Riesgo de CA mamario y Terapia Hormonal actual

por

Manuel Neves-e-Castro

VI Congreso Colombiano de Menopausia

Colombia, Marzo 3, 2005

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

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

Menopause

HORMONES AND CANCER

Proceedings of the 2nd International Symposium
of the Portuguese Menopause Society

Edited by
M. Neves-e-Castro
Reproductive Medicine Clinic, Lisbon, Portugal
and
B. G. Wren
Sydney Menopause Centre, Sydney, Australia

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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)

1. Background

Placebo controlled randomised clinical trials are considered to be the gold standards to assess the real risks and benefits of chronic treatments. This

0.7 and 0.8 cases per 1,000 woman / years a figure that is easier to interpret. It would suggest that if 1000 women were treated during one year there would be less than one woman with an adverse effect.

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

Women's Health Initiative

per 1000 pts over 5 years

	CHRT *Event*	No HRT *Event*	Changes
Coronary Heart Disease	17	13	+4
Stroke	13	9	+4
Pulmonary Embolism	8	4	+4
Invasive Breast Cancer	17	13	+4
Colorectal Cancer	5	8	-3
Hip Fracture	4	6	-2
Global Index	82	72	

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 !

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 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%)

Roussouw 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 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).

“HRT started at age 55 for 10 years can prolong life”.

“One excess breast cancer case is likely to occur per 5-6 averted cases of first myocardial infarction or hip fracture”.

Moerman CJ, Vanhout BA, BonneuxL, et al. J Intl Med 2000;248(2):143-150

The risks and benefits of HRT

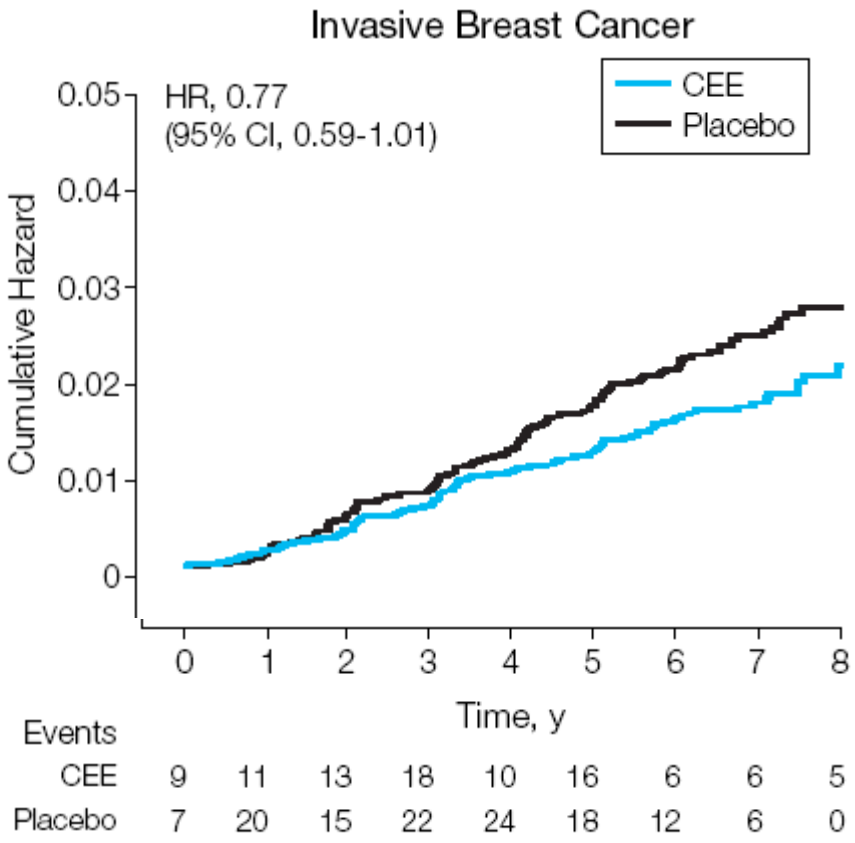
	Women aged 50-69 yrs	Women aged 60-69 yrs
Excess incidence per 1000 HRT users over 5 yrs		
Breast cancer	3.2	4.0
Stroke	1.2	4.0
Pulmonary embolism	1.6	4.0
Total excess	6/1000	12/1000
	1 in 170 users	1 in 80 users
Reduction in incidence per 1000 HRT users over 5 yrs		
Colorectal cancer	1.2	3.0
Hip fracture	0.5	2.5
Total deficit	1.7/1000	5.5/1000
	1 in 600 users	1 in 180 users
Overall balance	**Net excess**	**Net excess**
	4.3/1000	**6.5/1000**
	1 in 230 users	**1 in 150 users**

Table 1. Estimated change in incidence of risks and benefits for 5-year use of HRT[25].

Compstom JE. J Musculoskel Neuron Interact 2004;4(2):187-190

“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



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

Second thoughts on the WHI study: the effect of age on the safety HRT

Table 1 WHI estrogen-only arm, 2004. Serious side-effects of estrogen therapy in women commencing at age 50–59 compared with a placebo group

Coronary heart disease	decreased by 42%	16 cases vs. 29 cases
Breast cancer	decreased by 28%	25 cases vs. 35 cases
Colorectal cancer	decreased by 41%	8 cases vs. 14 cases
Stroke	increased by 8%	19 cases vs. 19 cases
Deaths	decreased by 27%	34 cases vs. 47 cases
Venous thromboembolism	increased by 22%	18 cases vs. 15 cases
Global index	decreased by 20%	104 cases vs. 132 cases

Studd J. Climacteric 2004;7:412-414

Statement from the Council on Hormone Education on the Results of the Estrogen-only Study of the WHI

The current results are favorable for younger menopausal women in terms of no increase in CHD, a decrease in breast cancer incidence, and a reduction in hip fractures. Because this study was carried out in older women, the council encourages more refined trials in a younger aged population.

Speroff L et al. CME Newsletter;April 2004

Estrogenoterapia en minidosis Hasta 20 años de seguimiento Evaluación comparativa del riesgo de cancer endometrial y mama con no usuarias

Soihet S et al. email:sszmd@terra.com.pe

Estrogenoterapia en Minidosis

Durante **20 años fueron seleccionadas 2814 pacientes** y recebieron ETR, EE.CC. de 0.3 a 0.625 mgs. o estradiol sintético de 1 a 2 mgs.

Soihet S et al. email:sszmd@terra.com.pe

Estrogenoterapia en Minidosis

Hemos passado **más de 20 años** en nuestra serie **sin neoplasia endometrial** y **solamente un caso de cáncer de mama a los doce años consecutivos de ETR en 2814 casos.**

Soihet S et al. email:sszmd@terra.com.pe

Estrogenoterapia en Minidosis

En el presente estudio prospectivo mayor de 20 años se demostró que el riesgo de malignidad de endometrio es mínimo y que **en mama** en el presente estudio **es mayor el riesgo de cáncer en las no usuarias que en las que recibieron estrógeno.**

Soihet S et al. email:sszmd@terra.com.pe

Riesgo relativo de cancer de mama con H T R

Investigadores	Riesgo Relativo
HOOVER Y CLS 1976	1.30
SARWERTLL Y COLS 1977	0.82
ROSS Y COLS 1980	1.10
JICK Y COLS 1980	0.90
HULKA Y COLS 1980	0.80
GAMBRELY Y COLS 1981	0.34
BRINTON Y COLS	1.24
KELSEY Y COLS 1981	0.90
HULKAY COLS 1982	1.20
HIATT Y COLS 1984	1.90
KAUFMAN Y COLS 1984	0.80
LA VECHIA Y COLS 1986	1.60
BRINTON Y COLS 1986	1.40
HUNT Y COLS 1987	1.70
WINGO Y COLS 1987	0.80
BERGKVIST Y COLS 1987	1.10
SOIHET Y COLS 2000	0.80

Soihet S et al. email:sszmd@terra.com.pe

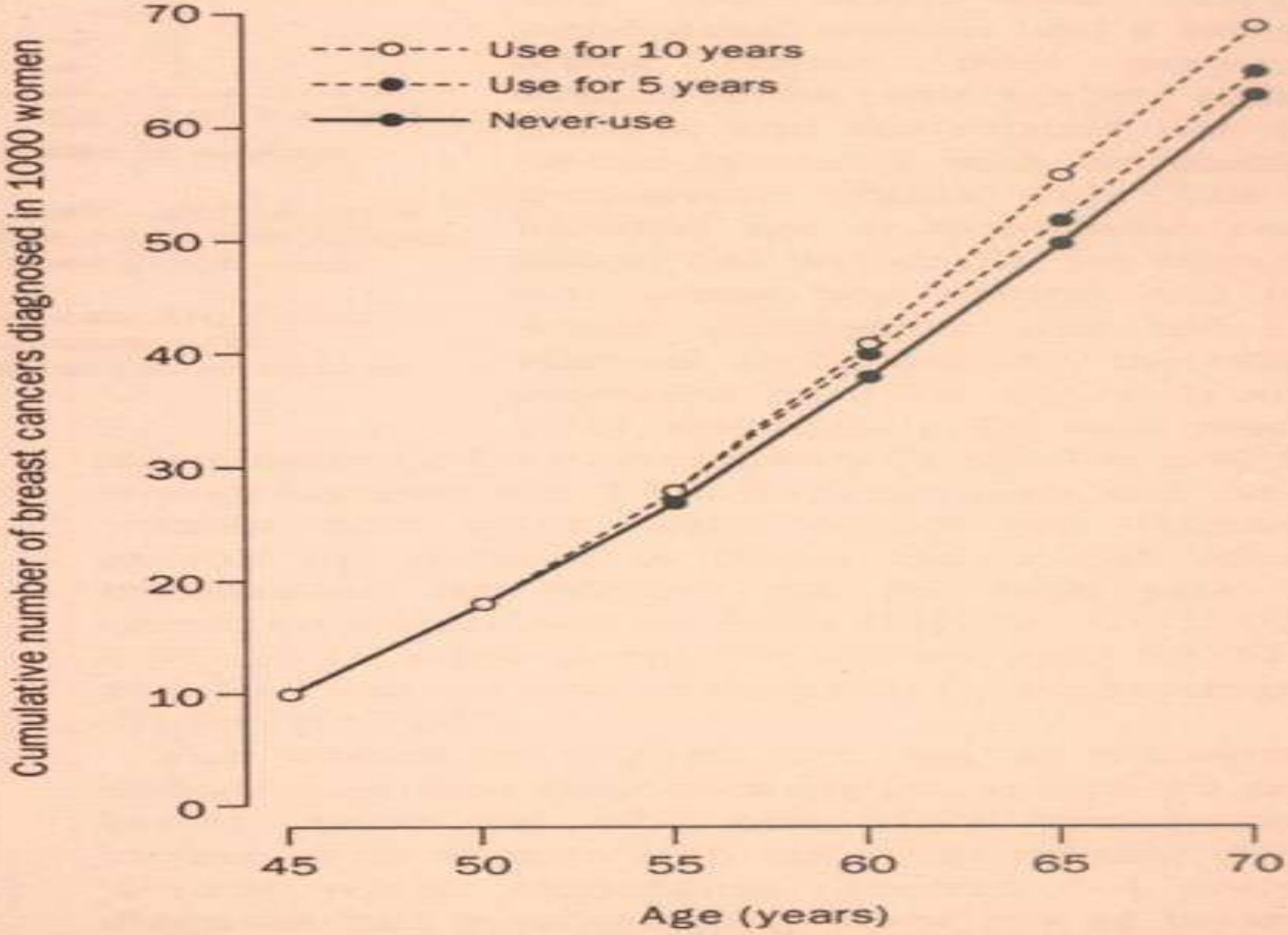


Figure 9: Estimated cumulative number of breast cancers diagnosed in 1000 never-users of HRT, 1000 users of HRT for 5 years, and 1000 users of HRT for 10 years

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

O risco do cancro da mama aumenta com a idade

Idade (anos)	Risco
30	½ x
40	1 x
50	2 x
60	3 x
70	4 x

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

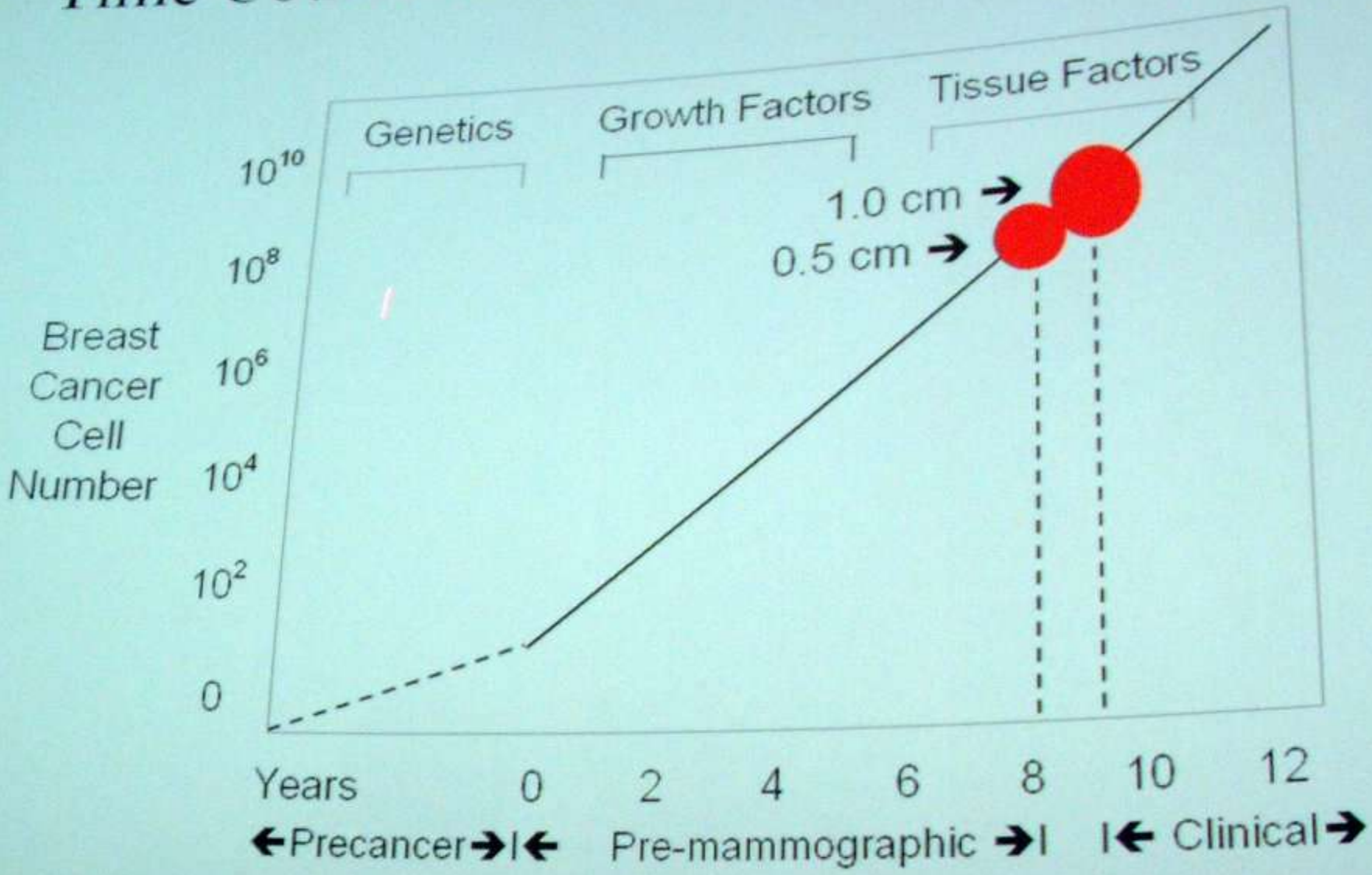
Million Women Study

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*

Risk of breast cancer by time in MWS

Time Course of Breast Cancer Development



ts from Mittra et al 2000. BMJ; 321:1071-3

Occult Breast Cancer

Breast malignancy was found in 22 women (20%)

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

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**

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

HRT and RR of DEATH from BREAST CANCER

(MW Study,2003)

- AR *never users* 238/2894 = 0.0822
- AR *current users* 191/3202 = 0.0597
- RR = 0.0597/0.0822 = **0.73**

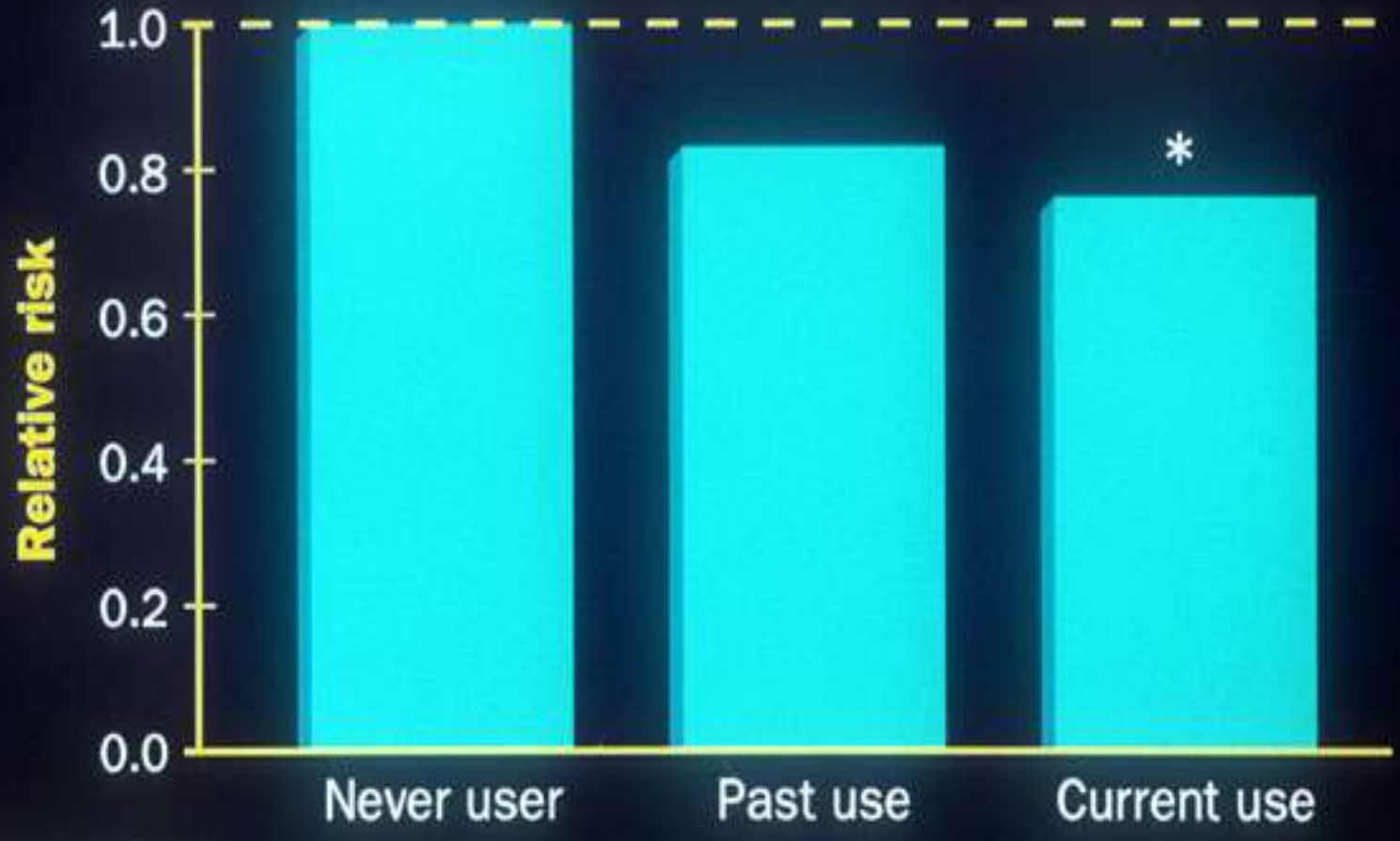
- RR for *mortality* = 1.22
- RR for *morbidity* =1.66
- RR for *dying from BC* = 1.22/1.66 = **0.73**

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***

Risk of Death from Breast Cancer Among ERT/HRT Users



*statistically significant

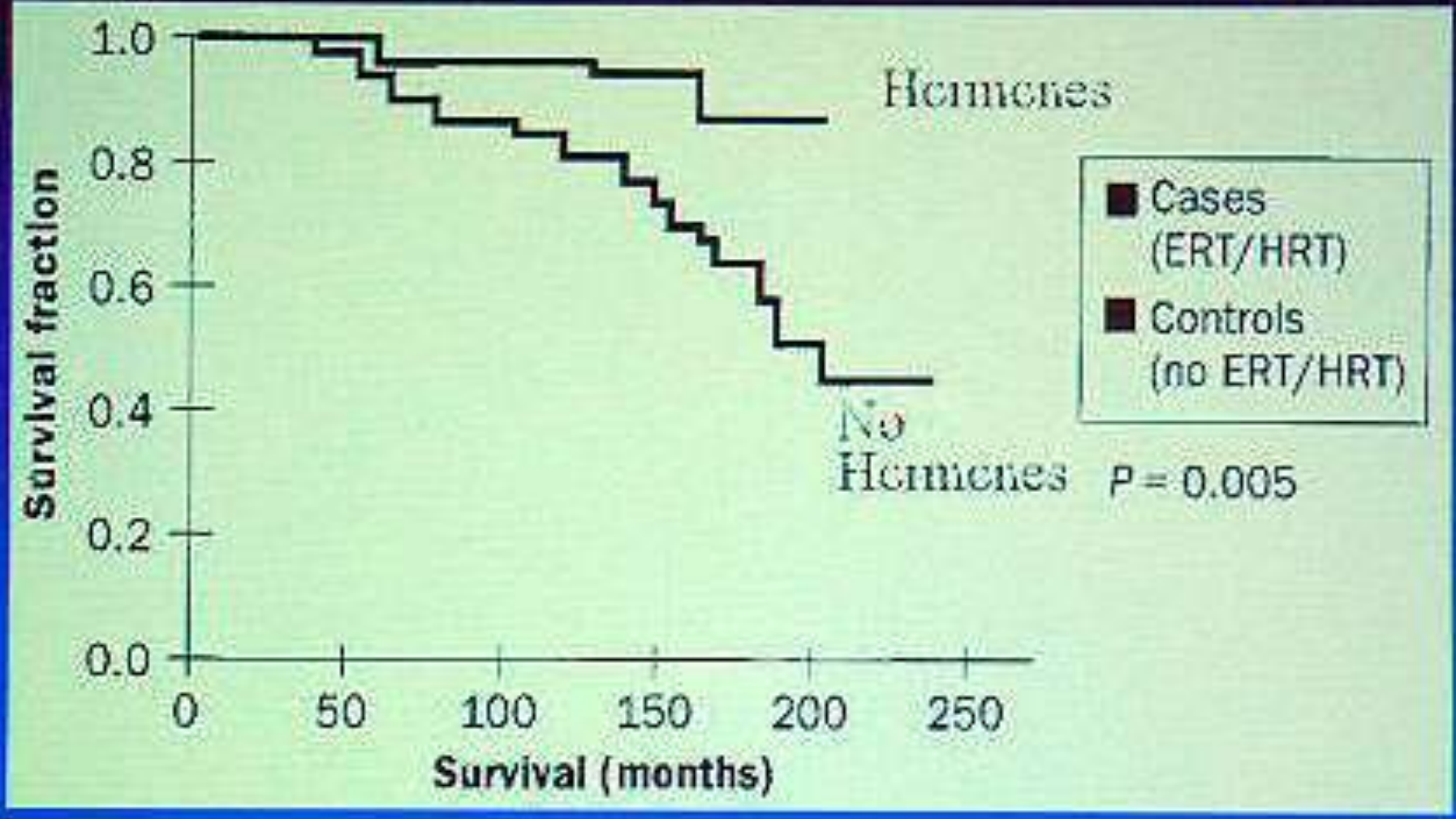
Grodstein et al. *N Engl J Med.* 1997;336:1769.

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 Cancer Survivors:
Results: Kaplan Meier Survival Analysis



DiSaia et al. Am J Clin Oncol Dec 2000

“Recurrent breast cancer was found in 9% of HRT users and 15% of nonuser”.

O’Meara ES et al

Estrogen replacement therapy in patients with early breast cancer

The mortality rates from breast cancer for the ERT users was 4.28% compared with 22.3% in the nonusers.

Natrajan PK and Gambrell RD. Am J Obstet Gynecol 2002;187:289-95

How to decrease potential risks?

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

A physiologic role for testosterone in limiting estrogenic stimulation of the breast.

- These findings suggest that treatment with a balanced formulation including all ovarian hormones may prevent or reduce estrogenic cancer risk in the treatment of girls and women with ovarian failure.

Dimitrakakis C et Al. Menopause 2003;10(4):292-8

Association between alcohol consumption and postmenopausal breast cancer: results of a case-control study in Montreal, Quebec, Canada.

Women who started to drink wine on or before the age of 40 were at a **2.5 times increased risk** (95% CI 1.4-4.4). *CONCLUSIONS:* Our findings provide further support for a **positive association between the risk of postmenopausal breast cancer and alcohol consumption.**

Lenz SK et al.Cancer Causes Control 2002;13(8):701-10

Mediterranean Diet, Lifestyle Factors, and 10-Year Mortality in Elderly European Men and Women

The combination of 4 low risk factors lowered the all-cause mortality rate to 0.35 (95% CI, 0.28-0.44). In total, *lack of adherence to this low-risk pattern was associated with* a population attributable risk of **60% of all deaths, 64% of deaths from coronary heart disease, 61% from cardiovascular diseases, and 60% from cancer.**

Knoops K et al. JAMA 2004;292:1433-9

Intake of fruits, vegetables and selected micronutrients in relation to the risk of breast cancer

Our study suggests that **high intake of certain vegetables and fruits may be associated with a reduced risk of breast cancer.**

Malin A et al. Internat Journal of Cancer 2003;105:413-8

Tea, circulating estrogens and breast cancer

"We recently provided the first set of human evidence that **breast cancer risk is significantly inversely associated with tea intake**, largely confined to intake of green tea."

"***Green tea may have down-regulatory effects on circulating sex-steroid hormones,***
whereas black tea may have up-regulatory effects ."

Wu A. et al. *Carcinogenesis 2005*.

Tea, circulating estrogens and breast cancer

Levels were

13% lower in regular green-tea drinkers (25.8 pg/ml)

and

19% higher in regular black tea drinkers (35.0 pg/ml).

Wu A. et al. *Carcinogenesis 2005*.

Recreational Physical Activity and the Risk of Breast Cancer in Postmenopausal Women

Women who engaged in the equivalent of 1.25 to 2.5 hours per week of brisk walking **had an 18% decreased risk of breast cancer** (RR, 0.82; 95% CI, 0.68-0.97) compared with inactive women.

McTiernan A et al. JAMA 2003;290:1331-6

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

Aspirin could be used to prevent cancer

The researchers found that the incidence of the three types of cancer in people who had taken aspirin regularly for at least five years was a third that in people who had not taken aspirin (odds ratio 0.33 (0.13 to 0.82)).

London O. BMJ 2003;326:565

Aspirin could be used to prevent cancer

Three recently published studies indicate that aspirin, already enjoying a second lease of life in the prevention of heart disease, may soon become a first line of defence against cancer.

London O. BMJ 2003;326:565

Breast Cancer and NSAID's WHI -1

"Our results indicate that the regular use of aspirin, ibuprofen, or other NSAIDs may have a significant chemopreventive effect against the development of breast cancer. *The analysis indicated that NSAID use was associated with a significant decrease (22%) in breast cancer risk."*

Harris R et al. Cancer Research 2003;63:6096-6101

Breast Cancer and Nonsteroidal Anti-Inflammatory Drugs: Prospective Results from the Women's Health Initiative1

COX-2 induction may promote breast cancer development by enhancing local estrogen biosynthesis, and COX-2 inhibition may reverse the process.

Harris R et al. Cancer Research 2003;63:6096-6101

Combined effect of oral contraceptive use and hormone replacement therapy on breast cancer risk in postmenopausal women

OC users were not at increased risk regardless of subsequent HRT exposure.
HRT users who had used OCs previously *did not have a higher risk of breast cancer* than women with no exposure to OCs

Norman SA et al. Cancer Causes Control 2003;14(10):933-43

Combined effect of oral contraceptive use and hormone replacement therapy on breast cancer risk in postmenopausal women

The increase in risk ***with CHRT*** was stronger in women who had never used OCs in the past than in women who had used OCs

Norman SA et al. Cancer Causes Control 2003;14(10):933-43

Inhibitory effect of *statins* on the proliferation of human breast cancer cells.

The present data indicate that **statins may possess anticancerogenic properties concerning the development of *breast cancer in postmenopausal women.***

Muck AO et al. Int J Clin Pharmacol Ther 2004;42(12):695-700

Inhibitory effect of statins on the proliferation of human breast cancer cells.

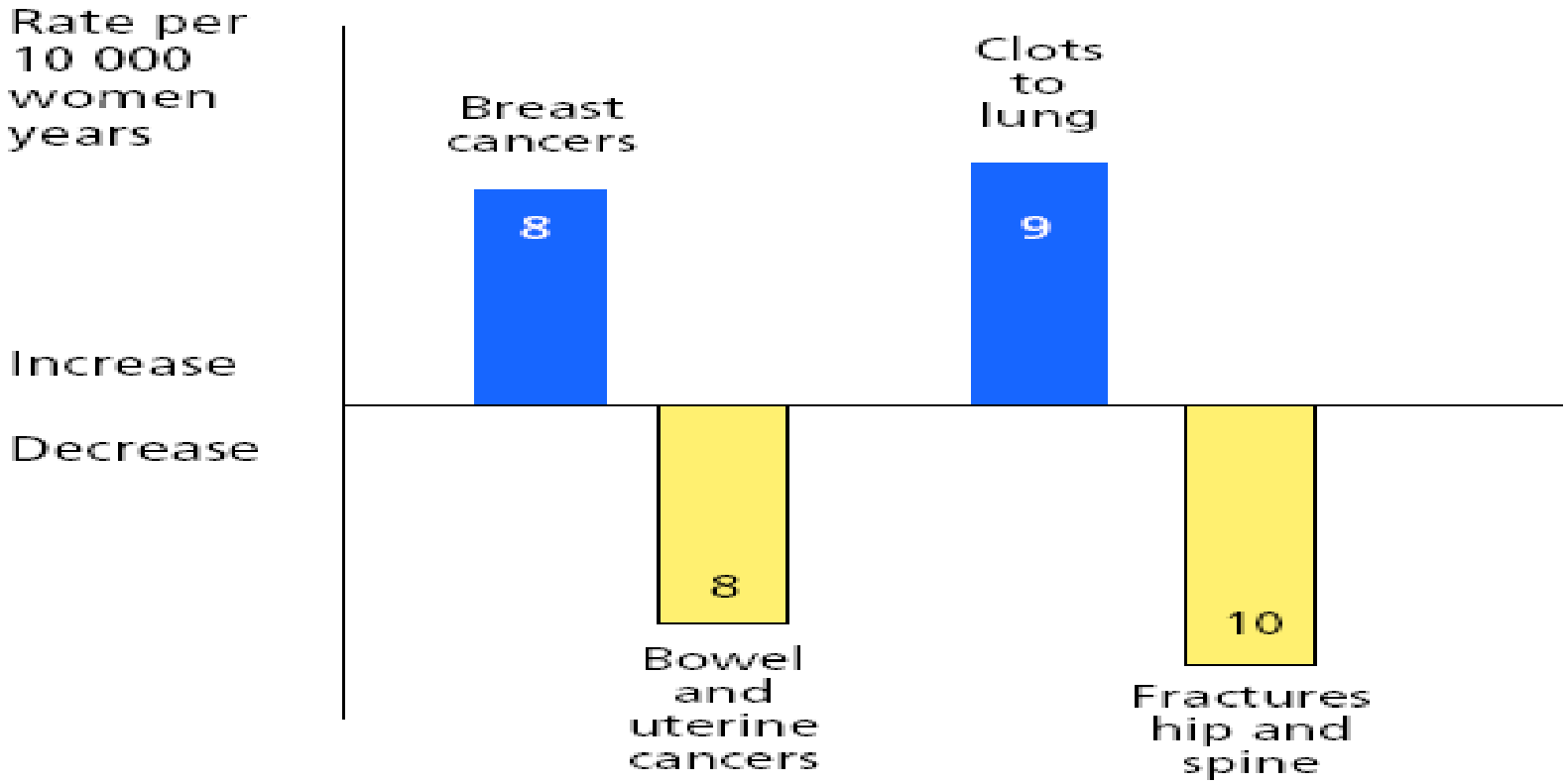
Atorvastatin **and** ***fluvastatin*** **were able to inhibit the proliferation of MCF-7 cells in the absence of estradiol.**

This effect seems to depend on an apoptotic statin effect.

Muck AO et al. Int J Clin Pharmacol Ther 2004;42(12):695-700

Fig. 2

Summary of significant risks and benefits after 5 years of HRT*



* Although increased stroke and heart attacks were seen in the US WHI population, this population had many pre-existing risk factors for these problems. The effect of HRT on the blood vessels of younger, healthier women around menopause requires further study.

Adapted from US WHI Study, 2002 [1]

MacLennan AH. Australian Prescriber 2003;26(1):8-10

Making decisions about benefits and harms of medicines

The balance between benefit and harm in medicine is neither simple or static.

Conclusions derived from clinical trials (however rigorously conducted) may not apply to individual patients for a host of genetic, physiological, psychological and sociocultural reasons.

Greenhalgh T et al. BMJ 2004;329:47-50

Cognitive biases in perception of benefit and harm

Distinguishing between small probabilities

We cannot meaningfully compare very small risks (for example, of different adverse effects) such as 1 in 20 000 and 1 in 200 000. Expressing harm as relative rather than absolute risk dramatically shifts the subjective benefit-harm balance because the risk of harm seems greater.

Greenhalgh T et al. BMJ 2004;329:47-50

Cognitive biases in perception of benefit and harm

Probability vs. Frequency

Poor decision making is exacerbated by the use of absolute and relative probabilities judgment biases are less common when information is presented as **frequencies**.

Greenhalgh T et al. BMJ 2004;329:47-50

Making decisions about benefits and harms of medicines

How information is framed (a treatment that “saves eight lives out of 10” seems better than one that “fails save two in every 10”) is one reason why even objective evidence can be interpreted differently in different contexts.

Greenhalgh T et al. BMJ 2004;329:47-50

Cognitive biases in perception of benefit and harm

Acceptable risk

Some risks (such as a lung cancer from smoking) are subjectively viewed as more acceptable than others (such as a vaccine damage), even when the probabilities of occurrence are in the other direction.

Greenhalgh T et al. BMJ 2004;329:47-50

Women are not statistics!

They must be treated *individually*

CONCLUSIONS

- Exercise
- Nutrition (“polymeal”)
- Aspirin
- Statins (“polypill”)
- Oral contraceptives
- Hormonal Therapy

MNC/05