

# Something has changed? The literature from 2008 to present?

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Rome Oct 7, 2011: Post-menopausal hormone therapy  
and women's information

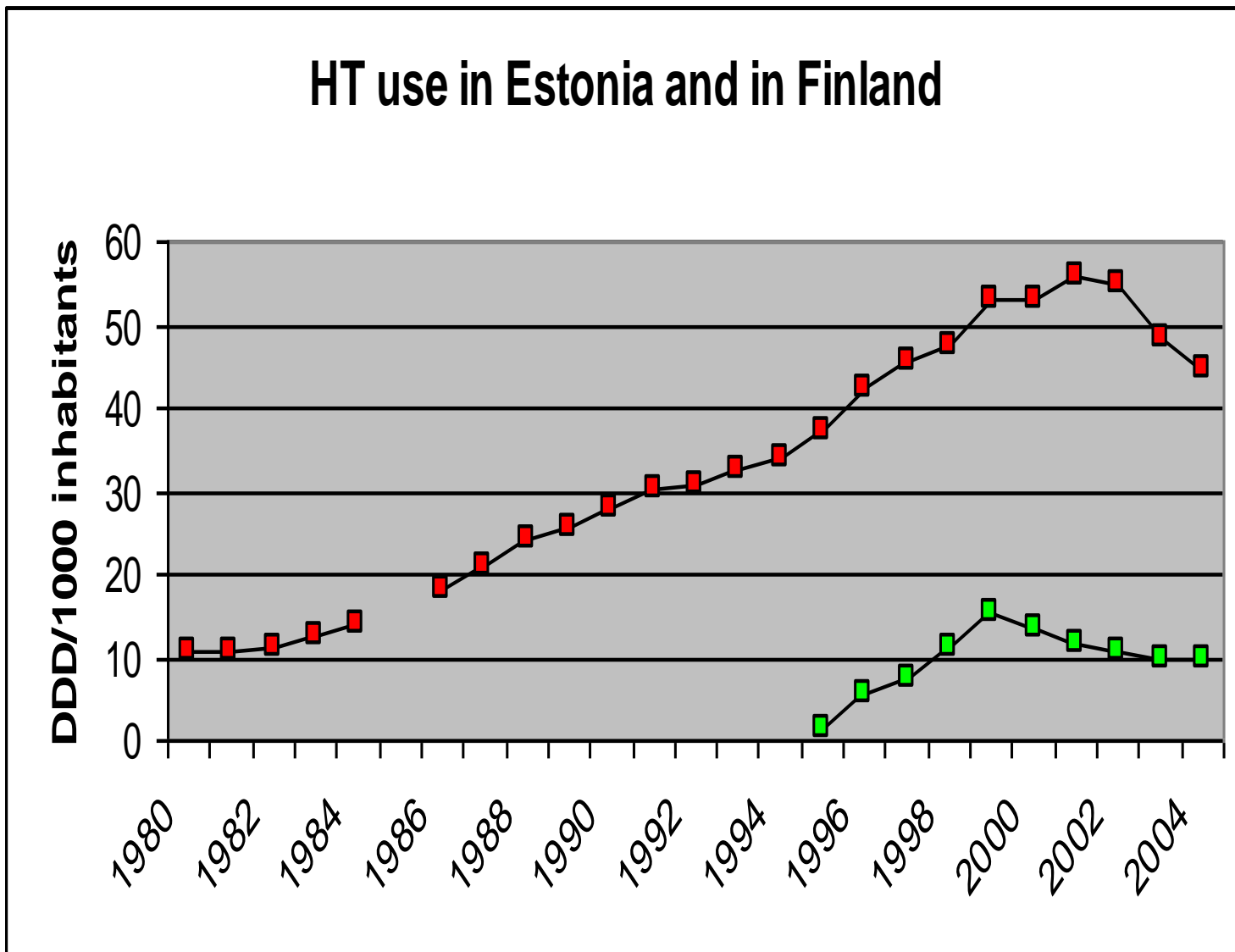
# 1. Introduction

- I will discuss of disease outcomes
- Symptoms; no change in knowledge: HT reduces symptoms among *many (but not all)* menopausal symptomatic women, estrogen also among non-symptomatic??; quality of life =?
- Use of health services and costs: increased? (very little information )
- I will answer the title question at the end, but to understand it, we need history
- My background: physician, long experience in epidemiology and health services research, including health technology assessment

## 2. Scientific knowledge < 2002

- Useful for menopausal symptoms (hot flashes, dry vagina)
- Disease impacts poorly known
- Prevents osteoporosis/ fractures
- Does not prevent cardiovascular disease among women at risk (HERS)
- Likely to increase breast cancer
- Does not look promising for disease prevention

# HT sales in Finland 1980-2004



# WHI 2002 and 2005

Combined HRT: Trial interrupted prematurely. Overall health risks exceeded benefits... 5.2 year follow-up among healthy postmenopausal US women. All cause mortality was not affected....this regimen should not be initiated or continued for primary prevention of CHD ( coronary heart disease)

Estrogens only: Trial interrupted prematurely. Does not protect from cardiovascular diseases; risk of stroke increased.

# FDA recommendations of HT

## Indications up to 2002

1. vasomotor symptoms (moderate to severe)
2. vulvar and vaginal atrophy
3. prevention of osteoporosis

## Indications in 2003

1. no change
2. topical products preferred
3. - consideration should be given to non-estrogen products
  - only if a significant risk of osteoporosis

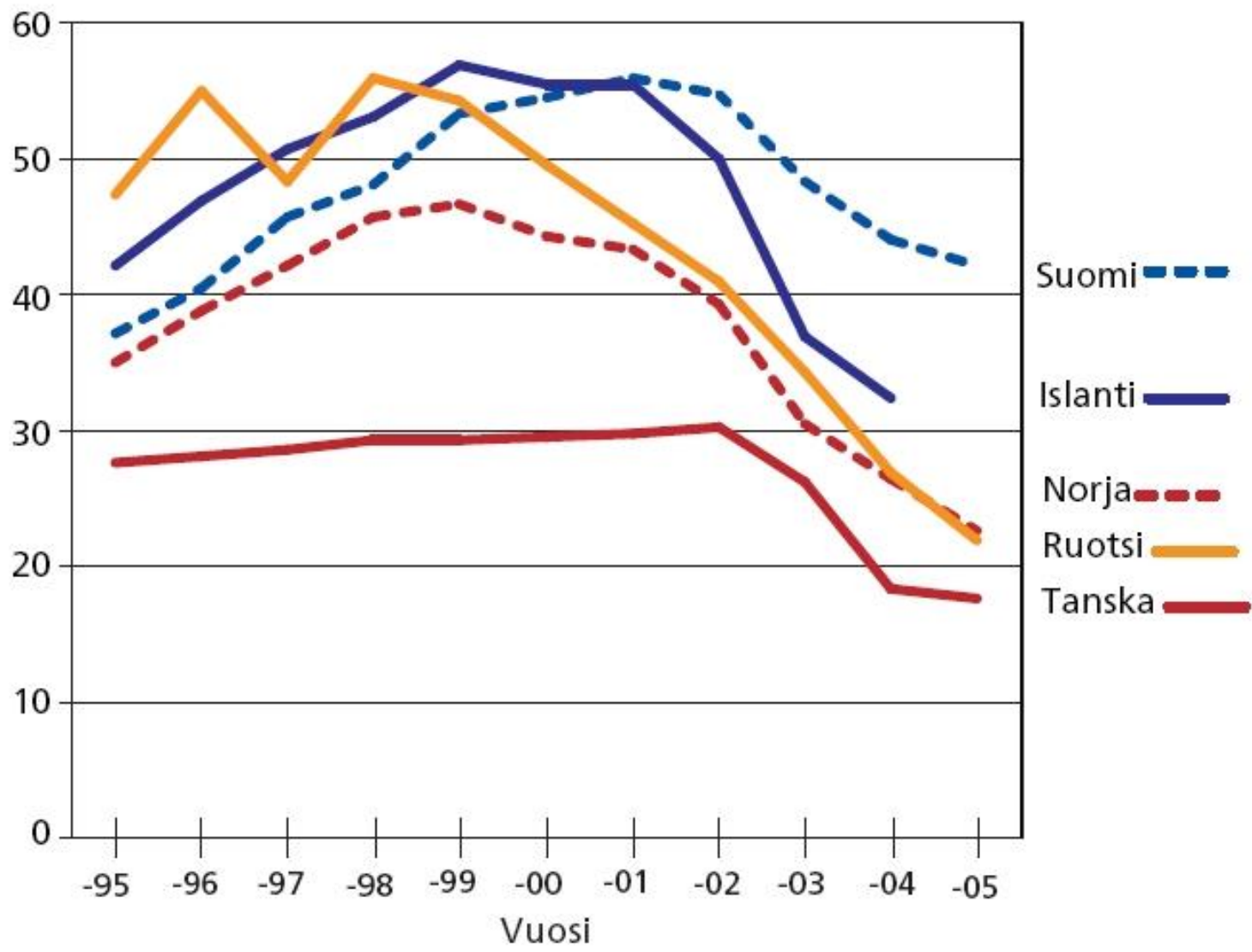
## Warning box in 2003 to all HT products

- heart attacks, strokes, blood clots, breast cancer
- not approved for preventing heart disease

# Prescribing and use 2002-2008

- Notable drop in prescribing/ use of HT
- Extent of drop varied: high in USA
- Nordic countries (similar in population and culture): sales in DDD (defined daily doses) next slide
- Italy: big drop

Kulutus  
DDD / 1 000





## 5. Knowledge of diseases by 2008

- HT (combined) is not good for "sick women": women in high risk of (further) cardiovascular events and breast cancer
- Among healthy women HT (combined or estrogen only) does not prevent cardiovascular events
- Among healthy women HT (combined) increases risk of breast cancer; estrogen only does not
- Many questions open, particularly from estrogens only
- All good data from two drugs, both containing conjugated estrogens (CEE)

## 6. What new since 2008?

1. Follow-up of WHI
  2. Long-term results of EPHT (unpublished)
  3. Results from WISDOM
  4. Many observational results
- > Nothing unexpected
- Data of some new health outcomes
  - What happens after stopping treatment among exposed?
  - Data for timing hypothesis

# Type of data

- Reanalysis of WHI (until exposure stops):  
new diseases
- Subgroup analysis
- What happens after the trial is over
- Data from WISDOM and EPHT
- Data from cohorts (e.g. Million Women's study)
- (Laboratory studies)

# EPHT trial 2001-7 (exposure 2004)

Mortality	0.98	0.51-1.89
Coronary heart disease	1.03	0.86-1.24
Cerebrovascular disease	1.22	0.89-1.68
Bone fractures	0.71*	0.57-0.89
Cancer	1.21	0.81-1.80
(n=1 778)		

# Publications from WHI

- <http://www.nhlbi.nih.gov/whi/references.htm>

Hormone Therapy trial (x2) results, n= 88

30 publications 2008 or later (Sept. 13, 2011)

(+ Publications from the cohort and diet trial)

- Are WHI publications from WHI? NIH researchers were required to give the original data to Wyeth (and others?)  
Publications from WHI data come now also from industry. Marketing/ manipulation of data? → **difficult to judge**

# Scientific knowledge of HT disease effects >2008, I

	E + P	E
Deaths	~	~
Disease index	increase	~
CHD (coronary heart disease)	increase	~
Deep vein thrombosis	increase	increase NS
Stroke	increase	increase NS
Diabetes	protection	protection?

# Scientific knowledge of HT disease effects > 2008 II

	E + P	E
Breast cancer	increase	protection
Benign breast proliferating dis.	increase	increase
Endometrial cancer	protection	--
Ovarian cancer	increase	??
Cervical cancer	??	??
Lung cancer deaths	increase	increase NS
Colorectal cancer fatality	~	~
Total cancer	~	~

# Scientific knowledge of HT disease effects > 2008 III

	E + P	E
Cognitive probl. (Alzheimer)	increase	~
Fractures	protection	protection
Gallbladder disease	increase	increase
Other specific cancers	?	?
Rheumatoid arthritis (comb.)	~ (protection)	~ (protection)
Kidney stones (comb.)	increase	increase
Age-related macular deg.	~	~
Mental illnesses (not symptoms)	?	?
Other specific diseases	?	?



# New data of disease outcomes

- Lung cancer deaths: increased (E+P/ WHI)
- Breast cancer fatality: increased (HR 1.96) (E + P/ WHI)
- Breast cancer protection: stat. sign (E /WHI)
- Breast cancer diagnosis: deteriorates + more false positives (E+P/ WHI)
- Breast cancer risk highest among young (Million women study)
- Benign breast disease: increase
- Colorectal cancer fatality: no protection
- Kidneys stones: increase
- Rheumatoid arthritis: protection? (NS)

# What happens after stopping treatment (WHI), E + P

- Cardiovascular: no new risk
- Breast cancer: risk continues same level/  
excess risk reduces
- Endometrial cancer: protection remains, NS
- Colorectal cancer: protection disappears
- Fractures: protection disappears
- Dementia/cognitive: remains same
- Deaths: remain same
- Global index: remains same
- Other diseases: ?

# What happens after stopping treatment (WHI), E alone

- Cardiovascular: no new risk
- Breast cancer: protection continues
- Colorectal cancer: remains same
- Fractures: protection disappears
- Dementia/cognitive: ?
- Deaths: remains same
- Global index: remains same

# Subgroup analysis

- Done by state at randomization; not prior hypothesis
- Not very useful; numbers getting low
- + Large number of comparison (particularly by cardiovascular risk factors) --> chance?
- **Studies by:** inflammatory, lipid, thrombotic, genetic, + other biomarkers, estrogen receptors, prior HT therapy, subclinical coronary artery disease etc.
- Can one trust them? Wyeth involvement
- One subgroup is timing

# Timing: if started at menopause

- One subgroup is timing: is HT impact different if started soon after menopause (most RCT: women with wide range of ages)
- Reanalysis of WHI and other studies (also cohorts)

# 50-59 year old, reanalysis of WHI

	E+P		E	
	OR	CI	OR	CI
coronary dis.	1.29	0.79-2.12	0.63	0.36-1.09
stroke	1.41	0.75-2.65	0.89	0.47-1.69
thromboemb.	<b>2.27*</b>	1.19-4.33	1.22	0.62-2.42
Breast ca	1.20	0.80-1.82	0.72	0.43-1.21
Colon ca	0.79	?	0.59	0.25-1.41
Femur fracture	0.17	0.02-1.43	5.04	0.59-43.2
Death *combined	0.69	0.44-1.07	0.71	0.46-1.11
(n)		2839+2683		1637+1673

# Breast cancer, cohort

- E+P: smaller risk if late start (5yr+ after menopause, RR=1.53) than if early start (<5yr before menopause, RR=2.04)
- E: no risk (RR=1.05) if late start
- E: increased risk (RR =1.43) if early start

(Beral et al Lancet 2011)

- Similar findings from WHI cohort (Prentice et al 2008)

# Timing: if started at menopause

- Suggestion: early start **may** reduce coronary heart disease and increase breast cancer risk.
- Other diseases, e.g. stroke =?
- **Not useful for prevention strategies**
- May be useful when deciding about individual woman's treatment (for troublesome symptoms)
- Important for knowledge (pathogenesis)



# A leading Finnish expert 2010

- "HT started in right time (early enough) will prevent loosing bone and muscular strength and **will reduce the risk of cardiovascular diseases and dementia** (Alzheimer). Furthermore combined therapy (E+P) reduces the risk of uterine and colon cancer"
- text to general audience, leading Finnish newspaper, paid attachment (O Y-K, HS ilmoitusliite).

# 7. What next

- Confusion continues?
- Gynecologists again dare to show their support to HT as a preventive drug?
- HT use: not (yet) increased in Finland (DDD)
- USA: low dose HT increased ?
- Italy=?

Further reliable scientific data unlikely → HT in preventive policy: is HT the best way to improve the health of older women?

- Diet, exercise, substance use, social activities etc

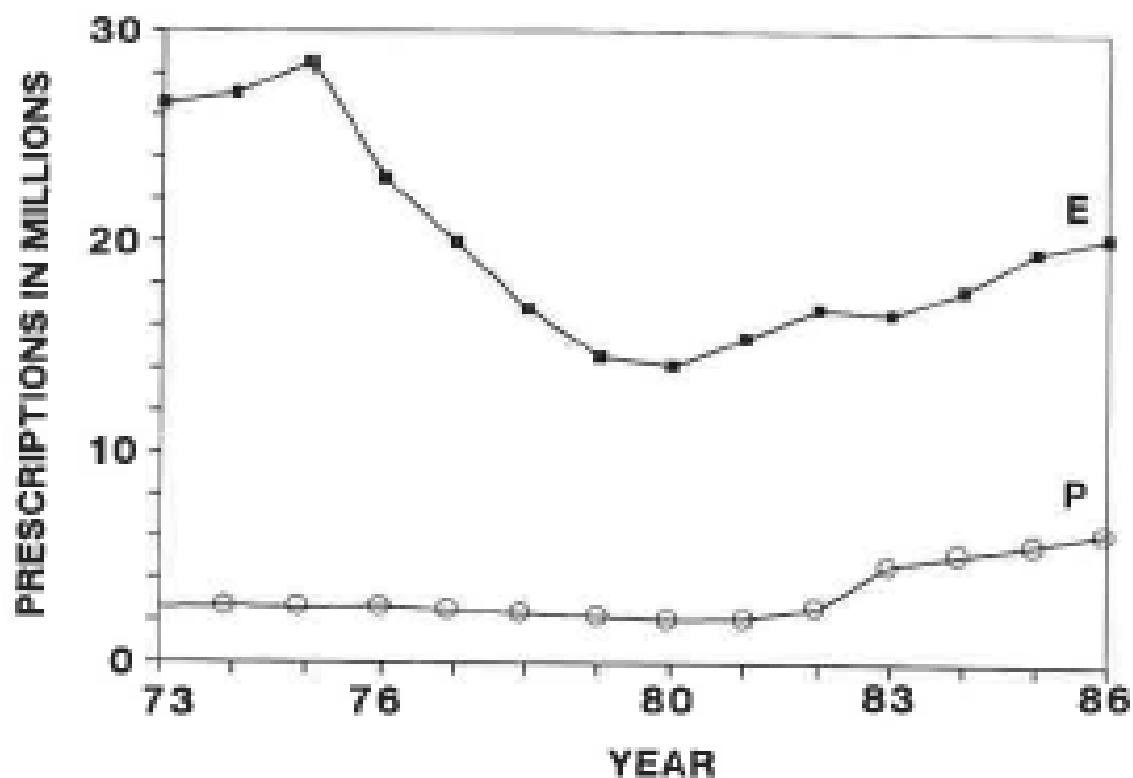


Figure 1. Numbers of dispensed prescriptions (in millions) containing estrogens (E) and progestins (P) in 1973-1986 (15).

# Current open questions

1. Effect of regimens other than Premarin and Prempro
2. Timing: if started at the time of menopause
3. Several diseases: metabolic (diabetes, liver, gallbladder, kidney etc), psychiatric *diseases*, musculoskeletal (rheumatism etc), specific cancers other than breast, lung and colon

*(practically same as 2008)*

# Selection bias to therapy

67% “GOOD” ADHERERS\*      15 %      16 %

33% “POOR” ADHERERS      28 %      26 %

Adjusted OR death =0.64 attributable to compliance

\* > 80 % prescribed dose  
NEJM 1980; 303: 1038-1041

*CDP- RCT; secondary prevention of CHD with clofibrate, males 30-60 (n=2789), 5 yr Mortality Adjusted for 40 baseline characteristics, Placebo Group*

Similar findings for WHI: *Curtis et al 2011*

- Thank you

# Outline

1. Introduction
2. Scientific knowledge < 2002
3. WHI Women's Health Initiative trial (+ other evidence)
4. 2002- open questions
5. Knowledge of diseases by 2008
6. What new since 2008?
7. What next

# History of HRT/ HT

- (Female) hormone drug therapy during and after menopause, HRT = HT
- Estrogens (+ progestins + other)
- 80 yr + for symptoms
- 40 yr + against aging
- 30 yr + for preventing diseases
- extracts, DES, other synthetic
- North America (USA) --> Western & Northern Europe --> whole world



# HT indications/ adverse effects

Have included all major chronic diseases

- cardiovascular diseases
- cancers
- dementia
- depression
- fractures
- diabetes, other metabolic diseases

# Knowledge basis

- tradition (< 1962 no efficacy requirement in drug licensing); group effect (estrogenic properties) enough to show
- epidemiological non-experimental research
- small scale trials
- beneficial effects on metabolism
- marketing

## (Other trials)

- Nachtigall et al.  
1979: +
- Hemminki et al.  
1997: ?
- HERS 1998: -
- Interim report from  
WHI 2000: 0
- WHI 2002: -
- WH1-2 2004: -

Small secondary  
prevention trials

EVTET 2000: -

WEST 2001: 0

PAPWORTH 2002

ESPRIT 2002

etc.

# (The Nurses' Health Study)

121,700 females age 30-55 in 1976-1994, risk of cardiovascular deaths

**OR (95% CI)**

	<b>Never</b>	<b>Current HRT</b>	<b>Past HRT use</b>
<b>Crude</b>	<b>1.0</b>	<b>0.35 (0.25-0.49)</b>	<b>0.84(0.67-1.05)</b>
<b>Adjusted</b>	<b>1.0</b>	<b>0.47 (0.32-0.69)</b>	<b>0.99 (0.75-1.30)</b>

# Physicians' views Finland < 2002

- Gynecologists very enthusiastic, internists and GPs somewhat
- Both disease prevention and subjective well-being and aging
- Recommended especially to women with cardiovascular risk or disease
- Recommendations for long therapies
- In 1989: useful against heart diseases: gyn. 74%, internists 52% (in 1995: 98% and 88%)

### 3. WHI Women's Health Initiative trial

- **Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial.**
- [Rossouw JE](#), [Anderson GL](#), [Prentice RL](#), [LaCroix AZ](#), [Kooperberg C](#), [Stefanick ML](#), [Jackson RD](#), [Beresford SA](#), [Howard BV](#), [Johnson KC](#), [Kotchen JM](#), [Ockene J](#); [Writing Group for the Women's Health Initiative Investigators](#). [JAMA](#). 2002 Jul 17;288:321-33.

## *(WHI, Women's health initiative, combined HT)*

- 16 000 "healthy" women; RCT, 8 yr prevention of cardiovascular diseases
- stopped after 5 yrs: ineffective, harms
- 7 extra heart infarcts per year per 10 000 women
- 8 extra breast cancers
- 8 extra brain insults
- 18 extra deep vein thrombosis
- less colon cancer and fractures

**Table 2 Hazard ratios (HR) and 95% confidence intervals (CIs) for various clinical outcomes in the estrogen plus progestin and estrogen-alone trials<sup>a</sup>**

	Hypothesized effect	E+P			E-alone		
		HR	95% CI	AR	HR	95% CI	AR
CHD (39, 45)	↓	1.24	1.00–1.54	+6	0.95	0.79–1.15	–3
Stroke (32, 68)	↔↓	1.31	1.02–1.68	+8	1.37	1.09–1.73	+12
Pulmonary embolism (20, 21)	↑	2.13	1.45–3.11	+10	1.37	0.90–2.07	+4
Venous thromboembolism (20, 21)	↑	2.06	1.57–2.70	+18	1.32	0.99–1.75	+8
Breast cancer (15, 63)	↑	1.24	1.02–1.50	+8	0.80	0.62–1.04	–6
Colorectal cancer (16, 70)	↓	0.56	0.38–0.81	–7	1.08	0.75–1.55	+1
Endometrial cancer (1)		0.81	0.48–1.36	–1	NA		
Hip fractures (13, 44)	↓	0.67	0.47–0.96	–5	0.65	0.45–0.94	–7
Total fractures (13, 44)	↓	0.76	0.69–0.83	–47	0.71	0.64–0.80	–53
Total mortality (70, 74)	↓	0.98 <sup>c</sup>	0.82–1.18	–1	1.04 <sup>c</sup>	0.91–1.12	+3
Global index <sup>b</sup> (70, 74)		1.15 <sup>c</sup>	1.03–1.28	+19	1.01 <sup>c</sup>	1.09–1.12	+2
Diabetes (9, 46)		0.79	0.67–0.93		0.88	0.77–1.01	
Gall bladder disease (17)	↑	1.59	1.28–1.97		1.67	1.35–2.06	
Stress incontinence (31)		1.87	1.61–2.18		2.15	1.77–2.62	
Urge incontinence (31)		1.15	0.99–1.34		1.32	1.10–1.58	
Peripheral artery disease (37, 38)		0.89	0.63–1.25		1.32	0.99–1.77	
Probable dementia (60, 61)	↓	2.05	1.21–3.48		1.49	0.83–2.66	

<sup>a</sup>Abbreviations: AR, attributable risk per 10,000 person years; E+P, estrogen plus progestin; E-alone, estrogen alone; HR, hazard ratio; CI, confidence interval. Hazard ratio estimates are based on proportional hazards analysis stratified by age (five-year categories) and randomization in the dietary modification trial.

<sup>b</sup>Global index defined for each woman as the time to the earliest diagnosis of CHD, stroke, pulmonary embolism, breast cancer, colorectal cancer, endometrial cancer (for E+P), hip fractures, and death from other causes.

<sup>c</sup>Based on an average 5.2 and 6.8 years of follow-up for E+P and E-alone, respectively. All others based on an average of 5.6 (E+P) and 7.1 (E-alone) years of follow-up.



# Other evidence

- Further analysis from WHI
- Results from WISDOM (UK based) and EPHT (Estonia)
- Some small trials
- Non-experimental epidemiologic research

## 4. 2002- open questions

1. Do different regimens differ? Most research with CEE (Premarin\* and Prempro\*)
2. Were WHI women "healthy"?/ timing
3. Timing: if started at the time of menopause...
4. Effect on several diseases: metabolic (diabetes, liver, gallbladder, kidney etc), psychiatric *diseases*, musculoskeletal (rheumatism etc), specific cancers (other than breast, lung and colon) etc

# Do different regimens differ?

- weak evidence from trials: similar effects with other regimens (only limited outcomes and low power)
- breast cancer: cohorts and time trends: impact varies by regimen
- endometrial cancer: impact varies by regimen
- Other:?

# Were WHI women "healthy"?

- much debate, a source of criticism
- relates to timing hypothesis
- data from our Estonian trial: results on healthier (and younger women) similar to WHI (low power)
- no convincing data of younger women (not likely to come?); reanalysis of WHI =?
- Who is healthy at 50 years?

# 2002- gynecologists views

- Mixed
- WHI results were against current thinking
- Strong lobby by industry (and some experts) for HT and belittling WHI; positive opinion leaders made visible
- “Every woman has symptoms”, off-label marketing indirectly
- Selective publications, ghost-writing, ordered papers, bought experts (court cases: FDA archives) see e.g. Adriane Fugh-Berman

# Scientific knowledge of HT disease effects < 2008, I

	E + P	E
Deaths	~	~
Disease index	increase	~
CHD (coronary heart disease)	increase	~
Deep vein thrombosis	increase	increase
Stroke	increase	increase
Diabetes	protection	protection?

# Scientific knowledge of HT disease effects < 2008 II

	E + P	E
Breast cancer	increase	(protection NS)
Endometrial cancer	(protection NS)	--
Ovarian cancer	(increase NS)	??
Cervical cancer	??	??
Lung cancer	?	?
Colorectal cancer	protection	~
Total cancer	~	~

# Scientific knowledge of HT disease effects < 2008 III

	E + P	E
Cognitive probl. (Alzheimer)	increase	increase (?)
Fractures	protection	protection
Gallbladder disease	increase	increase
Other specific cancers	?	?
Age-related macular degeneration	~	~
Mental illnesses (not symptoms)	?	?
Other specific diseases	?	?