Something has changed? The literature from 2008 to present?

Elina Hemminki

National Institute for Health and Welfare, Helsinki, Finland

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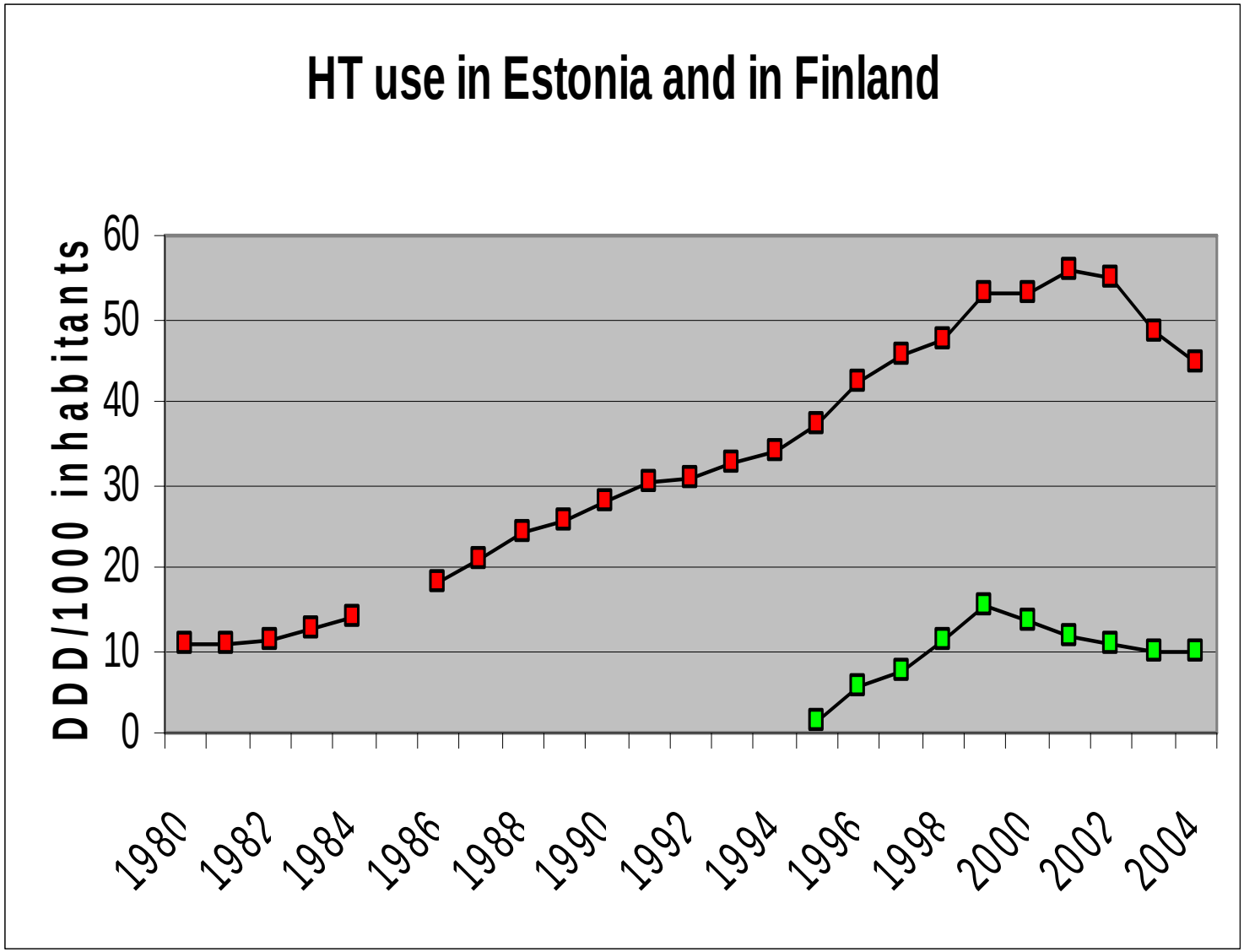
1. Introduction

- 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 increases 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

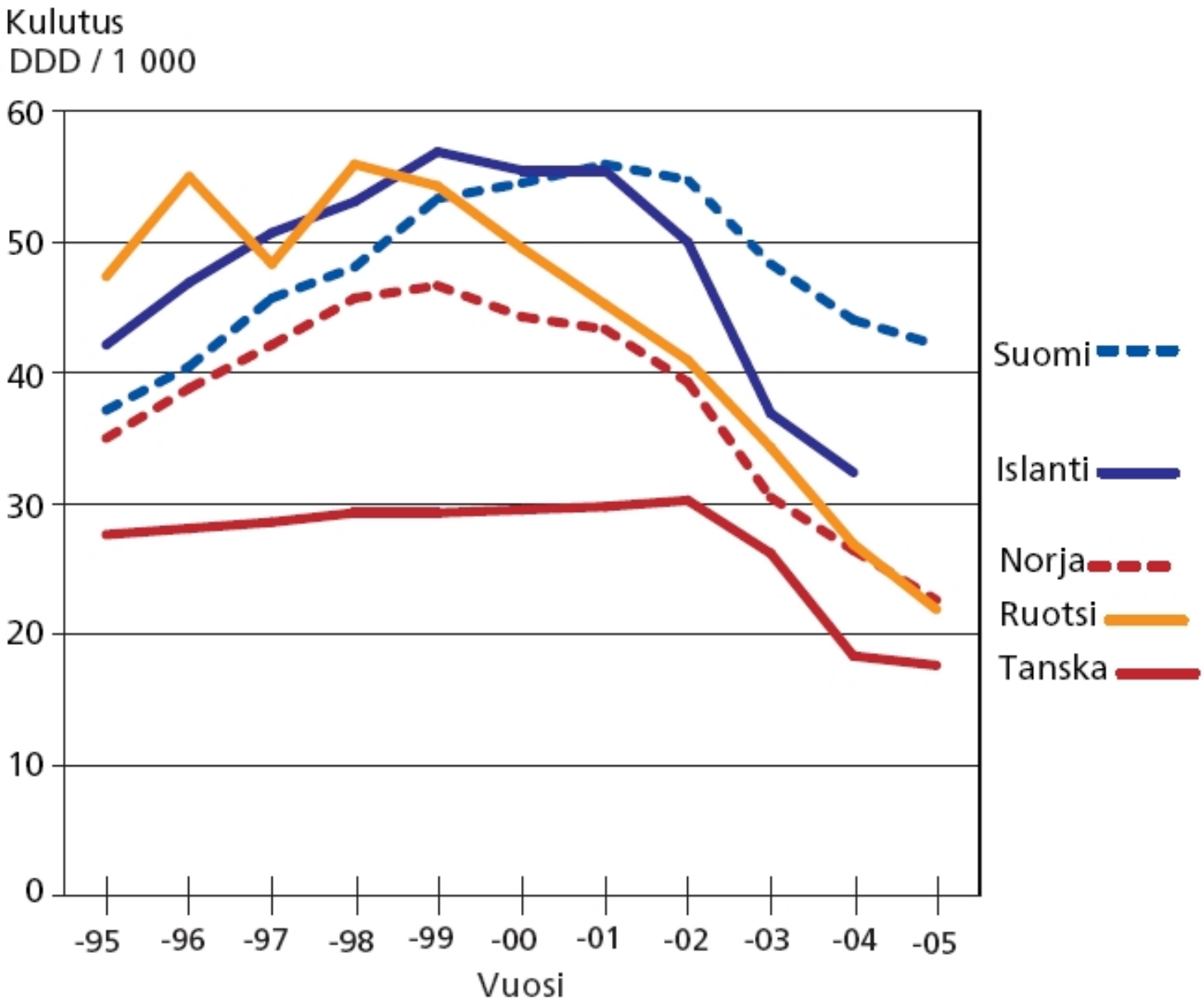
1. no change
2. topical products preferred
3. - consideration should be given to non-estrogen products
   - only if a significant risk of osteoporosis

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
60
50
40
30
20
10
0
-95
-96
-97
-98
-99
-00
-01
-02
-03
-04
-05
Vuosi
Suomi
Islanti
Norja
Ruotsi
Tanska

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 given the original data to Wyeth (and others?) Publications form 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 prolif.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.	**2.27***	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 cardiovasular 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

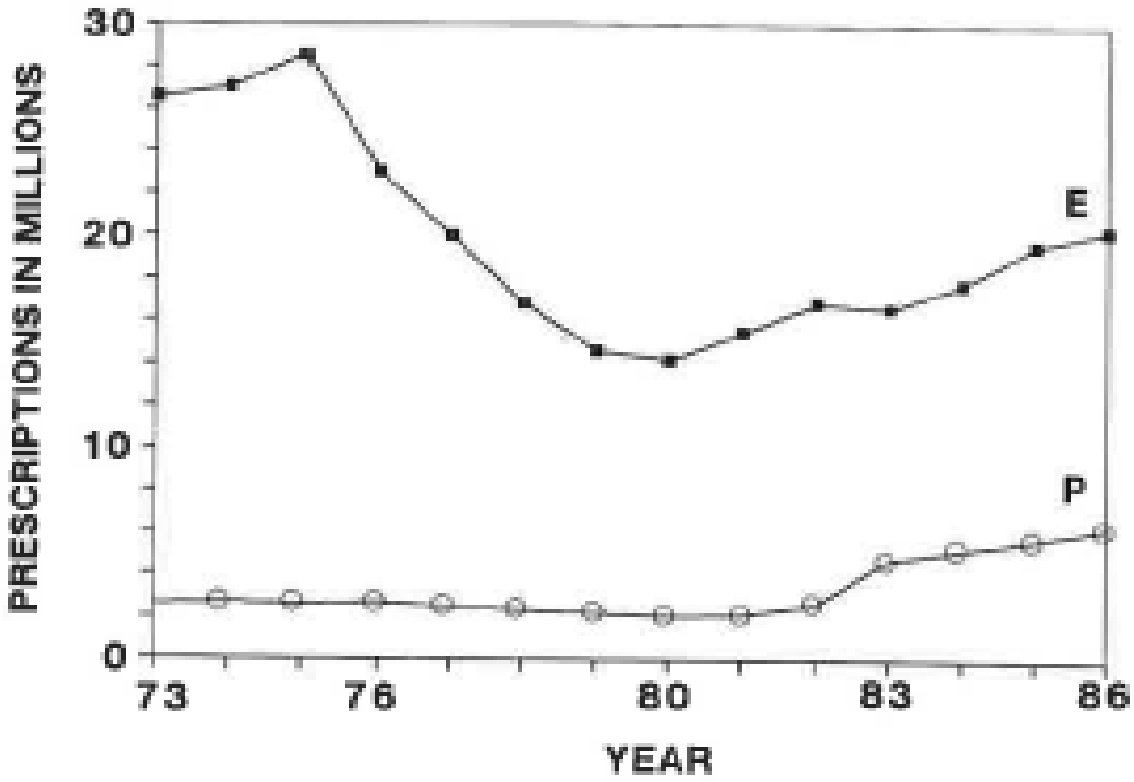


Figure 1. Numbers of dispensed prescriptions (in millions) containing estrogens (E) and progestins (P) in 1973–1986 (15).

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” AHDERERS	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
- benficial 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)

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

NEJM 1997;336:1769-75

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 vain 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[a]

	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[c]	0.82–1.18	−1	1.04[c]	0.91–1.12	+3
Global index[b] (70, 74)		1.15[c]	1.03–1.28	+19	1.01[c]	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	

[a]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.

[b]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.

[c]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	?	?