O Estado da Arte

VI Reunião Cientifica

da

Sociedade Portuguesa de Menopausa

por

Manuel Neves-e-Castro

no

Dia Mundial da Menopausa

18.10.2003

Therapy	Was	Now
Using estrogen with or without hormone	*Hormone replacement* therapy **(HRT)**	**Menopausal therapy (MHT)**
Using estrogen alone	Estrogen replacement therapy **(ERT)**	Estrogen therapy **(ET)**
Using estrogen with a progestin	*Hormone replacement* therapy **(HRT)**	**Estrogen-progestin therapy (EPT)**

Menopause: *An Update, 2003*. National Institute on Aging, NIH, USA

Rank	All American Women	African American	Asian/Pacific Islanders	Caucasian	Hispanic/Latina	Native Americans/ Alaskans
1st	**Heart Disease**	Heart Disease	Cancer	Heart Disease	Heart Disease	Heart Disease
2nd	**Cancer**	Cancer	Heart Disease	Cancer	Cancer	Cancer
3rd	Cerebrovascular Diseases (includes stroke)	Cerebrovascular Diseases (includes stroke)	Cerebrovascular Diseases (includes stroke)	Cerebrovascular Diseases (includes stroke)	Cerebrovascular Diseases (includes stroke)	Unintentional Injuries
4th	Chronic Obstructive Pulmonary Diseases	Diabetes Mellitus	Pneumonia and Influenza	Chronic Obstructive Pulmonary Diseases	Diabetes Mellitus	Diabetes Mellitus
5th	Pneumonia and Influenza	Pneumonia and Influenza	Unintentional Injuries	Pneumonia and Influenza	Unintentional Injuries	Cerebrovascular Diseases (includes stroke)
6th	Diabetes Mellitus	Unintentional Injuries	Diabetes Mellitus	Unintentional Injuries	Pneumonia and Influenza	Pneumonia and Influenza
7th	Unintentional Injuries	Chronic Obstructive Pulmonary Diseases	Chronic Obstructive Pulmonary Diseases	Diabetes Mellitus	Chronic Obstructive Pulmonary Diseases	Chronic Liver Disease and Cirrhosis
8th	Alzheimer's Disease	Septicemia	Suicide	Alzheimer's Disease	Conditions Originating in the Perinatal Period	Chronic Obstructive Pulmonary Diseases
9th	Nephrilis, Nephrotic Syndrome, and Nephrosis	Nephrilis, Nephrotic Syndrome, and Nephrosis	Nephrilis, Nephrotic Syndrome, and Nephrosis	Nephrilis, Nephrotic Syndrome, and Nephrosis	Chronic Liver Disease and Cirrhosis	Nephrilis, Nephrotic Syndrome, and Nephrosis
10th	Septicemia	HIV/AIDS	Conditions Originating in the Perinatal Period	Septicemia	Congential Anomalies	Septicemia

Women’s Health Statiscal Information

deg487

Human Reproduction Vol.18, No.12 pp. 1–7, 2003

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DEBATE—continued

Menopause in crisis post-Women's Health Initiative? A view based on personal clinical experience

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Menopausal women should not consider that hormonal treatment is an obligatory long-term commitment. Estrogen-based treatments are extremely effective for vasomotor symptom relief and for vaginal atrophy. HRT also is one of several effective methods for the primary prevention of osteoporosis. If trials were done early after the menopause when the endothelium is likely still to be intact, estrogen-based treatment might be shown to prevent coronary heart disease. However, greater efficacy is to be expected from smoking cessation, proper nutrition, exer-

TABLE 1

Risks and benefits of CEE/MPA compared with placebo

Risks of CEE/MPA	No. of **additional** cases/year per 10,000 women
Coronary heart disease	7
Stroke	8
Invasive breast cancer	8
Pulmonary embolism	8
Benefits of CEE/MPA	**No. of fewer cases/year per 10,000 women**
Colorectal cancer	6
Hip fractures	5
Total fractures	44

Source: Writing Group for the Women's Health Initiative Investigators[1]

Michelle P. Warren.Putting WHI into perspective.Council on Hormone Education, Vol.1(2), 2003

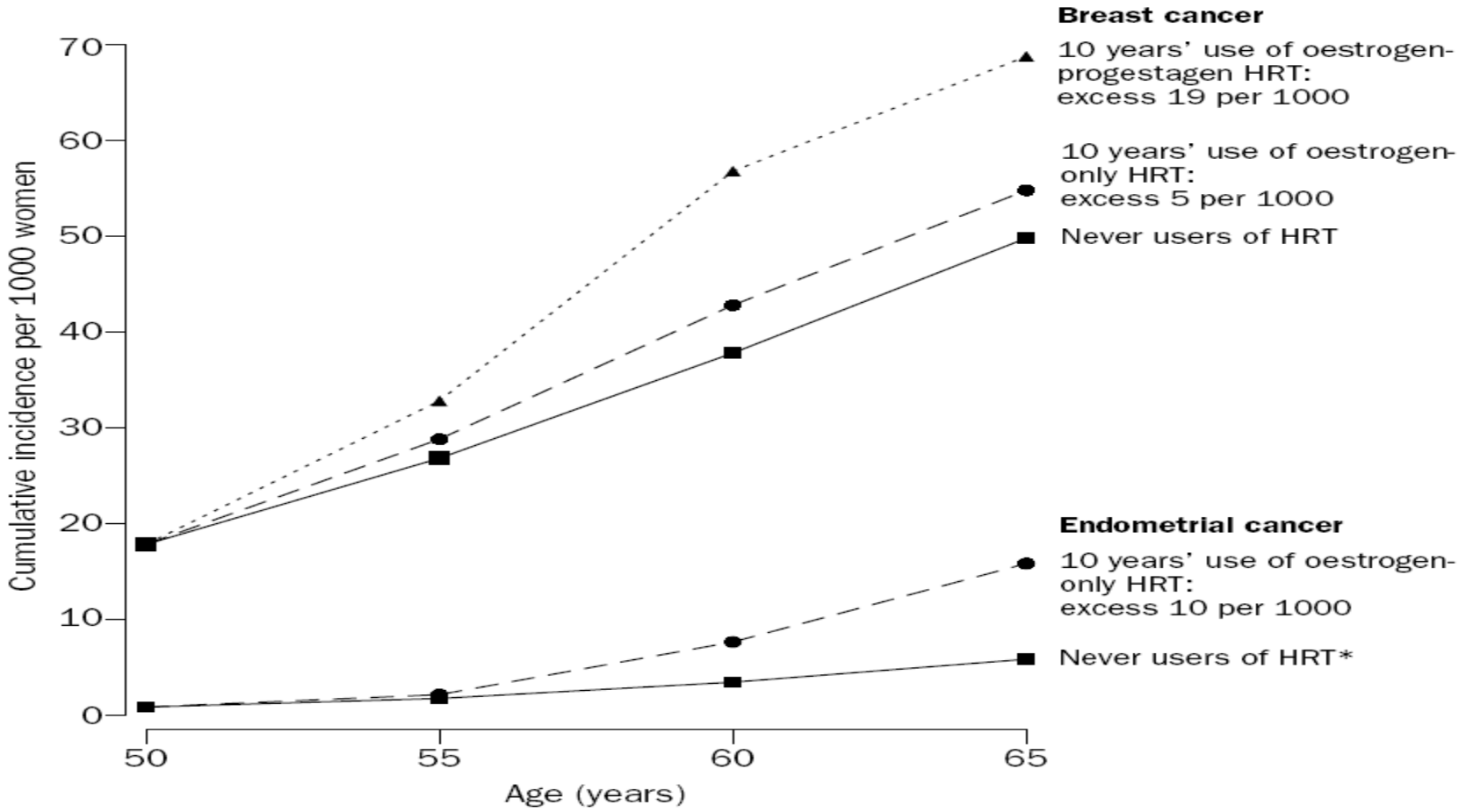


Figure 7: **Estimated cumulative incidence of breast and endometrial cancer per 1000 women in developed countries who never used HRT and who used HRT for 10 years, beginning at age 50 years**

*10 years' use of oestrogen-progestagen HRT estimated to result in little change in culmulative incidence of endometrial cancer.

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

The risk of breast cancer in relation to total duration of use was

	<5 years	*>5 years*
Oestrogen	1.21	1.34
Oestrogen+progestagen	1.70	2.21
Tibolone	1.32	1.57

Neves-e-Castro M. Some comments to the “Million Women Study”. Letter to the Editor of Climacteric, 2003

	Estimated cumulative incidence of breast cancer				
	Never users of HRT	Duration use of oestrogen only		Duration use of oestrogen-progestagen	
		5 years	10 years	5 years	10 years
Up to age (years)					
50	18	18	18	18	18
55	27	28·5	29	34	34
60	38	39·5	43	44	57
65	50	51·5	55	56	69
Excess cumulative incidence per 1000 HRT users (95% CI)	0	1·5 (0–3)	5 (3–7)	6 (5–7)	19 (18–20)

Table 2: **Cumulative and excess incidence of invasive breast cancer in 1000 women who had never used and ever used HRT, based on incidence rates typical of developed countries**

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

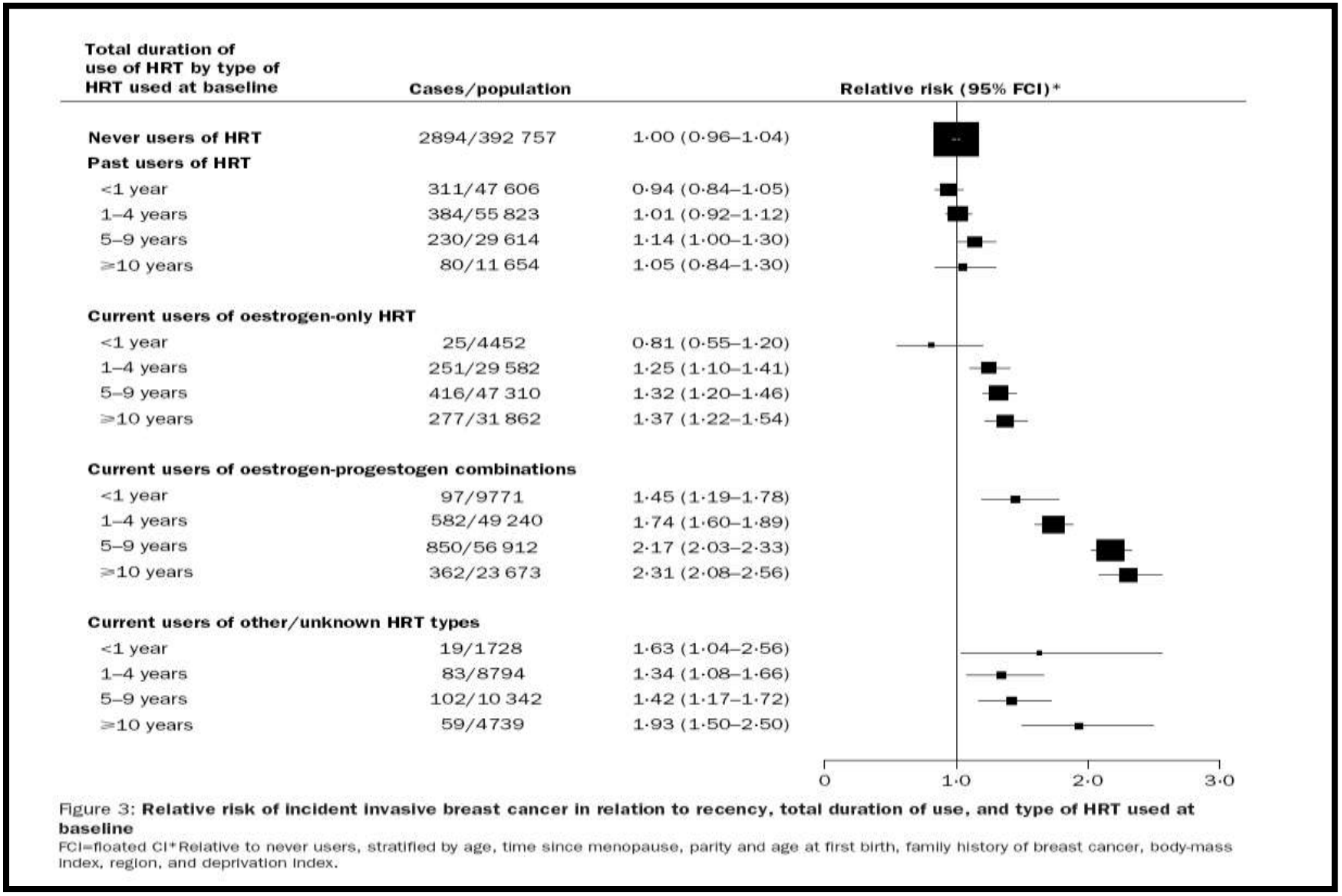


Figure 3: **Relative risk of incident invasive breast cancer in relation to recency, total duration of use, and type of HRT used at baseline**

FCI=floated CI*Relative to never users, stratified by age, time since menopause, parity and age at first birth, family history of breast cancer, body-mass index, region, and deprivation index.

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

Total duration of use of HRT by type of HRT used at baseline	Cases/population	Relative risk (95% FCI)*	NNH
Never users of HRT	2894/392 757	1·00 (0·96–1·04)	
Past users of HRT			
<1 year	311/47 606	0·94 (0·84–1·05)	1.111
1–4 years	384/55 823	1·01 (0·92–1·12)	1.000
5–9 years	230/29 614	1·14 (1·00–1·30)	714
≥10 years	80/11 654	1·05 (0·84–1·30)	2.000
Current users of oestrogen-only HRT			
<1 year	25/4452	0·81 (0·55–1·20)	1.250
1–4 years	251/29 582	1·25 (1·10–1·41)	400
5–9 years	416/47 310	1·32 (1·20–1·46)	312
≥10 years	277/31 862	1·37 (1·22–1·54)	270
Current users of oestrogen-progestogen combinations			
<1 year	97/9771	1·45 (1·19–1·78)	222
1–4 years	582/49 240	1·74 (1·60–1·89)	135
5–9 years	850/56 912	2·17 (2·03–2·33)	85
≥10 years	362/23 673	2·31 (2·08–2·56)	76
Current users of other/unknown HRT types			
<1 year	19/1728	1·63 (1·04–2·56)	158
1–4 years	83/8794	1·34 (1·08–1·66)	294
5–9 years	102/10 342	1·42 (1·17–1·72)	238
≥10 years	59/4739	1·93 (1·50–2·50)	107

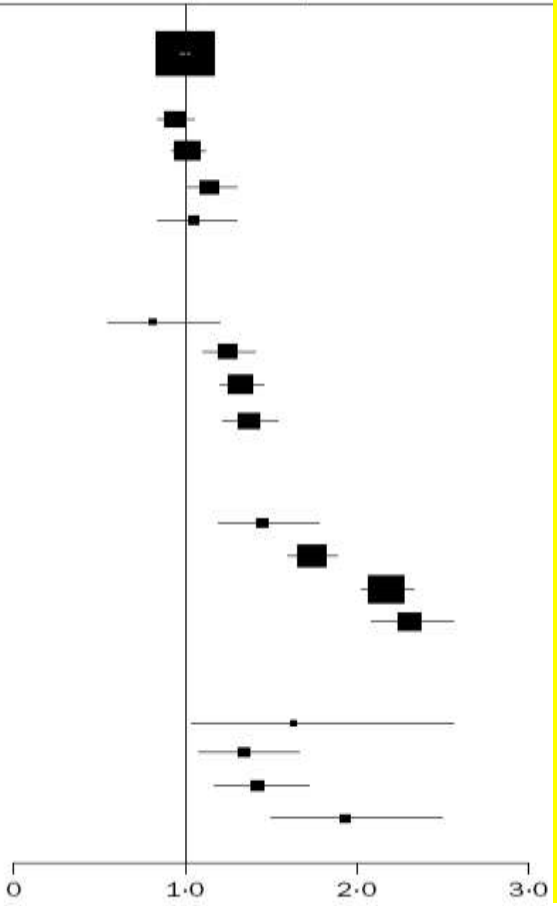
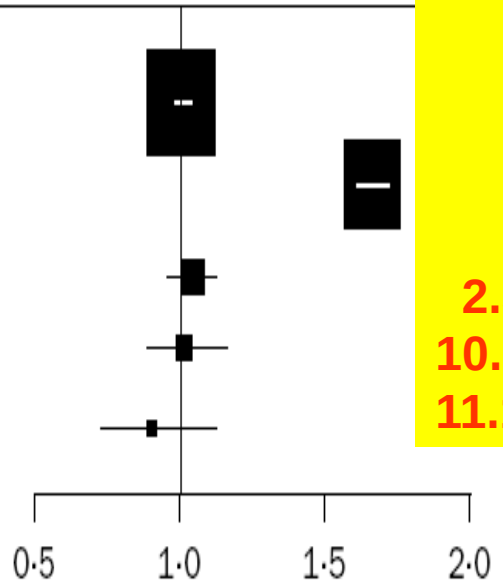


Figure 3: **Relative risk of incident invasive breast cancer in relation to recency, total duration of use, and type of HRT used at baseline**

FCI=floated CI*Relative to never users, stratified by age, time since menopause, parity and age at first birth, family history of breast cancer, body-mass index, region, and deprivation index.

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

HRT use at baseline	Cases/population	Relative risk (95% FCI)*	NNH
Never users	2894/392 757	1·00 (0·97–1·04)	
Current users	3202/285 987	1·66 (1·60–1·72)	151
Last use <5 years previously	579/81 875	1·04 (0·95–1·12)	2.500
Last use 5–9 years previously	207/29 395	1·01 (0·88–1·16)	10.000
Last use ⩾10 years previously	79/12 568	0·90 (0·72–1·12)	11.111



χ^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**

FCI=floated CI. *Relative to never users, stratified by age, time since menopause, parity and age at first birth, family history of breast cancer, body-mass index, region, and deprivation index.

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

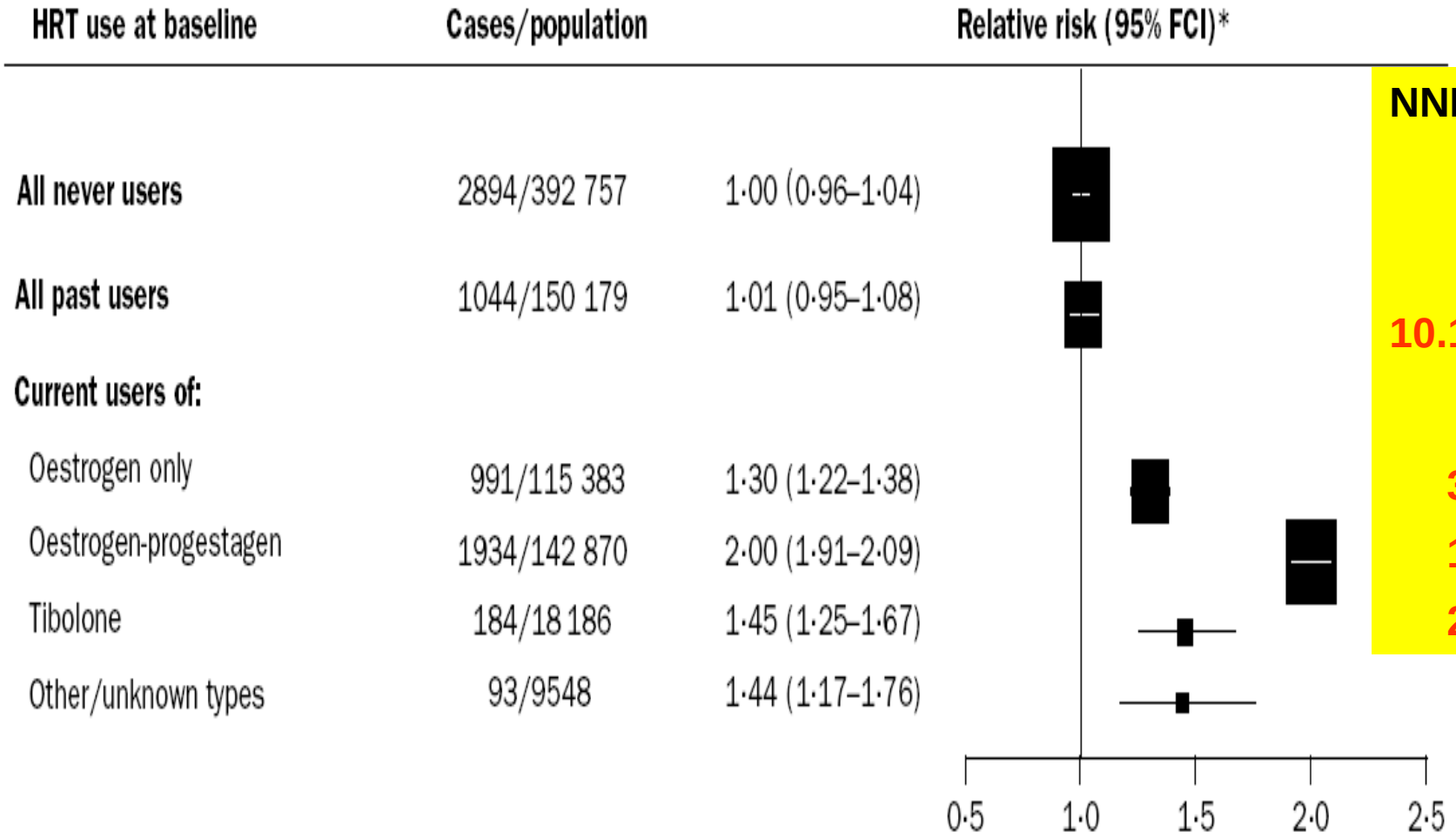


Figure 2: **Relative risk of incident invasive breast cancer in relation to recency and type of HRT used**

FCI=floated CI. *Relative to never users, stratified by age, time since menopause, parity and age at first birth, family history of breast cancer, body-mass index, region, and deprivation index.

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

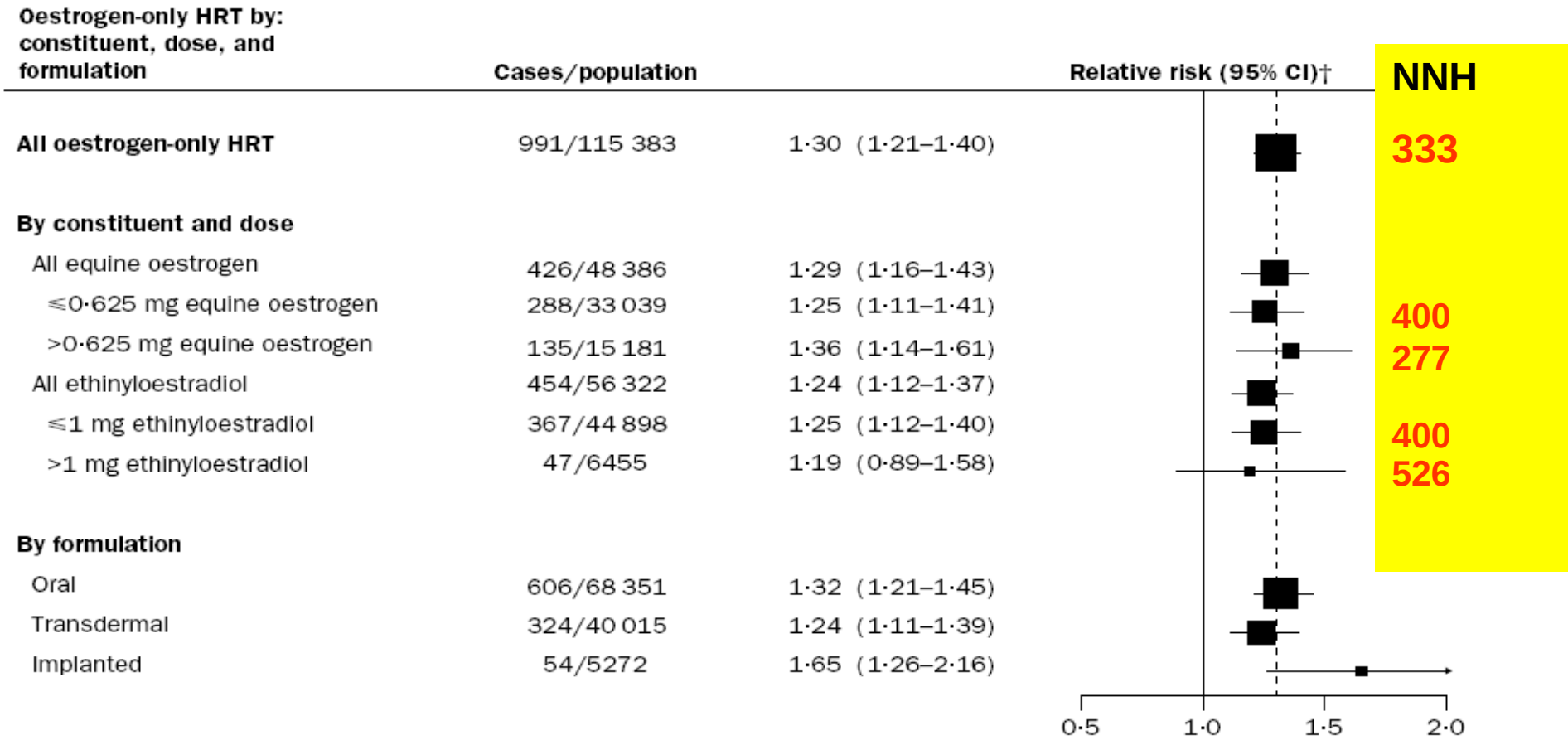


Figure 4: **Relative risk of incident invasive breast cancer by constituent, dose, and formulation of oestrogen only HRT preparation used at baseline***

*Dotted line represents overall relative risk for current users of oestrogen-only preparations compared with never users at baseline. Full information on specific constituents and their formulation was not available for some women. †Relative to never users, stratified by age, time since menopause, parity and age at first birth, family history of breast cancer, body-mass index, region, and deprivation index.

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

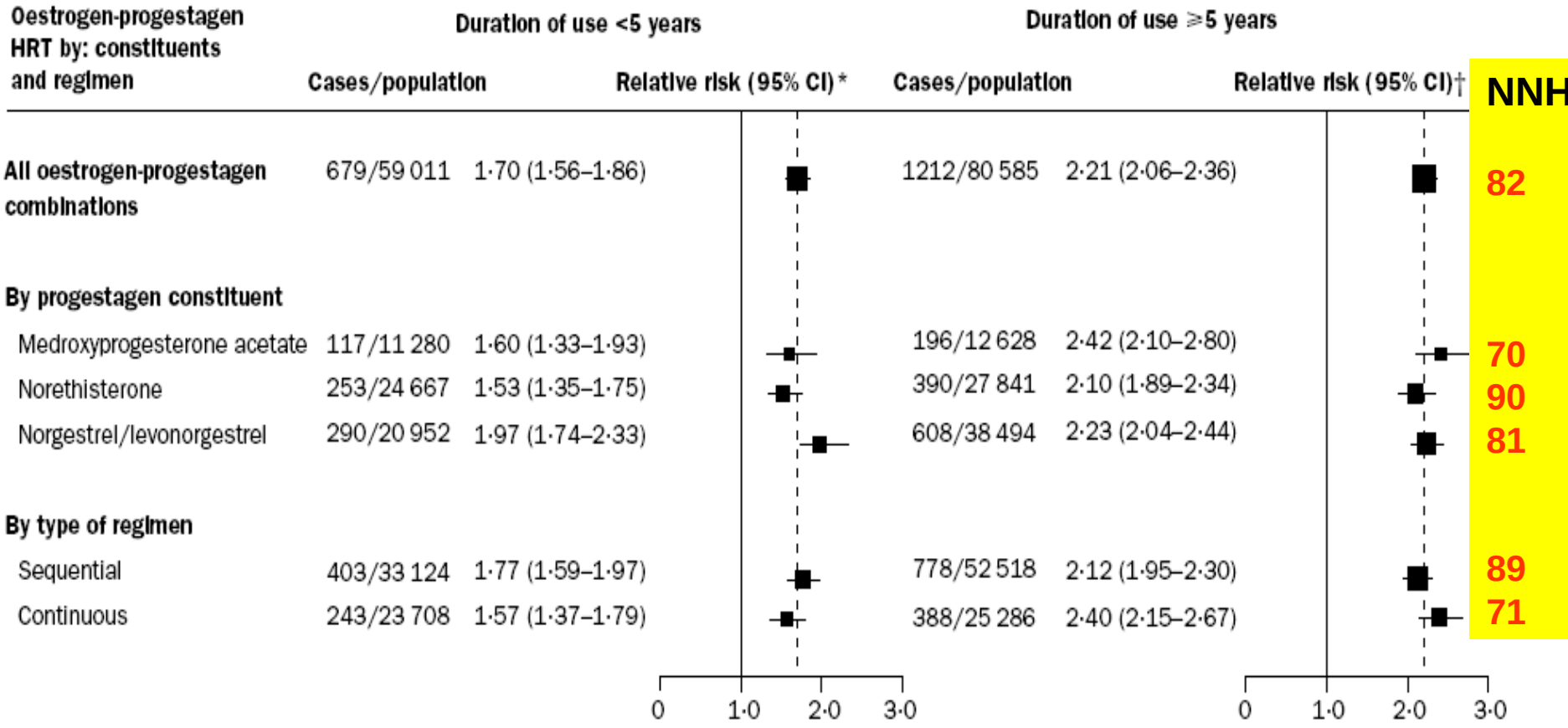


Figure 5: **Relative risk of incident invasive breast cancer by constituent and regimen of oestrogen-progestagen combination HRT used at baseline***

*Dotted line represents overall relative risk for current users of oestrogen-progestagen preparations compared with never users at baseline. Full information on specific constituents and their formulation was not available for some women. †Relative to never users, stratified by age, time since menopause, parity and age at first birth, family history of breast cancer, body-mass index, region, and deprivation index.

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

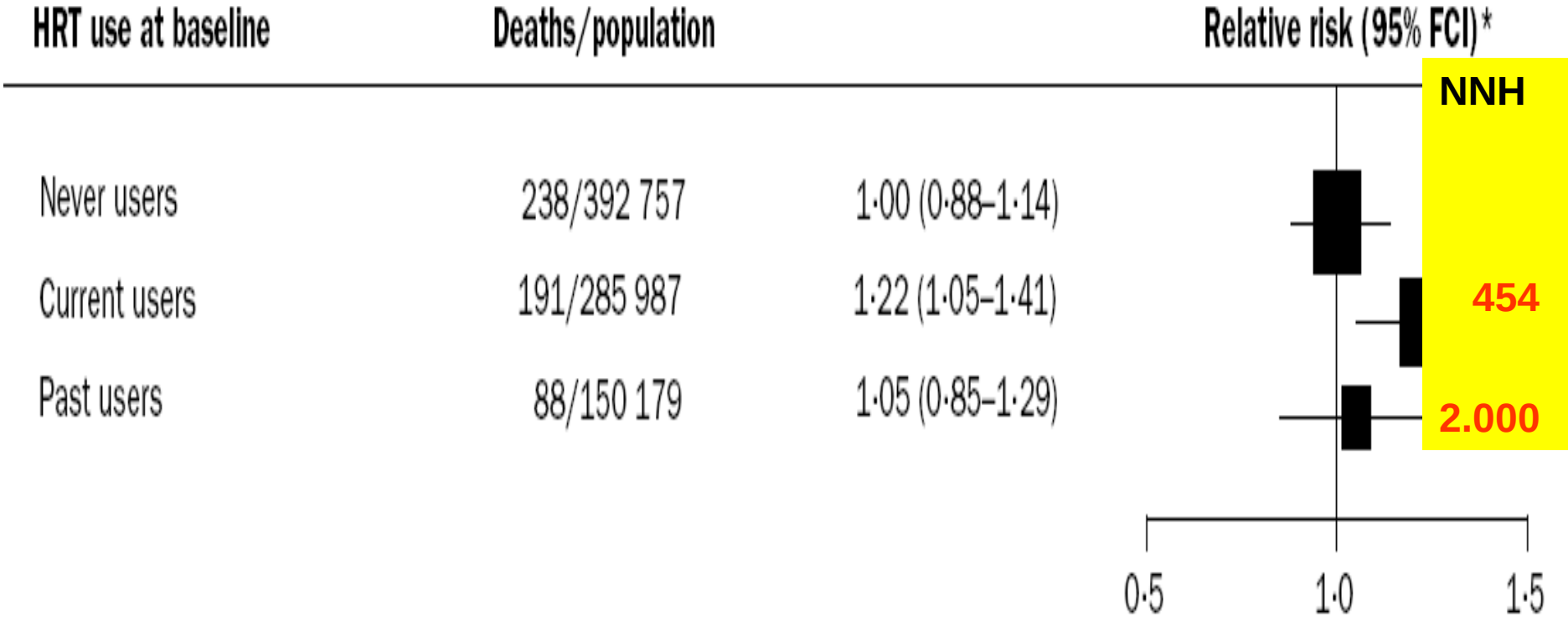


Figure 6: **Relative risk of fatal breast cancer in relation to use of HRT at baseline**

FCI=floated CI. *Relative to never users, stratified by age, time since menopause, parity and age at first birth, family history of breast cancer, body-mass index, region, and deprivation index.

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

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 Vol.362;419-427, 2003

If one goes to Fig .2 there are 3202 current users and 2894 never users of HRT from Fig 6 one sees that there were 191 deaths among current users and 238 among never users. One interesting interpretation is the following estimate of RR's of death: *"for never users (deaths/breast cancer cases): 238/2894 =* ***0.0822****. For current users (deaths/breast cancer cases): 191/3202 =* ***0.0597****. This shows a RR of 0.73 for current users versus never users " And the same source goes on "you can also divide the RR for mortality (1.22) by the RR for morbidity (1.66) in order to get the RR of 0.73 which provides you with the RR of dying from breast cancer. This* ***challenges the conclusions of the authors that the RR of dying from breast cancer is 1.22. In our opinion it is 0.73"*****.**

Manuel Neves-e-Castro,M.D.

As with the WHI reports, much emphasis and publicity has been given to the relative risks and percentage increases of 30 - 200%, whereas absolute figures provide a more suitable perspective of the risk. The additional cancers associated with estrogen only being 1.5 after 5 years and 5 after 10 years and for CEPT the figures are 6 and 19 respectively per 1,000 women by the age of 65 years. Or put another way, a doctor would need to give CEPT to 116 women for 5 years, or 53 women for 10 years, to see one extra case of breast cancer. These figures were derived, not by comparing breast cancer incidence in users and non-users in the study, but by estimating the cumulative

David W Sturdee, Alastair H MacLennan. Is combined Estrogen/Progestogen Hormone Therapy worth the risk? (editorial) Climacteric, 2003

Nevertheless, these new data from MWS are consistent with those from WHI and other observational studies and can not be ignored. Women who are currently taking HT and especially CEPT should discuss their perceived benefits of continuing and balance these against the apparent greater risks than previously thought. There is no indication for all women to stop HT as suggested in the editorial[9] accompanying MWS. HT remains by far the best treatment for climacteric symptoms and for many

David W Sturdee, Alastair H MacLennan. Is combined Estrogen/Progestogen Hormone Therapy worth the risk? (editorial) Climacteric,2003

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

Tibolone data in perspective

	Million Women Study	GPRD Study
Observation period	1996 – 2001	1992 – 1998
Breast cancers	9364	7192

Relative Risk (95% CI)

Tibolone	1.45 (1.25 – 1.67)	1.02 (0.78 – 1.33)
ET	1.30 (1.21 – 1.40)	0.97 (0.86 – 1.08)
EPT	2.00 (1.88 – 2.12)	1.21 (1.21 – 1.30)[1]
		[1]Sequential EPT only

The conclusions of these studies suggest that the **“safe “ woman (NNH between 600-1000 women)** to initiate HRT 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 a Body Mass Index > 30 (to be protected from breast cancer). 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, Vol.18(12):1-7

O Estado da Arte…
é a Sabedoria:

- é estar bem informado
- é ser critico do que se lê
- é não emitir opiniões infundadas
- é praticar uma Boa Medicina Holística