Menopause and beyond: recent advances in climacteric

by

Manuel Neves-e-Castro

Lisbon - Portugal

12th World Congress on Human Reproduction

Venice, March 2005
The controversies about the present management of the climacteric are due to:

- a **lack of culture** that prevents a correct criticism of the published results
- a **bad practice of medicine** that ignores the woman in her totality
- a **political lobies** from the *NIH*
- a **lack of scientific honesty** manifested by many of the WHI writers
- **lobies from several pharmaceutical industries** through the activities of many well known doctors that “offer” themselves to transmit their “messages”
Part 1. Women’s health after WHI.
Reports from the Amsterdam Menopause Symposium, October 2-4, 2004.

Part 2. Transatlantic confrontation of options.
The Menopausal Stars

The U.S.A. “team”

The USA Vision

Chair: M. Neves-e-Castro and Mario de Sousa

09.00-09.30 – Controversies about HRT – Lessons from Monkey Models
Th. Clarkson, Wake Forest Univ.

09.30-10.00 – Appropriate Use of Hormones Should Alleviate Concerns Regarding CV and Breast Cancer Risks
R. Lobo, Columbia Univ

10.00-10.30 – Implications of clinical trials for CVD in younger women
Jacques Rossouw, NIH/NHLBI/WHI

10.30-11.00 Coffee Break

11.00-11.30 – Menopausal Therapy and Cancer Risk in the WHI
R. Chlebowski, WHI

11.30-12.00 - The state of the Art in the USA
L. Speroff, Portland. Or

12.00-13.00 - Debate and Discussion
Chair: J. Stevenson (UK) and S. Palacios (Sp)
The European “team”

The European Vision

Chair: Mario de Sousa and M. Neves-e-Castro

14.30-15.00 – WHI and Cardioprotection: Looking Beyond the Figures
   A.Pines, II

15.00-15.30 – Hormone Therapy and Breast Cancer: What is the Problem?
   P.Kenemans, NI

15.30-16.00 – Do Estrogens Really Increase Breast Cancer Risk?
   H. Kuhl, D

16.00-16.30 – Coffee Break

16.30-17.00 Strategy in Osteoporosis Management Following WHI
   D.Barlow, UK

17.00-18.00 Debate and Discussion
   Chair: A. Genazzani (I) and J. Calaf (Sp)

18.00 - Conclusions
   M.Neves-e-Castro
CONCLUSIONS
We believe that as to CHD, both the primate studies and clinical evidence suggest strongly that HT can be preventive if started very early after the menopause, preferably after a regimen of oral contraceptives given during the perimenopausal years.

Clarkson TB. *Fertil Steril* 2004;81:1498-1501
Stampfer MJ. *NAMS* 2004;PS#2
Victory R et al. *Fertil Steril* 2004;82:O-130
However, the E only arm of WHI strongly suggests that an estrogen only medication is not only **devoid of risk** but may even be **protective**.

This is supported by previous investigations of pregnancy following breast cancer or HT in breast cancer survivors.

WHI Group *J Am Med Assoc* 2004;291:1701-1712  
O’Meara et al. *J N C l* 2001  
Nananda F Col et al.*J Clin Oncol*;2001:19:2357-2363
Recent reports did not find, for continuous combined treatments, any increased risk of either CHD or breast cancer.

The difference from WHI being that women were younger, symptomatic and with lower body weights.

Heikkinen J. *NAMS* 2004, Abstract LB38
Lobo R. *Arch Int Med* 2004;164:482-484
We reemphasize the need to implement very important collateral measures, like
- normalization of body weight,
- abstention from tobacco,
- low alcohol consumption,
- exercise,
- Mediterranean diet,
etc.
In conclusion, and in the light of present evidence, doctors and women should be reassured that the suggested HT’s for the relief of symptoms in the menopause are safe and very effective.
WHI
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

MENOPAUSE AND THE HEART

Proceedings of an International Symposium organized by the
PORTUGUESE MENOPAUSE SOCIETY

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NEW YORK

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Menopause
HORMONES AND CANCER
Proceedings of the 2nd International Symposium of the Portuguese Menopause Society

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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)
• **Results:**

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

• **Discussion:**

  “**the substantial risks** for CVD and breast cancer” (?)
“The breast cancer findings are reported as statistically insignificant but are regarded as clinically relevant!”

Utian W. Menopause Management 2003;12:9-10
**WHI results calculated as**

<table>
<thead>
<tr>
<th>Condition</th>
<th>NNT/1 year</th>
<th>NNH/1 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD</td>
<td></td>
<td>1428</td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
<td>1250</td>
</tr>
<tr>
<td>VTE</td>
<td></td>
<td>588</td>
</tr>
<tr>
<td><strong>Breast Cancer</strong></td>
<td></td>
<td><strong>1250</strong></td>
</tr>
<tr>
<td>Colon Cancer</td>
<td></td>
<td>1667</td>
</tr>
<tr>
<td><strong>Osteoporotic fractures</strong></td>
<td></td>
<td><strong>227</strong></td>
</tr>
<tr>
<td><em>(totals)</em></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

“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
Stroke

“In women 50-59 years not taking HT, ischemic stroke is expected to occur in 3 out of 1000 women during 5 years. Five years use of HT would yield 1 additional case of stroke/ 1000 women”

Effects of conjugated Equine Estrogen in Postmenopausal Women with Hysterectomy. JAMA, 2004;291:1701-1712
NAMS position statement on estrogen and progestagen use in peri-and postmenopausal women

Revised breast cancer statements indicate that the risk of breast cancer probably increases with EPT use but not with ET use.
Second thoughts on the WHI study: the effect of age on the safety HRT

<table>
<thead>
<tr>
<th>Condition</th>
<th>Effect</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary heart disease</td>
<td>decreased by 42%</td>
<td>16 cases vs. 29 cases</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>decreased by 28%</td>
<td>25 cases vs. 35 cases</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>decreased by 41%</td>
<td>8 cases vs. 14 cases</td>
</tr>
<tr>
<td>Stroke</td>
<td>increased by 8%</td>
<td>19 cases vs. 19 cases</td>
</tr>
<tr>
<td>Deaths</td>
<td>decreased by 27%</td>
<td>34 cases vs. 47 cases</td>
</tr>
<tr>
<td>Venous thromboembolism</td>
<td>increased by 22%</td>
<td>18 cases vs. 15 cases</td>
</tr>
<tr>
<td>Global index</td>
<td>decreased by 20%</td>
<td>104 cases vs. 132 cases</td>
</tr>
</tbody>
</table>

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.
The E only arm of the WHI was stopped!

Why ?! ...
It seems that if one additional breast cancer had been found in the placebo group the results of the study would have been shown as statistically very significative!
Thus...

the WHI/NIH team would have been forced to declare that:

• **Estrogens do not induce breast cancer**, and that

• **Estrogens protect the breast from cancer!**
Why did they not want the study to be finished and come to such important conclusions?...

Was it due to the need of some investigators to continue receiving million of dollars?...
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

Breast Cancer Cell Number

Years

Genetics       Growth Factors       Tissue Factors

1.0 cm

0.5 cm

Precancer ↔ I ↔ Pre-mammographic ↔ I ↔ Clinical ↔

Data 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
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
## Breast Cancer

### MWS data compared to other publish data

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>EPT</td>
<td>2.00</td>
<td>1.21¹</td>
<td>1.15²</td>
<td>1.24³</td>
<td>1.22</td>
<td>1.26</td>
</tr>
<tr>
<td>ET</td>
<td>1.30</td>
<td>0.97</td>
<td>0.99²</td>
<td>1.06³</td>
<td>0.84</td>
<td>ongoing 4</td>
</tr>
<tr>
<td>Tibolone</td>
<td>1.45</td>
<td>1.02</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

¹Seq EPT ²≤ 5 y use ³Per 5y use ⁴> 6 y
HRT and RR of DEATH from BREAST CANCER
(MW Study, 2003)

- **AR never users**: \( \frac{238}{2894} = 0.0822 \)
- **AR current users**: \( \frac{191}{3202} = 0.0597 \)
- **RR** = \( \frac{0.0597}{0.0822} = 0.73 \)
- **RR for mortality** = 1.22
- **RR for morbidity** = 1.66
- **RR for dying from BC** = \( \frac{1.22}{1.66} = 0.73 \)
## Fatal Breast Cancers

<table>
<thead>
<tr>
<th></th>
<th>Case-death</th>
<th>Case-No death</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Current use</strong></td>
<td>191</td>
<td>3011</td>
</tr>
<tr>
<td><strong>Never use</strong></td>
<td>238</td>
<td>2656</td>
</tr>
</tbody>
</table>

**RR=0.71 (95% CI 0.58-0.87)**

Risk of Death from Breast Cancer Among ERT/HRT Users

- Never user: Relative risk 1.0
- Past use: Relative risk 0.8
- Current use: Relative risk 0.6

*statistically significant

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>86</td>
<td>172</td>
</tr>
<tr>
<td>5yr survival</td>
<td>97%</td>
<td>86%</td>
</tr>
<tr>
<td>10yr survival</td>
<td>93%</td>
<td>75%</td>
</tr>
</tbody>
</table>
HRT in Breast Cancer Survivors: Results: Kaplan Meier Survival Analysis

![Survival curve graph showing comparison between cases and controls with and without hormones.](image)

“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.

What has been learned from the major observational studies and clinical trials?

*the first lesson*

systematically administered progestagens may in part suppress some of the beneficial effects of estrogens and may also slightly increase the risk of breast cancer after treatments with duration greater than five years.

MNC/05
What has been learned from the major observational studies and clinical trials?

*the second lesson*

*estradiol*, when given alone to hysterectomized women, did not appear to minimally affect the risk for breast cancer when compared with controls.
What has been learned from the major observational studies and clinical trials?

**the third lesson**

*Metabolic effects* of estrogens and progestagens, as a whole, *can differ depending on the route of administration*, i.e. oral vs. parenteral, and on the combination of both, in a sequential regimen or in continuous combined administration.

MNC/05
What has been learned from the major observational studies and clinical trials?

**the fourth lesson**

Hormonal treatments are the first choice for vasomotor symptom relief as long as they are needed (on and off assessment). *They should not be used for the secondary prevention of CVD*, when atheroma plaques are already present.
What has been learned from the major observational studies and clinical trials?

the fourth lesson (cont.)

Conversely, they may protect from CVD if started early during the transition into the post menopause. Hormonal treatments are preventive of osteopenia and osteoporosis at any stage in life.

MNC/05
Postmenopausal former oral contraceptives users may have lower rates of heart disease

702 postmenopausal women enrolled in the WISE.

Use of oral contraceptive in the past was an independent negative predictor of CAD severity ($P=0.04$ after adjustment for smoking, aspirin use, lipid lowering medication, and socioeconomic variables (model $R^2=0.19$))

14th Annual Meeting of the North American Menopause Society. Abstract P-51
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

What has been learned from the major observational studies and clinical trials?

**the fifth lesson**

Estrogens *may prevent degenerative lesions of the CNS* since, so far, they seem to be the only available drugs with nerve growth effects.
How to decrease potential risks?
TABLE 2. Breast cancer cases in women using testosterone compared with major studies

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Age</th>
<th>Cases/100,000 woman-years</th>
<th>Years observed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schairer et al\textsuperscript{10} (E/P)</td>
<td>1,854</td>
<td>57.4 y</td>
<td>628</td>
<td>10.2</td>
</tr>
<tr>
<td>WHI\textsuperscript{6} (E/P)</td>
<td>8,506</td>
<td>63.2 y</td>
<td>380</td>
<td>5.2</td>
</tr>
<tr>
<td>Million Woman\textsuperscript{5} (E/P)</td>
<td>142,870</td>
<td>55.9 y</td>
<td>521</td>
<td>2.6</td>
</tr>
<tr>
<td>Million Woman\textsuperscript{5} never-users</td>
<td>392,757</td>
<td>55.9 y</td>
<td>283</td>
<td>2.6</td>
</tr>
<tr>
<td>Adelaide (E/P/T)</td>
<td>347</td>
<td>57 y</td>
<td>293</td>
<td>5.9</td>
</tr>
</tbody>
</table>

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.
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.

What about the best treatments during the climacterium and beyond?

However, little attention is paid to other pharmacological interventions (non hormonal) and strategies that have been shown to be important for the prevention of such diseases and to maintain or improve health.
HRT is not possible ...

- When it is not wanted by women.
- When women do not feel the need.
- When there are contraindications.
Pharmacologic interventions

- Symptomatic

- Preventive
  - Primary
  - Secondary
Nurses’s Health Study

from 1980 to 1994 CHD ↓ 31%

↓ Smoking ↓ 13%
↑ Obesity ↑ 8%
↑ THS ↓ 9%
↑ Better nutrition ↓ 16%

“It appears that half of the benefits in the prevention of cardiovascular diseases are not hormone related”!

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

Among individuals aged 70 to 90 years, adherence to a mediterranean diet lifestyle is associated with a more than 50% lower rate of all-causes and cause-specific mortality.

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

Franco O et al. BMJ 2004;329:1447-50
Doctors could retrain as *Polymeal* chefs or wine advisers

*Polymeal*—an evidence based menu that includes *wine, fish, dark chocolate, fruits, vegetables, garlic,* and *almonds*—promises to be an effective, safe, cheap, and tasty solution to reducing cardiovascular morbidity and increasing life expectancy.

*Polymeal* could reduce cardiovascular disease by more than 75%.

Franco O et al. BMJ 2004;329:1447-50
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).

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
## RELATIVE RISK OF BREAST CANCER BY BODY WEIGHT

<table>
<thead>
<tr>
<th>Age at Diagnosis</th>
<th>&lt;60</th>
<th>60-69</th>
<th>70+</th>
</tr>
</thead>
<tbody>
<tr>
<td>35-49</td>
<td>1.00</td>
<td>0.54</td>
<td>1.16</td>
</tr>
<tr>
<td>50-59</td>
<td>1.00</td>
<td>1.22</td>
<td>1.43</td>
</tr>
<tr>
<td>60-69</td>
<td>1.00</td>
<td>1.61</td>
<td>1.81</td>
</tr>
</tbody>
</table>

from deWaard et al, 1964, 1978
Moderate exercise cuts breast cancer biomarkers in postmenopausal women

Increased physical activity significantly reduces serum estrogens in postmenopausal women and thus may reduce the risk of breast cancer.

McTiernan A. Cancer Res 2004;364:2923-8
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
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.”

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 defense against cancer.

London O. BMJ 2003;326:565
Breast Cancer and Nonsteroidal Anti-Inflammatory Drugs: Prospective Results from the Women’s Health Initiative

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

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.

Effect of statins combined with estradiol on the proliferation of human receptor-positive and receptor-negative breast cancer cells

Statins can inhibit the proliferation of receptor-positive and -negative human breast cancer cells but failed to completely abrogate the E2-induced proliferation of receptor-positive breast cancer cells.

Mueck AO et al. Menopause 2003;10(4):332-6
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.

The Polypill

Wald N and Law M. BMJ 2003;326:1419-25
A strategy to reduce cardiovascular disease by more than 80%

One third of people taking this pill from age 55 would benefit, gaining on average about 11 years of life free from an IHD event or stroke.

Wald N and Law M. BMJ 2003;326:1419-25
Table 4 Prevalence of participants in randomised trials reporting symptoms attributable to the Polypill components (in doses specified in table 1)

<table>
<thead>
<tr>
<th>Drug or vitamin</th>
<th>% of participants with symptoms*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any symptoms</td>
</tr>
<tr>
<td>Statin(^1)</td>
<td>0.1</td>
</tr>
<tr>
<td>Thiazide(^6)</td>
<td>2.0</td>
</tr>
<tr>
<td>Angiotensin II receptor antagonist(^5)</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>Calcium channel blocker(^6)</td>
<td>1.6</td>
</tr>
<tr>
<td>Folic acid</td>
<td>&lt;&lt;0.1</td>
</tr>
<tr>
<td>Aspirin (see table 3)</td>
<td>3.9</td>
</tr>
</tbody>
</table>

*Percentage in treated group minus percentage in placebo group.
Fig. 2
Summary of significant risks and benefits after 5 years of HRT*

<table>
<thead>
<tr>
<th>Rate per 10 000 women years</th>
<th>Breast cancers</th>
<th>Clots to lung</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>Decrease</td>
<td>8</td>
<td>10</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Rate per 10 000 women years</th>
<th>Bowel and uterine cancers</th>
<th>Fractures hip and spine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase</td>
<td>8</td>
<td>10</td>
</tr>
</tbody>
</table>

* 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
NAMS position statement on estrogen and progestagen use in peri- and postmenopausal women

No single trial should be used to set public health policy. The practice of medicine must ultimately be based on the interpretation of the entire body of evidence currently available, given that there will never be adequate clinical trials to cover all populations, eventualities, and regimens.
NAMS position statement on estrogen and progestagen use in peri-and postmenopausal women

Place no limit on ET/EPT treatment duration, provided it is consistent with treatment goals; if monitored regularly, no stipulation is made regarding when to reduce or stop therapy.
Are there risks?

It is crucial that information be given about the difference between relative risks and absolute risks, since the latter are the major cause of misinformation and alarmism, being the favorites of the media...
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
<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Relative risk</th>
<th>Increase incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight-normal weight : obesity</td>
<td>1 : 2.5</td>
<td>+ 150%</td>
</tr>
<tr>
<td>Age at menopause - 42yrs : 52 yrs</td>
<td>1 : 2.0</td>
<td>+ 100%</td>
</tr>
<tr>
<td>Age at menarche – 14 yrs: 11 yrs</td>
<td>1 : 1.3</td>
<td>+ 30%</td>
</tr>
<tr>
<td>Parity – multiparous : nulliparous</td>
<td>1 : 1.3</td>
<td>+ 30%</td>
</tr>
<tr>
<td>Age at first birth – 20 yrs : 35 yrs</td>
<td>1 : 1.4</td>
<td>+ 40%</td>
</tr>
<tr>
<td>Oral contraceptives – never user:ever user</td>
<td>1 : 1.1</td>
<td>+ 10%</td>
</tr>
<tr>
<td><strong>Hormone replacement-never:5 or more yrs</strong></td>
<td>1 : 1.3</td>
<td>+ 30%</td>
</tr>
<tr>
<td>Alcohol consumption-none:≥20 g daily</td>
<td>1 : 1.3</td>
<td>+ 30%</td>
</tr>
<tr>
<td>Serum lipids – normal : raised</td>
<td>1 : 1.6</td>
<td>+ 60%</td>
</tr>
<tr>
<td>Physical activity – activate : inactive</td>
<td>1 : 1.2</td>
<td>+ 20%</td>
</tr>
</tbody>
</table>
A modern gynecologist must ...

know how to identify risk factors and to modify them in order to prevent diseases.
Look for risk factors

- Cardiovascular
- Cancer
- Bone
- CNS
Years of healthy life can be increased 5-10 years, WHO says

We need to concentrate on the major risks if we are to improve healthy life expectancy by about 10 years, and life expectancy by even more.

Alan Lopez, Ph.D., WHO Senior Science Advisor and co-director of the WHO report (2002)
TABLE 3. *Modifiable and nonmodifiable CHD risk factors*

<table>
<thead>
<tr>
<th>Modifiable</th>
<th>Nonmodifiable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cigarette smoking</td>
<td>Increasing age (men ≥ 45 y; women ≥ 55 y)</td>
</tr>
<tr>
<td>Hypertension (blood pressure ≥140/90 mm Hg or on antihypertensive medication)</td>
<td>Family history of premature CHD (male first-degree relative &lt; 55 years; female first-degree relative &lt; 65 years)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td></td>
</tr>
<tr>
<td>Obesity</td>
<td></td>
</tr>
<tr>
<td>Physical inactivity</td>
<td></td>
</tr>
</tbody>
</table>

Women are not statistics!
They must be treated individually
Evidence based medicine: does it make a difference?

Like any technology, evidence based medicine carries risks and benefits and can be used appropriately or inappropriately.

Schon CR et al. BMC Health Serv Res 2003;3(1):14
Evidence informed practice

• It is clearly time to change “evidence based medicine” to “evidence informed practice”.

• I suggest the era of evidence informed rather than evidence based medicine has arrived.

Evidence Based Medicine

and/or

Medicine Based Evidence?

Manuel Neves-e-Castro
Evidence Based Medicine or Intelligent Based Medicine?

Lucas Viana Machado
“He who learns, but does not think is lost. He who thinks, but does not learn is dangerous”.

Confucius
If we both **learn** and **think** we will neither be **lost** nor **dangerous** to our postmenopausal women patients”

Wenger NK. *Am J Geriatr Cardiol* 2000;9:204-9
“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)
What are the best recommendations of the climacteric woman’s doctor?

1. Understand what is happening to the body during the climacteric and the postmenopause
2. Mental occupation
3. Physical exercise
4. Proper nutrition (moderate consumption of red wine, and abundant fish, vegetables, fruits, soy, milk, garlic, chocolate, etc)
5. Keep the body mass index (BMI) within normal limits
6. Keep a normal girdle/hip ratio, waist circumference
7. Refrain from smoking
8. Keep a normal blood pressure
9. Keep the blood lipids within normal values (statins?)
10. Examine the breasts (palpation, inspection, mammography)
Which is the best treatment?

In general terms, is the one that is wisely indicated, if not contraindicated, after balancing benefits and risks, of all strategies and interventions, hormonal or not. It must be aimed at specific objectives and targets that will be monitored at regular intervals in order to determine its efficacy and to estimate the occurrence of any side effects, a condition that will determine its duration.
Which is the best treatment?

Patient needs and preferences are decisive, based on the doctors’ advice. Let it not be forgotten that although many treatments are available, they are nevertheless not indispensable. Doctors have the duty to give their best unbiased information to their patients so that they may make the right choices and then be compliant.

The woman is the decision maker, if the doctor sees no contraindication.

Thus, the best treatment is what she has chosen.
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.
The take-home message is:
(3)

- No answers from ongoing clinical trials are indispensable to practice today a good Medicine!
HT appears to be the best form of pharmacologic treatment to improve brain function, as well as to reduce the risk of colon cancer. It is probably the best preventive strategy for osteoporosis.

With this in mind,

limiting HT to the treatment of climacteric symptoms only is unjustified.

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
Science is the search for truth.
It is not a game in which one tries to beat his opponent, to do harm to others

Linus Carl Pauling, 1958