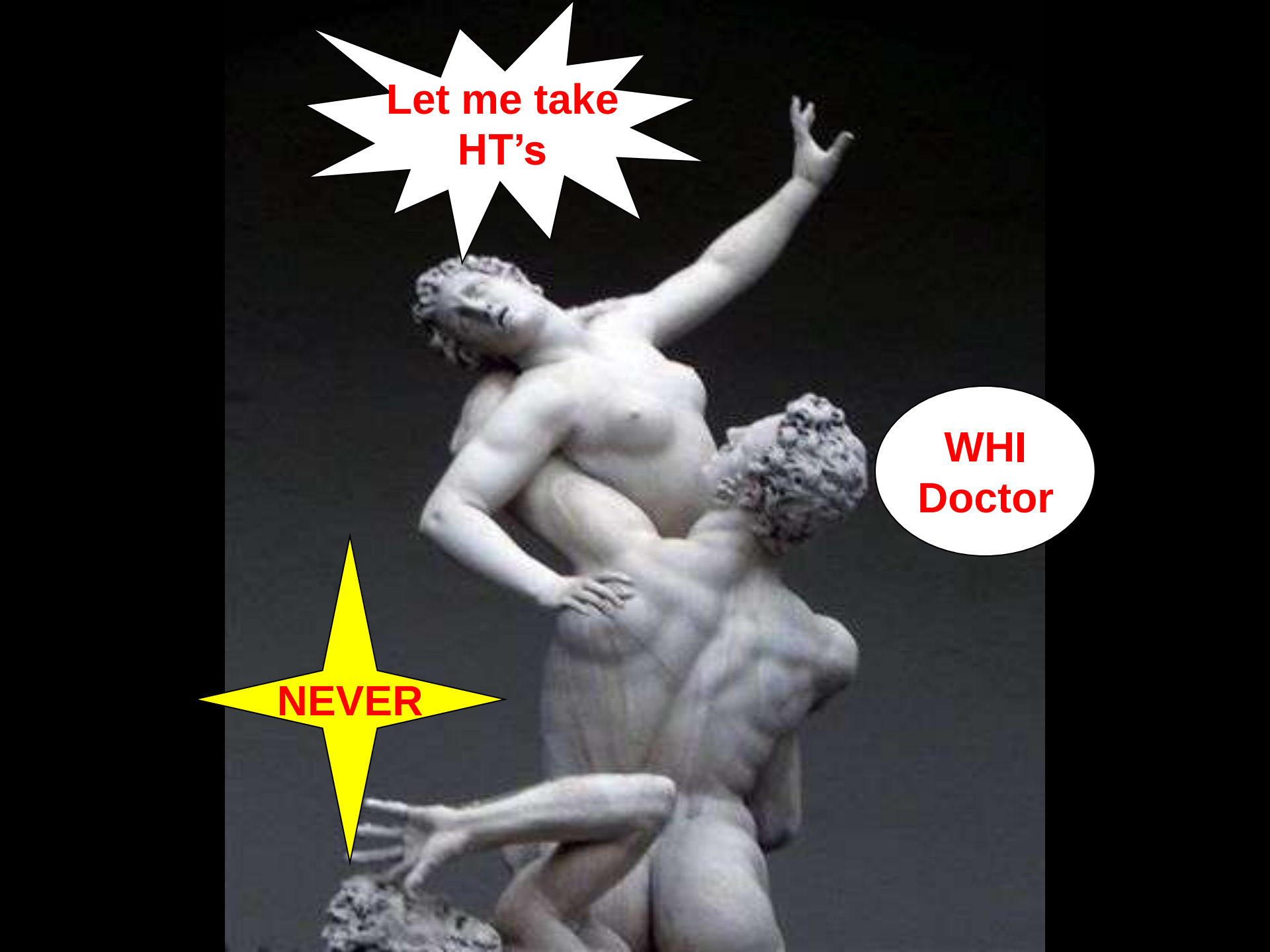
Let me take HT's
WHI Doctor
NEVER

por isso ...
Mário de Sousa

foi ler o

Hamlet

Ser ou não ser…

Porque sim?

Porque não?

por

Manuel Neves-e-Castro

VII Reunião Cientifica

da

Sociedade Portuguesa de Menopausa

Viseu, 16 Outubro 2004

To Know …

What is it?

It is the selective and critical acquisition of information and its concerted integration in our mind.

Are we being well informed?

or

“well” misinformed? …

Information is based on Epidemiological studies

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

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Epidemiological studies

1. Descriptive studies
2. Analytical studies
3. Experimental studies

1. Descriptive Studies

- Who has the disease?
- What is the disease?
- Why did the condition arise?
- When does the disease occur?
- Where does the diseases occur?
- What is the clinical importance of report?

2. Analytical Studies

- **Cross- sectional**
- **Observational :**

  Case control **(starts from a disease and looks back in time at exposure)**

  Cohort studies **(from exposure to outcome; natural history of disease) (NHS)**

then ...

How to screen

what is true and

what is not ?...

The “language” of the results

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

Example of Absolute Risk

- ***If you buy*** **one** ***lottery ticket*** **you will have a one in 1 million chance of winning**
- ***If you buy five lottery tickets*** **your chances are five fold higher or 5 in one million**
- **Your chances of winning are increased by five fold (relative risk)**

Relative Risk

The risk of an event occuring under certain circumstances compared to the risk under other circumstances

Attributable or Excess Risk

The difference between underlying risk and risk when receiving HT is called the attributable or excess risk

Do not confuse…

Relative Risk

with

Absolute Risk!

Conclusion

- **Relative risk is a *confusing* word and is only important if the absolute chances of an event are high**
- **Attributable or excess risk is the thing that one should be most concerned about**

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*

?

3. Experimental Studies

- Controlled randomized trials (WHI)
- Crossover trials

Confidence interval (C.I.)

A 95% C.I. signifies that there is a 95% chance that the population "true value" lies between the two limits.

If C.I. crosses the "line of no difference" the point at which a benefit becomes a harm (i.e.1) then one can conclude that the results are not statiscally significant

Does

“Statistically Significant”

always equate to

“Clinically Relevant”?

Utian W. Menopause Management 2003;12:9-10

p Value

Is the *probability* of obtaining the observed relative risk by chance

(*p* must be < 0.05)

Type of association

- Spurious
- Indirect
- Causal
    - Strenght of association
    - Consistency
    - Dose response relationship
    - Specificity
    - Biological plausibility

Validity

Internal: the study measured what is set out to measure

External: the results can be extrapolated to one's patients

Observational research (NHS) may have

poorer internal validity

better external validity

Randomized controlled trial (WHI)

better internal validity

poorer external validity

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)

WHI

(JAMA 2002;288:321-331)

- **Results:**

  "the difference reaches **"almost nominal** statistical significance" ***(i.e. not statistically different!)***

- **Discussion:**

  "**the substantial risks** for CVD and breast cancer" (?!...)

Thus…

“The breast cancer findings are reported as statistically insignificant but are regarded as clinically relevant!”

Utian W. Menopause Management 2003;12:9-10

Do not confuse…

Morbidity

with

Mortality

Breast cancer
WHI

RR 1.26 ARC 0.30% / 10.000 / yr

C.I. (1.00 – 1.59) ART 0.38% / 10.000 / yr

Attributable risk = 8/10.000 / yr

= 1/1.250 / yr

NNH = 1.250 / yr

Breast cancer
HERS

RR= 1.27 ARC = 0,59% / 10.000 / yr

C.I.(0,84-1.94) ART = 0,47% / 10.000 / yr

Attributable risk = 12 / 10.000 / yr

= 1 / 833 / yr

NNH = 833 / yr

"The nurse's study and ones like it could be right and the Women's Health Initiative could be wrong, or vice-versa"

Rossouw J, 2003

”May be each study is wrong. May be estrogen, in pills, is not the chemical to focus on”

Rossouw J, 2003

“If each is right it may be because the women in the two types of studies are different in a way that researchers have not yet figured out”.

Rossouw J, 2003

“It is quite possible that both are correct. The different results may hinge on the differences between the women who joined the studies”

Grodstein F, 2003

Occult Breast Cancer

Clinically occult **in situ BC's are frequent in young and middle-aged women.**

Nielsen M *et al*-Br J Cancer 1987;*56*:814-9

Occult Breast Cancer

Breast malignancy was found in 22 women (20%)

Nielsen M *et al*-Br J Cancer 1987;*56*:814-9

Occult Breast Cancer

Malignancy was significantly more frequent among women

. aged more than 40 years

. with late age at first full-term pregnancy

. with alcohol abuse

. with steatosis or cirrhosis of the liver

Nielsen M *et al*-Br J Cancer 1987;*56*:814-9

HRT and Breast Cancer

Pregnancy Following Breast Cancer
Gelber 2001

	Cases	Controls
	86	172
5yr survival	97%	86%
10yr survival	93%	75%

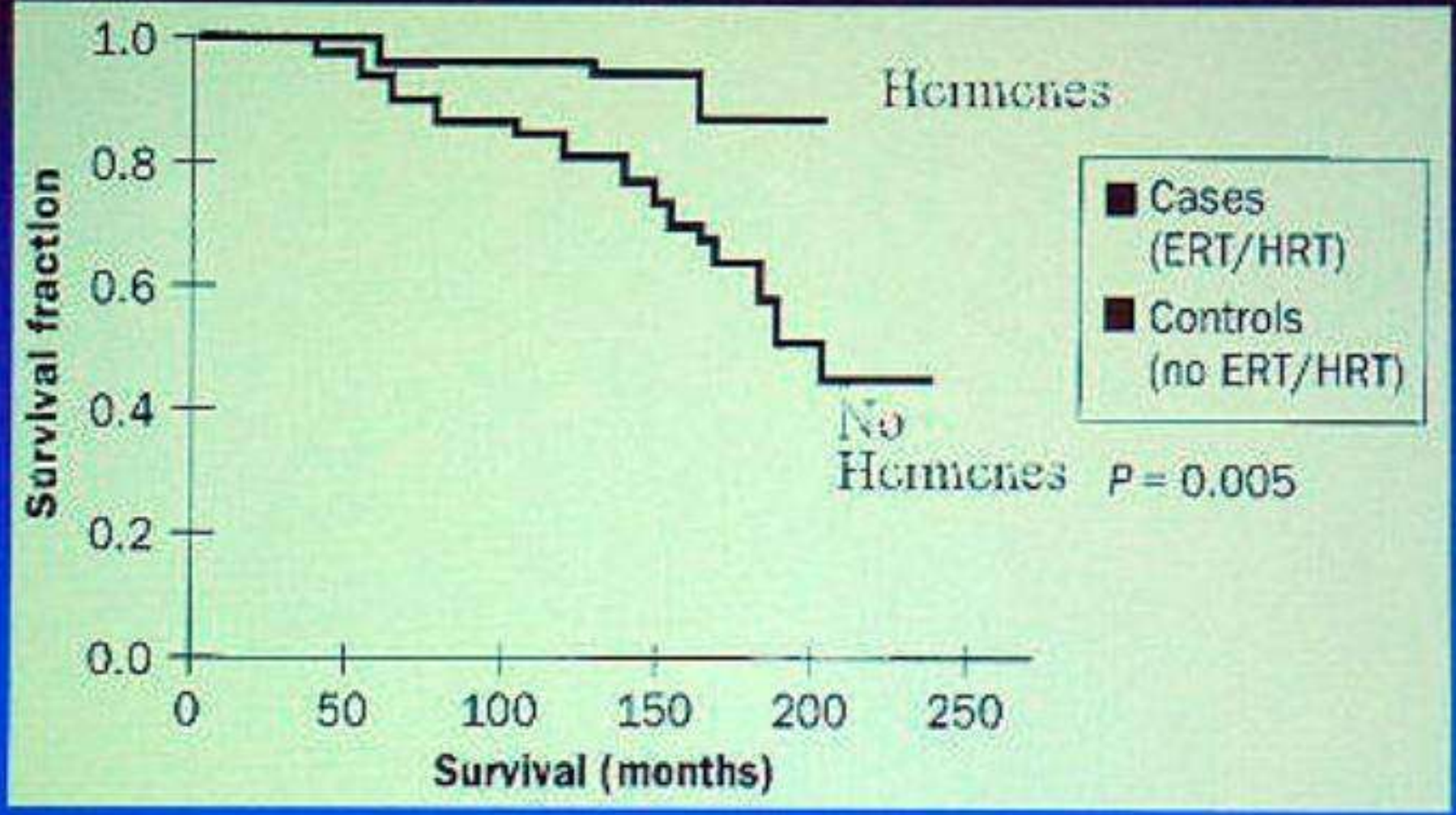
HRT in Breast Survivors: results:Matched Analysis

174 breast cancer cases taking estrogen matched 4:1 controls with cancer not taking Estrogen.

	Cases (ERT/HRT)	Controls (no ERT/HRT)
recurrence	17/1000	30/1000
Br cancer deaths	5/1000	16/1000
Total deaths	16/1000	30/1000

O'Meara et al, JNCI 2001

HRT in Breast Cancer Survivors:
Results: Kaplan Meier Survival Analysis



DiSaia et al. Am J Clin Oncol Dec 2000

The conclusions of these studies suggest that the *"safe " woman* (NNH between 600-1000 women) to initiate HT is

- between 50-59 years of age
- with vasomotor symptoms
- less than 10 years after the menopause
- being treated with statins
- with a good lipid profile and
- with a Body Mass Index >25

Neves-e-Castro M. **Menopause in crisis post-Women's Health Initiative? A view based on personal clinical experience.** ***Human Reproduction 2003;18:1-7***

This is precisely the profile of the great majority of women who come for consultation after their menopause.

Therefore *it seems that what most gynecologists are doing to their predominant population of patients is not unsafe and contributes not only to a good quality of life but to prevention, as well.*

Neves-e-Castro M*. Menopause in crisis post-Women's Health Initiative? A view based on personal clinical experience. *Human Reproduction 2003;18:1-7

“Each time we learn something new, the astonishment comes from the recognition that we were wrong before.

In truth, whenever we discover a new fact, it involves the elimination of old ones.

WE ARE ALWAYS, as it turns out, fundamentally IN ERROR.”

Lewis Thomas

English Biologist (1913-1993)

The take-home message is: (1)

Prescribe postmenopausal hormonal treatments

when clinically indicated,

***if not contraindicated*!**

The take-home message is: (2)

- The prescription of long-term hormonal treatments must depend always on a benefit/risk analysis *in comparison with other non-hormonal medications and strategies*.

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The take-home message is: (3)

- ***No answers*** **from ongoing clinical trials** ***are indispensable*** **to practice today a good Medicine !**

MNC/02

Preventing a woman from the benefits of a

sound postmenopausal hormone therapy

because of the fear of rare side effects

does not seem to be satisfactory Medicine...

M.Neves-e-Castro, 2000

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!

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