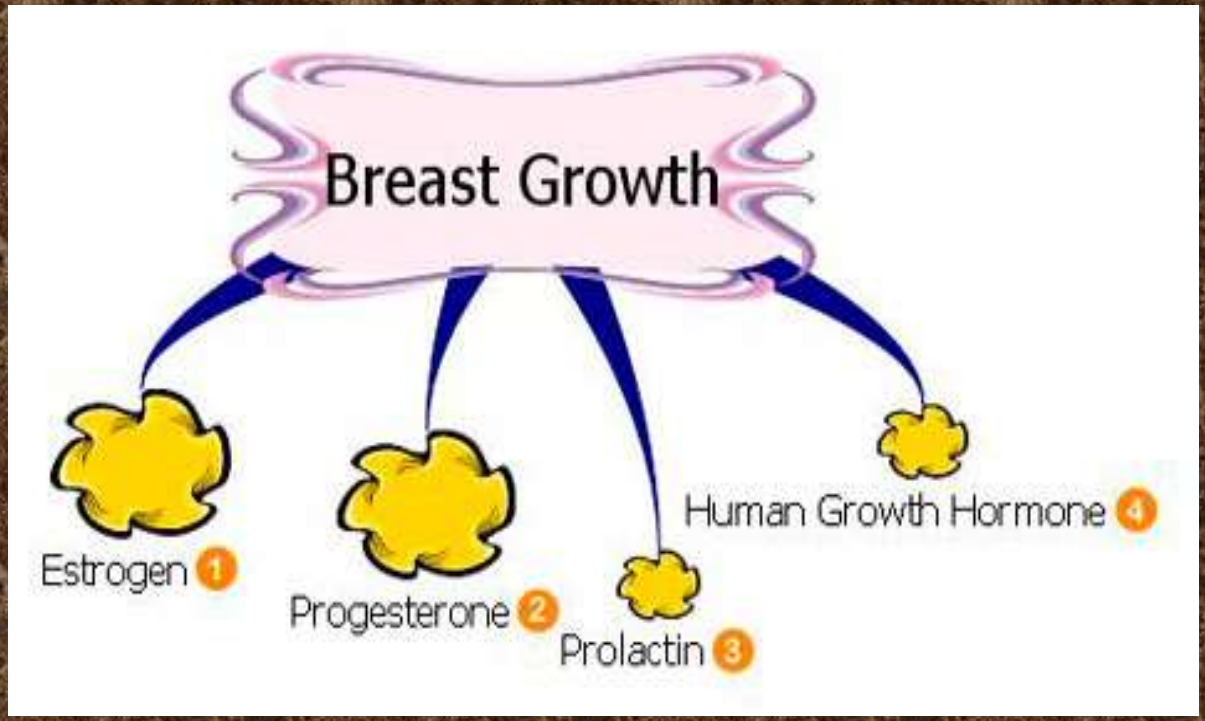
HRT and Breast

Dr.Shobhana Mohandas.MD.DGO.FICOG
Sun Medical Centre
Thrissur
Kerala

Breast and Hormones



Progesterone Stimulates the Lobular system

Estrogen stimulates The duct system

EFFECT OF HORMONES ON BREAST

Proliferation,differentiation,regression

Endogenous ovarian hormones play central roles in breast development and breast cancer

Predispose to malignant change

Increase in prolif activity, thickness of acinar & ductal epithelium

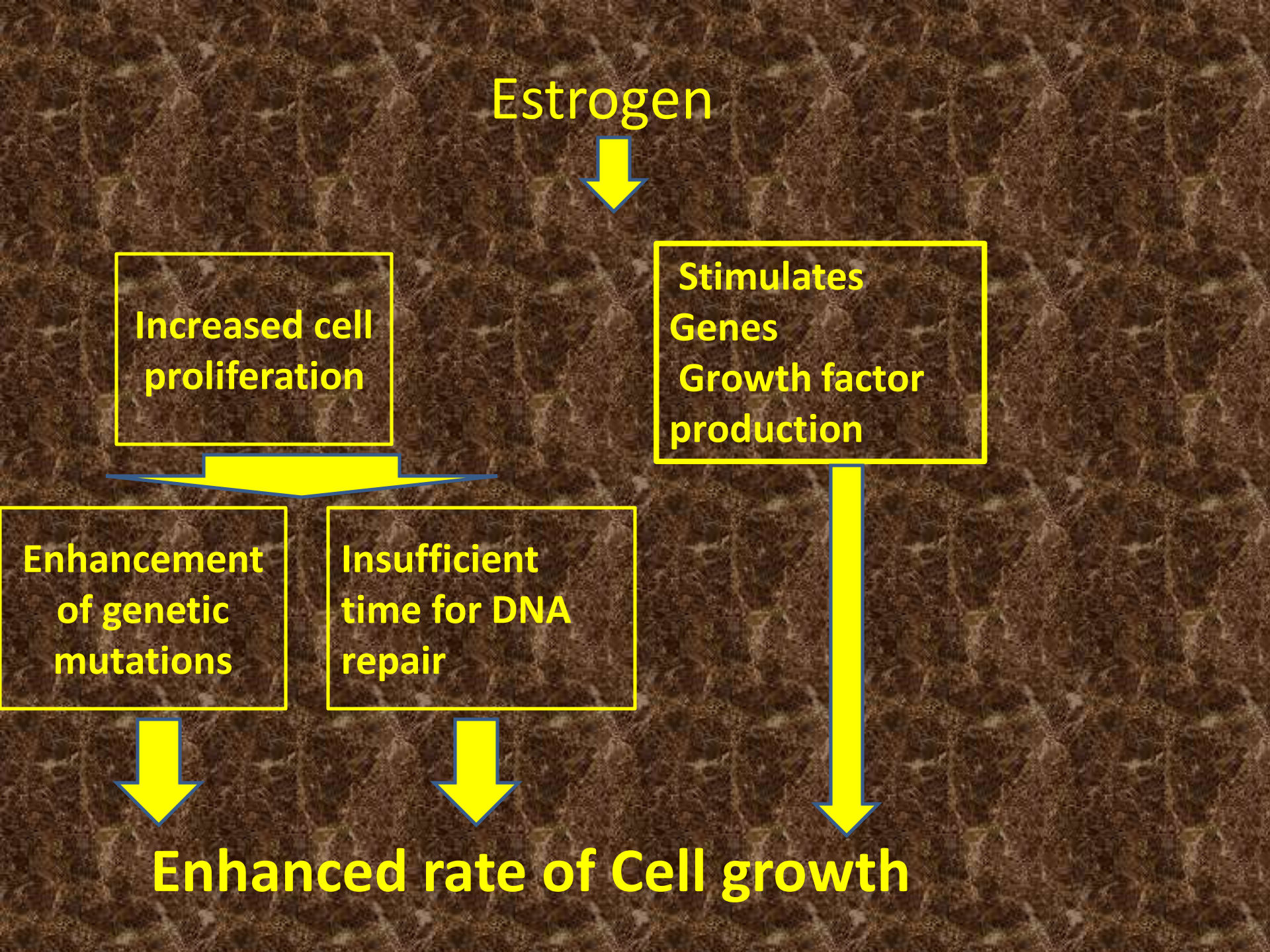
EFFECT OF HORMONES ON BREAST

E2 : Hyperplastic epith morph, decreases apoptotic cells

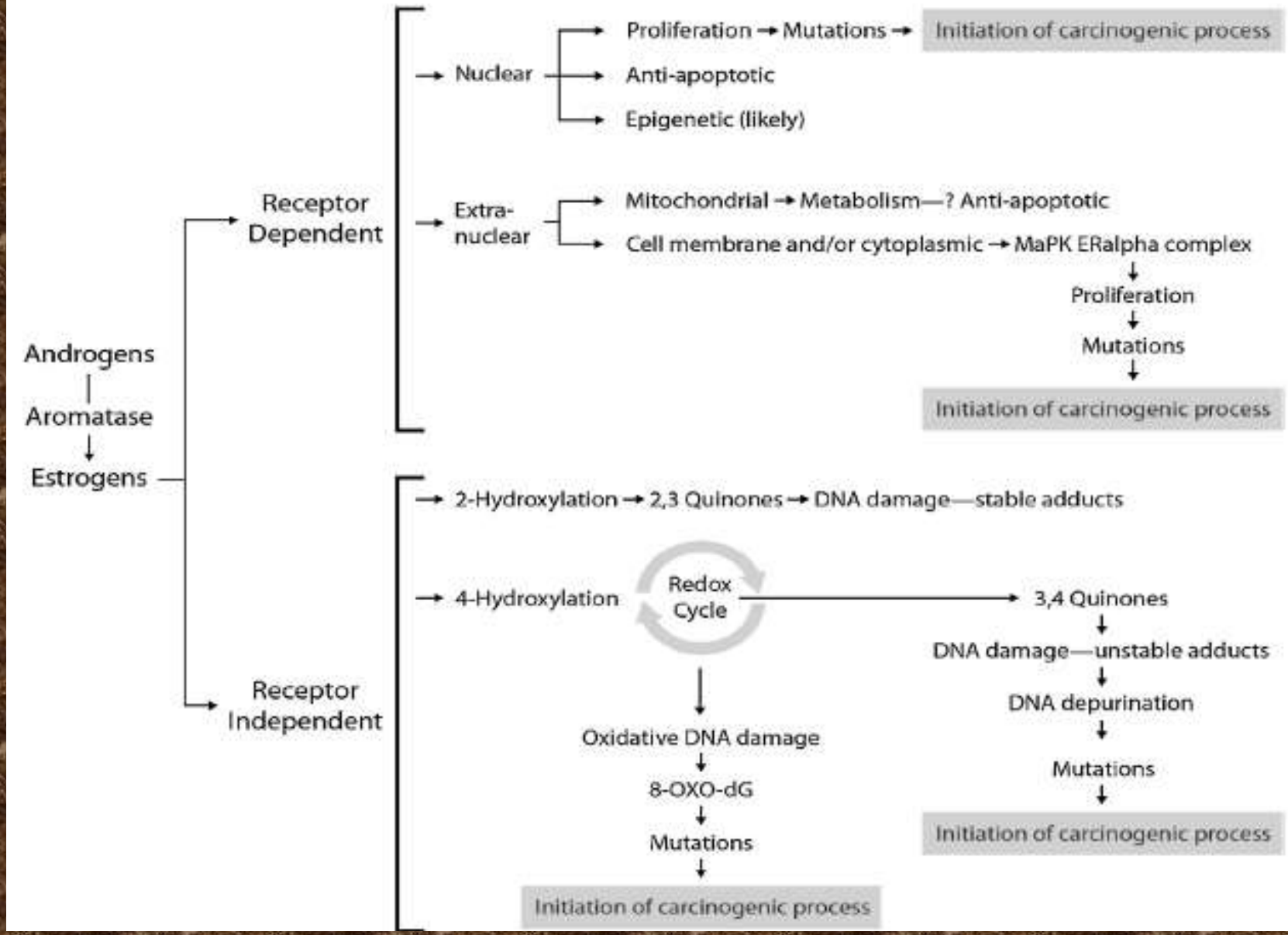
MPA : Hypersecretory single layered Epithelium.

E2+MPA : Multilayered, organised Epithelium.

Tibolone: Inhibits sulphatase activity, Increases apoptosis,decreases cell proliferation


Estrogen
Increased cell proliferation
Stimulates Genes Growth factor production
Enhancement of genetic mutations
Insufficient time for DNA repair
Enhanced rate of Cell growth

Pathways to Estrogen Carcinogenesis



- Oophorectomy at 35 years reduces risk of breast Cancer by 75%.
- Women have 100 times more risk for breast cancer
- Plasma estra-diol levels
- Age at menopause,
- First live birth
- Early menarche

Progesterone

Progesterone controls proliferation and morphogenesis of the luminal epithelium.

Progesterone also drives expansion of stem cells by paracrine signals to generate progenitors required for alveologenesis

Breast epithelium proliferates most during the luteal phase of the menstrual cycle.

During mid-to-late pregnancy, progesterone has another role to suppress secretory activation until parturition

Alteration in Progesterone/PR signalling pathways

Patient tumor samples and clinical studies indicates that Progesterone is a risk factor for breast cancer . It contributes To cell proliferation in breast cancer.

Molecular and Cellular Endocrinology 357 (2012) 4–17

Increase of BC risk with oral synthetic progestins,

not with

Progesterone and Dydrogesterone.

In

Maturitas 65 (2010) 183–189

Genetic disposition to polymorphism of key metabolic enzymes with a resultant formation of toxic metabolites.

In otherwise healthy metabolic conditions,sex steroids are not known to damage DNA.

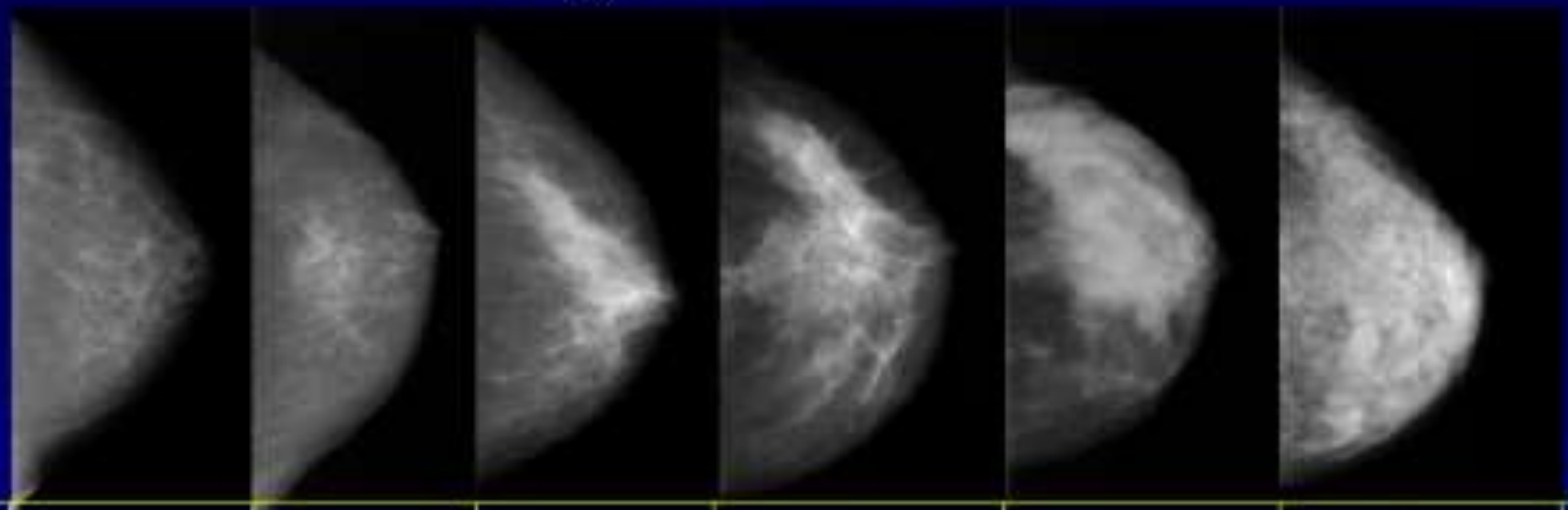
Mortality is reduced in breast cancer women with HRT exposure.

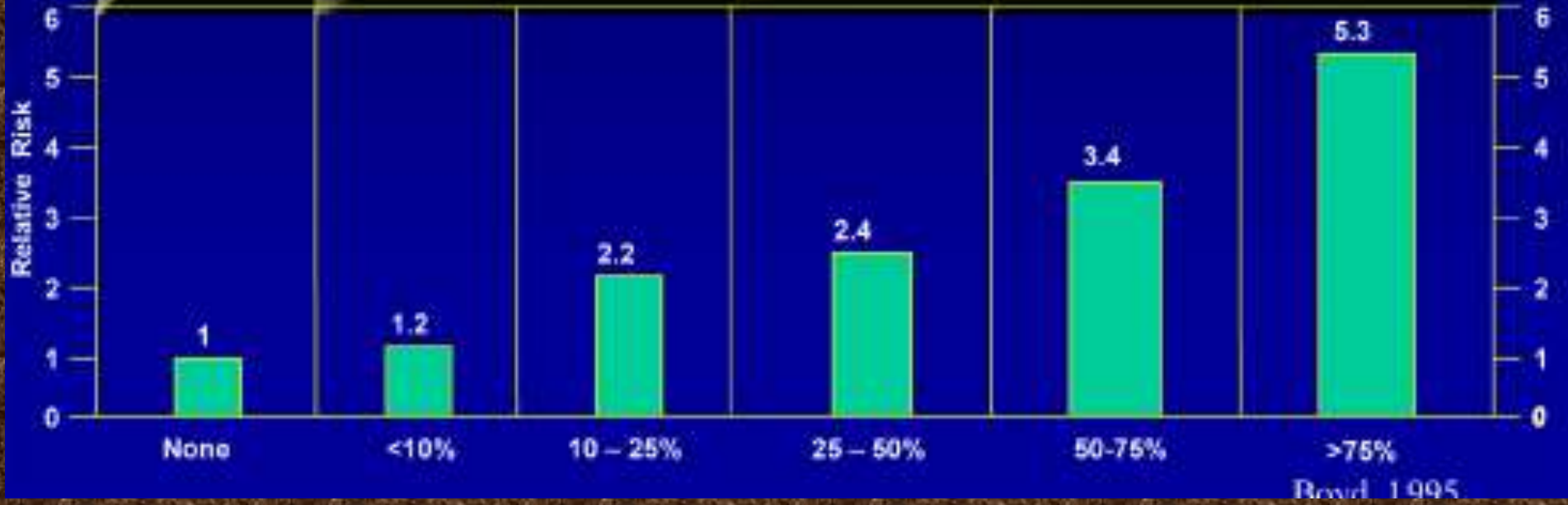
Maturitas 43 Suppl. 1 (2002) S35–S52

Obesity increases risk of breast cancer by

Increased estrogen production

Boyd Classification





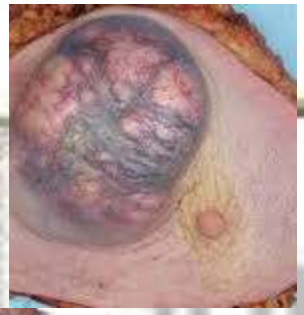
2002

W H I Trial

Trial on the effect of O & P on Menopause was stopped

Stroke

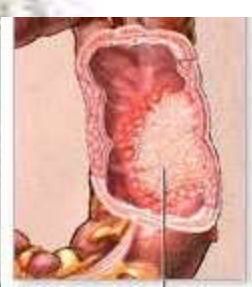
Breast cancer



Myocardial infarction

Increased Risk

Colo Rectal Cancer



Hip Fracture

Decreased Risk

2004

Oestrogen only Arm

10,739 hysterectomized women randomized
To
unopposed conjugated oestrogen or placebo

Decreased risk of Breast cancer with Oestrogen

Data accumulated over the past ten years suggest that E can induce apoptotic cell death in tumors deprived of estrogen long term

Average age of women in the WHI study were 61

RJ Santen, Menopausal hormone therapy Http: //dx.doi.org/10.1016/j.jsbmb.2013.06.010

In postmenopausal women aged 50–59 years taking combined oestrogen and progestogen HRT over 5 years

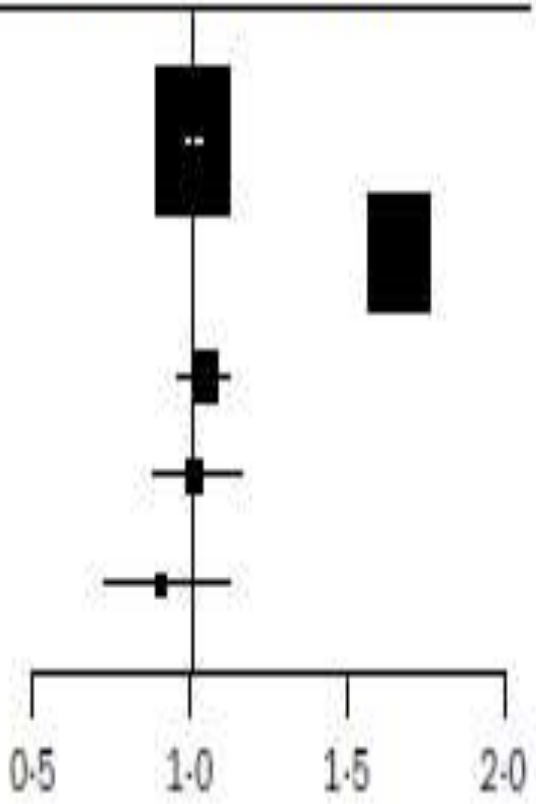
3 additional cases per 1000 women

Risk is not significantly increased over 3 years of use

Million Women's Study 2004

Never HRT	Oestrogen only	Tibolone only	Oest+ Progesterone
1.2 (1-1.48)	1.3 (1.21–1.40)	1.45 (1.25–1.68).	1.8 (1.88-2.12)

HRT use at baseline	Cases/population	Relative risk (95% FCI)*
Never users	2894/392 757	1·00 (0·97–1·04)
Current users	3202/285 987	1·66 (1·60–1·72)
Last use <5 years previously	579/81 875	1·04 (0·95–1·12)
Last use 5–9 years previously	207/29 395	1·01 (0·88–1·16)
Last use ⩾10 years previously	79/12 568	0·90 (0·72–1·12)



χ^2 for heterogeneity between ever users=161·5, p<0·0001

Figure 1: **Relative risk of incident invasive breast cancer in relation to recency of use of HRT**

Current users of oestrogen-progestogen combinations

<1 year	97/9771	1·45 (1·19–1·78)
1–4 years	582/49 240	1·74 (1·60–1·89)
5–9 years	850/56 912	2·17 (2·03–2·33)
≥10 years	362/23 673	2·31 (2·08–2·56)

OBJECTIONS TO MWS

Data collected by questionnaire

No follow up

50% ever users : High percentage

Excess breast cancers in first year ??

No increase in past users ?

? Selection bias for Tibolone users

Studd JW : Progress in Obstetrics& Gynaecology 16

Autopsy studies showed
Undiagnosed breast cancers in 7% of healthy women

Mammographic detection range

1.44 cm in <40 years

0.88cm in >70yrs with fatty breast

Mean tumour doubling time is 100 days

Only 6% of new tumours will be detectable in 7 years

WHI and MWS show growth of existing tumours

Breast cancer in HRT users

Less virulent compared to

Breast cancer in Non users

Estrogen Receptor blockers

- Tamoxifene
- Letrozole

Improve only Estrogen receptor positve tumours

Can Estrogen Receptor

Negative patients take HRT?

Severe Menopausal symptoms

A meta-analysis of 10 uncontrolled observational and 11 case-controlled studies involving **1558** **breast cancer survivors**

HRT users

Non HRT users

No Difference in recurrence

TIBOLONE

Tibolone, does not increase mammographic density,

Effective

Could be a treatment option for women persistently seeking help

LIFT

Long-Term Intervention on Fractures with Tibolone

Randomized placebo-controlled trial

Breast-cancer incidence was significantly reduced after 3 years

LIBERATE

Livial Intervention Following Breast Cancer; Efficacy, Recurrence and Tolerability Endpoints

Non-inferiority of tibolone to placebo re: risk of recurrence in breast cancer patients with climacteric complaints

FRENCH COHORT STUDY 2008

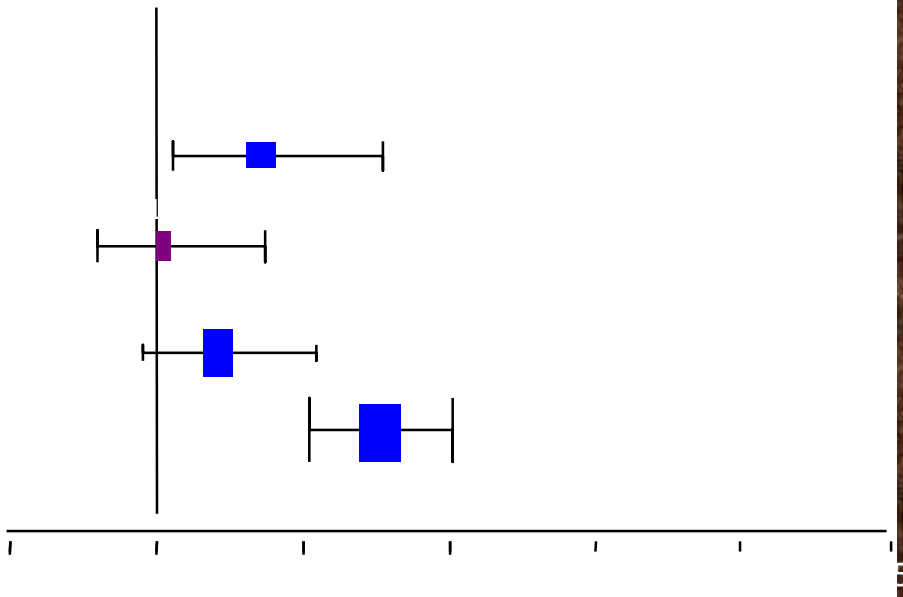
Estrogene

alone RR=1,29

+ micronized progesterone RR=1

+ dydrogesterone RR=1,16

+ other progesterone RR=1,69



No increased breast cancer risk with percutaneous estrogen + natural progesterone association (RR=1)

Fournier,Breast Canc Res Treat,2008;.

Breast Cancer

Perception

All types of HRT cause an increased risk of breast cancer within a short duration of use.

- **Evidence**
- **After 5 years' use of combined estrogen and progestogen, the WHI cohort showed a small increase in risk of breast cancer of about eight extra cases per 10,000 women per year. Risk was not increased in first-time hormone users. [A]**
  - Chlebowski RT. *JAMA* 2003;289:3243
  - Stefanic ML. *JAMA* 2006;295:1647

Breast Cancer

Perception

The reported decline in breast cancer rates in the US following the publication of the WHI data proves that HRT causes cancer.

- **Evidence**

- **A decline in the incidence of breast cancer in the USA started before the WHI publication and can be partially related to fluctuation in screening. There has been no decline in breast cancer registration in the UK following the Million Women Study report, nor in Norway, Canada, the Netherlands and countries with stable screening programs. [B]**
  - *Li CI. Cancer Epidemiol Biomarkers Prev* 2007;16:2773
  - *Kliewer EV. NEJM* 2007;357:509; Zahl PH. *NEJM* 2007;357:510

INDIAN MENOPAUSE SOCIETY Consensus 2008

EPT (>4 years) assoc with
inc risk of detection of Ca breast
EPT does not appear to initiate malignant transformation, but to potentiate it
Ca breast detected during HRT use usually less aggressive with more favourable prognosis

APMF GUIDELINES 2008
HRT and Breast Cancer

- Oestrogen/progestogen therapy for up to 5 years does not add significantly to lifetime risk of breast cancer.
- Beyond that time, the increase in risk is small, and comparable to other risks such as being obese or drinking more than 2 standard drinks of alcohol per day
- Oestrogen-only therapy for up to 7 years does not significantly increase breast cancer risk.
- Young postmenopausal women starting on combined HRT for the first time should be advised that breast cancer risks do not appear to increase in the first 7 years of use.
- Hysterectomized women on unopposed oestrogen are not at increased risk of breast cancer and some may even have a small reduction in risk.

INTERNATIONAL MENOPAUSE SOCIETY

Data on HRT in women with a family history of breast cancer is inconclusive

Individual risk to be assessed

BREAST CANCER SURVIVORS

Consider in some women whose quality of life impaired by estrogen deficiency

Risk of recurrence must be explained

Fair trial with alternative therapies given prior to starting HRT

Lowest effective dose for shortest duration

CONCLUSION

Relationship bet use of HRT & breast cancer only after 4 yrs of use

Do not deny short term, low dose HRT to symptomatic women

ET in hysterectomised women does not increase risk

Tibolone may be a better choice

Prudent to withhold HRT in breast cancer survivors