WHI, HERS y otros estudios: Su significado en la clinica diária

III Congreso Ecuatoriano de Climaterio
Menopausia y Osteoporosis

por

Manuel Neves-e-Castro

(*Lisboa-Portugal)*

Julho, 2003

Machala

The published studies

. HERS 1 and 2

. WHI

. Oxford Breast Cancer

. HOPE

. What do we know?

Information is based on

. **Observational studies (*retrospective*)**

. **Clinical trials (*prospective*)**

and

. **Experimental studies**

“in vitro”

“in vivo” **animals**

women

Epidemiological studies

- How were they performed?
- What similarities do they have with our clinical practice?
- How to interprete them?

The “language” of the results

. Absolute risks
. Relative risks
. Number needed to treat (NNT)
. Number needed to harm (NNH)
. Number needed to screen (NNS)
. Events per woman / years
. Events per total number of women

What is

a woman /year ?!

100 woman/years = *100* *women treated during 12 months*

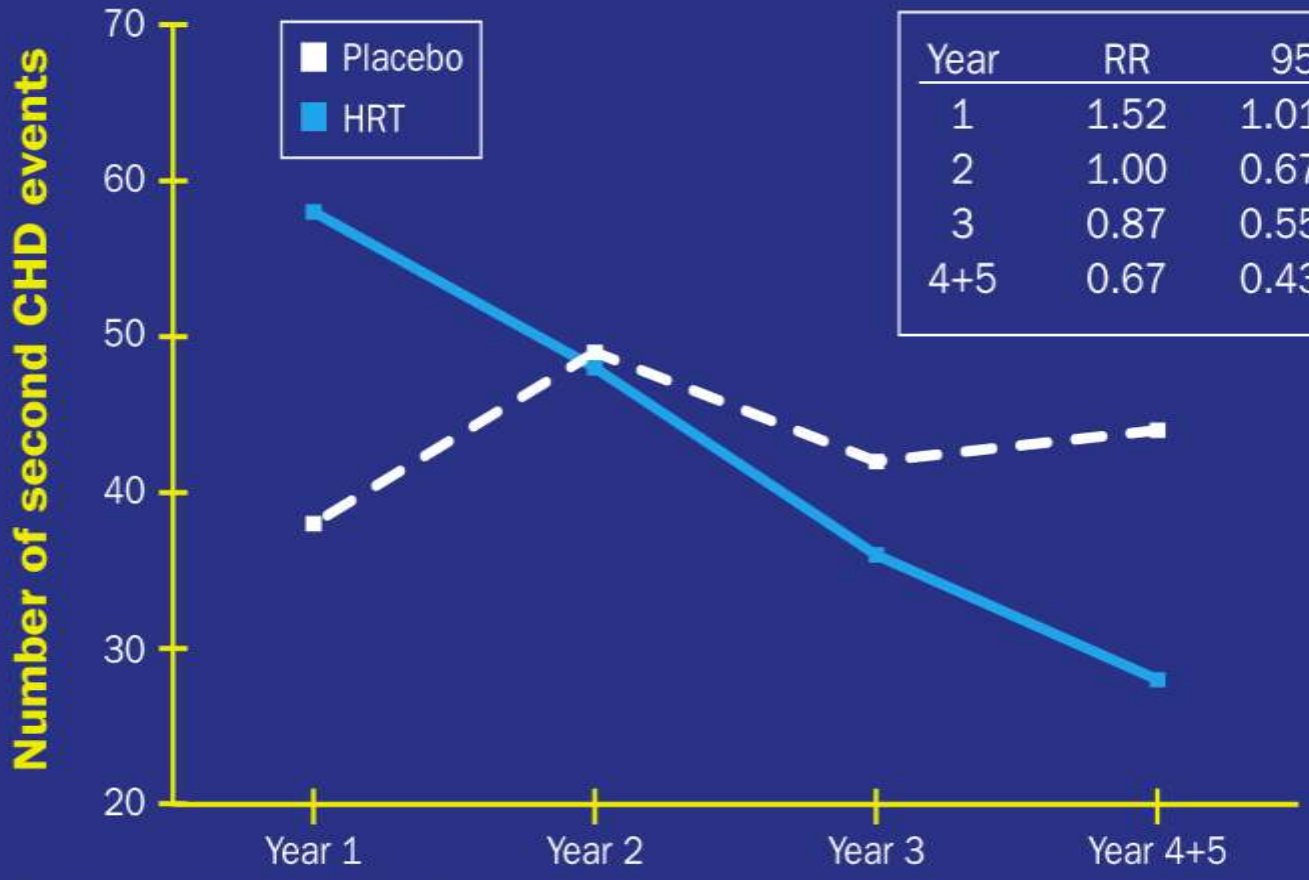
is it the same as

100 woman/years = *400* *women treated during 3 months*

?

The HERS

Effect of HRT vs Placebo on Second CHD Events (HERS)



Year	RR	95% CI	
1	1.52	1.01–2.29	*
2	1.00	0.67–1.49	
3	0.87	0.55–1.37	
4+5	0.67	0.43–1.04	

*P = .009, for trend-time analysis

Hulley et al. *JAMA*. 1998;280:605.

"The HERS study group was really very sick: "established coronary disease was defined as evidence of one or more of the following: coronary artery bypass graft surgery, percutaneous coronary revascularization, or angiographic evidence of at least a 50% occlusion of *one more major coronary arteries"!*

Hulley S, Grady G, Bush T, et al. JAMA 1998;280:605-13

"It is not conceivable that older women *("participant range in age from 44 to 79 years")* are kept on a treatment that is obviously excessive," as pointed out by S.Hulley et al.

Neves-e-Castro M. Maturitas 2001;38(3):235-237

“Breast discomfort and vaginal bleeding were reported directly to the gynaecology staff” …

“For women who stopped taking HERS medication, the risk of primary CHD events was <u>elevated in the first month after stopping use of medication</u>”?!

Hulley S, Grady D, Bush T, et al. JAMA 1998;280:605-13

“The RH comparing risk of the primary CHD outcome in the hormone and placebo group was similar”.

Hulley S, Grady G, Bush T, et al. JAMA 1998;280:605-13

"HERS did not evaluate the effect of estrogens plus progestin therapy, in women without CHD, and it is not known whether our findings apply to healthy women. It is also not known whether the use of different progestin or of estrogens alone would have been beneficial".

Hulley S, Grady G, Bush T, et al. JAMA 1998;280:605-13

“The discrepancy between the finding of HERS and the observational studies may also reflect important differences between the study populations and treatments”.

Hulley S, Grady G, Bush T, et al. JAMA 1998;280:605-13

“Perhaps post-menopausal hormone therapy is beneficial in women who have not yet developed coronary disease but not in women who already have it”.

Grady D, Hulley SB. Ann Intern Med 2000;133:999-1001

Cardiovascular contradictions …

. **HERS II**

- **smokers!** ***(less risk?)***
- **living alone** ***(more risk?)***
- **digitalis users** ***(more risk?)***

"The observed lower event rate in smokers compared with non smokers in the hormone group is intriguing" !...

There is "a higher event rate among users of digitalis in the hormone group compared with the placebo groups" !...

Furberg CD, et al. Subgroup Interactions in the Heart and Estrogen/Progestin Replacement Study. *Circulation* 2002;105:917-922.

In the HERS Study "it is difficult to explain why hormone therapy would increase the risk of coronary events in women with less than 3 live births and in those living alone"!

Furberg CD, et al. Subgroup Interactions in the Heart and Estrogen/Progestin Replacement Study. *Circulation* 2002;105:917-922.

The authors of these reanalysis of the HERS Study conclude that they "did not identify any sub groups of HERS participants in which postmenopausal treatment was clearly beneficial or harmful".

Furberg CD, et al. Subgroup Interactions in the Heart and Estrogen/Progestin Replacement Study. *Circulation* 2002;105:917-922.

The WHI

The "Estrogen plus Progestin" arm of the *Women's Health Initiative* randomised control trial was suspended .

NOT the "Estrogen only" arm!

“the increased risk of breast cancer for each woman in the WHI study who was taking the estrogen plus progestin therapy was actually very small: less than a tenth of 1 percent per year” (0.1%)

Rossouw J. Release of the Results of the Estrogen PlusProgestin Trial of the Women’s Health Initiative: Findings and Implication. Press Conference Remarks July 9, 2002.
http://www.nhlbi.nih.gov/whi/hrtupd/roussouw.htm

The WHI

The women in the study were older: the mean age was 63.

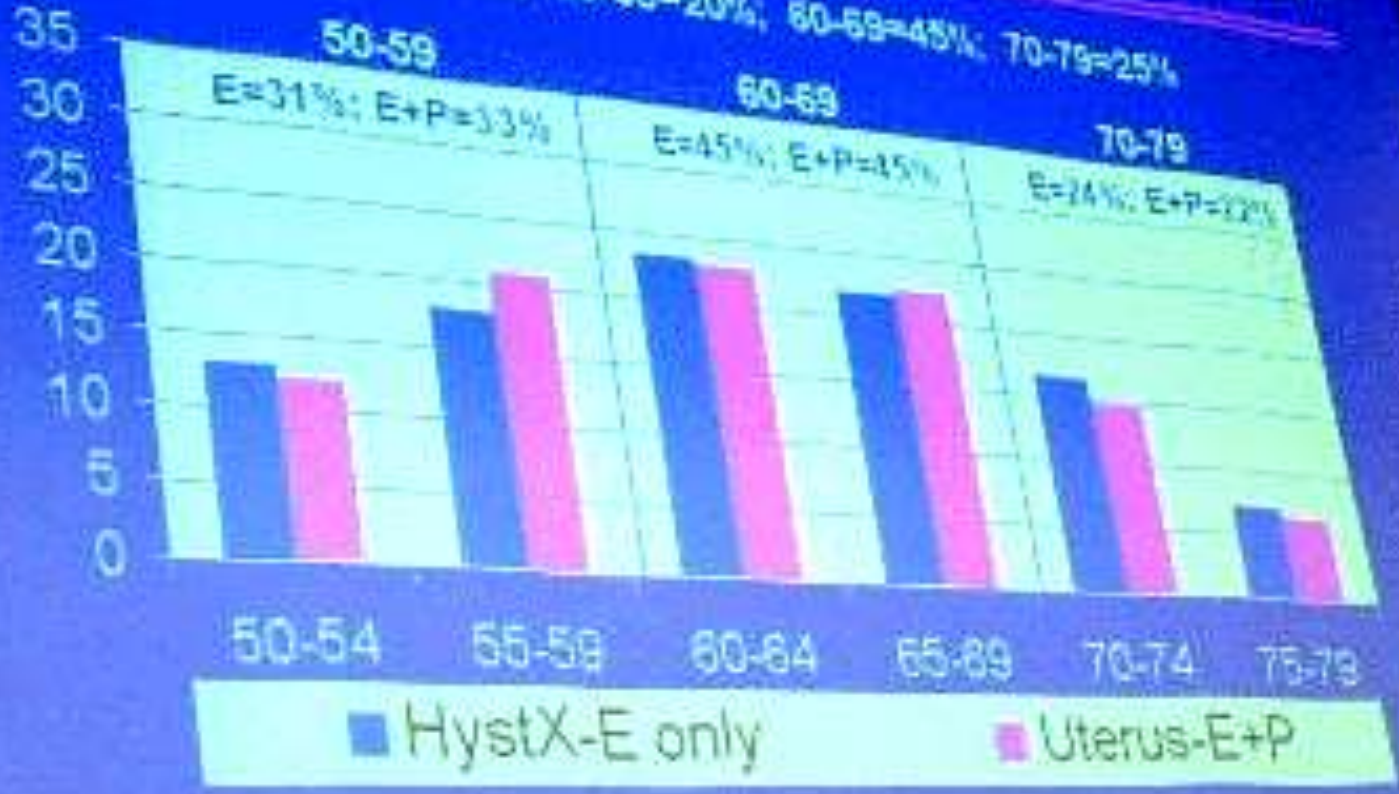
Thus, they were past the age of menopausal symptoms.

Thacker HL. The case for hormone replacement: New studies that should inform the debate.Cleveland Clinic Journal of Medicine 2002;69(9):670-678

WHI HRT: Baseline Age Distribution

Mean ± SD: HystX-E only = 63.6 ±7.3; Uterus-E+P = 63.3 ±7.1

Goal: 50-54 = 10%; 55-59=20%; 60-69=45%; 70-79=25%



The WHI

The study was not an efficacy trial.

but rather

a preventive trial.

Thacker HL. The case for hormone replacement: New studies that should inform the debate.Cleveland Clinic Journal of Medicine 2002;69(9):670-678

If Absolute Risks are plotted as percentages,

instead of the additional

8 strokes

7 heart attacks

8 breast cancers ***per 10.000 woman/year***

one would have, respectively

0.08

0.07

0.08 ***cases per 100 woman/year***

a figure that is easier to interpret

Summary:

- Long-term HRT leads to a small increase in breast cancer incidence:
  - Age 50–59 years, 3.2 extra cases per 1000 users over 5 years; and
  - Age 60–69 years, 4 extra cases per 1000 users over 5 years.
- Long-term HRT leads to a reduction in colorectal cancer incidence:
  - Age 50–59 years, 1.2 fewer cases per 1000 users over 5 years; and
  - Age 60–69 years, 3 fewer cases per 1000 users over 5 years.
- Long-term HRT does not appear to affect mortality.

WHI results calculated as

	NNT/1 year	NNH/1 year
CHD		1428
Stroke		1250
VTE		588
Breast Cancer		1250
Colon Cancer	1667	
Osteoporotic fractures (totals)	227	

Neves-e-Castro M (2003) "*WHI* menopause is in a *crisis*?" *Human Reproduction (submitted)*.

“The absolute excess risk events included in the global index was 19 per 10.000 person/years”

(1.9 events per 1.000 w/ys !)

Writing Group for the Women’s Health Initiative Investigators. Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women. *JAMA* 2002;288(3):321-333

WHI report stresses that "the results do not necessarily apply to lower dosages of those drugs, to other formulations of oral estrogen and progestin or to estrogens and progestins administered through the transdermal route"

Writing Group for the Women's Health Initiative Investigators. Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women. *JAMA* 2002;288(3):321-333

The recommendations of the WHI writing group are mainly focused on public rather than individual health

"Those data describe increased risk of an entire population, not the increased risk for individual women"

Rossouw J. Release of the Results of the Estrogen Plus Progestin Trial of the Women's Health Initiative: Findings and Implication. Press Conference Remarks July 9, 2002. *http://www.nhlbi.nih.gov/whi/hrtupd/roussouw.htm*

"THE WHI study authors took pains to emphasize that women should not be unduly alarmed. The increased risks in WHI applied to an entire population of women, not to increased risks for individual women – which were very small, less than a tenth of 1 percent per year".

(The American College of Obstetricians and Gynecologists, special Task Force on Hormone Replacement Therapy, July 2002).

WISDOM trial vs WHI

"No strong ethical or scientific reasons to stop the trial"

"still important questions about the balance of risks and benefits from taking HRT long-term that have not yet been answered.

Committee in charge of the WISDOM trial, Britain's Medical Research Council

WISDOM trial vs WHI

WISDOM unanimously concluded that WHI's evidence that hormone replacement therapy raises the risk of heart disease is *not convincing*. The US researchers have not determined the size of the risks reliably. This split, according to many observers, reflects a *difference between cultures* as much as a *disagreement over the science*.

Collins R.Despite safety concerns, UK hormone study to proceed. Science 2002;297:492

The HOPE Study

>2600 healthy, symptomatic, with intact uterus

At 2 years

No increase in venous thromboembolism was seen in the large group of relatively healthy postmenopausal women

Thacker HL. The case for hormone replacement: New studies that should inform the debate.Cleveland Clinic Journal of Medicine 2002;69(9):670-678

The HOPE Study

There were improvements in measures of coagulation and fibrinolysis in all the active-treatment groups.

Thacker HL. The case for hormone replacement: New studies that should inform the debate.Cleveland Clinic Journal of Medicine 2002;69(9):670-678

The HOPE Study

The lower dose (CEE 0.3 mg + MPA 1.5 mg) favorably affects the lipid profile, does not adversely affect carbohydrate metabolism, and maintains skeletal health.

HERS II vs WHI

ELSEVIER

Maturitas 42 (2002) 255–258

MATURITAS

THE EUROPEAN MENOPAUSE JOURNAL

www.elsevier.com/locate/maturitas

Results from WHI and HERS II - Implications for women and the prescriber of HRT

Manuel Neves-e-Castro *, Göran Samsioe, Martina Dören, Sven O Skouby

On behalf of the European Menopause & Andropause Society (EMAS)


GRAYLYN
CONFERENCE
CENTER
WAKE FOREST
UNIVERSITY

Effect on the risk of CHD

WHI **Significant increased risk**

RR 1.29 (CI 1.02-1.63); **29 %** increased risk

AR 0.37% vs 0.30% (ie, **37** vs **30** events annually per 10.000 women)

HERS **Nonsignificant decreased risk**

RR 0,99 (CI 0.84-1.17); 1% decreased risk

AR 3.66% vs 3.68% (ie, 366 vs 368 events annually per 10.000 women)

"Unlike HERS which showed no benefit or harm after 6.8 years of hormone use, WHI found more heart disease in women taking the combined therapy after 5.2 years."

"This is a key finding because WHI results apply to healthy women while HERS involve women with heart disease"

Rossouw J. Release of the Results of the Estrogen Plus Progestin Trial of the Women's Health Initiative: Findings and Implication. Press Conference Remarks July 9, 2002. *http://www.nhlbi.nih.gov/whi/hrtupd/roussouw.htm*

"The findings in WHI for stroke are consistent with but somewhat more extreme than those of HERS" .

This is puzzling since the HERS participants where definitely sicker (CV) than those in WHI, supposed to be CV disease free.

Writing Group for the Women's Health Initiative Investigators. Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women. *JAMA* 2002;288(3):321-333

“More recent epidemiological studies continue to supply evidence that long-term postmenopausal hormone therapy may reduce the risk for CAD in healthy women”

Hu FB, Grodstein F. Postmenopausal hormone therapy and the risk of cardiovascular disease: the epidemiologic evidence. *Am J Cardiol* 90(1) Supl.1:F26-F29

National Registry of Myocardial Infarction

HRT remained associated with improved survival

OR = 0.65 (CI: 0.59- 0.72)

Shipak MG et al.Hormone Therapy and in-hospital survival after myocardial infarction in postmenopausal women. Circulation 2001;104:2300-2304

National Registry of Myocardial Infarction

Women with MI who had used postmenopausal HRT had a lower mortality rate:

7.4% vs 16,2% in nonusers

Shipak MG et al.Hormone Therapy and in-hospital survival after myocardial infarction in postmenopausal women. Circulation 2001;104:2300-2304

You need healthy endhotelium to respond to estrogen.

Beneficial effects of hormonal treatment are progressively diminished with increasing atherosclerosis.

Speroff L.WHI Trial Arm with E/P Finds An Increase In Breast Cancer . Ob/Gyn Clin Alert August 2002;19(4):25-32

Effect on the risk of stroke

WHI **Significant increased risk**

RR 1.41 (CI 1.07-1.85); **41%** increased risk

AR 0.29% vs 0.21% (ie, **29** vs **21** events annually per 10.000 women)

HERS **Nonsignificant increased risk**

RR 1.09 (CI 0.88-1.35); **9** % increased risk

AR 2.12% vs 1.95% (ie, 212 vs 195 events annually per 10.000 women)

Effect on the risk of breast cancer

WHI **Nonsignificant increased risk**

RR 1.26 (CI 1.00-1.59); **26%** increased risk

AR 0.38% vs 0.30% (ie, **38** vs **30** events annually per 10.000 women)

HERS **Nonsignificant increased risk**

RR 1.27 (CI 0.84-1.94); 27% increased risk

AR 0.59% vs 0.47% (ie, 59 vs 47 events annually per 10.000 women)

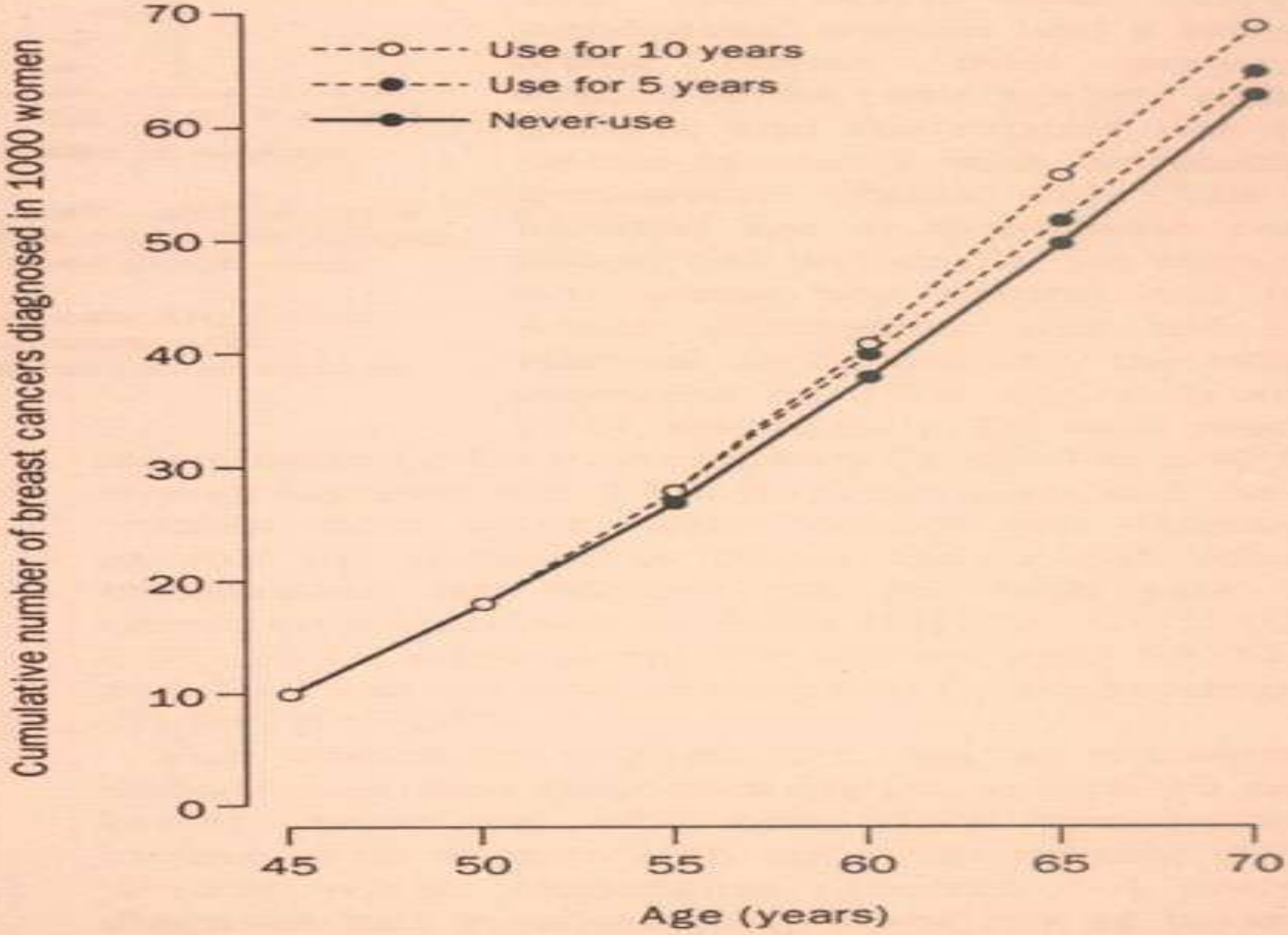


Figure 9: Estimated cumulative number of breast cancers diagnosed in 1000 never-users of HRT, 1000 users of HRT for 5 years, and 1000 users of HRT for 10 years

Estimated numbers for 1000 women in Europe or North America, with assumption that HRT use began at age 50.

Breast Cancer and HRT

CGHFBC-Lancet 1997;350:1047-59

Cumulative incidence/1000 women

(starting at age 50)

5 years	***2*** **new cases**
10 years	***6*** **new cases**
15 years	***12*** **new cases**

Do not confuse…

Relative Risk

with

Absolute Risk!

Do not confuse…

Morbidity

with

Mortality

Epidemiological Studies

PLEASE!

Do not read only the tittles

Do not read only the abstracts

Do read the full paper

Be critical!

Make up your own mind!

MNC

Selections

of the

Readers's Digest

“High quality observational studies may extend evidence over a wider population and are likely to be dominant in the identification of harms”

Barton S.-Which clinical studies provide the best evidence? The best RCT still trumps the best observational study. *BMJ* 2000:321:255-6

The WHI decision to stop the estrogen progestin arm does not minimally affect a wise clinician's decision as to the best clinical care of a postmenopausal woman.

"***More recent epidemiological studies continue to supply evidence that long-term postmenopausal hormone therapy may reduce the risk for CAD in healthy women***"

Hu FB, Grodstein F. Postmenopausal hormone therapy and the risk of cardiovascular disease: the epidemiologic evidence. *Am J Cardiol* 90(1) Supl.1:F26-F29

The WHI is an important study.

However,

it does not introduce new rules to good clinical

Interventions investigated…

Only "*hormone replacement therapy*"!...

Thus,

Studies based *ONLY* on the use of hormones do not reflect good clinical practice!...

A menopausal woman is a middle-aged woman

As a menopausal woman:

She is hypoestrogenic and will suffer, at various levels, from its consequences.

MNC

As a mid-age woman:

She will suffer from the process of natural ageing, both from a biological and a psychological perspective.

Attention!

Please remember:

our main target is mature woman's health and disease prevention *by all means*,

drug and non-drug related.

CONCLUSION

There is only one medicine.

What must we learn…

How to practice

GOOD

MEDICINE!