Preventing Breast Cancer in HT users

by
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Portuguese Menopause Society
September 2004

I am also PRO!...

because HT

does not increase breast cancer,

and overall,

its benefits out weight its risks !

The Risks

White woman's risk of death between the ages of 50 and 94 are:

31.0% from heart disease

2.8% from breast cancer

2.8% from hip fracture

Brinton LA, Schairer C. N Engl J Med.1997;336:1769-1775

WHI

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

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

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

"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

“Women considering taking CEE should be counseled about an *increased risk of stroke* but can be reassured about no excess risk of heart disease or breast cancer for at least 6.8 years of use.”

Effects of conjugated Equine Estrogen in Postmenopausal Women with Hysterectomy.JAMA, 2004;291:1701-1712

Breast Cancer

"The increased risk of breast cancer with longer-term exposure, however, seems to be limited in most studies to lean women (ie, BMI<25kg/m2)."

"ET part of the WHI trial has showed no increased the risk of breast cancer"

EMAS Statement 2004.

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

"A subsequent analysis by the WHI of the full 5-year period has already shown that there was not a statistically significant increase in breast cancer and the apparent increase in the cardiovascular hazard, new breast cancer incidence and thromboembolic event frequency risk in year five ***had occurred because of a transient fall in the rates of these events/diagnoses in the*** **placebo group,** ***rather than a rise in the estrogen + progestin group"***

Rossouw JE, *et al*. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *J Am Med Assoc* 2002;288:321–33

WHI

"In any case, the lack of statistically significant differences between groups after the full duration of the WHI trial makes conclusions regarding the value of HT highly uncertain and *devalues or invalidates the conclusions* from the initial publication from which so many clinical implications have been drawn."

Position Statement *International Menopause Society, 2004*

http://www.imsociety.org

MWS

- **Breast cancer diagnosed on average 1.2 years after recruitment**

- **Average time between diagnosis and death was 1.7 years *(thus, advanced disease at time of diagnosis)***

Banks E. J Epidemiol Biostat 2001;6:357-63

Breast Cancer

MWS data compared to other publish data

	MWS (2003)	GPRD (2002)	Beral (1997)	Ross (2000)	Weiss (2002)	WHI (2003)
EPT	2.00	1.21[1]	1.15[2]	1.24[3]	1.22	1.26
ET	1.30	0.97	0.99[2]	1.06[3]	0.84	ongoing[4]
Tibolone	1.45	1.02				
		[1]Seq EPT	[2] ≤ 5 y use	[3]Per 5y use		[4]> 6 y

Breast Cancer
Million Women Study

The follow-up for breast cancer diagnosis was just over 2½ years, meaning that these breast cancers were almost certainly pre-existent at the start of the observational period.

Press Release from the *British Menopause Society, 2003*

DISCORDANCE AMONG STUDIES

- **WHI** – delayed increase in risk (>2 years)

- **MWS** – immediate increase in risk

  Risk desapearing > than 1 year after stoping HT

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Million Women Study: On-Off-Phenomenon

Shortly after cessation of treatment, past users had no increase in breast cancer incidence or **mortality**. Given the long latency time between tumour induction and detection, plus the fact that **cancer is**, by definition, **an autonomous process that does not cease by stopping exposure**, how can these findings be explained?

.

J. Dinger: Letter to the editor of Lancet (Oct 2003) – refused -.

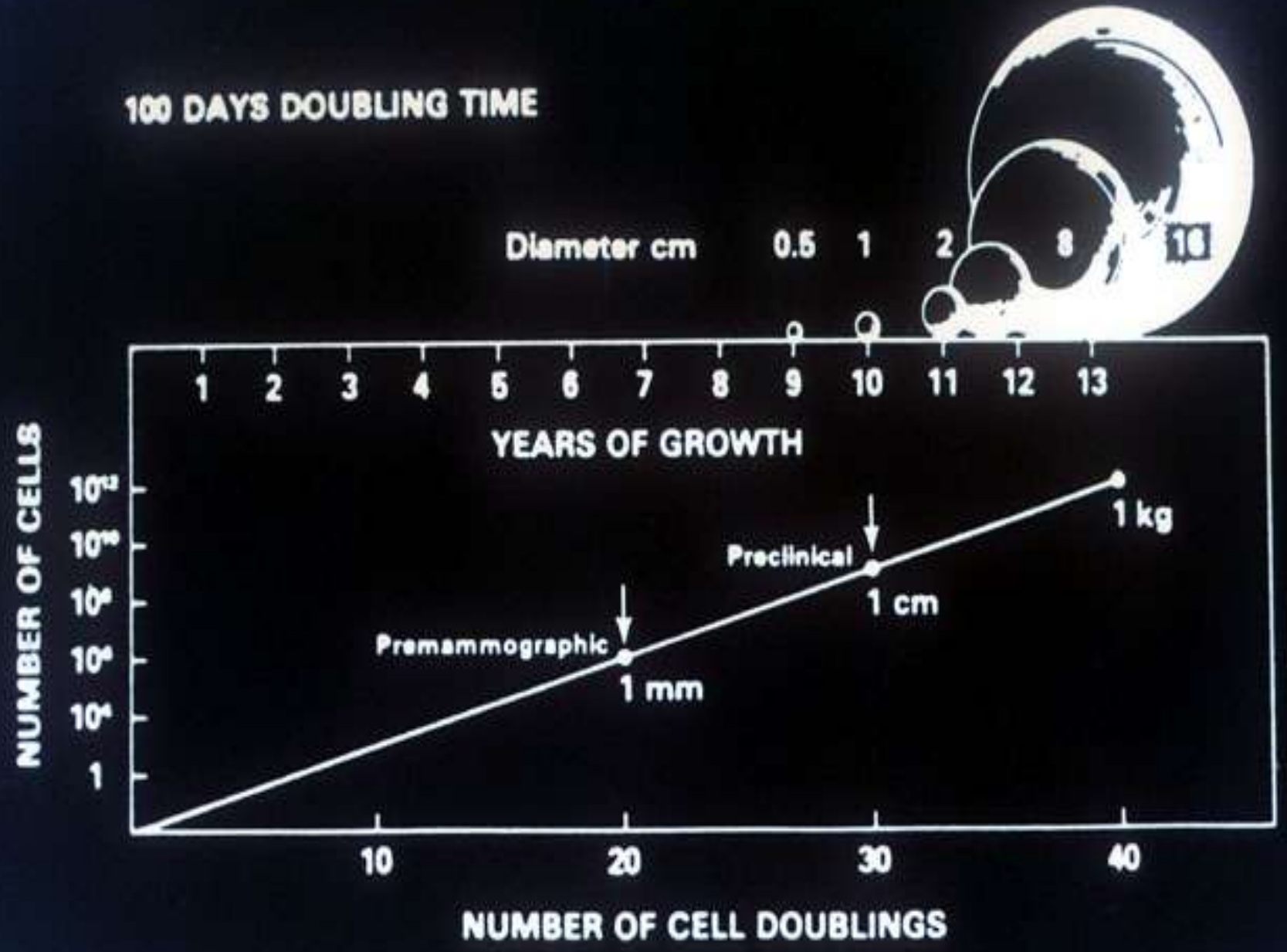


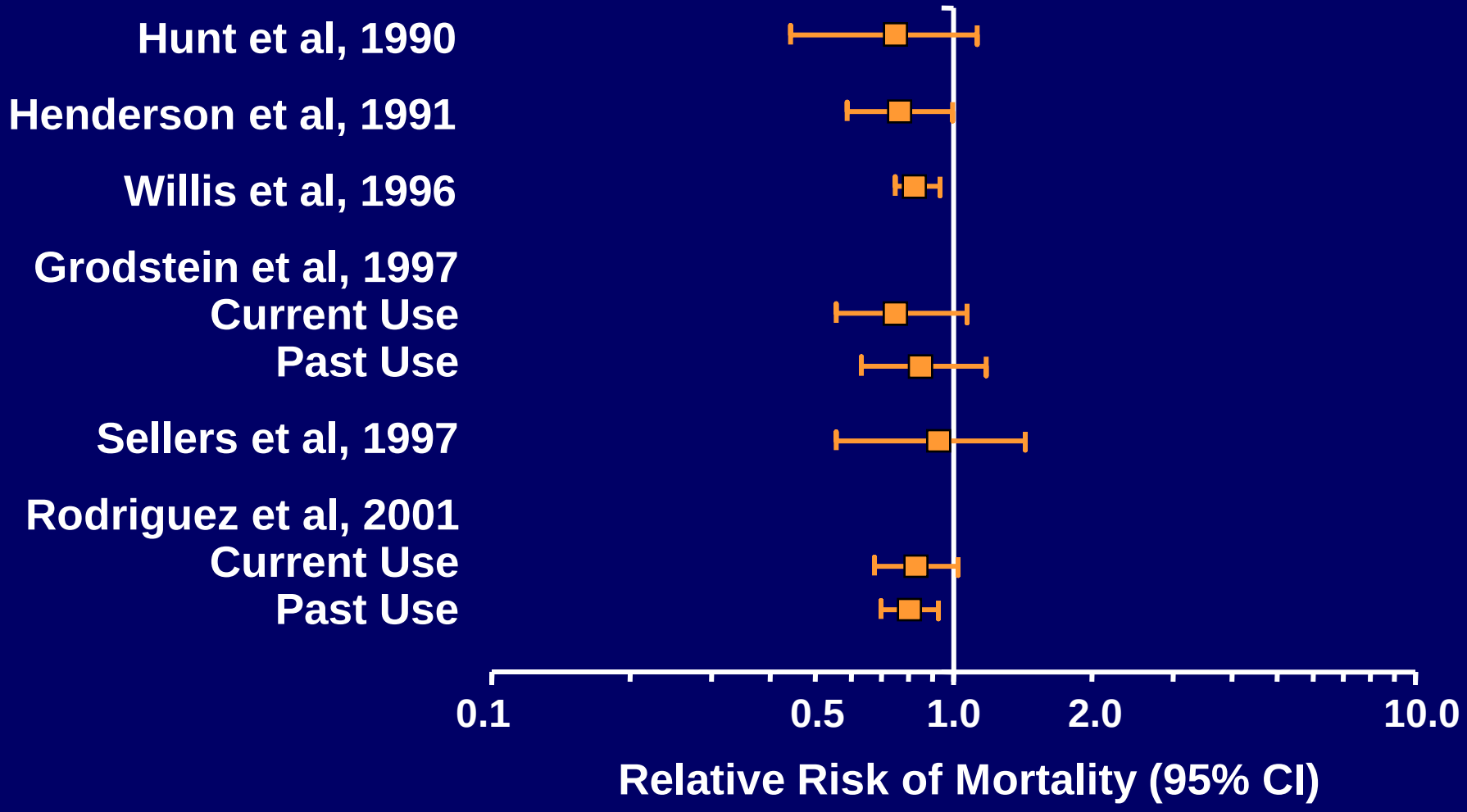
Figure 17–2. The long preclinical existence of breast cancer based on tumor doubling time. (*From Gullino PM: Cancer 1977;39:2697.*)

Fatal Breast Cancers

	Case-death	Case-No death	
Current use	**191**	**3011**	**3203**
Never use	**238**	**2656**	**2894**
RR=0.71 (95% CI 0.58-0.87)			

Million Women Study Collaborators. Breast Cancer and hormone replacement therapy in the Million Women Study. ***Lancet 2003;362:419-427***

Results for Breast Cancer Mortality With ET/HT Use Show Consistency



Breast Cancer

The possibility that contemporary HT causes an increase in breast cancer is not clarified by either the WHI or the MWS and remains to be resolved

Position Statement ***International Menopause Society, 2004***

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%

HABITS STUDY

Hormonal replacement therapy after breast cancer- is it safe?

A randomised comparison

Trial stopped

Holmberg L, Anderson H. Lancet 2004;363:

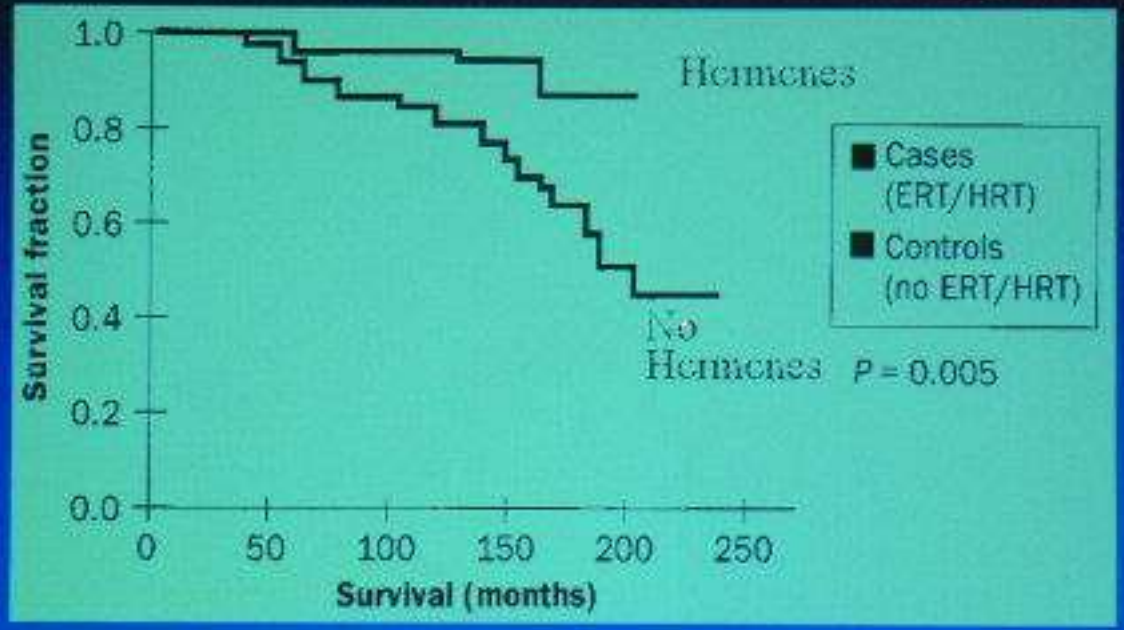
HRT in Breast Survivors: results:Matched Analysis

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

“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 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

HRT and Breast Cancer link still unclear

Bush TL et al -*Hormone replacement therapy and breast cancer: a qualitative review.* Obstet Gynecol 2001;98:498-508

"The evidence did not support the hypotheses that estrogen use increases the risk of breast cancer and that combined hormone therapy increases the risk more than estrogen only. Aditional observational studies are unlikely to alter this conclusion".

BREAST CANCER

Risk factor	***Relative risk***	***Increase incidence***
Body weight-normal weight : obesity	1 : 2.5	+ 150%
Age at menopause - 42yrs : 52 yrs	1 : 2.0	+ 100%
Age at menarche – 14 yrs: 11 yrs	1 : 1.3	+ 30%
Parity – multiparous : nulliparous	1 : 1.3	+ 30%
Age at first birth – 20 yrs : 35 yrs	1 : 1.4	+ 40%
Oral contraceptives – never user:ever user	1 : 1.1	+ 10%
Hormone replacement-never:5 or more yrs	**1 : 1.3**	***+ 30%***
Alcohol consumption-none:≥20 g daily	1 : 1.3	+ 30%
Serum lipids – normal : raised	1 : 1.6	+ 60%
Physical activity – activate : inactive	1 : 1.2	+ 20%

R. Santen, 2004

RELATIVE RISK OF BREAST CANCER BY BODY WEIGHT

Age at Diagnosis	Weight (Kg)		
	<60	60-69	70+
35-49	1.00	0.54	1.16
50-59	1.00	1.22	1.43
60-69	1.00	1.61	1.81

from deWaard et al ,1964,1978

How to decrease potential risks?

How to decrease potential risks

- Age at begining (window of oportunity)
- BMI
- Parenteral estradiol (transdermal, subcutaneous)
- Parenteral progesterone (vaginal, IUD)
- Adition of testosterone or dihidrotestosterone
- Tibolone
- Raloxifene
- Aspirin
- Statins
- hCG ? (Russo, Bo Schoultz)

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TABLE 2. *Breast cancer cases in women using testosterone compared with major studies*

	N	Age	Cases/100,000 woman-years	Years observed
Schairer et al[10] (E/P)	1,854	57.4 y	628	10.2
WHI[6] (E/P)	8,506	63.2 y	380	5.2
Million Woman[5] (E/P)	142,870	55.9 y	521	2.6
Million Woman[5] never-users	392,757	55.9 y	283	2.6
Adelaide (E/P/T)	347	57 y	293	5.9

Current E/P users are analyzed in comparison with never-users (from the Million Woman Study) and E/P/T users from Adelaide, South Australia. Citations refer to the "References" section at the end of the article. WHI, Women's Health Initiative; E/T, estrogen + testosterone; E/P/T, estrogen + progestin + testosterone.

Dimitrakakis C et al. Menopause 2004;11:531-535

Testosterone induced down-regulation of mammary epithelial proliferation and ERgene expression.

This suggests that **the addition of testosterone might reduce the risk of breast cancer associated with estrogen-progestin therapy in postmenopausal women.**

Zhou J, Ng S, et al. Testosterone inhibits estrogen-induced mammary epithelial proliferation and suppresses estrogen receptor expression. FASEB J 2000;14:1725–1730

In an estrogen replete environment **androgens oppose the unfavorable effects of estrogen in breast tissue**.

Consistent with this concept, tibolone

Yue W, Berstein LM, et al. The potential role of estrogen in aromatase regulation in the breast. J Steroid Biochem Mol Biol 2001;79:157–164

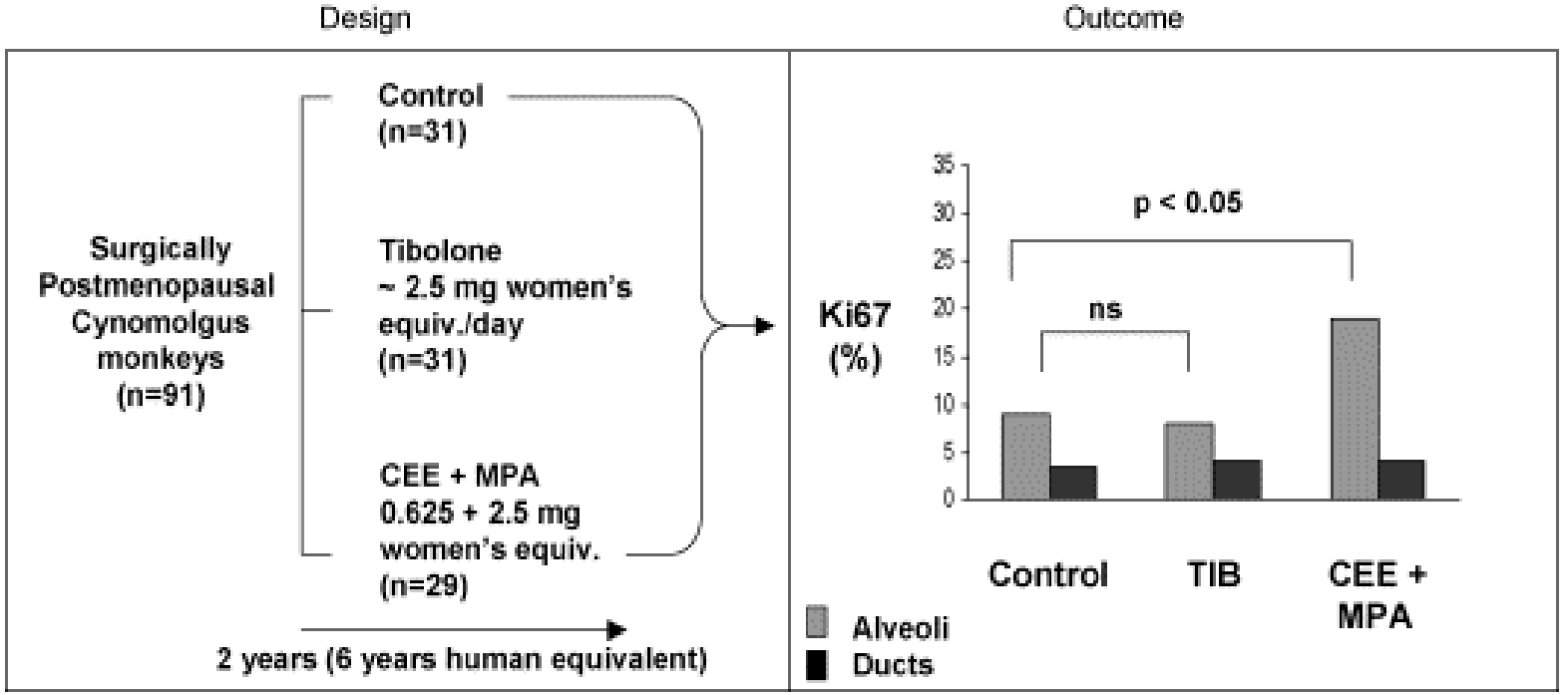

Fig. 6. Comparison of HT with exogenous progestogen (MPA) vs. endogenously derived progestogen (Δ4-ketoisomer of tibolone) on expression of Ki67 proliferation marker in breast epithelial tissue of surgically postmenopausal monkeys in surgically postmenopausal cynomolgus monkeys. Monkeys were treated with tibolone or conjugated equine estrogens (CEE) plus medroxyprogesterone acetate (MPA), for 2 years. Data are expressed as mean percent Ki67 M1B antibody stained cells. Data are modified from Cline et al. [40].

Aspirin and Breast Cancer

"Women who took aspirin seven or more times a week had a 26 percent lower risk of developing breast cancer than women who did not take it".

Terry MB et al. JAMA 2004;291:2433-2440

The Benefits

The Benefits

- **Osteoporosis**
- **Colon Cancer**
- **CHD *(Nurses Health Study, primate models)***
- **Alzheimer**
- **Quality of life (physical, mental, sexual)**

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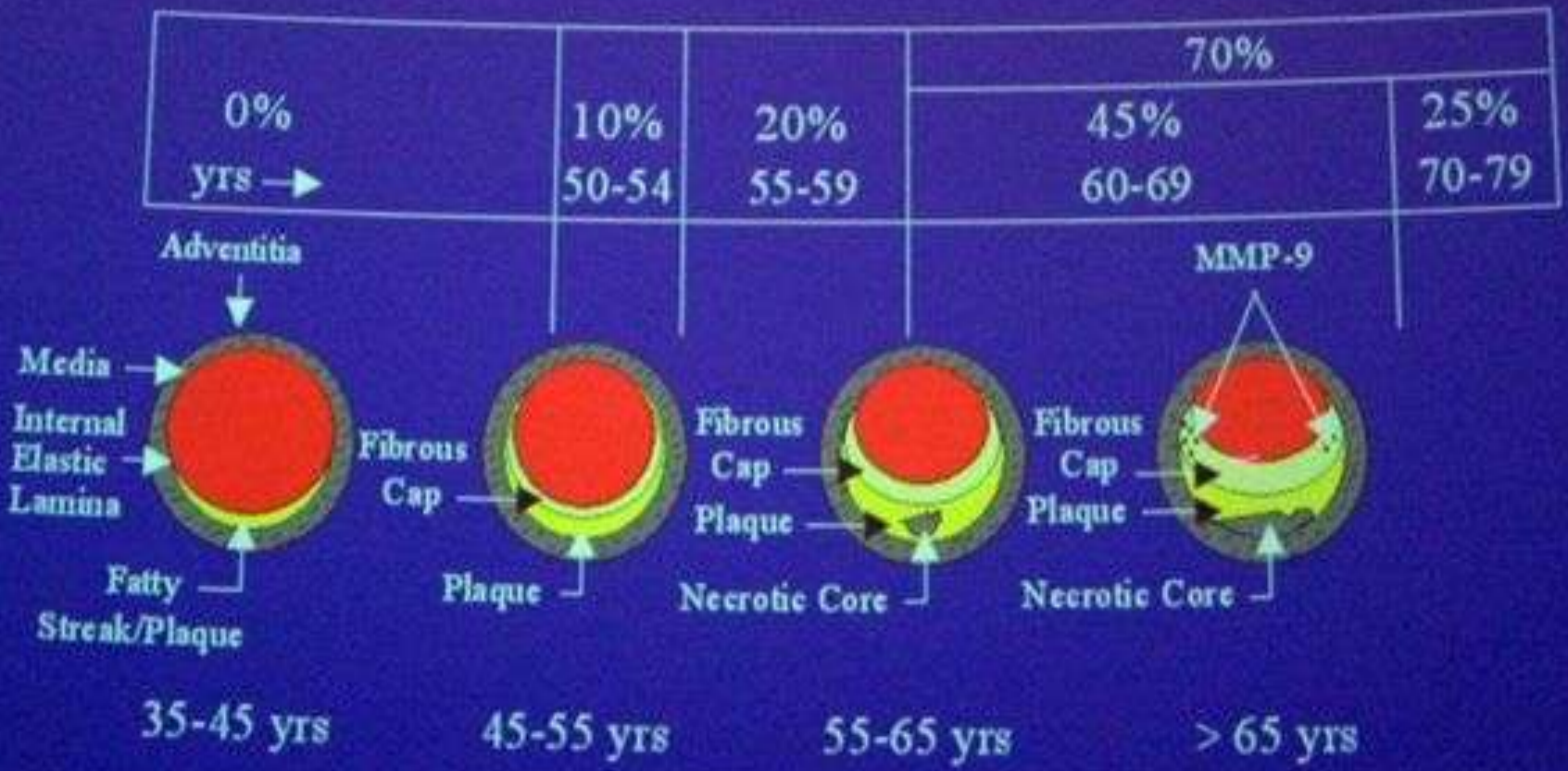
“The *Nurse’s Health Study* investigation of primary prevention indicates that hormone therapy may be associated with coronary benefits”.

Grodstein F, Manson JE, Colditz GA et al Ann Intern Med 2000:133;933-41

When "Primary Prevention" Starts

Relation of Age Distribution in WHI to Stage of Progression of Coronary Artery Atherosclerosis



With thanks to Tom Clarkson

The Truth?

"The objective of both basic and clinical science is to know the truth".

"Every epidemiologic study, no matter how good or how large, gives only one view of the truth".

"It takes many views to come close to seeing the truth"

Bush TL. *Int J Fertil*.2001;46:56-59

“Not everything that can be counted *counts*;

and not everything that *counts* can be counted”

Albert Einstein

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*.

MNC/02

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