Hormone therapy and breast cancer: conflicting evidence

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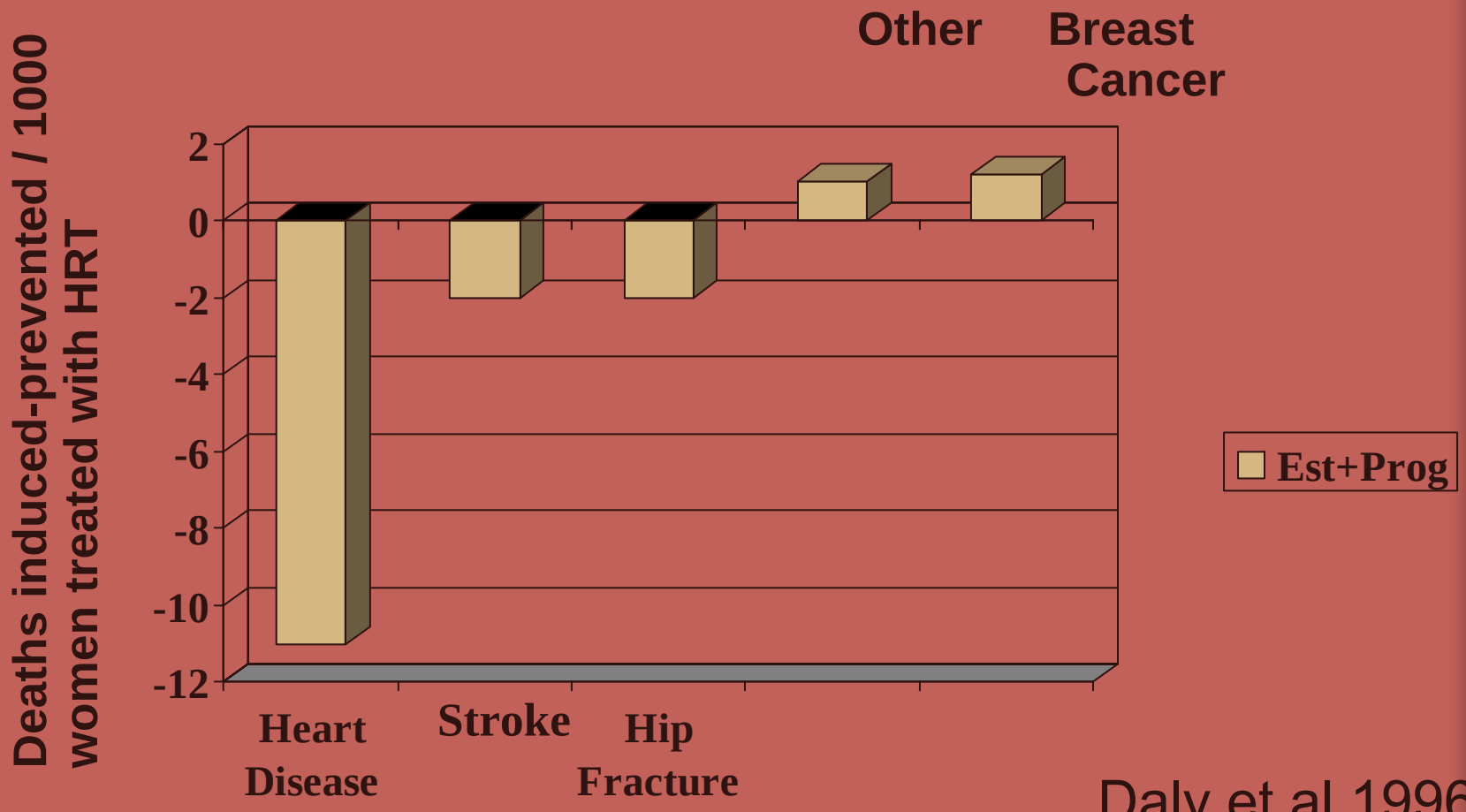
The world of hormone therapy in the 1990's

- 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



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?

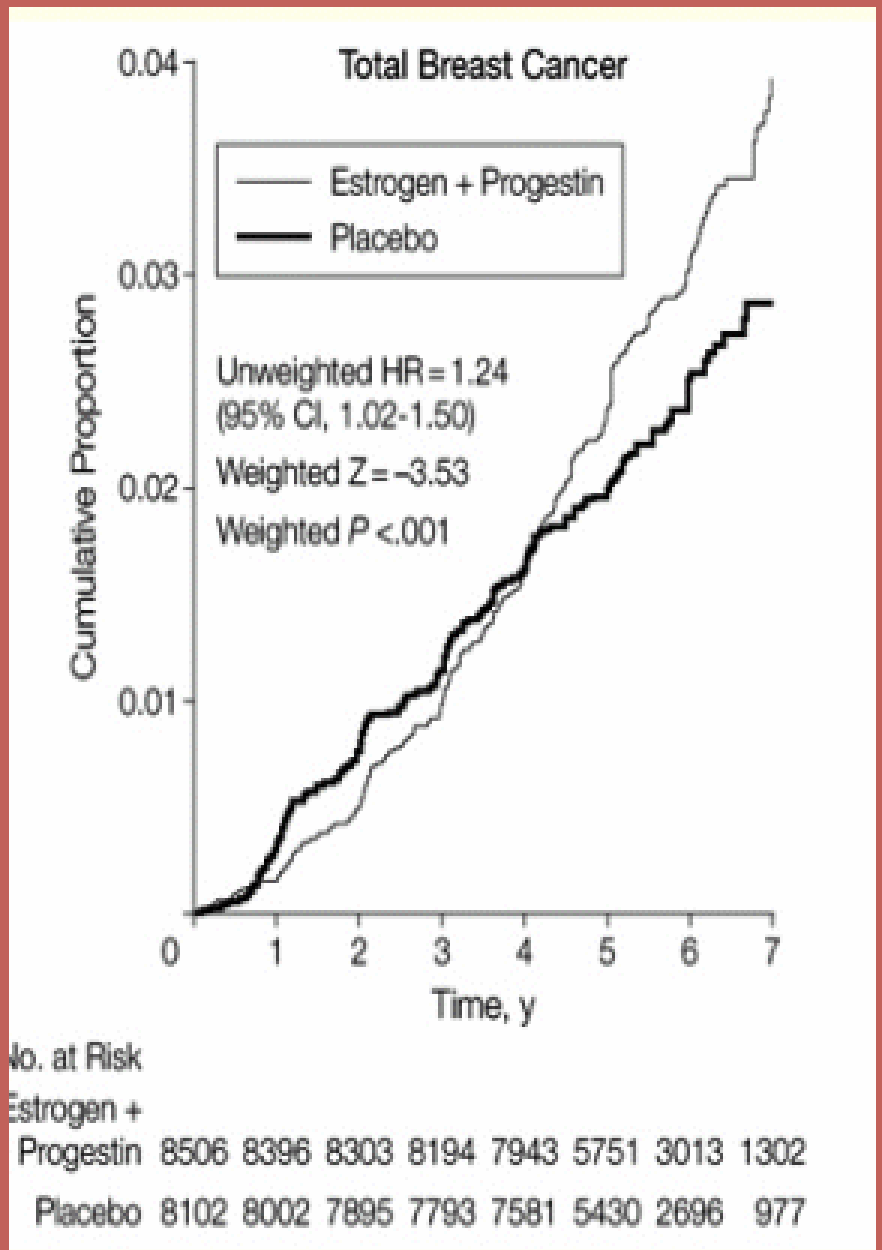
- Age: 50-79 years with mean of 63 years
- 70% overweight, 45% BMI ≥ 30
- Ethnically diverse
- 20% prior HRT use, 6% current users

WHI results for HRT: July 2002

Cases per 10,000 women per year

	HRT	placebo	Additional events/1,000	NNT for 1 additional event
Breast cancer	**38**	**30**	**+8**	**1250**
Heart disease	37	30	+7	1430
Stroke	26	13	+7	1250
DVT	29	21	+8	550
Fracture	10	15	-5	2000
Colorectal cancer	10	16	-6	1667

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

Articles

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

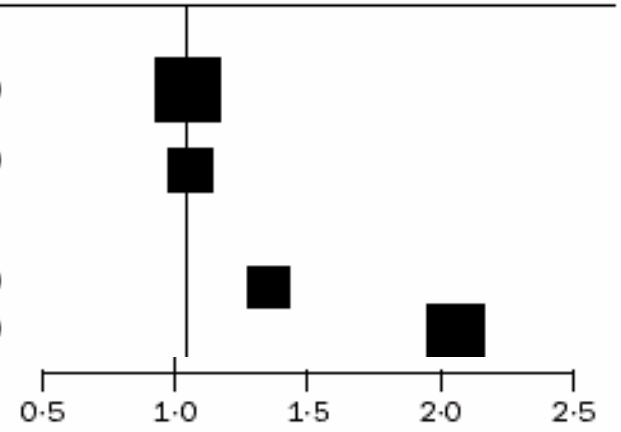
Million Women Study Collaborators

THE LANCET • Vol 362 • August 9, 2003 • www.thelancet.com

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

HRT use at baseline	Cases/population	Relative risk (95% FCI)*
All never users	2894/392 757	1·00 (0·96–1·04)
All past users	1044/150 179	1·01 (0·95–1·08)
Current users of:		
Oestrogen only	991/115 383	1·30 (1·22–1·38)
Oestrogen-progestagen	1934/142 870	2·00 (1·91–2·09)



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

Mortality from BC in MWS

HRT use at baseline	Deaths/population	Relative risk (95% FCI)*
Never users	238/392 757	1·00 (0·88–1·14)
Current users	191/285 987	1·22 (1·05–1·41)
Past users	88/150 179	1·05 (0·85–1·29)

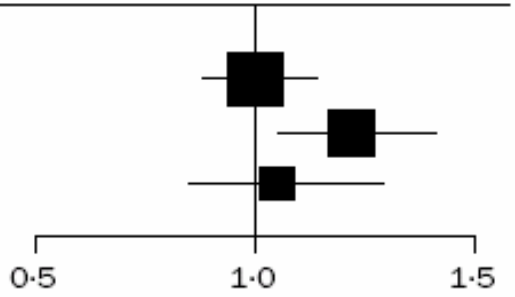


Figure 6: **Relative risk of fatal breast cancer in relation to use of HRT at baseline**
FCI=floated CI. *Relative to never users, stratified by age, time since menopause, parity and age at first birth, family history of breast cancer, body-mass index, region, and deprivation index.

Authors conclusions

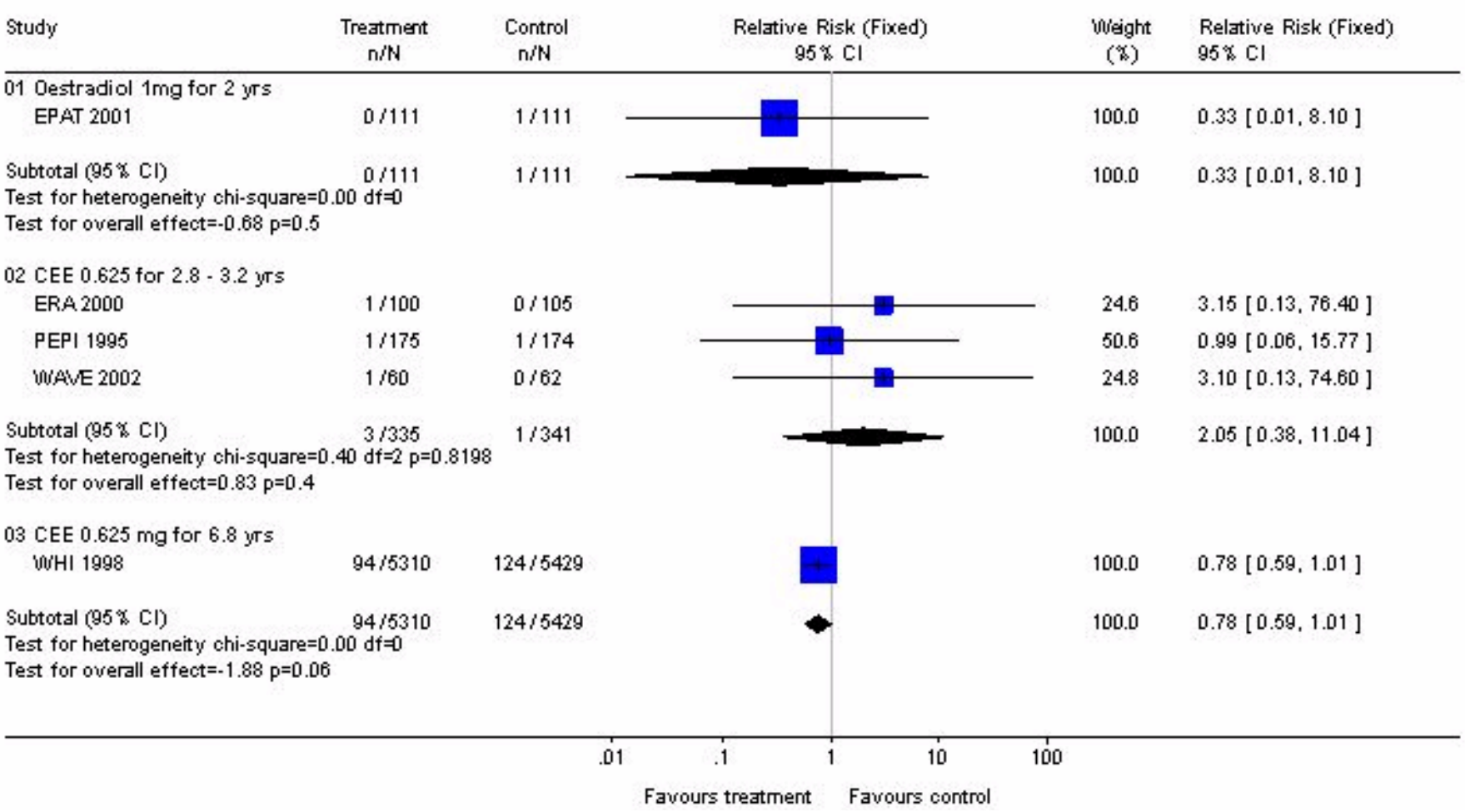
- 10 years of HRT is estimated to result in
  - 5 additional cancers per 1000 users of E only
  - 19 additional cancers per 1000 users of E+P
- Use of HRT by women 50-64 yrs in UK in past decade has resulted in an estimated 20,000 extra breast cancers (15,000 from E + P)

Summary of WHI and MWS: RR

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

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)



WHI and MWS: consistency?

	WHI	MWS
BC Δ E+P	Increased	Increased
BC mortality E+P	No difference	Increased
BC Δ E only	No difference	Increased
BC mortality E only	Not reported	Not reported

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

BMI Kg/m^2	RR of BC Δ MWS	MWS	WHI 2004
< 25	1.36 (1.14-1.63)	45%	21%
25-29	1.14 (0.94-1.40)	37%	34%
≥ 30	0.99 (0.73-1.34)	18%	45%

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

Lancet Editorial Dec 2004

"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. "