Hormone therapy and breast cancer: conflicting evidence

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The world of hormone therapy in the 1990’s

Throughout the 1970s, 1980s and 1990s long term use of HRT was widely recommended for women after the menopause

- Suggested Benefits: prevention of hot flushes, osteoporosis, heart disease, ageing, improved cognition
- Possible harms: breast cancer, venous thromboembolism
Balancing the benefits and harms

Deaths induced-prevented / 1000 women treated with HRT

Heart Disease
Stroke
Hip Fracture
Other
Breast Cancer

Daly et al 1996
HRT and Breast Cancer is not a new story......

- Berquivist (1992) RR of breast cancer in HRT users 1.6
- Nurses Health study (1995) RR 1.45 after >5 years use of HRT
- Lancet Collaborative meta analysis (1997) RR 1.35 after >5 years of HRT
Lancet Collaborative Group

Meta analysis of 51 observational studies on breast cancer risk and HRT use
52,000 women with breast cancer
Majority on ERT
Adjusted for age of menopause
Main findings:
- RR of breast cancer diagnosis 1.35 after 5 + years of HRT
- No increased risk in past users (>5 years)
- Risk greater in slim women than overweight (BMI >25) women
- Family history of breast cancer did not increase risk
- No increased risk of mortality
- No difference between ERT and HRT
Design of WHI study

POPULATION:
- 16,608 women aged 50 to 79 years
- Population based sample (recruited from mailing and media awareness)
- Heterogeneous group – minimal exclusions
- Washout period before trial
- Two study groups: HRT and ERT
What sort of women were in the trial?

- Age: 50-79 years with mean of 63 years
- 70% overweight, 45% BMI $\geq 30$
- Ethnically diverse
- 20% prior HRT use, 6% current users
### WHI results for HRT: July 2002

**Cases per 10,000 women per year**

<table>
<thead>
<tr>
<th>Condition</th>
<th>HRT</th>
<th>Placebo</th>
<th>Additional events/1,000</th>
<th>NNT for 1 additional event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer</td>
<td>38</td>
<td>30</td>
<td>+8</td>
<td>1250</td>
</tr>
<tr>
<td>Heart disease</td>
<td>37</td>
<td>30</td>
<td>+7</td>
<td>1430</td>
</tr>
<tr>
<td>Stroke</td>
<td>26</td>
<td>13</td>
<td>+7</td>
<td>1250</td>
</tr>
<tr>
<td>DVT</td>
<td>29</td>
<td>21</td>
<td>+8</td>
<td>550</td>
</tr>
<tr>
<td>Fracture</td>
<td>10</td>
<td>15</td>
<td>-5</td>
<td>2000</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>10</td>
<td>16</td>
<td>-6</td>
<td>1667</td>
</tr>
</tbody>
</table>

No overall increase in death rates at 5.2 years of follow up.
Prior use of HRT increased risk cf with no prior use of HRT

- HR 2.13 (1.15-3.94) for prior use
- HR 1.06 (0.81-1.38) for no prior use

Adherent to therapy increased risk

- HR 1.49
ERT only study: 2004

- No effect on BC diagnoses reported after 6.8 years follow up
  - HR 0.77 (nominal 95%CI 0.59-1.01 and adjusted 95% CI 0.57-1.06)
- Mortality from BC: no difference but no HR provided
Million Women Study – Aug 03

- 1996-2001: National Health Service Breast Screening Programme invited women to take part prior to entry
- 1084110 women, 50-64 years
- 50% of women had used HRT
- 18 % had BMI ≥ 30

Breast cancer and hormone-replacement therapy in the Million Women Study

Million Women Study Collaborators
Million Women Study

Relative Risk

- E only: 1.3 (1.21-1.40)
- E+P: 2.0 (1.88-2.12)

Current users of HRT cf never users

- Diagnosis of BC: adj RR 1.66 (1.58-1.75)
- Mortality from BC: 1.22 (1.00-1.48)

Past users of HRT: no increased risk

No differences: formulations and delivery systems

<table>
<thead>
<tr>
<th>HRT use at baseline</th>
<th>Cases/population</th>
<th>Relative risk (95% FCI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>All never users</td>
<td>2894/392 757</td>
<td>1.00 (0.96-1.04)</td>
</tr>
<tr>
<td>All past users</td>
<td>1044/150 179</td>
<td>1.01 (0.95-1.08)</td>
</tr>
<tr>
<td>Current users of:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oestrogen only</td>
<td>991/115 383</td>
<td>1.30 (1.22-1.38)</td>
</tr>
<tr>
<td>Oestrogen-progestagen</td>
<td>1934/142 870</td>
<td>2.00 (1.91-2.09)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>HRT use at baseline</th>
<th>Deaths/population</th>
<th>Relative risk (95% FCI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never users</td>
<td>238/392 757</td>
<td>1.00 (0.88–1.14)</td>
</tr>
<tr>
<td>Current users</td>
<td>191/285 987</td>
<td>1.22 (1.05–1.41)</td>
</tr>
<tr>
<td>Past users</td>
<td>88/150 179</td>
<td>1.05 (0.85–1.29)</td>
</tr>
</tbody>
</table>

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.
Authors conclusions

- 10 years of HRT is estimated to result in
  - 5 additional cancers per 1000 users of E only
  - 19 additional cancers per 1000 users of E+P

- Use of HRT by women 50-64 yrs in UK in past decade has resulted in an estimated 20,000 extra breast cancers (15,000 from E + P)
## Summary of WHI and MWS: RR

<table>
<thead>
<tr>
<th></th>
<th>WHI – E+P</th>
<th>WHI – E only</th>
<th>MWS – E+P</th>
<th>MWS – E only</th>
</tr>
</thead>
<tbody>
<tr>
<td>Br Ca Δ</td>
<td>1.26 (1.02-1.56)</td>
<td>0.79 (0.61-1.02)</td>
<td>2.0 (1.88-2.12)</td>
<td>1.3 (1.21-1.40)</td>
</tr>
<tr>
<td>BC mortality</td>
<td>0.95 (0.24-38.1)</td>
<td>Not reported</td>
<td>1.22 (1.05-1.41)</td>
<td>Not reported</td>
</tr>
<tr>
<td>Time frame</td>
<td>5.6 years</td>
<td>6.8 years</td>
<td>4.1 years</td>
<td>4.1 years</td>
</tr>
</tbody>
</table>

Not reported
Cochrane Review

Review: Long term hormone therapy for perimenopausal and postmenopausal women
Comparison: 05 All women (Selected outcomes: cancer, cholecystic disease, fractures)
Outcome: 02 Breast cancer: Oestrogen-only HT (moderate dose)

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>Relative Risk (Fixed) 95% CI</th>
<th>Weight (%)</th>
<th>Relative Risk (Fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>01 Oestradiol 1mg for 2 yrs EPAT 2001</td>
<td>0 / 111</td>
<td>1 / 111</td>
<td>[0.33, 0.01, 8.10]</td>
<td>100.0</td>
<td>[0.33, 0.01, 8.10]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>0 / 111</td>
<td>1 / 111</td>
<td>[0.33, 0.01, 8.10]</td>
<td>100.0</td>
<td>[0.33, 0.01, 8.10]</td>
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<tr>
<td>Test for heterogeneity chi-square=0.00 df=0</td>
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<tr>
<td>Test for overall effect=-0.68 p=0.5</td>
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<td></td>
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</tr>
<tr>
<td>02 CEE 0.625 for 2.8 - 3.2 yrs ERA 2000</td>
<td>1 / 105</td>
<td>0 / 105</td>
<td>[3.15, 0.13, 76.40]</td>
<td>24.6</td>
<td>[3.15, 0.13, 76.40]</td>
</tr>
<tr>
<td>PEPI 1995</td>
<td>1 / 174</td>
<td>1 / 174</td>
<td>[0.99, 0.06, 16.77]</td>
<td>50.6</td>
<td>[0.99, 0.06, 16.77]</td>
</tr>
<tr>
<td>WAVE 2002</td>
<td>1 / 140</td>
<td>0 / 140</td>
<td>[3.10, 0.13, 74.60]</td>
<td>24.8</td>
<td>[3.10, 0.13, 74.60]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>3 / 335</td>
<td>1 / 341</td>
<td>[2.05, 0.38, 11.04]</td>
<td>100.0</td>
<td>[2.05, 0.38, 11.04]</td>
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<tr>
<td>Test for heterogeneity chi-square=0.40 df=2 p=0.8198</td>
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<tr>
<td>Test for overall effect=0.83 p=0.4</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>03 CEE 0.625 mg for 6.8 yrs WHI 1998</td>
<td>94 / 5310</td>
<td>124 / 5429</td>
<td>[0.78, 0.59, 1.01]</td>
<td>100.0</td>
<td>[0.78, 0.59, 1.01]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>94 / 5310</td>
<td>124 / 5429</td>
<td>[0.78, 0.59, 1.01]</td>
<td>100.0</td>
<td>[0.78, 0.59, 1.01]</td>
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<td>Test for heterogeneity chi-square=0.00 df=0</td>
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<tr>
<td>Test for overall effect=-1.88 p=0.06</td>
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<tr>
<td></td>
<td>WHI</td>
<td>MWS</td>
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</tr>
<tr>
<td>BC Δ E+P</td>
<td>Increased</td>
<td>Increased</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BC mortality E+P</td>
<td>No difference</td>
<td>Increased</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BC Δ E only</td>
<td>No difference</td>
<td>Increased</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BC mortality E only</td>
<td>Not reported</td>
<td>Not reported</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Possible explanation for the differences

- **Study design**
  - RCT versus observational

- **Power**
  - 16,000 women versus 1,000,000

- **US vs UK pop**
  - Differences in screening etc

- **Prior use of hormones**
  - 72% E+P (WHI), 52% E (WHI) versus 50% in MWS

- **Younger age in MWS**
  - Mean 63yrs E+P (WHI), 63 E (WHI) versus 56 years (MWS)

- **BMI**
  - Women in WHI study heavier than women in MWS
Explanation for the differences: BMI amongst Estrogen only in MWS

<table>
<thead>
<tr>
<th>BMI Kg/m²</th>
<th>RR of BC Δ MWS</th>
<th>MWS</th>
<th>WHI 2004</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 25</td>
<td>1.36 (1.14-1.63)</td>
<td>45%</td>
<td>21%</td>
</tr>
<tr>
<td>25-29</td>
<td>1.14 (0.94-1.40)</td>
<td>37%</td>
<td>34%</td>
</tr>
<tr>
<td>≥ 30</td>
<td>0.99 (0.73-1.34)</td>
<td>18%</td>
<td>45%</td>
</tr>
</tbody>
</table>
Weight and breast cancer

- Overweight women have increased risk of breast
- In MWS trial women with BMI < 25 had increased risk
Conclusions

Authors of trial concluded that:

- HRT should not be used for long-term disease prevention because the benefits were not sufficient to justify the risks.
- On balance the harm of HRT was greater than the benefit (global index)
- The trial was not designed to assess the effects of HRT for short term use to control menopausal symptoms
Intervention/comparison

Combined HRT study
- Conjugated equine oestrogens 0.625mg/day + medroxyprogesterone acetate 2.5mg/day in 1 tablet
- Placebo tablet, 1 tablet
- Participants and study staff blinded but unblinding occurred because of need to treat bleeding

Estrogen only study
- Women who had undergone hysterectomy
- Conjugated equine oestrogens 0.625mg/day
- Placebo tablet
Time period of trial

- Recruitment from 1993 – 1998
- Average follow up 5.2 years
- Planned duration 8.5 years (until 2005)
- Trial stopped early because:
  - Test statistic for invasive breast cancer exceeded the stopping boundary
  - Global index statistic supported risks exceeding benefits
Outcomes

Primary
- CHD rates – HRT expected to be a benefit
- Invasive breast cancer rates – HRT expected to be a harm

Other outcomes
- Hip fracture and other fracture rates
- Stroke rates
- VTE rates
- Endometrial cancer rates
- Colorectal cancer rates
- Total death rates
- Global index
But the HRT story is an all too familiar one in modern medicine. A new drug is found to be potentially useful in a large proportion of the population. Hypotheses for extended use, in the case of HRT to prevent cardiovascular disease and bone fractures, are generated from observational studies. Its use is then heavily promoted beyond the initial indication. Rigorously conducted randomised studies with long enough follow-up are scarce or lacking. Harm and risk are uncovered many years after widespread use.