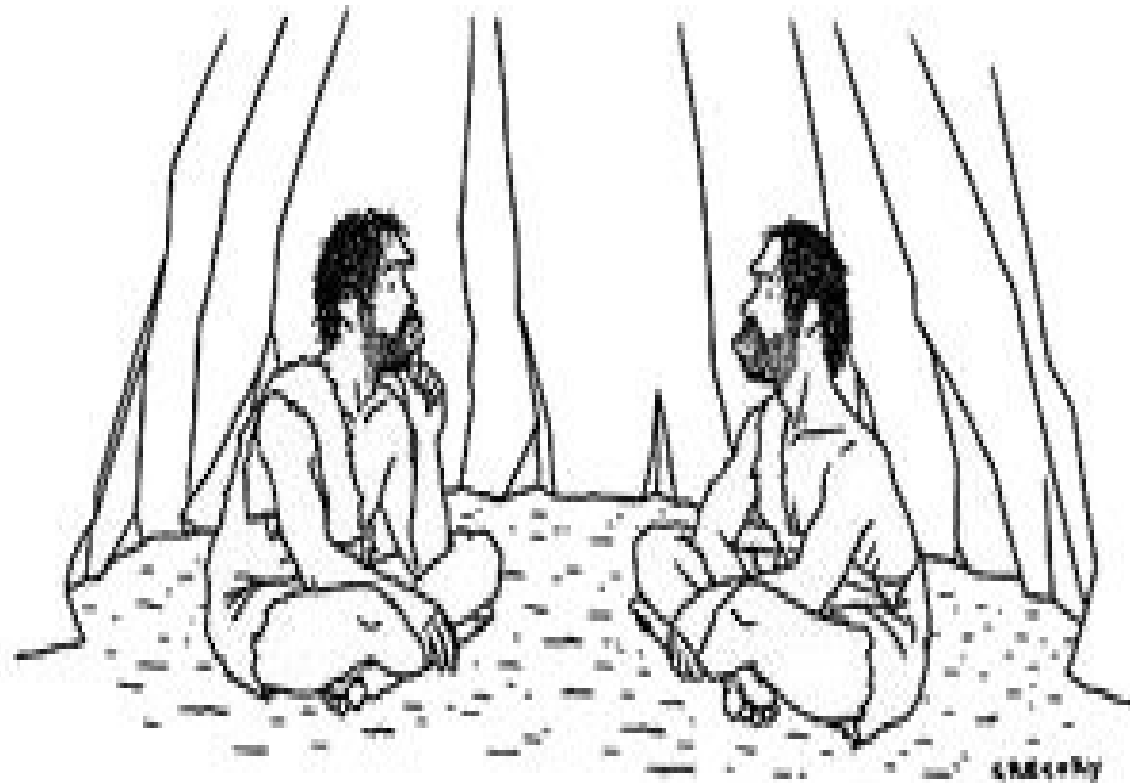


# HRT myths and realities



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*“Something’s just not right—our air is clean, our water is pure, we all get plenty of exercise, everything we eat is organic and free-range, and yet nobody lives past thirty.”*



GLOBAL  
WARMING  
IS  
HOGWASH!!

NO BASIS IN FACT!!



A TOTAL  
MYTH!!!



WAG HANDELSMAN  
© 2008 NEWS 24/7

HE  
MELTED...



2002

# WHI Trial

Stopped  
after  
5.2 years

Stroke



Breast cancer



Colo  
Rectal  
Cancer



Hip  
Fracture



Myocardial  
infarction

Decreased  
Risk

Increased  
Risk



**2004**

**Oestrogen only Arm**

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

**Decreased risk of Breast cancer with  
Oestrogen**

# 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 Cl. Cancer Epidemiol Biomarkers Prev 2007;16:2773  
Kliwer EV. NEJM 2007;357:509; Zahl PH. NEJM 2007;357:510*

# Million Women's Study 2004



Million + women undergoing mammography answered questions



Never HRT

**1.2**

(1-1.48)

Oestrogen only

**1.3**

( 1.21-1.40)

Tibolone only

**1.45**

(1.25-1.68).

Oest+  
Progesterone

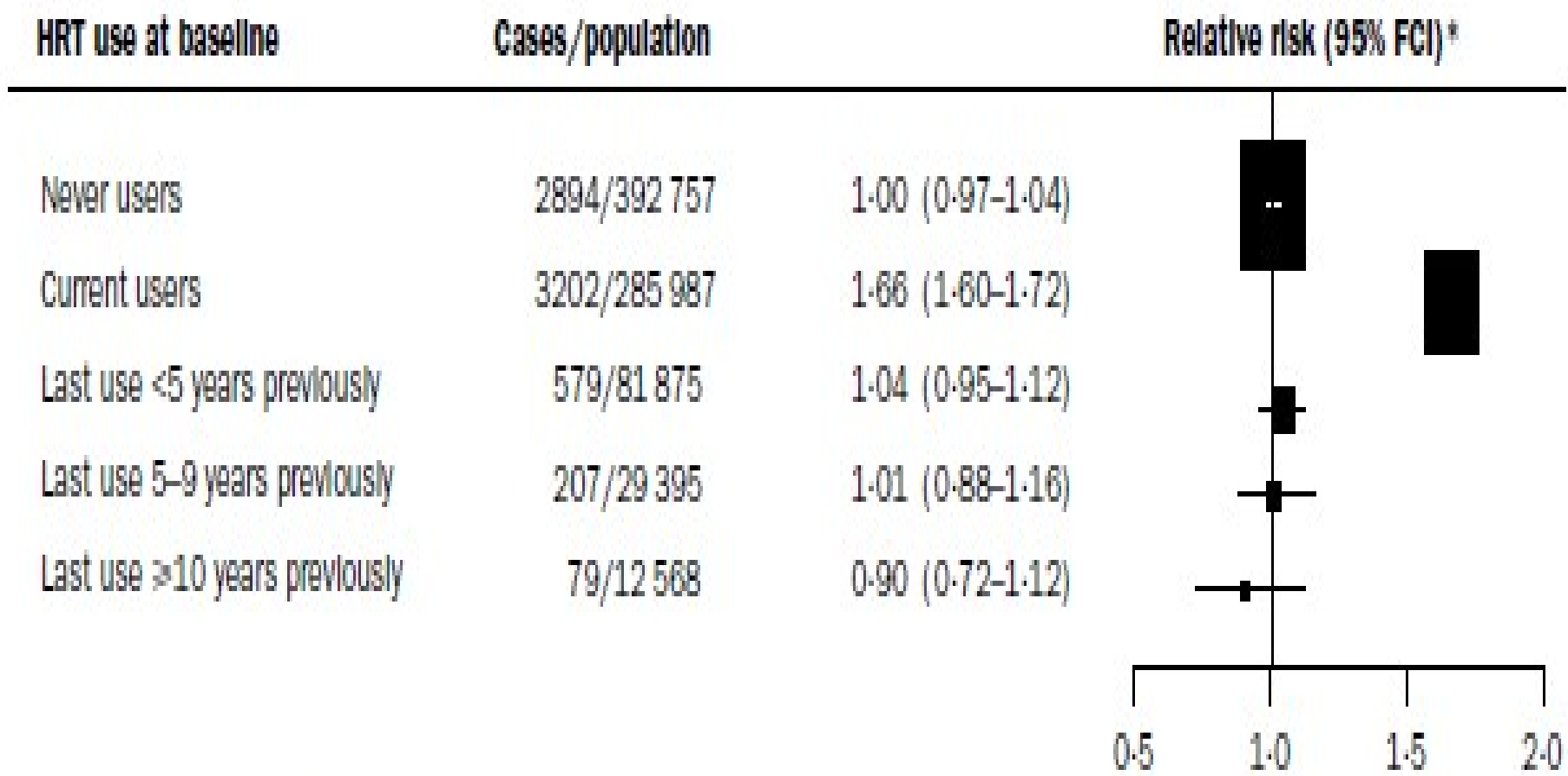
**1.8**

(1.88-2.12)

Half the women had used HRT;

9364 incident invasive breast cancers after an average of 2.6 years

and 637 breast cancer deaths were registered and 4.1 years of follow-up,



$\chi^2$  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)

# Breast Cancer-Risks

Age in years	Baseline risk/1000	% risk
<50	18	2
50-60	38	4
61-70	63	6.5

- 50-80yrs - % Prevalence of undiagnosed breast cancer in autopsy specimen is 7%
- Women who never took HT-→Prevalence
- Increase in Urban

Use of HRT before **the** diagnosis of breast cancer results in more favorable primary tumors, with a lower incidence of recurrences and a better overall survival rate.

Probably due to normalized bone metabolism by the use of HRT, which may lower the conditions of tumor cell seeding therapy

Am J Obstet Gynecol 2007;196:342.e1-342.e9.

HRT users developed breast cancer at a younger age than nonusers; HRT use was associated with the development of biologically more favorable cancers than those that developed in nonusers; and overall and disease-free survival rates were higher in HRT users than nonusers.

© 2009 Published by The American Journal of Surgery, Vol 197, No 3, March 2009 by Elsevier Inc.



# Habits trial

**Hormonal Replacement After Breast Cancer—Is it Safe?)**

**Randomized, non-placebo-controlled HT for menopausal symptoms with non-horm among women with previously treated breast cancer**

**HRT after breast cancer**

**No HRT after breast cancer**

**Stopped After 2 years  
Significant hazard of HRT found**

Data Monitoring Co. HABITS (hormonal replacement therapy after breast cancer: is it safe?), a randomised comparison: trial stopped. Lancet 2004; 363: 453-5.

# Stockholm trial

Women with breast cancer who were disease free

On HRT  
No= 188

Not on HRT  
No= 190

After 4 years, no increased recurrence

Continued for 10 years

On HRT  
No= 60

11 local  
recurrence

12 distant  
metastasis

14  
contralateral  
breast cancer

Control  
No= 48

15 local  
recurrence

12 distant  
metastasis

4  
contralateral  
breast cancer

# **LIBERATE**

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

## **LIBERATE:**

(Livial intervention following breast cancer: Efficacy, Recurrence and Tolerability Endpoints)

**2002 - 2004**

**3098 :1556 (T)1542 (P)**

**3.1 years**

**237 of 1556 (T) (15.2%)**

**165 of 1542 (P) (10.7%)**

**Tibolone increases the risk of  
recurrence in breast cancer  
patients**

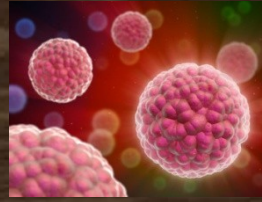


**Cancer research**

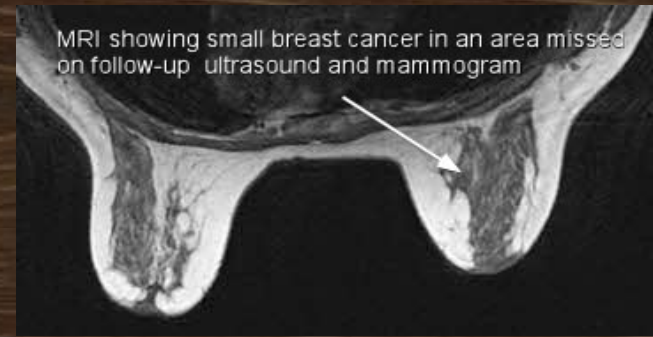


**Single Cell**

**5-10 years.**



**5-10mm lesion**



**Majority of HRT associated tumours are slowly growing and lesions are well differentiated.**

**This period (5-10year)  
may be too short to  
permit the detection of  
tumors primarily induced  
by HRT.**

# Hormone Dependent Carcinogen

The Possibilities → Preclinical

Estrogen

Tumour initiation

Intranuclear  $\alpha$   $\beta$  receptors

DNA

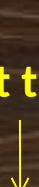
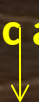
Mitotic activity

Proliferation

Occult tumour

Estradiol late stage promotor

Clinical tumour



WHI and MWS reported.

↑ In breast Ca starts Immediately  
after HRT use

If hormones caused it rise should  
have come later .

After stopping HRT, ↓  
Growth rate rapidly

If hormones caused it, decrease  
should come much later....

In summary, HRT is hence more likely to be a tumor promoter than  
a de novo-inducer of breast cancers.

# EFFECT OF HORMONES ON BREAST

**E2 : Hyperplastic epith morph, dec apoptotic cells**

**MPA : Hypersecretory single layered epith**

**E2+MPA : Multilayered, organised epith**

**Tibolone: Inhibits sulphatase activity, inc apoptosis, dec in cell prolif**



# **HRT AND BENIGN BREAST DISEASE**

**Mastalgia**

**Promotion of Breast cysts**

**No evidence of inc risk of Ca**

# Not all progestins are bad

In a cohort study including  
80,377 women Fournier et al.

found  
an increase of BC risk with  
oral synthetic progestins,

but not with  
progesterone and  
dydrogesterone

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**

**Current clinical guidelines  
suggest**

**HRT should be contraindicated in cancer survivors.**

**In light of available evidence, we should rethink in women with severe  
symptoms**

**Will HRT act in the presence of Tamoxifene.**

**Yes: Stockholm trial: in one subgroup.**



**OC pills with 20microgram ethinyl estradiol plus a progesterone**

**Avoid in women who smoke, are obese, have migraines, or have hypertension.**

**5 mg Ethinyl estradiol**

**=**

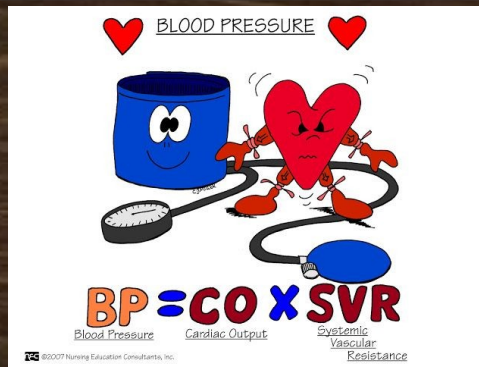
**0.625mg Conjugated estrogen**

**1 COC pill**

**=**

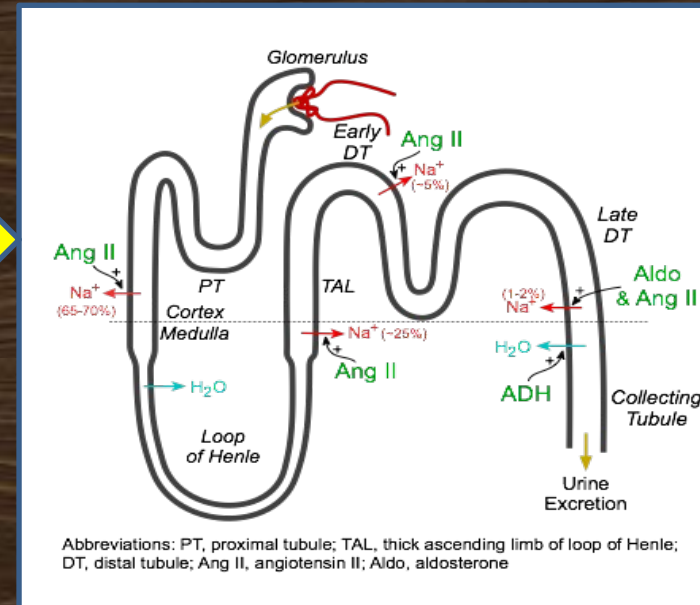
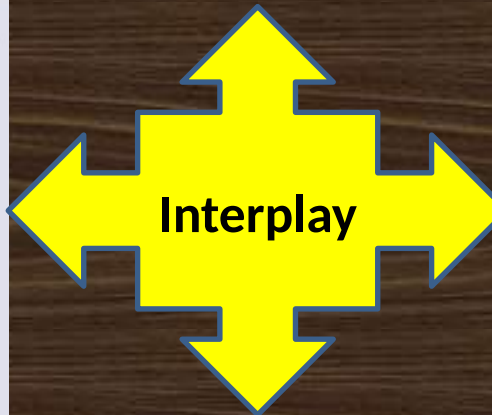
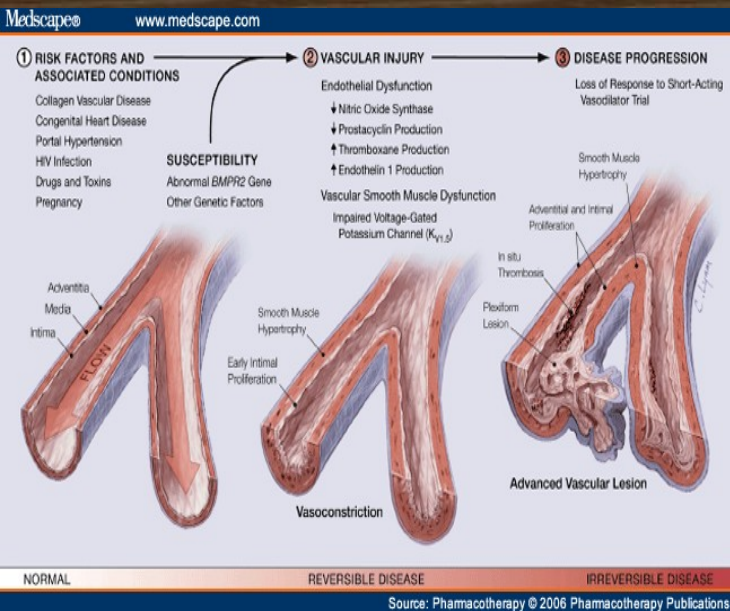
**4 tablets of conj.estrogen**

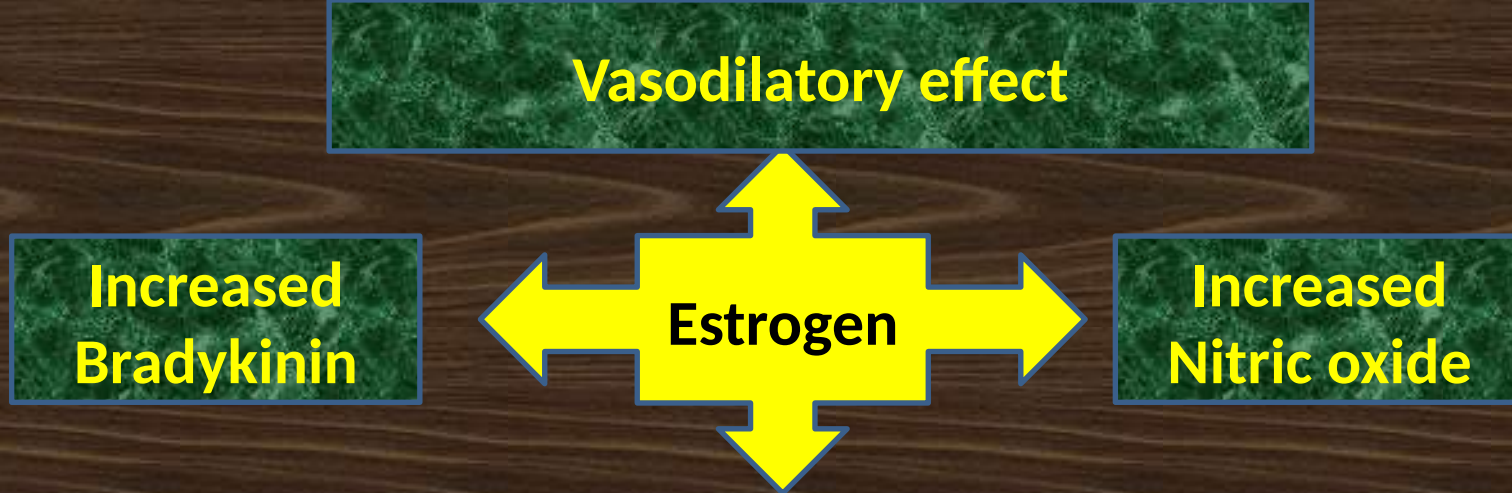
# HRT and hypertension



## Peripheral vascular resistance

## Volume regulatory mechanism





Women with HRT had reduced left ventricular cavity dimensions, diminished resting aortic blood flow velocity, and lower resting-mean and post-exercise blood pressures

HRT would be expected to leave blood pressure unchanged or to actually promote a blood-pressure reduction in post-menopausal normotensive and hypertensive women.

Hormone replacement therapy and blood pressure in normotensive and hypertensive women  
Nephrology Dialysis Transplantation. Vol 16, Issue 5, PP 888-890



**Patients with hypertension**

**Raloxifene**

**Comb.HRT**

**Placebo**

**Decreased BP and carotid-femoral  
PWV(pulse wave velocity)**

**Excerpta Medica Inc.  
(Am J Cardiol 2004;94:1453-1456)**



Age 50-59



1<sup>st</sup> year E use improves blood lipids

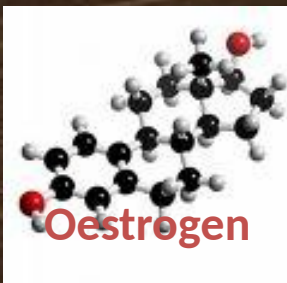
Framingham study

Older age



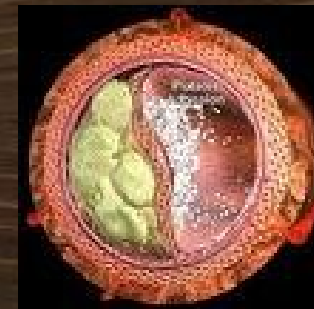
Increased incidence of MI

# Timing hypothesis



Prothrombotic action

Proinflammatory action



Atherosclerotic  
plaque

**Estrogen appears to improve arterial compliance  
independently of BP within 4 weeks.**

Maturitas 45 (2003) 293/298

# HRT in a patient with fibroid

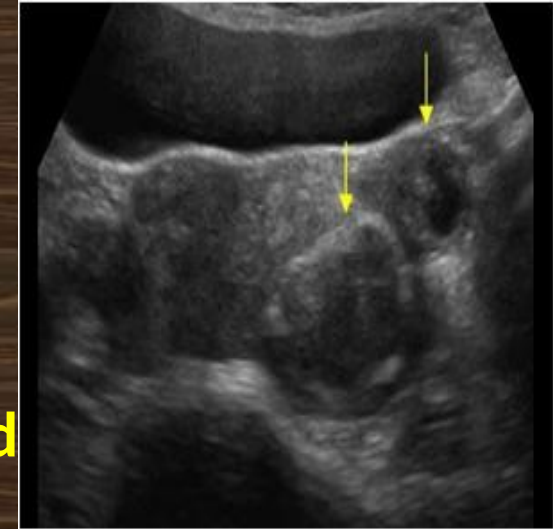
**3 year study .**

**Women with and without fibroid were given HRT**

**In the first two years, fibroid volume increased more in the HRT group**

**In the third year the increase was not marked at end of the third year study, one of 34 and three of 34 women increased fibroid volume over 25% compared with baseline in HRT non-users and users, respectively.**

**Maturitas 2002 Sep 30;43(1):35-9.**



# Should progesterone be given after vaginal creams?

Most specialists agree that after two years of use of either of the very low dose preparations, a short course of progestogen (e.g. 12 days of norethistrone 5mg tds) should be given and if no withdrawal bleeding occurs when the progestogen is stopped, unopposed oestrogen treatment can be continued. If bleeding occurs, the endometrium should be investigated (by ultrasound and biopsy).



