Modern concepts of managing women in perimenopause and postmenopausal period

by

Manuel Neves-e-Castro

Lisbon/Portugal

3rd Slovenia-Croatian Symposium on Menopause and Andropause

April 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
- **political lobbies** from the *NIH*
- a **lack of scientific honesty** manifested by many of the WHI writers
The “Menopausal Stars“

1. Women’s health after WHI. Reports from the Amsterdam Menopause Symposium, October 2-4, 2004.


The U.S.A. “team”

1. R. Chlebowski
2. J. Rossow
3. R. Lobo
4. Th. Clarkson
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”

1. D. Barlow
2. H. Kuhl
4. P. Kenemans
4. A. Pines
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
Some of the 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
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

Edited by
M. Neves-e-Castro, MD
Reproductive Medicine Clinic, Lisbon, Portugal
and
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University of Berne, Switzerland
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Wake Forest University, NC, USA
P. Collins, MD
National Heart and Lung Institute, London, UK

The Parthenon Publishing Group
International Publishers in Medicine, Science & Technology
NEW YORK LONDON
Menopause
HORMONES AND CANCER
Proceedings of the 2nd International Symposium
of the Portuguese Menopause Society

Edited by
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The Parthenon Publishing Group
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PORTUGAL ABAIXO DA MÉDIA EUROPEIA

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<td>Espanha</td>
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Número de casos por cada 100 mil mulheres
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” (?)...
“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>
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<tr>
<td>CHD</td>
<td>1428</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>1250</td>
<td></td>
</tr>
<tr>
<td>VTE</td>
<td>588</td>
<td></td>
</tr>
<tr>
<td>Breast Cancer</td>
<td>1250</td>
<td></td>
</tr>
<tr>
<td>Colon Cancer</td>
<td>1667</td>
<td></td>
</tr>
<tr>
<td>Osteoporotic fractures</td>
<td>227</td>
<td></td>
</tr>
<tr>
<td>(totals)</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*
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

<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>

Studd J. Climacteric 2004;7:412-414
Revised breast cancer statements indicate that the risk of breast cancer probably increases with EPT use but not with ET use.
The E only arm of the WHI was **stopped** !...

**Why ?**

**Why ?? ! ...**

**Why ??? ...**
“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.”

“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”

*EMAS Statement; 2004.*
The E only arm of the WHI was stopped !...

Why ?

Why ?? ! ... 

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 millions 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

- Relative Risk
  - 0 months: 1
  - 12 months: 2
  - 18 months: 3
  - 24 months: 1
  - 36 months: 1
  - 48 months: 1

- Months:
  - 0
  - 12
  - 18
  - 24
  - 36
  - 48

Line graph showing the relative risk over time in MWS.
Time Course of Breast Cancer Development

![Graph showing the time course of breast cancer development with markers for genetic, growth factor, and tissue factor events. The graph illustrates the progression from precancer to clinical stages, with key milestones at 0.5 cm and 1.0 cm.]
Occult Breast Cancer in medico-legal autopsies

Breast malignancy was found in 22 women (20%)

Nielsen M et al-Br J Cancer 1987;56:814-9
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>
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</thead>
<tbody>
<tr>
<td>Current use</td>
<td>191</td>
<td>3011</td>
</tr>
<tr>
<td>Never use</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

*statistically significant

# HRT and Breast Cancer

**Pregnancy Following Breast Cancer**

*Gelber 2001*

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

Survival fraction vs Survival (months)

Cases (ERT/HRT)
Controls (no ERT/HRT)

No Hormones $P = 0.005$

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

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
BMI and Breast Cancer

In our study the effect of hormone use on breast cancer appeared to be similar across categories of BMI, contradicting previous findings that the increase in risk associated with HRT’s primarily concerns underweight women.

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

**the second lesson**

Estrogens, 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. parentheral, and on the combination of both, in a sequential regimen or in continuous combined administration.
Breast Cancer

Estrogens and Progestagens

• The association between HRT use and breast cancer risk most likely varies according to the types of progestagens used.

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.

MNC/05
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.
Postmenopausal hormone therapy: critical reappraisal and unified hypothesis

HRT is associated with less coronary atherosclerosis in postmenopausal women. HT may be cardioprotective, if initiated before the onset of atherosclerosis.

Akhrass F et al. J Clin Endocrinol Metab 2003; 88:5611–5614
Impaired Endothelial Function in Young Women with Premature Ovarian Failure: Normalization with Hormone Therapy

Early onset of endothelial dysfunction associated with sex steroid deficiency may contribute to the increased risk of cardiovascular disease and mortality in young women with premature ovarian failure. \textit{Hormone therapy restores endothelial function within 6 months of treatment.}

Hormone therapy and coronary artery calcification in asymptomatic postmenopausal women: the Rancho Bernardo Study

Barrett-Connor E. Menopause 2005;12:40-8
FIG. 1. Odds ratios for the association of *current* and *past vs never* HT and other CHD risk factors with increasingly severe coronary artery calcification among 204 asymptomatic postmenopausal women. Units: age = 10 y; LDL/HDL ratio = 1; pulse pressure = 10 mm Hg; FPG (fasting plasma glucose) = 20 mg/dL; current smoking = *yes* vs *no*. 
FIG. 2. Age-adjusted proportions of women with CACS (coronary artery calcification score) >100 by duration of HT use among 127 asymptomatic postmenopausal women. *P < 0.01 vs 10-15 y and >15 y.
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 R2=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.
IADRD: Estrogens Exhibits Neuroprotective effect in preliminary analysis of Swedish Data

Preliminary analysis of data from the Swedish Twin Registry suggests that estrogen is neuroprotective and the effect is not related to length of estrogen therapy.

Estrogen use was significantly related to better cognitive functioning (odds ratio [OR]=0.43 95% confidence interval [CI]=0.26, 0.70)

Postmenopausal Estrogen Use Affects Risk for Parkinson Disease

- Estrogen therapy has been associated with *improved cognitive functioning, a reduced risk of dementia in women with Parkinson disease* (PD), and a *decreased risk of Alzheimer disease*.
- Postmenopausal estrogen therapy may be associated with a *reduced risk of PD in women*.

Fig 2. Relative risk of Alzheimer’s disease in ERT users. Courtesy of R. A. Greene, MD. Advanced Reproductive Endocrinology Services; Redding Medical Center. Prepared April 2000.
How to decrease potential risks?
<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Age</th>
<th>Cases/100,000 woman-years</th>
<th>Years observed</th>
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<tbody>
<tr>
<td>Schairer et al$^{10}$ (E/P)</td>
<td>1,854</td>
<td>57.4 y</td>
<td>628</td>
<td>10.2</td>
</tr>
<tr>
<td>WHI$^6$ (E/P)</td>
<td>8,506</td>
<td>63.2 y</td>
<td>380</td>
<td>5.2</td>
</tr>
<tr>
<td>Million Woman$^5$ (E/P)</td>
<td>142,870</td>
<td>55.9 y</td>
<td>521</td>
<td>2.6</td>
</tr>
<tr>
<td>Million Woman$^5$ 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?

There is a general tendency to consider that *sex steroid hormones* are the only instruments with which to treat women when they enter in the climacteric phase of their lives...
What about the *best treatments* during the climacterium and beyond?

This is assumption is shared by both **women and physicians**. Otherwise the ongoing discussions that have exploded all over the world would not have been centered only in the risks/benefit assessment of hormonal treatments…
What about the best treatments during the climacterium and beyond?

The **climacteric**, due to hormonal causes and aging, is also a time of the onset of several risk factors for diseases that may be manifested later in life, mainly cardiovascular diseases (CVD), osteoporosis, degenerative diseases of the central nervous system (CNS), to name only the major ones that may have impact in the duration and quality of life.
What about the **best treatments** during the climacterium and beyond?

**Epidemiological studies**

There are abundant studies that confirm the **increased incidence of such diseases** in **untreated women** as well as many other studies about the **benefit/risk** analyses of the hormonal treatments to which these women have been submitted.
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.
Sometimes

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
Olive oil and red wine antioxidant polyphenols inhibit endothelial activation... 

...thus partially explaining atheroprotection from Mediterranean diets.

Carluccio MA et al. Arteriosclerosis, Thrombosis and Vascular Biology 2003;23:622
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!

The *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
<table>
<thead>
<tr>
<th>Age at Diagnosis</th>
<th>&lt;60</th>
<th>60-69</th>
<th>70+</th>
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<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><strong>1.00</strong></td>
<td><strong>1.61</strong></td>
<td><strong>1.81</strong></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
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
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
A Randomized Trial of Low-Dose Aspirin in the Primary Prevention of Cardiovascular Disease in Women

Ridker PM et al. NEJM 2005;352:1-12
Figure 1. Cumulative Incidence Rates of the Primary End Point of Major Cardiovascular Events.

A major cardiovascular event was defined as a nonfatal myocardial infarction, a nonfatal stroke, or death from cardiovascular causes.
Figure 2. Cumulative Incidence Rates of Stroke, Myocardial Infarction, Ischemic Stroke, and Hemorrhagic Stroke.
“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.”

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.

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

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.

The *Polypill*

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&lt;sup&gt;1&lt;/sup&gt;</td>
<td>0.1</td>
</tr>
<tr>
<td>Thiazide&lt;sup&gt;16&lt;/sup&gt;</td>
<td>2.0</td>
</tr>
<tr>
<td>Angiotensin II receptor antagonist&lt;sup&gt;15&lt;/sup&gt;</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>Calcium channel blocker&lt;sup&gt;16&lt;/sup&gt;</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.
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
What is already known on this topic

Four risk factors (LDL cholesterol, blood pressure, homocysteine, and platelet function) that can be reduced by drugs or vitamins account for most cardiovascular disease.

Apart from aspirin, the use of such agents has focused on people with high levels of the risk factor.

Wald N and Law M. BMJ 2003;326:1419-25
What this study adds

Intervening on all four risk factors reduces heart attacks and strokes by over 80%.

To achieve this large effect in a population requires a combination treatment taken by everyone above a specified age (say 55) and younger people with a clinical history of occlusive arterial disease.

A combination pill containing six active components could be widely used.

Each component has been used in medical practice for more than 10 years with substantial evidence on safety and efficacy.

Wald N and Law M. BMJ 2003;326:1419-25
And now...
in 2005
The new American way ... 
or ... 
a 180° rotation! ...
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 former are the major cause of misinformation and alarmism, being the favorites of the media…
General Risks  With which we are “at home”

RISK INCREASING

Totally safe - For all practical purposes  Risk effectively Zero  Minimal  Very low  Low  Moderate  High  Very high

- Risk of dying at some point in life
- Risk of drowning in tub this year
- Cancer risk from eating charbroiled steak once a week for 1 year
- Risk of dying on a single trip on any scheduled civilian airline
- Annual risk of being bitten by a dog
- Risk of death from accidents at home in 1 year
- Extra risk of cancer from 1 light beer a day for 1 year
- Risk of injury due to skiing slopes in one season
- Risk of mother dying in birth of single child
- Extra risk of cancer from living in Zermatt compared to Lisbon for 1 year

THE PALING PERSPECTIVE SCALE
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www.riskcomm.com
### Medical Risks

The magnitude of women’s main health risks after menopause

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>Risk Description</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Totally safe</td>
<td>For all practical purposes</td>
<td></td>
</tr>
<tr>
<td>Risk effectively</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zero</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minimal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very low</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very high</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Risk of 60 year old woman dying within the year:** 1 in 110
- **Chance of woman (aged 50-60) getting breast cancer in any one year:** 1 in 833
- **Chance a woman (aged 50-60) getting first heart attack in any one year:** 1 in 250
- **Chance of woman dying from breast cancer in any one year:** 1 in 3,700
- **Chance of woman dying from heart attack in any one year:** 1 in 714
- **Chance of woman (finally) dying from breast cancer:** 1 in 33
- **Chance of woman (finally) dying from heart attack:** 1 in 7

**NOTE:** We can only show you average numbers. Whether your results will be positive or negative is impossible to predict and is dependent on many factors influencing individual health.

---

THE PALING PERSPECTIVE SCALE
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www.riskcomm.com
Various risk factors influencing Breast Cancer Risk

**Risk factors for Breast Cancer**

- **Hormonal**
  - Breast Density
  - Plasma E2
  - Bone Density
  - Late First Birth
  - Post-menopausal weight gain
  - Late Menopause
  - Waist Hip Ratio
  - Menarche < age 12
  - Hormonal Treatment E-P
  - HT E alone
  - OVX < age 35
- **Non-hormonal**
  - Physical activity (recreational)
  - Alcohol
  - Smoking

**Lung Cancer**

- Smoking

**References**

4. CGHFBC, Br J Cancer, 2002; 87: 1234-1245; Chan-Wendy, Y, cs, Ann Intern Med, 2002; 137; 798-804
We can only show you averages. It is impossible to predict whether your results will be positive or negative.
What you need to know about breast cancer and hormonal treatment for menopausal symptom relief

One thousand women (mean age 63) during 1 year

Women who do not get breast cancer: 997

Indicates the number of women in the general population who will get breast cancer anyway = 3 in 1000

Additional risk for women who take hormone therapy (estrogen+progestagen) = 0.8 in 1000 or less than one woman in thousand

Women who do not get breast cancer: 997

Indicates the number of women in the general population who will get breast cancer anyway = 3 in 1000

Indicates the number of women who might be protected against getting breast cancer by using estrogen only therapy = 0.6 in 1000

Data adapted from the WHI, JAMA 2004; 291: 1701-12

Risk for a postmenopausal woman developing breast cancer over a five year period is 15 out of 1000. The additional risk if they also take hormonal treatment during 5 years is 4 out of 1000. At the age of 65, finally 30 out of 1000 women will have got breast cancer. This is called the cumulative risk. Most women (70-80%) do survive from breast cancer.
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>
<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
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)
What are the best recommendations of the climacteric woman’s doctor?

• **For vasomotor symptoms and night sweats** take a sequential E+P medication, the most inert being an E-patch + oral or vaginal natural progesterone (alternatively, a progestagen loaded IUD). If hysterectomized take only E (no need for P)

• **If libido is still down**, add testosterone or switch E+P to tibolone.

• **If breasts are tender and dense**, adjust dosages or use tibolone instead of E (+P)
What are the best recommendations of the climacteric woman’s doctor?

• Use vaginal estrogens if vagina is dry and if there is dispareunia
• If osteoporetic one may add bisphosphonates or tibolone
• Check stools for occult blood and do the first colonoscopy at age 50 and thereafter at 5 year intervals.
• Last but not least, enjoy life and help other women to do what you are doing.
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.*

Mortality Associated with HRT in younger and older women

Hormone Replacement Therapy *reduced total mortality in trials with mean age of participants under 60 years.*

*No change in mortality was seen in trials with mean age over 60 years.*

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