Trends in hormone replacement therapy use (all formulations) over time in the USA

Once upon a time…HRT

Kevin Z et al. J Epidemiol Community Health 2012

Women's Health Initiative Trial

16.608 donne in post-menopausa non isterectomizzate (1993-1998)

- **8506 HRT combinata continua (0.625 mg CE + 2.5 mg MPA)**
- **8102 placebo**

Nel trial WHI la popolazione in studio aveva caratteristiche sfavorevoli come età media elevata (63 anni), BMI medio elevato (28.5) e patologie pregresse come diabete e ipertensione arteriosa

Età media: 63.3 anni

Follow up mediano: 5.6 anni

Primary outcome: incidenza di *coronary heart disease* (infarto miocardico e morte per CHD)

Primary adverse outcome: incidenza di carcinoma mammario

Writing Group for the Women's Health Initiative Investigators JAMA 2002

Methods: Women with an intact uterus ($n = 16{,}608$) were randomized to CEE+ MPA therapy or placebo for a median of 5.6 years; women with hysterectomy ($n = 10{,}739$) were randomized to CEE-alone therapy or placebo for a median of 7.2 years. Both cohorts have been followed for 18 years.

The Women's Health Initiative trials of menopausal hormone therapy: lessons learned

Menopause, Vol. 27, No. 8, 2020

JoAnn E. Manson, MD, DrPH, NCMP,[1] Shari S. Bassuk, ScD,[1] Andrew M. Kaunitz, MD, NCMP,[2] and JoAnn V. Pinkerton, MD, NCMP[3]

Health outcomes in the overall study population in the Women's Health Initiative estrogen-progestin and estrogen-alone trials,

Outcome	Estrogen-progestin trial					Estrogen-alone trial				
	CEE+MPA # events per 10,000 PY	Placebo # events per 10,000 PY	Difference[b] per 10,000 PY	HR (95% CI)	*P*	CEE # events per 10,000 PY	Placebo # events per 10,000 PY	Difference[b] per 10,000 PY	HR (95% CI)	*P*
Cardiovascular disease										
Coronary heart disease[c]	41	35	6	1.18 (0.95-1.45)	0.13	55	58	−3	0.94 (0.78-1.14)	0.53
Myocardial infarction	35	29	6	1.24 (0.98-1.56)	0.07	44	45	−1	0.97 (0.79-1.21)	0.97
Coronary revascularization[d]	42	45	−3	0.95 (0.78-1.16)	0.64	68	67	1	1.00 (0.83-1.19)	0.96
Stroke	33	24	9	1.37 (1.07-1.76)	0.01	45	34	11	1.35 (1.07-1.70)	0.01
Pulmonary embolism	18	9	9	1.98 (1.36-2.87)	<0.001	14	10	4	1.35 (0.89-2.05)	0.15
Deep vein thrombosis	25	14	12	1.87 (1.37-2.54)	<0.001	23	15	7	1.48 (1.06-2.07)	0.02
Cardiovascular mortality	17	15	2	1.08 (0.78-1.48)	0.65	29	28	1	1.01 (0.78-1.31)	0.95
All cardiovascular events[e]	170	152	19	1.13 (1.02-1.25)	0.02	251	224	27	1.11 (1.01-1.22)	0.03
Cancer										
Breast cancer	43	35	9	1.24 (1.01-1.53)	0.04	28	35	−7	0.79 (0.61-1.02)	0.07
Colorectal cancer	10	17	−6	0.62 (0.43-0.89)	0.009	17	15	2	1.15 (0.81-1.64)	0.44
Endometrial cancer	6	7	−1	0.83 (0.49-1.40)	0.49	NA	NA	NA	NA	NA
Cancer mortality	27	24	3	1.10 (0.86-1.42)	0.44	33	34	−1	0.96 (0.75-1.22)	0.72
All cancer types[f]	127	124	4	1.02 (0.91-1.15)	0.69	109	117	−8	0.93 (0.81-1.07)	0.30
Other outcomes										
Hip fracture	11	17	−6	0.67 (0.47-0.95)	0.03	13	19	−6	0.67 (0.46-0.96)	0.03
All fracture	161	212	−51	0.76 (0.69-0.83)	<0.001	153	214	−61	0.72 (0.64-0.80)	<0.00
Diabetes	72	88	−16	0.81 (0.70-0.94)	0.005	134	155	−21	0.86 (0.76-0.98)	0.02
Gallbladder disease	131	84	47	1.57 (1.36-1.80)	<0.001	164	106	58	1.55 (1.34-1.79)	<0.00
Probable dementia[g]	46	23	23	2.01 (1.19-3.42)	0.01	44	29	15	1.47 (0.85-2.52)	0.17
Other (non-CVD, noncancer) mortality[h]	7	12	−5	0.59 (0.39-0.90)	0.01	17	13	4	1.34 (0.93-1.94)	0.12
All-cause mortality	52	53	−1	0.97 (0.81-1.16)	0.76	80	77	3	1.03 (0.88-1.21)	0.68
Global index[i]	189	168	20	1.12 (1.02-1.24)	0.02	208	204	4	1.03 (0.93-1.13)	0.63

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2020 The North American Menopause Society.

The Women's Health Initiative trials of menopausal hormone therapy: lessons learned

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Tempo dal momento della menopausa: CCE+MPA

CHD

- **< 10 anni: HR 0.90** (95% IC 0.56-1.56, p=0.08)
- **10-20 anni: HR 1.19** (95% IC 0.83-1.70, p=0.08)
- **> 20 anni: HR 1.52** (95% IC 1.07-2.17, p=0.08)

INFARTO MIOCARDICO

- **< 10 anni: HR 0.91** (95% IC 0.54-1.52, p=0.01)
- **10-20 anni: HR 1.16** (95% IC 0.79-1.69, p=0.01)
- **> 20 anni: HR 1.99** (95% IC 1.32-3.02, p=0.01)

Il rischio di CHD e infarto miocardico aumenta all'aumentare del tempo trascorso dal momento della menopausa

HRT and Breast cancer: WHI Trial

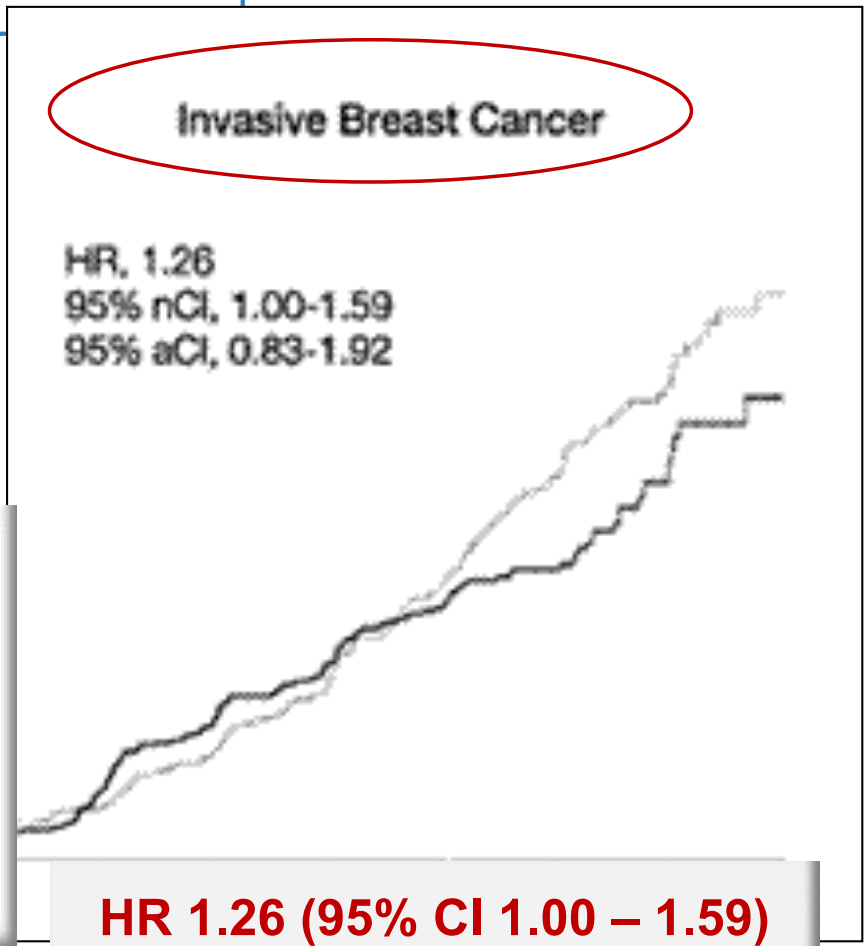
Chlebowski JAMA July 2002

Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women
Principal Results From the Women's Health Initiative Randomized Controlled Trial

BC Incidence ↑
BC mortality
?

The Women's Health Initiative (WHI): *the largest Randomised placebo-controlled trial of* ***HRT in post menopausal women***
CEE, 0.625mg/d +MPA, 2.5mg/d (n = 8506)
vs
placebo (n = 8102)

- 40 clinical sites in USA
- **Mean intervention time 5.6 years**
- **Mean follow up 7.9 years**
- **Increase of BC incidence in pts who received E+P**
- **BC mortality non reported** (short FUP period)

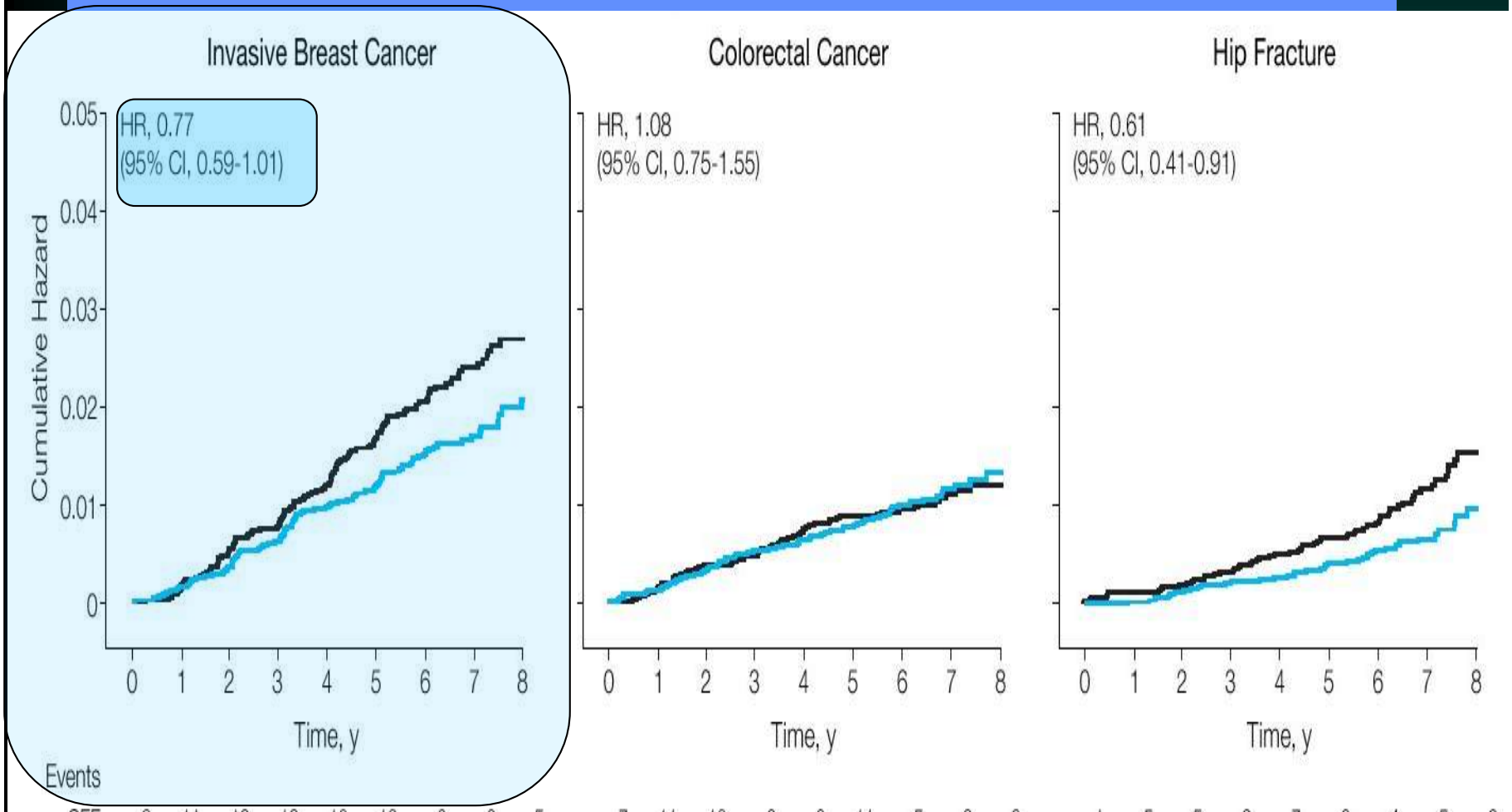


HR 1.26 (95% CI 1.00 – 1.59)

WHI trial - Estrogen only

JAMA 2004; 291: 1701-1712

Kaplan-Meier estimates of cumulative hazards for selected clinical outcomes



JAMA | Original Investigation

Association of Menopausal Hormone Therapy With Breast Cancer Incidence and Mortality During Long-term Follow-up of the Women's Health Initiative Randomized Clinical Trials

Rowan T. Chlebowski, MD, PhD; Garnet L. Anderson, PhD; Aaron K. Aragaki, MS; JoAnn E. Manson, MD, DrPH; Marcia L. Stefanick, PhD; Kathy Pan, MD; Wendy Barrington, PhD; Lewis H. Kuller, MD; Michael S. Simon, MD; Dorothy Lane, MD; Karen C. Johnson, MD; Thomas E. Rohan, MBBS; Margery L. S. Gass, MD; Jane A. Cauley, PhD; Electra D. Paskett, PhD; Maryam Sattari, MD; Ross L. Prentice, PhD

WHI trial
-E_2 Only
-E+P

WHI LONG TERM FU (20.3 years)

DESIGN, SETTING, AND PARTICIPANTS Long-term follow-up of 2 placebo-controlled randomized clinical trials that involved 27 347 postmenopausal women aged 50 through 79 years with no prior breast cancer and negative baseline screening mammogram. Women were enrolled at 40 US centers from 1993 to 1998 with follow-up through December 31, 2017.

INTERVENTIONS In the trial involving 16 608 women with a uterus, 8506 were randomized to receive 0.625 mg/d of conjugated equine estrogen (CEE) plus 2.5 mg/d of medroxyprogesterone acetate (MPA) and 8102, placebo. In the trial involving 10 739 women with prior hysterectomy, 5310 were randomized to receive 0.625 mg/d of CEE alone and 5429, placebo. The CEE-plus-MPA trial was stopped in 2002 after 5.6 years' median intervention duration, and the CEE-only trial was stopped in 2004 after 7.2 years' median intervention duration.

MAIN OUTCOMES AND MEASURES The primary outcome was breast cancer incidence (protocol prespecified primary monitoring outcome for harm) and secondary outcomes were deaths from breast cancer and deaths after breast cancer.

After more than 20 years of median cumulative follow-up, mortality information was available for more than 98%.

JAMA. 2020;324(4):369-380. doi:10.1001/jama.2020.9482

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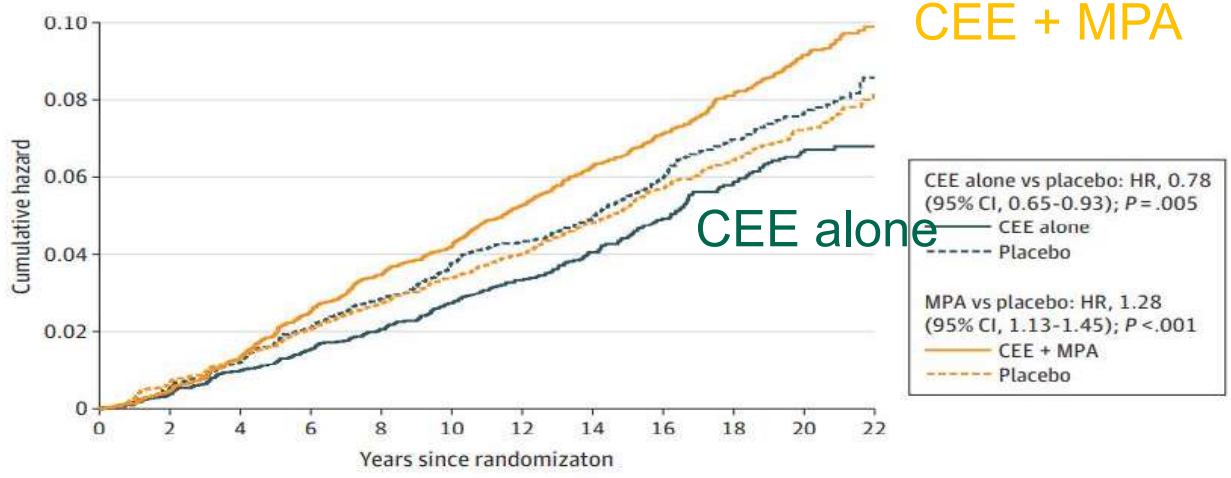
JAMA July 2020

WHI FU 20.3 years

CEE alone → Incidence: 238 cases vs 296 cases HR 0.78; **P = .005**
Mortality: 30 deaths vs 46 deaths HR, 0.60 **P = .04**

CEE plus MPA → Incidence: 584 cases vs 447 cases HR, 1.28 **P < .001**
Mortality: 71 deaths vs 53 deaths HR, 1.35 P= .11

Figure 1. Kaplan-Meier Estimates for the Association of Menopausal Hormone Therapy With Invasive Breast Cancer During Cumulative Follow-up



No. at risk

CEE + MPA												
CEE + MPA	8506	8329	8114	7802	7016	6248	5743	5006	4517	4143	3239	881
Placebo	8102	7916	7726	7472	6700	5944	5515	4808	4360	3991	3159	769
CEE alone												
CEE alone	5310	5167	5010	4845	4271	3673	3378	2873	2565	2307	1811	496
Placebo	5429	5280	5105	4915	4307	3717	3387	2892	2567	2307	1807	498

HRT and breast cancer: are all the treatments alike?

Potential differences may exist in breast cancer risk with ET, EPT, and CEE combined with bazedoxifene therapies.

Different types of estrogen or progestogen, as well as **different formulations, doses, timing of initiation, durations of therapy** and patient characteristics, may play a role in HT's effect on the breast.

NAMS Position Statement 2022

The **cancer risk of HRT differs depending on many factors**, so **treatment should be individualized** to identify the most appropriate dose, regimen, duration, and route of administration, using the best available evidence, with **periodic reevaluation of the woman's benefit-risk profile**

- Estrogens only
- Estrogens plus progestins
- Route of E administration
  - oral
  - transdermal
- Type of progestin
- Type of estrogen
- Sequential/continuous regimen

medicina

MDPI

Review

Current Evidence of the Oncological Benefit-Risk Profile of Hormone Replacement Therapy

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Received: 28 June 2019; Accepted: 3 September 2019; Published: 7 September 2019

check for updates

BMS Consensus Statement
The Risks and Benefits of HRT before and after a Breast Cancer Diagnosis
Jo Marsden, Hugo Pedder on behalf of The British Menopause Society with acknowledgement to Professor Richard Santen

(2020). Risks and benefits of hormone replacement therapy before and after a breast cancer diagnosis. *Post-Reproductive Health*. https://doi.org/10.1177/2053369120934026

University of BRISTOL

Key points

In women with a low underlying risk of breast cancer (i.e. most of the population), the benefits of HRT for up to 5 years' use for symptom relief will exceed potential harm

- Unopposed oestrogen is associated with no, or little change in risk but this may be influenced by age at initiation
- There is no evidence of a dosage effect with oestrogen
- Vaginal oestrogen is not associated with an increased risk
- Combined HRT can be associated with an increased risk, which appears duration dependent
- Whilst risk with continuous combined HRT may be greater that with sequential HRT, the difference in risk is small and may be offset by protection against endometrial cancer
- Avoidance of synthetic progestogens in combined preparations may minimise risk