women and to follow them for 5 years, **it was stopped** on Dec 17, 2003, after a median follow-up of slightly longer than two years.
- Recurrent or de novo breast cancer had developed in
26 women in the **HRT** group
7 women in the **no-HRT** group.

The HABITS trial was terminated because women with a history of breast cancer allocated to receive HRT for menopausal symptoms

- experienced **an unacceptably high risk of breast cancer** compared with breast-cancer survivors allocated to best symptomatic treatment without hormones.

HRT AFTER ENDOMETRIAL CANCER

- HRT after endometrial cancer (EMC) treatment is an uncertain subject with limited exploration among gynecologic cancer research. Because estrogen is a well-recognized etiologic factor of EMC, most physicians are probably reluctant to provide a replacement therapy, or limit its use to only a selected group of patients.
- HRT did not appear to increase the recurrence or death rates in EMC. However, most information came from retrospective studies with selection bias, or from a small prospective non-randomized study. The only randomized controlled trial of the Gynecologic Oncology Group could also not provide a definite answer regarding its safety and recommendation.
- In conclusion, on the basis of the currently available studies, HRT after EMC treatment does not appear to have an adverse effect on EMC. Nevertheless, because of a limitation of data, the physician should thoroughly consider all possible benefits and theoretical risks of recurrence or mortality in each individual to provide the best of care for their patients.

Tangjitgamol et al, 2008

HRT AFTER CERVICAL CANCER

- Association between use of HRT and cervical carcinoma has never been proven.

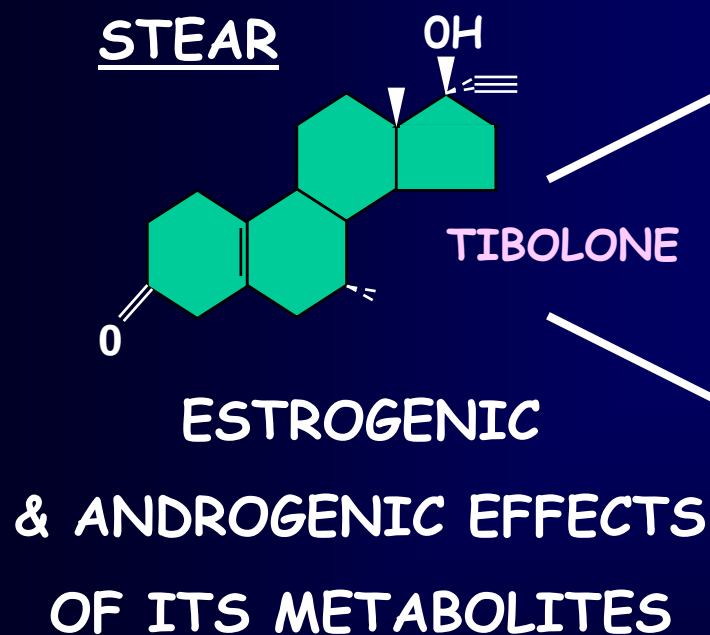
In 120 women treated for stages I-II cervical cancer HRT showed no change either in survival or disease free survival at 5 years [Ploch, 1997].

- In a case-control study, the group of women on HRT showed an overall RR of 2.1 (95% CI, 0.95-4.6) for adenocarcinoma versus 0.85 (95% CI, 0.34-2.1) for squamous cell carcinoma.

The risk was higher in case of estrogens alone: RR for adenocarcinoma 2.7 (95% CI, 1.1-6.8) versus 0.86 (95% CI, 0.26-2.8) for squamous cell carcinoma. With combined treatment the RR for adenocarcinoma was 1.1 (95% CI, 0.26-5.0) [Lacey et al, 2000].

- According to these data, treatment approach should be the same as for endometrial adenocarcinoma.

TIBOLONE & TARGET TISSUES RELEVANT TO MENTAL & SEXUAL WELL-BEING



NEUROENDOCRINE CIRCUITRIES

*(Hot-flushes, Mood,
Libido, Orgasm)*

VAGINAL & CLITORAL TISSUES

*(Sensations, Congestion,
Lubrication)*

TIBOLONE in breast cancer survivors

LIBERATE

(Livial Intervention following Breast cancer: Efficacy, Recurrence And Tolerability Endpoints)

Objective: The primary outcome variable is breast cancer recurrence. Secondary study outcomes include vasomotor symptoms, bone mineral density (BMD), health-related quality of life (HRQL) and overall survival.

Design: a randomized, placebo controlled, double-blind, parallel-group study

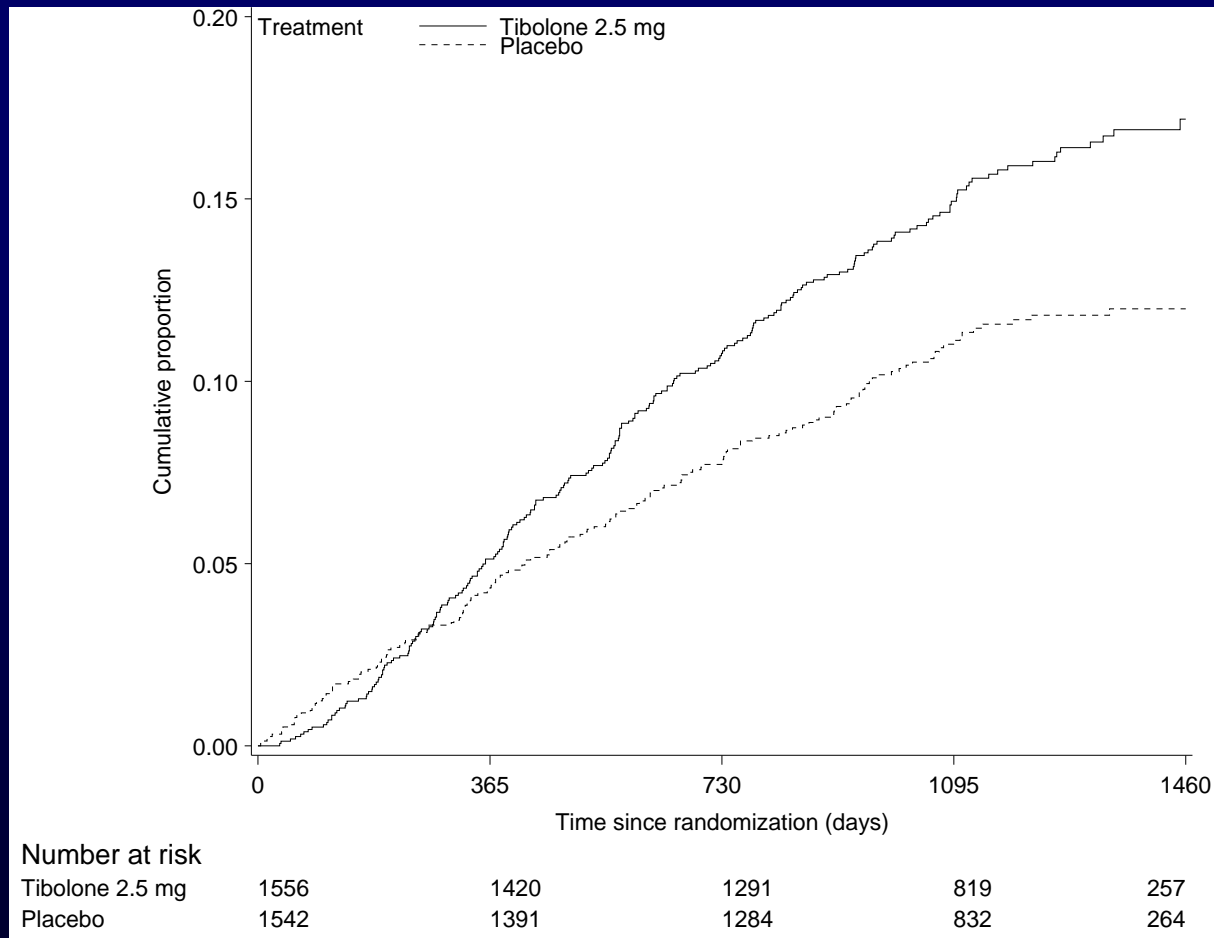
Setting: worldwide, July 2002 - December 2004 (stopped prematurely six months before the planned trial end)

Participants: 3148 women treated for breast cancer with climacteric complaints were randomised at 245 centres in 31 countries.

Results: at a median follow-up of 3.1 years, an increased risk of recurrence with the use of tibolone (HR 1.40 [1.14-1.70]) was demonstrated. The risk for breast cancer recurrence with tibolone was more evident in women with ER-positive tumor status than in women with an ER-negative tumor status.

Breast Cancer Recurrence (ITT)

HR Tibolone to Placebo [95% CI]



237 tibolone

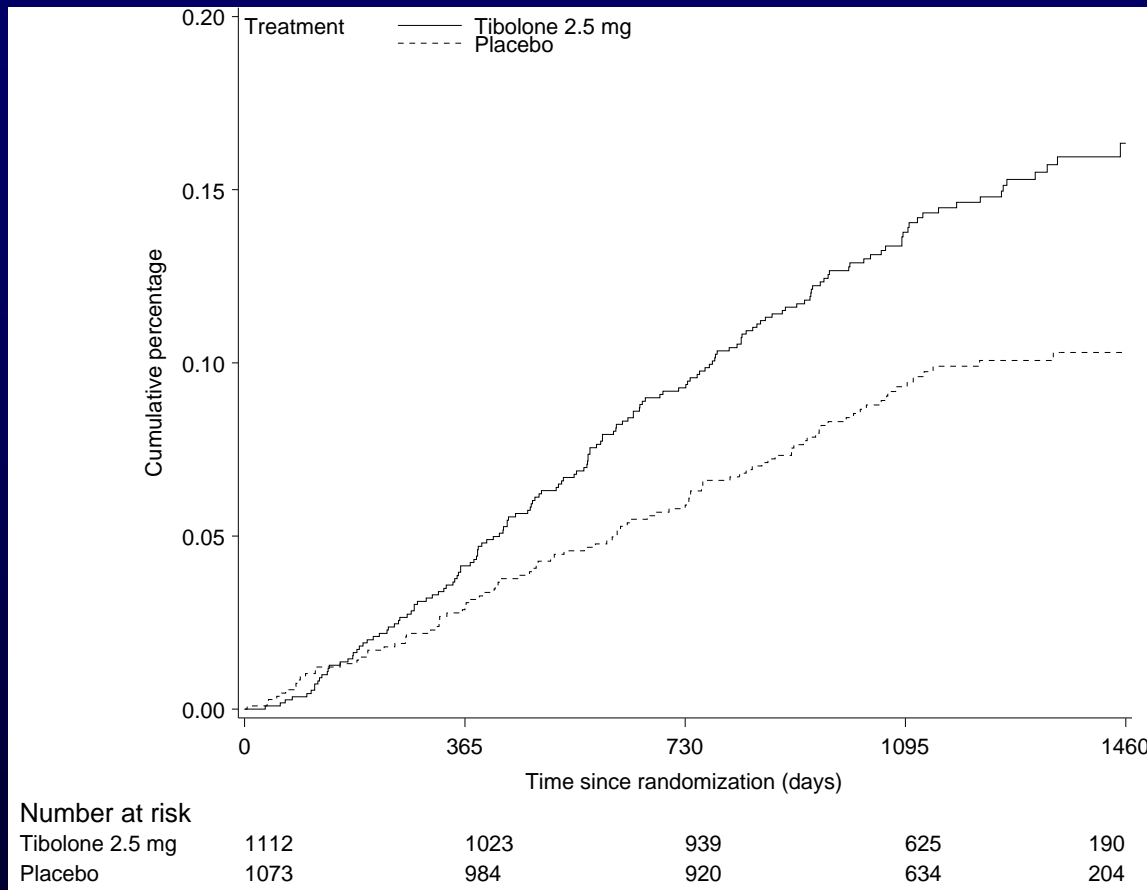
165 placebo

HR=1.40
95% CI: 1.14-1.70

Kenemans et al, 2009

Breast Cancer Recurrence (ITT)

Estrogen Receptor status Positive (n=2185)



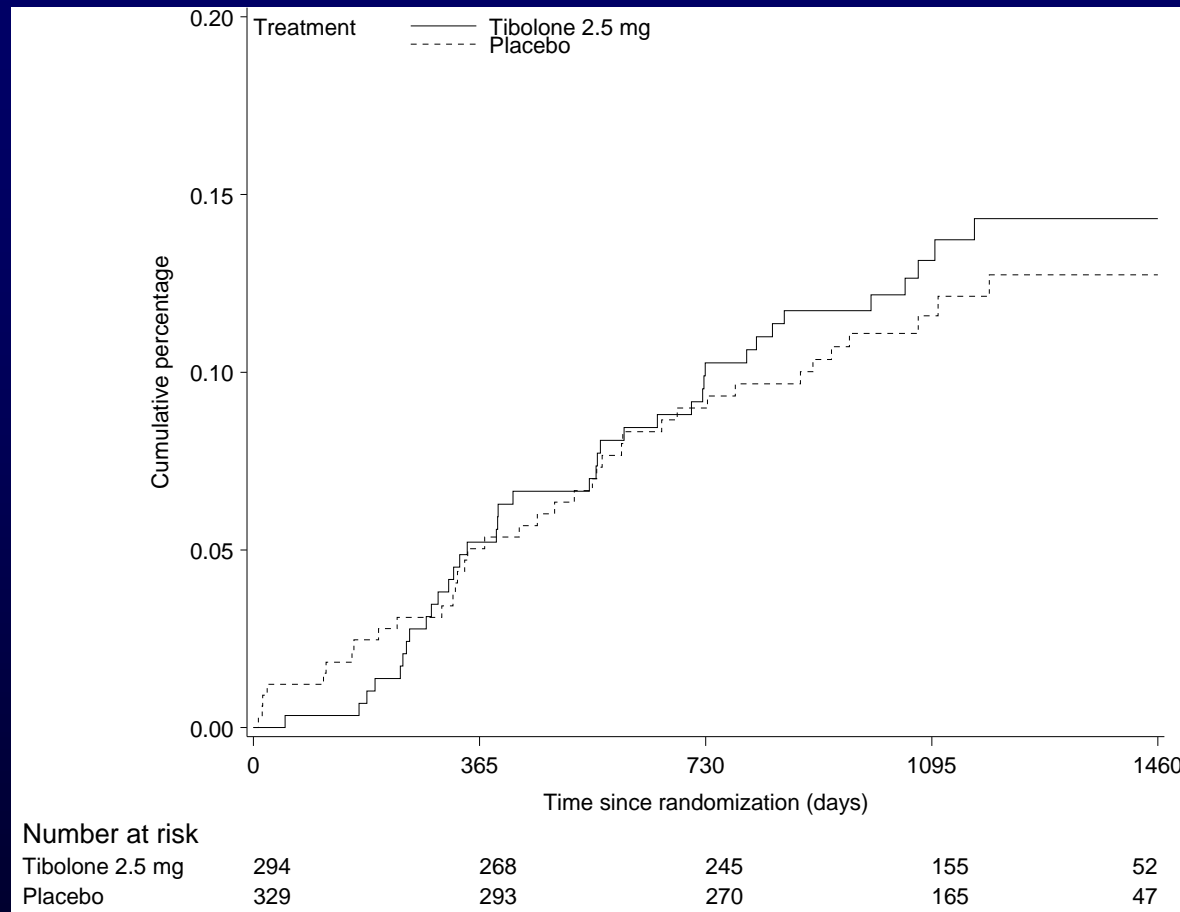
159 tibolone

99 placebo

HR=1.56
95% CI: 1.22-2.01

Breast Cancer Recurrence (ITT)

Estrogen Receptor status Negative (n=623)



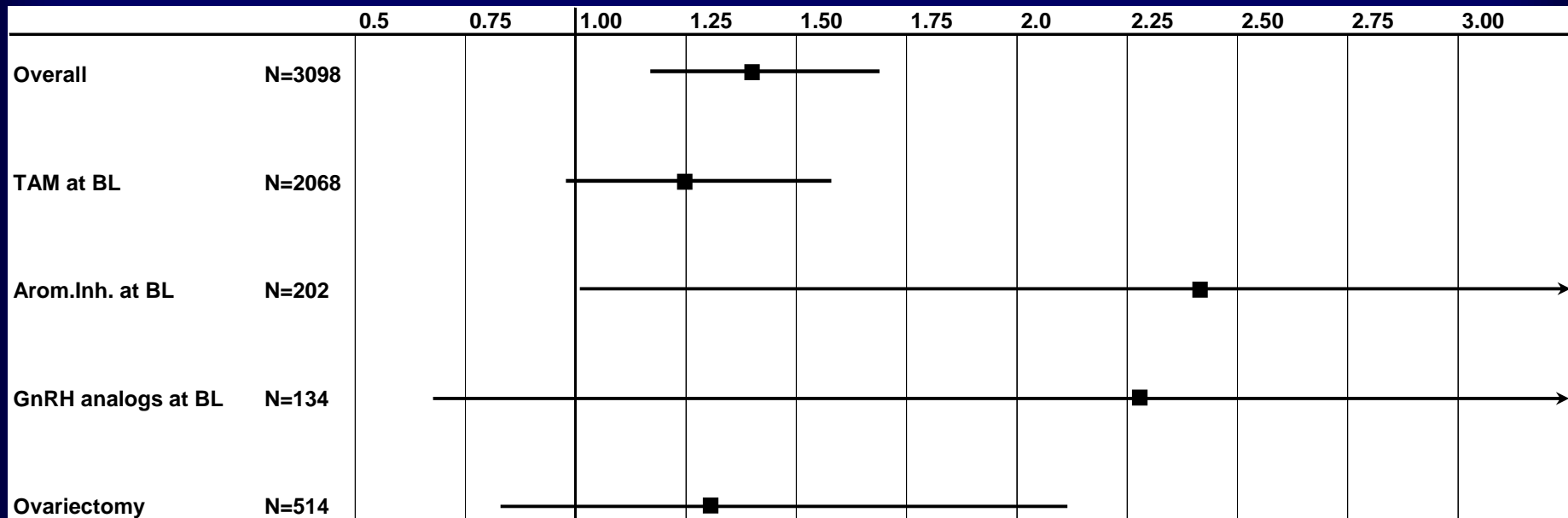
39 tibolone

37 placebo

HR=1.15
95% CI: 0.73-1.80

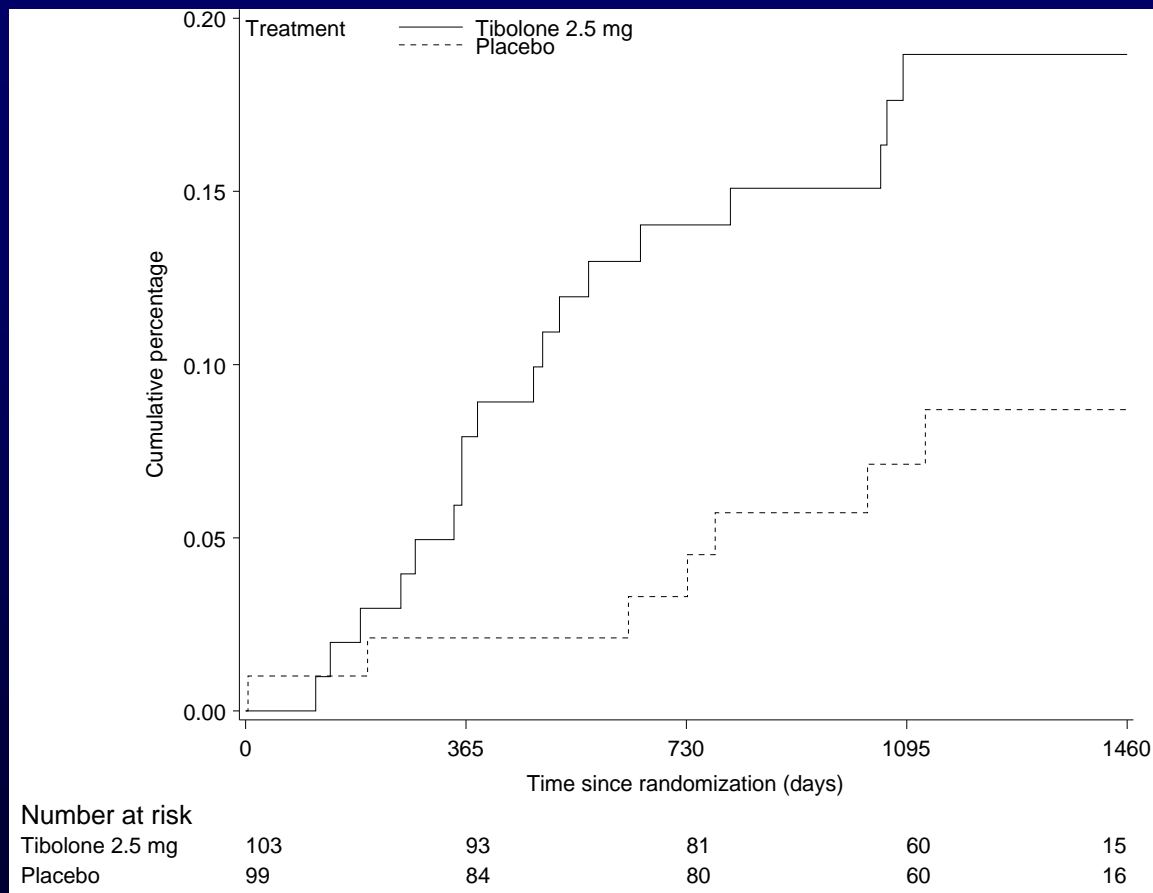
Breast Cancer Recurrence (ITT)

HR and 95% CI by Endocrine Therapy



Breast Cancer Recurrence (ITT)

Aromatase Inhibitor use at Baseline (n=202)



18 tibolone

7 placebo

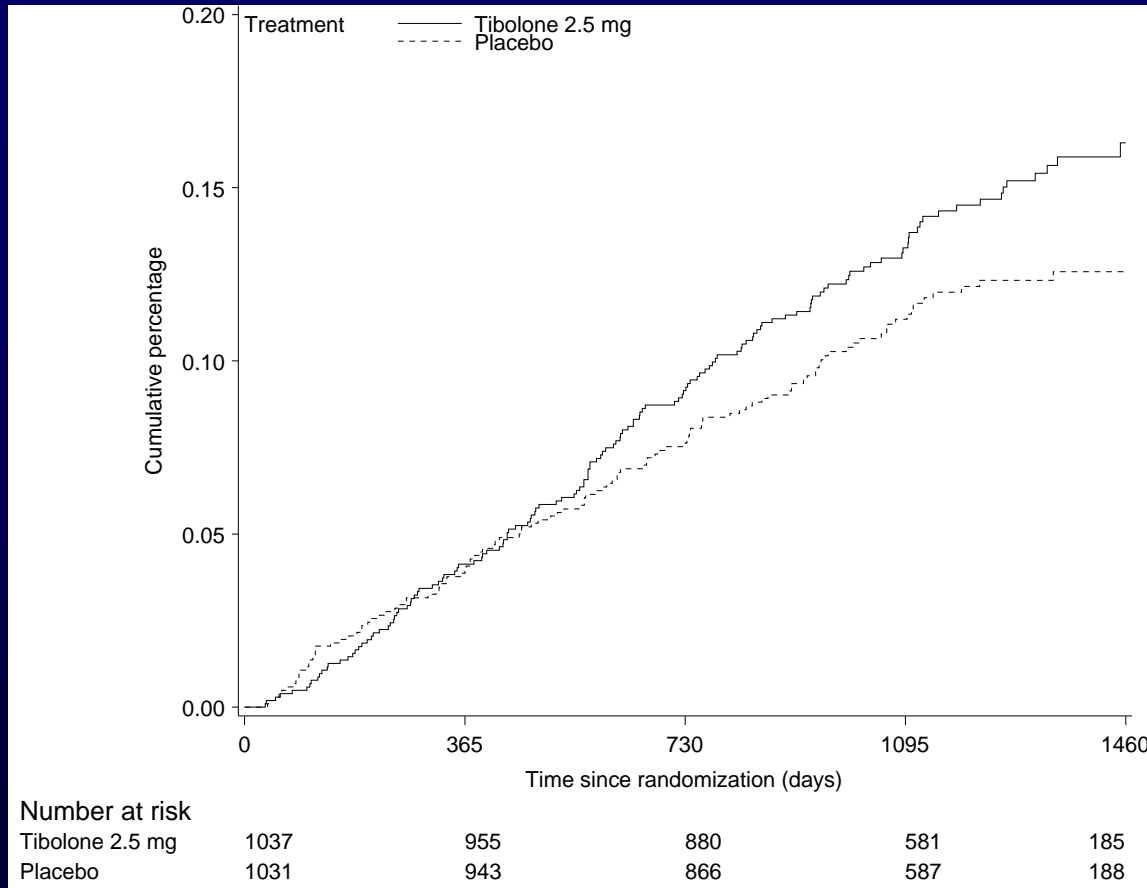
HR=2.42
95% CI: 1.01-5.79

Status at baseline

Kenemans et al, 2009

Breast Cancer Recurrence (ITT)

Tamoxifen use at Baseline (n=2068)



147 tibolone

116 placebo

HR=1.25
95% CI: 0.98-1.59

APHRODITE

(Transdermal Testosterone Patch Only)

Study Design

- Randomized, double-blind, multinational study over 12 months
 - Placebo or 150mg/day or 300mg/day transdermal testosterone patch given twice weekly
- Efficacy assessed through 24 weeks in 4-week frequency
- Hormone levels, adverse events and clinical labs evaluated over 12 months
- 814 postmenopausal women with HSDD were enrolled
 - 771 (95%) participants were included in the 24 week efficacy analysis

TESTOSTERONE IS PROVEN HELPFUL BUT BREAST SAFETY IS STILL LACKING!

RESULTS: At 24 weeks, the increase in the 4-week frequency of satisfying sexual episodes was significantly greater in the group receiving 300 microg of T per day than in the placebo group (an increase of 2.1 episodes vs. 0.7, $P < 0.001$) but not in the group receiving 150 microg/day (1.2 episodes, $P = 0.11$). The rate of androgenic adverse events - primarily unwanted hair growth - was higher in the group receiving 300 microg of T per day than in the placebo group (30.0% vs. 23.1%). Breast cancer was diagnosed in four women who received T (as compared with none who received placebo); one of the four received the diagnosis in the first 4 months of the study period, and one, in retrospect, had symptoms before undergoing randomization.

CONCLUSIONS: In postmenopausal women not receiving estrogen therapy, treatment with a patch delivering 300 microg of testosterone per day resulted in a modest but meaningful improvement in sexual function. The long-term effects of testosterone, including effects on the breast, remain uncertain.

TOPICAL USE OF HORMONAL & NON-HORMONAL PRODUCTS FOR FSD AT MENOPAUSE

- ✓ CEE/Estriol/other weak estrogen cream
- ✓ Estradiol tablets or ring
- ✓ Testosterone Cream
- ✓ Lubricants/Gels

→ *Local treatments improve the genital response but they do not directly affect the motivational aspects of sexual function & behaviour.*

LIVING VERSUS SURVIVING IN WOMEN WITH BREAST CANCER

➡ *Addressing sexual issues early in the disease trajectory may prevent or minimize subsequent negative effects*

INDIVIDUALIZED
COUNSELLING

TAILORED
MANAGEMENT

QUALITY
OF LIFE

