HORMONE THERAPY

A BALANCED VIEW??

Prof Greta Dreyer

-- PART 1 --

Definitions

- HRT hormone replacement therapy
- HT genome therapy
- ERT estrogen replacement therapy
- ET estrogen
- EPT estrogen progesterone therapy

Logical indications for HRT

- Perimenopausal symptoms:
  - Flashes
  - Dryness
  - Sleeping or mood disorders

- Osteoporosis
- QOL
- Depression

Decision to treat

- Certainty of diagnosis:
  - Clinical = good enough
  - FSH>30

- Severity of symptoms = indication
- No Contra-indications

- Idea of pro's and con's
- Idea of planned duration
- Holistic approach, preventative medicine

Holistic approach to the menopausal woman

- Modify lifestyle:
  - Exercise
  - Smoking
  - Alcohol
  - Obesity
  - Diet
  - Stress

Holistic approach

- Alternative medications proven to impact:
  - HT treatment
  - ACE I
  - LDA
  - Statins
  - Bisphosphonates
  - Calcium

WHI: HRT in 2003: JAMA 2002; 288:321-333

- About: The risks & benefits of:
  - Estrogen plus progestin in
  - Healthy postmenopausal women

- 16608 women with uterus
- Used for 5,2 yrs
- Age 50-79
- CEE 0,625mg & MPA 2,5mg vs placebo

- Stopped early: Risks > Benefits

WHI: HRT in 2003: JAMA 2002; 288:321-333

- Other leg:
  - 11739 on estr alone
  - Without uteri
  - Ends 3/2005
  - Health benefits outweights risks??
  - CEE 0,625mg vs placebo
  - Ongoing

WHI: HRT in 2003: JAMA 2002; 288:321-333

- Outcome measures per 10000 women yrs:
  - Cancer:
    - Breast
    - Colon
    - Other
- Stroke: RR1,4 = 40% incr risk (21 vs 29)
- Other TE events
- Coronary heart diseases
- Fracture and osteoporosis

Atherosclerosis issue

- Atherosclerosis Studies:
  - Progression equal
  - On angiography

- Estrogen alone:
  - Without statins
  - Slows progression

Clinical outcome measures - influences on CVD - WHI, HERS:

- HERS study:
  - Secondary prevention of CHD
  - 2763 used for 4,1 yrs
  - CEE & MPA
  - Failed to show benefit
  - Increased events in first (2) year
  - CVS and stroke

Clinical guidelines after WHI - study:

- Re-evaluation - long term use:
  - Continued benefit vs automatic renewal of script?
  - Increased risk with long term use:
    - Clotting tendency
    - Breast cancer
    - CHD

Clinical guidelines after WHI - study:

- Re-evaluation - long term use:
  - Options to consider:
    - Stop
    - Lower dosages
    - Alternative medications
    - Continue use - active decision

Important remaining issues:

- Estrogen only - better??
- Different regimens and routes
- Lower doses for reduced side effects
- Unopposed vs apposed
- Tibolone
- SERMs

-- PART 2 --

- This part of the lecture is additional information

ESTROGEN therapy PRO's and CON's

- **Prevention of skeletal complications**
  - **Fractures**
  - **Pain**
  - **Shortening**
  - Prevention vs
  - Treatment
  - Cost effective!

ESTROGEN therapy PRO's and CON's

- **Non-skeletal benefits**
  - **Climacterium**
  - Dementia
  - Carbohydrate metabolism
  - Lipid profile
  - Decrease in some cancers
  - Vascular status

ESTROGEN therapy PRO's and CON's

- **Thrombo-embolic disease**
  - increased risk RR 3.6
  - Trans-dermal?
  - Dose dependant
  - AGE dependant

ESTROGEN therapy PRO's and CON's

- Heart and blood vessels
  - Menopause is major risk factor for disease
  - Difficult to evaluate evidence
  - Interaction with existing risk factors
  - Age and type of HT differs widely
  - Clotting risk on existing vascular disease in elderly women major problem!
  - Possible prevention in younger women not sufficiently proven

PROGESTOGEN therapy PRO's and CON's

- **Coloncancer prevention**
- **Endometrial cancer prevention**
- Increased effect on bone
- Decreased effect on lipids and CVS
- **Breast cancer**
  - Risk increased with ~ 2% of the existing risk pa use after 5 years of use
  - Risk disappears after cessation of use

PROGESTOGEN-HORMONES

Classification

- A group of substances that are able to create a secretory pattern of estrogen primed endometrium
- According to derivation from parent compound.
- Natural progestins and various synthetic progestins

Classification

Parent compound	*Progestin*
Progesterone	Micronised progesterone
Retroprogesterone	Dydrogesterone
17α-Hydroxyprogest (pregnanes)	MPA, Megestrol acetate
17α-Hydroxyprogest (norpregnanes)	Nomegestrol acetate
19-Norprogesterone derivatives	Trimegestone
19-Nortestosterone derivatives	Norethisterone, LNG
Spirinolactone derivatives	Drospirenone

Pharmacological Profiles of Progestogens

	Progestogenic activity	Androgenic activity	Anti-androgenic activity	Anti-aldosterone activity	Gluco-corticoid activity
Progesterone	+	–	(+)	+	–
Drospirenone	+	–	+	+	–
Cyproterone	+	–	+	–	(+)
Levonorgestrel	+	(+)	–	–	–
Medroxyprogesterone	+	(+)	–	–	(+)
Norethisterone	+	(+)	–	–	–
Tibolone	+	+	–	–	–
Norgestimate	+	(+)	–	–	–
Dydrogesterone	+	–	–	–	–

Symbols: + relevant activity, (+) activity not clinically relevant, - no activity

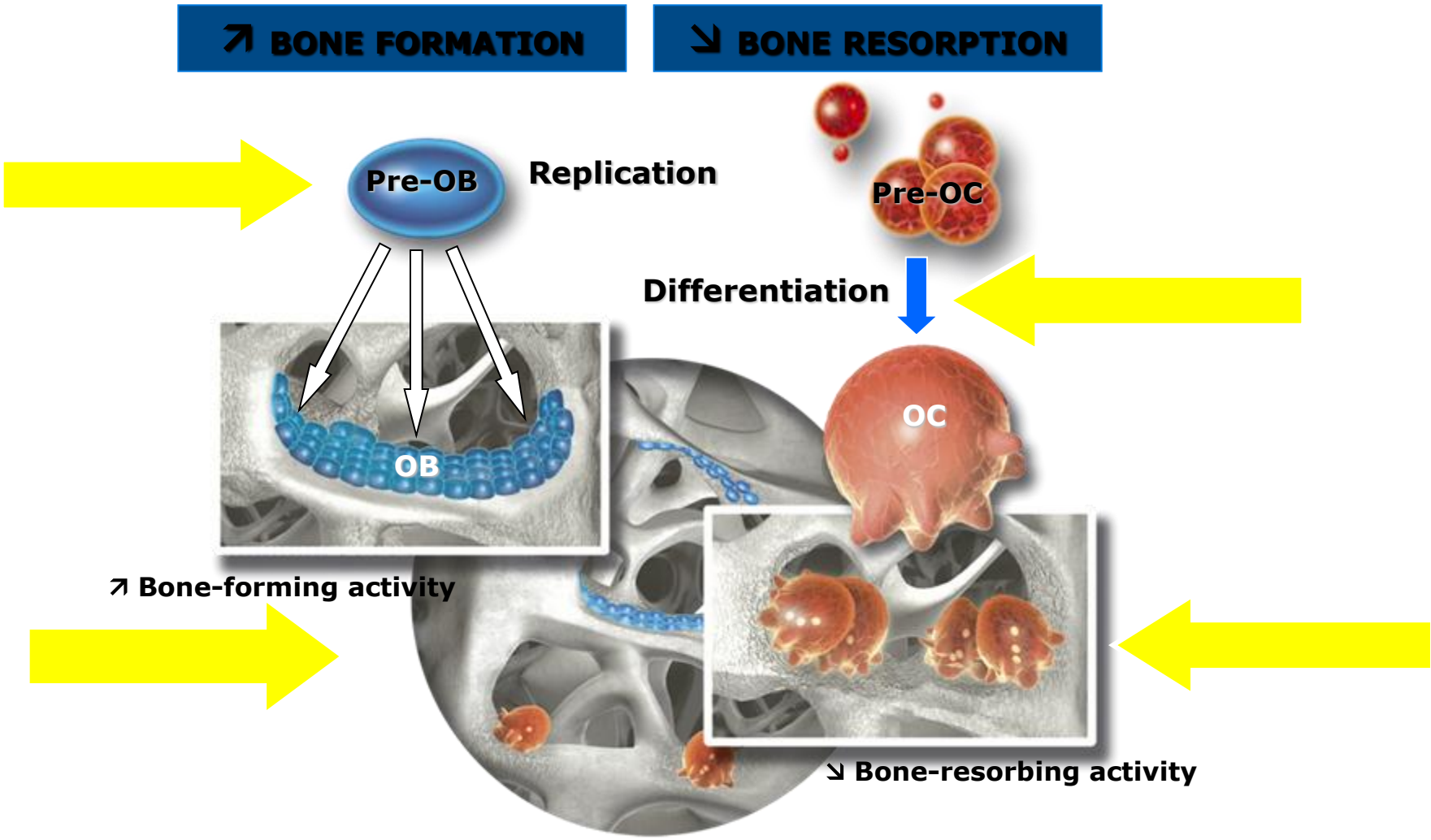
HORMONES and BONE

BONE PHYSIOLOGY

Estrogen:

- **Stimulatory effect on osteoblasts**
- **Positive effect on collagen**
- **Prevents bone resorption**
- **Significantly reduces bone turnover**
  - **inhibition of bone remodelling or architectural change**
  - **inhibits differentiation of osteoclasts**

Modes of action anti-osteoporosis interventions



Modified from Marie PJ et al. *Calcif Tissue Int.* 2001;69:121-129.

Published data on range of anti-fracture efficacy of bone agents

			Alendronate	Risedronate	Raloxifene	Estrogen	Strontium ranelate
Osteopenia			NS	NS	✓	✓	✓
Osteoporosis	Vertebral Fx		✓	✓	✓	✓	✓
	Peripheral Fx[#]		NS	✓	NS	✓	✓
	Hip Fx		✓	✓	NS	✓	✓
	≥ 80 years	Vertebral Fx	---	✓	---	---	✓
		Peripheral Fx	---	NS	---	---	✓

[#] Intention to Treat Population (ITT)

✓ Significant fx reduction vs placebo

NS Non-significant fx reduction vs placebo

— No data

Estrogen and the prevention of osteoporosis

- Most effective in first few years after the menopause
- Estrogen therapy that begins after age 60 and continues appears to offer a nearly equivalent bone-conserving benefit and might indeed be more cost-effective

Estrogen and the prevention of osteoporosis

- Many years of estrogen therapy are needed
- Worthwhile reduction in the fracture risk.
- After seven to ten years of use, reduction in fractures of the spine, hip and wrist more than 50%
- catch-up bone loss occurs after estrogen is discontinued

Estrogen and the prevention of osteoporosis

- HRT uptake and continuation is increased after demonstration of osteoporotic risk
- BMD is better maintained when estrogen replacement is combined with an adequate intake of calcium
- lower doses of oestrogen in combination with adequate calcium has adequate effect

Estrogen and the treatment of osteoporosis

- Estrogen therapy increases or preserves bone density in all areas of the skeleton
- Long-term use of estrogen replacement reduces the risk of hip fractures by 50-60% and the risk of vertebral fractures by 90%
- delayed estrogen replacement is unquestionably effective when continued for around 10 years or more

Estrogen and the treatment of osteoporosis

- Efficacy well estblished
- Relatively low acquisition cost
- Non-skeletal benefits
- HRT considered one of the first-line pharmacologic therapies for the treatment of established osteoporosis in post-menopausal women.

Estrogen and the treatment of osteoporosis

- Can effectively be combined with other anti-resorptive agents
  - Bisphosphonates
  - calcitonin for an additive therapeutic effect on
    - BMD
    - fractures and height loss
- When used as therapy for established osteoporosis, therapy should often continue indefinitely.

OTHER SEX HORMONES AND ANALOGUES

- **Progestogens**
  - **Responsible for increase in breast cancer risk**
  - **lowest effective dose**
  - **women with a uterus only**
  - **Negative cardiovascular effects**
  - **No important effect on bone**

OTHER SEX HORMONES AND ANALOGUES

- **Phyto-estrogens**
  - **Not currently recommended**

- **Androgens and anabolic steroids**
  - **increase bone density**
  - **negative effects on serum lipids, cardiovascular morbidity, liver function and hirsutism**
  - **frail, elderly patients**
  - **advanced osteoporosis**
  - **management of acute vertebral fractures.**

OTHER SEX HORMONES AND ANALOGUES

Tibolone

- prevent postmenopausal bone loss
- neutral on the endometrium and breast
- effective control of menopausal symptoms
- fracture data not available

SERMs

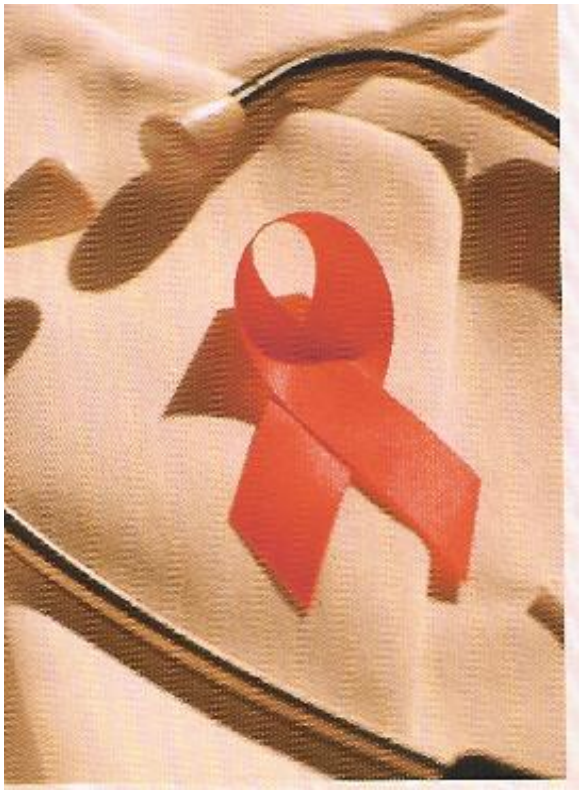
- prevent postmenopausal
- reduce the incidence of vertebral fractures
- risk of venous thromboembolism
- lower incidence of breast cancer
- climacteric symptoms

Risks and concerns of estrogen replacement therapy

- **Breast cancer**
  - Risk increased by approximately two percent per year of use after 5 years
  - Risk only increased when adding progestin
- **Thrombo-embolic disease**
  - increased 3.6 fold
- Cardiovascular system
  - Cardiac morbidity
  - stroke

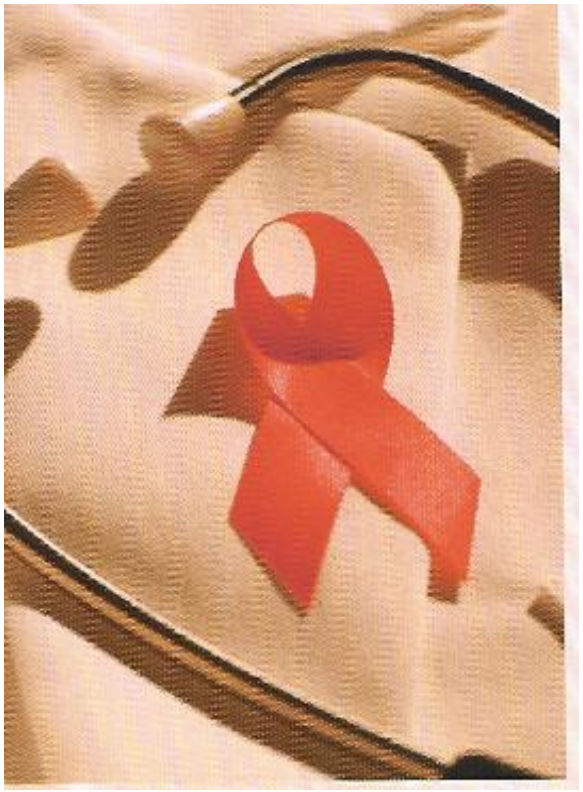
HORMONES and the BREAST

BREAST CANCER:



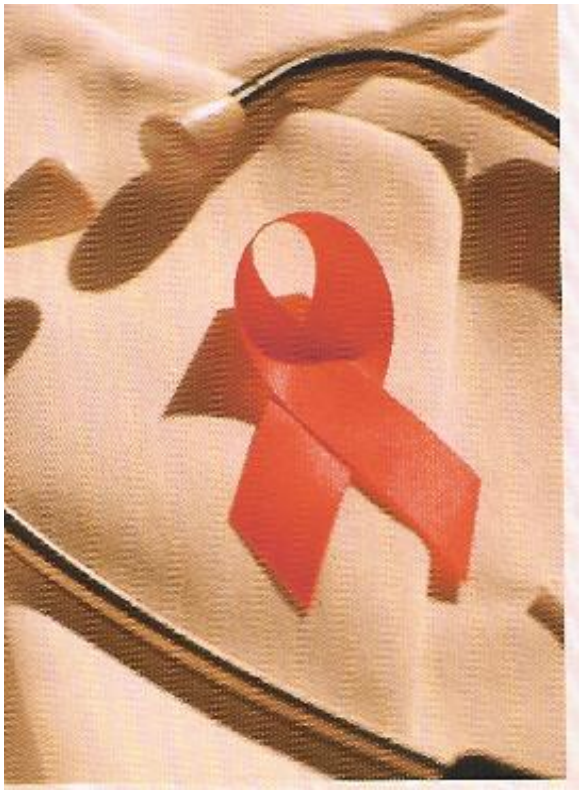
- **Hormone-related**
  - **Sex ratio**
  - **Hormonal risk factors**
- **Non-hormonal risk factors**
- **Epidemiological risk factors – not very helpful for the individual**

BREAST CANCER – hormonal risks:



- Gender
- Long reproductive span
- Obesity
- PCOS, infertility, anovulation
- ‘Long term’ use of combined HRT

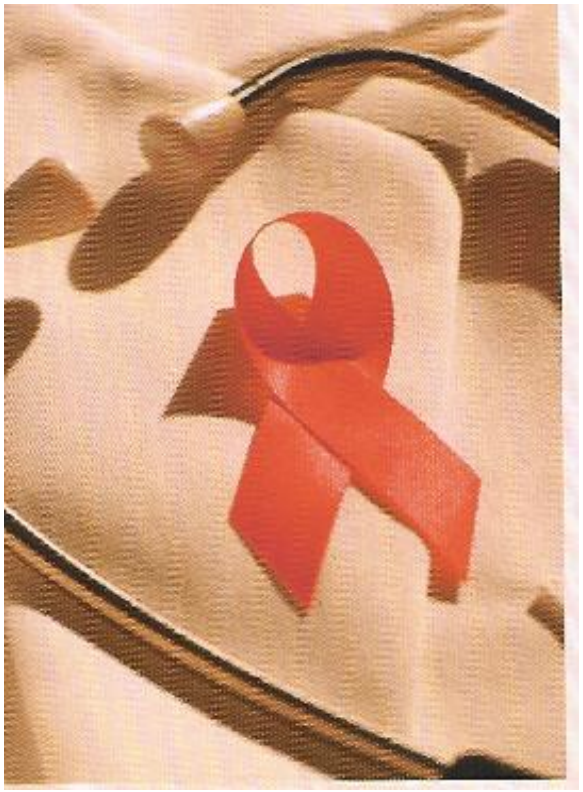
BREAST CANCER – hormonal risks:



Protective factors:

- **Early or surgical menopause**
- **Low BMI**
- **Anti-hormones**

BREAST CANCER – hormonal risks:



- Gender
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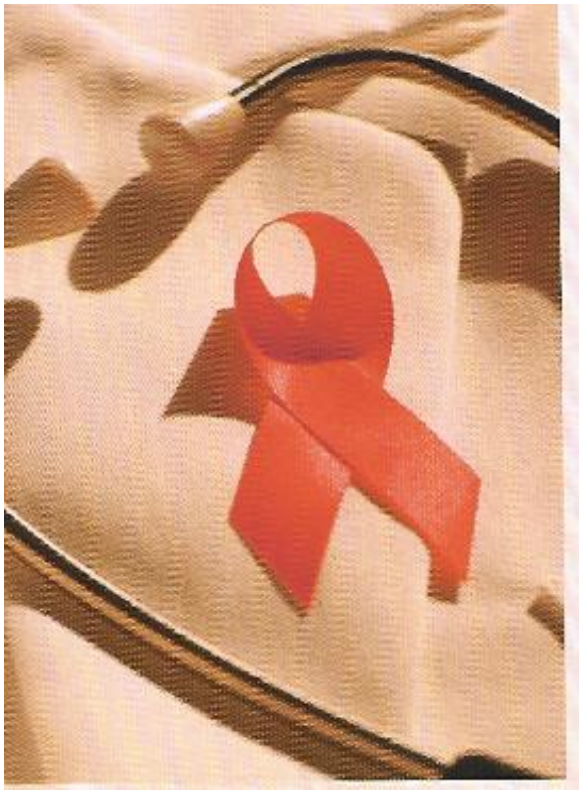
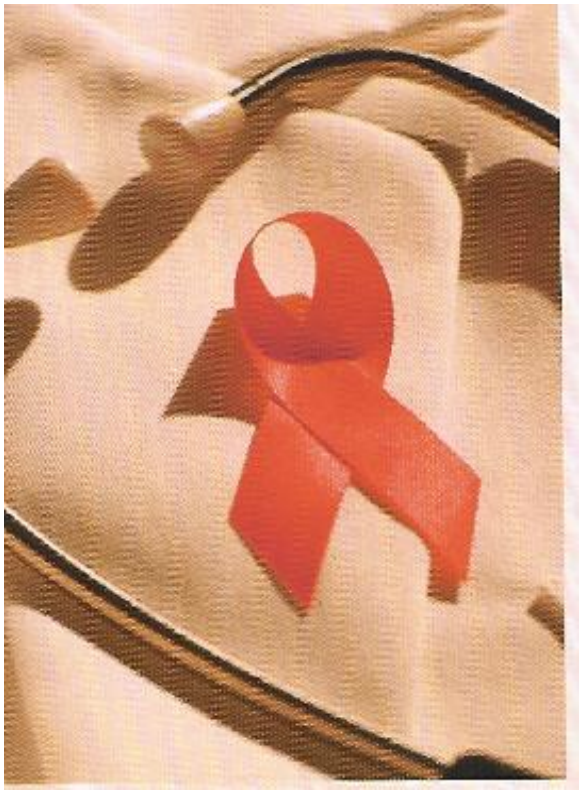
BREAST CANCER – non-hormonal risks:



- AGE
- Smoking
- Large breasts
- Diet high in animal fats
- White or Indian race

BREAST CANCER – non-hormonal factors:



Protective factors:

- **Exercise**
- **Anti-oxidant intake**
- **Fruit & vegetable intake**
- **Black race, oriental diet**

Demographics – hereditary breast cancer:

FAMILY HISTORY

- **Multiple cancers, >2 cases**
- **Mean age younger, below 40 yrs**
- **Multifocal or bilateral breast cancer**
- **Male breast cancer**
- **Multiple primary cancers, breast and ovarian cancer**

Risk Factors for Breast Cancer

	RR
First pregnancy (>30 yrs)	1.48
Body mass index (>29.68 kg/m^2)	1.48
College graduate	1.36
Alcohol use (>5 g/d)	1.16
Delayed menopause	1.14 (5 yrs)
HRT (current)	1.12 (5 yrs)*

* based on data from Collaborative Group on Hormonal Factors in Breast Cancer. *Lancet*. 1997;350:1047.

HORMONE THERAPY CONCLUSION

Therapeutic regimens:

- Hysterectomised women, **only estrogen** preparations
- Young postmenopausal women
  - **sequential regimen**
  - orally or transdermally
- **Later postmenopause**
  - continuous combined
  - amenorrhoea

ESTROGEN REPLACEMENT therapeutic guidelines:

- **Dosage**
  - lower dosage will be equally effective when combined with calcium therapy
- **Route of administration:**
  - transdermal route
  - optimise patient satisfaction
- **Clotting risk**:
  - Consider as contra-indication
  - Combine with anti-coagulants

Special indication:

- Early oophorectomy
- Premature ovarian failure
  - Low dose OC
  - Decreases all the risks of early ovarian failure

ESTROGEN REPLACEMENT: "best practise"

- **Per indication**
- **Individualize**
- **Dyration of treatment**
  - Symptoms – short term
  - Osteoporosis >7 years
- Progestogen separate question
  - Local?
  - Low dose?