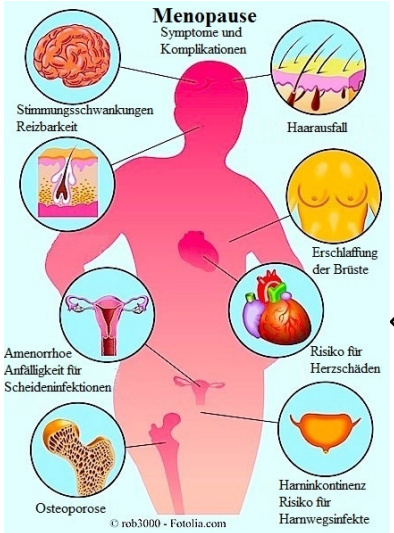
Menopause-beschwerden – Was Wann Wie Warum

Hornung R.



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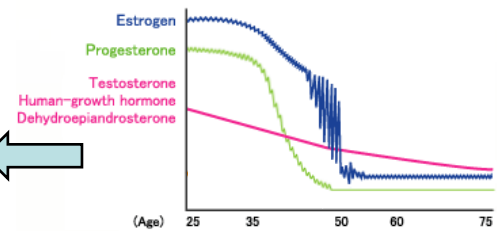


https://www.restartmed.com/wp-content/uploads/2016/09/age-related-decline-of-testosterone-in-women.png

Pflegekongress 2021: Menopausebeschwerden

Butenandt, Adolf Friedrich Johann
1903 – 1995; 1939 Nobelpreis für Sexualhormonforschung

TABLE 2. HRT and Breast Cancer: A Timeline of Relevant Events and Studies

1942: Researchers develop methods to extract large quantities of estrogen from the urine of pregnant mares, and Ayerst Laboratories launches Premarin (from PREgnant MARes' urINe), the first estrogen tablets.

1950s: Ayerst Laboratories begins a marketing campaign promoting the use of Premarin to lessen menopausal symptoms.

1966: New York gynecologist Robert Wilson publishes *Feminine Forever*, a best seller that promises youth, beauty, and a "full sex life" for menopausal women through the use of hormone therapy.

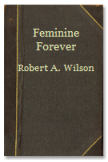
1975: Postmenopausal women on estrogen are found to have a 4- to 8-fold increase in the risk of uterine cancer.[1]

Mid 1980s: The addition of progestin to estrogen negates the increased risk of uterine cancer associated with estrogen alone.[2] By 1986, over 20 million prescriptions for non-contraceptive hormones are dispensed.[82]

1982: A study finds that estrogen is not associated with an increased risk of breast cancer.[83]

1974–1989: Of the 26 most cited reports during this period that have investigated the association between HRT or ERT and breast cancer

5 report an increased risk
7 report a decreased risk
14 report no significant association.[84]



Hormone Replacement Therapy: Real Concerns and False Alarms. Bluming, Avrum; Tavris, Carol. Cancer Journal. 15(

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2000: A retrospective study finds an increased risk of breast cancer among estrogen-only users, but only after 15 yr of use. A barely significant increased risk of breast cancer among combination estrogen-progestin users is found after 5 yr.[78]

2002: The Women's Health Initiative (WHI) terminates the estrogen-progestin arm of their study prematurely because they claim to have found an increased risk of breast cancer. This increased risk is, however, not statistically significant.[25]

2003: The WHI "confirms" its 2002 finding, reporting a small increased risk of breast cancer among women on HRT. Analysis of the data according to kind of cancer finds either no statistical significance or barely a 1% increased risk.[37]

2003: A British study, published in The Lancet, entitled "The Million Women Study," reports an increased risk of breast cancer in women taking ERT or HRT. However, they also find:

- No increase in risk of breast cancer in past users of either estrogen or estrogen-progestin, regardless of duration of use.
- The increased risk of breast cancer is found only in current users.
- The average period of follow-up is only 2.6 yr.[88]

2004: The WHI reports no increased risk of breast cancer associated with the use of estrogen alone.[89]

2006: The WHI reaffirms its 2004 finding of no increased risk of breast cancer among women taking estrogen, even after 7 yr. This time, they report that women who had used HRT in the past had a lower rate of breast cancer than women who had never taken hormones.[90]

2006: A study of 9000 Japanese women finds that HRT users are less likely to develop breast cancer than never-users.[91]

2006: A study reports no increase in breast cancer incidence among women who have been taking estrogen, even after 8 or more years.[92]

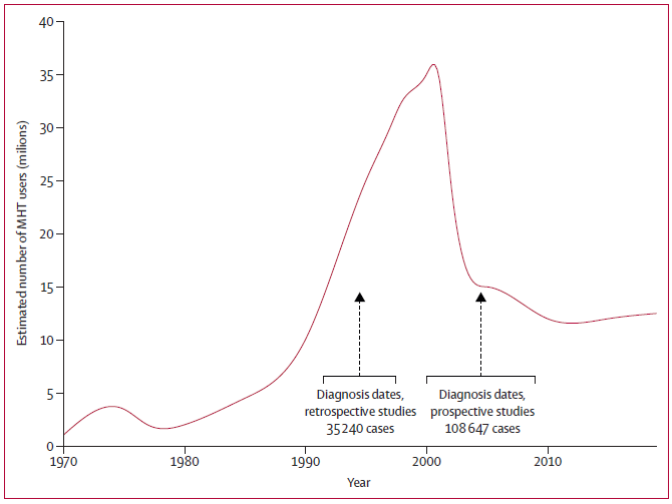
2006: The WHI now reports no increased risk of breast cancer even among women randomized to take combined estrogen and progestin.[93]

2008: The WHI reports that the risk of cardiovascular events, malignancies, breast cancers, and deaths from all causes was higher in the HRT group than in the placebo group even 3 yr after the women stopped taking HRT. However, none of the associations between HRT and breast cancer or mortality rates is statistically significant.[94]

2008: An observational study of 472 postmenopausal women who have a genetic predisposition to breast cancer, the BRCA1 mutation, finds that hormone use, either as HRT or ERT, is not associated with increased risk of breast cancer. On the contrary, it is associated with a decreased risk.[95]

2019: Lancet: Risiko Mammakarzinom: Östrogen-Gestagen mit Gest tgl > Östrogen-Gestagen mit Gest monatlich > Östrogen mono. → Östrogen vaginal ohne Risiko

HRT Einsatz und Einfluss der Studien zu Brustkrebs



Lancet 2019; 394: 1159–68

Beschwerden

↓

Hormone Replacement **Therapy**

HRT

Präparate + Dosierungen

- Oral
  - Sequentiell
  - Kontinuierlich
  - Östrogen – Monotherapie (nur bei hysterektomierten Frauen)
- Transdermal
  - Pflaster (sequentiell – kontinuierlich)
  - Creme (Östradiol → systemische Wirkung)

} Systemische Wirkung

- Intravaginal
  - Ovula / Creme (Estriol → lokal wirksam)

} Lokale Wirkung

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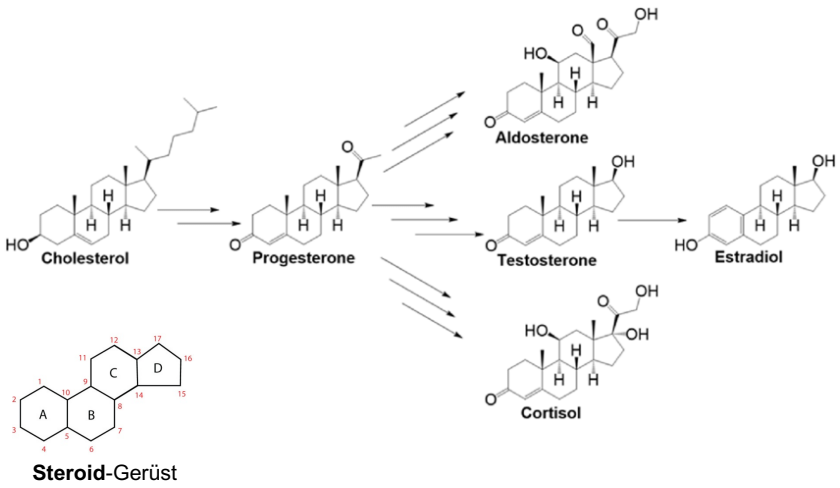

→ Gegenseitige Partialwirkungen der einzelnen Sexualsteroide

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Gestagen	Wirkung						
	gestagen	östrogen	antiöstrogen	androgen	antiandrogen	glukokortikoid	antimineralo-kortikoid
Progesteron	+	–	+	–	(+)	(+)	+
Dydrogesteron	+	–	+	–	–	–	(+)
Medroxy-progesteronacetat	+	–	+	(+)	–	+	–
Chlormadinonacetat	+	–	+	–	+	+	–
Cyproteronacetat	+	–	+	–	+	+	–
Dienogest	+	–	+	–	+	–	–
Desogestrel	+	–	+	+	–	–	–
Gestoden	+	–	+	+	–	+	(+)
Levonorgestrel	+	–	+	+	–	–	–
Lynestrenol	+	(+)	+	+	–	–	–
Norethisteron	+	(+)	+	+	–	–	–
Norgestimat	+	–	+	+	–	–	–
Drospirenon	+	–	+	–	+	–	+

Schindler AE et al: Maturitas 2003; 46(Suppl1): S7

Tab. 1: Das partielle Wirkungsspektrum von Gestagenen

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2. Estrogen Mono Präparate			oral
2.1 Mit niedrigerer Estrogendosis			
Estrofem N	28 Filmtbl.	1 mg Estradiol	Novo Nordisk
Progynova mite	84 Drg.	1 mg Estradiol	Bayer/Schering
2.2 Mit höherer Estrogendosis			
Femoston mono	28 Filmtbl.	2 mg Estradiol	Solvay Pharma
Estrofem N	28 Filmtbl.	2 mg Estradiol	Novo Nordisk
Progynova	28 Drg.	2 mg Estradiol	Bayer/Schering
2.3 Estriol			
Ovestin Ovula	Ovulum	0,5 mg Estriol	Essex Chemie
Ovestin Creme	Creme	1 mg Estriol	Essex Chemie
Ovestin Tabletten	30 Tbl.	1 mg Estriol	Essex Chemie
Ortho Gynest D	Ovulum	3,5 mg Estriol	Janssen Cilag

3. Gestagene			oral
3.1 Progesteron und -derivate			
Duphaston	20 Filmtbl.	10 mg Dydrogesteron	Solvay Pharma
Prodafem	84 Tbl. 30 Tbl.	2,5 mg MPA 5/-10 mg MPA	Pfizer
Progesteron	Amp.	2,5 mg Progesteronum	Streuli Pharma
Utrogestan	30 Kps. 15 Kps.	100 mg Progesteron 200 mg Progesteron	Vifor
3.2 Nortestosteronderivate			
Primolut N	30 Tbl.	5 mg NETA	Bayer/Schering

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1. Estrogene + Gestagene oral			
1.1 Zyklische Präparate			**Blutung**
1.1.1 Mit niedrigerer Estrogendosis			
Femoston 1 / 10 mg	14 + 14 Filmtbl.	1 mg Estradiol 1 mg Estradiol + 10 mg Dydrogesteron	Solvay Pharma
Mericomb	28 Filmtbl.	1 mg Estradiol 1 mg Estradiol + 1 mg NETA	Novartis Pharma
Novofem	16 + 12 Filmtbl.	1 mg Estradiol 1 mg Estradiol + 1 mg NETA	Novo Nordisk
1.1.2 Mit höherer Estrogendosis			
Femoston 2 / 10 mg	14 + 14 Filmtbl.	2 mg Estradiol 2 mg Estradiol + 10 mg Dydrogesteron	Solvay Pharma
Climen	11 + 10 Drg.	2 mg Estradiol 2 mg Estradiol + 1 mg Cyproteronacetat	Bayer/Schering
Cyclacur	11 + 10 Drg.	2 mg Estradiol 2 mg Estradiol + 0,5 mg Norgestrel	Bayer/Schering
Mericomb	28 Filmtbl.	2 mg Estradiol 2 mg Estradiol + 1 mg NETA	Novartis Pharma
Triaval	70 + 14 + 7 Tbl.	2 mg Estradiol 2 mg Estradiol + 20 mg MPA Hilfsstoffe	Orion Pharma
Trisequens N	12 + 10 + 6 Filmtbl.	2 mg Estradiol 2 mg Estradiol + 1 mg NETA 1 mg Estradiol	Novo Nordisk
1.2 Kontinuierlich kombinierte Präparate			**Keine Blutung**
1.2.1 Mit niedrigerer Estrogendosis			
Femoston conti	28 Filmtbl.	1 mg Estradiol + 5 mg Dydrogesteron	Solvay Pharma
Activelle	28 Filmtbl.	1 mg Estradiol + 0,5 mg NETA	Novo Nordisk
Angeliq	28 Filmtbl.	1 mg Estradiol + 2 mg Drospirenon	Bayer/Schering
Indivina	28 Tbl.	1 mg Estradiolvalerat + 2,5 mg MPA 1 mg Estradiolvalerat + 5 mg MPA	Orion Pharma
1.2.2 Mit höherer Estrogendosis			
Estranor Sandoz	28 Filmtbl.	2 mg Estradiol + 1 mg NETA	Sandoz
Indivina	28 Tbl.	2 mg Estradiol + 5 mg MPA	Orion Pharma
Kliogest N	28 Filmtbl.	2 mg Estradiol + 1 mg NETA	Novo Nordisk
Livial	28 Kaps. 28 Tbl.	1,25 mg Tibolonum 2,5 mg Tibolonum	Essex Chemie
Merigest	28 Filmtbl.	2 mg Estradiol + 0,7 mg NETA	Novartis Pharma

4. Estrogene + Gestagene			transdermal
4.1 Zyklische Präparate			
Estracomb TTS	Pflaster	50 µg Estradiol + 250 µg NETA/Tag	Novartis Pharma
Systen Sequi TTS	Pflaster	50 µg Estradiol + 170 µg NETA/Tag	Janssen Cilag
4.2 Kontinuierlich kombinierte Präparate			
Estalis	Pflaster	50 µg Estradiol + 140 µg NETA/Tag 50 µg Estradiol + 250 µg NETA/Tag	Novartis Pharma
Estragest TTS	Pflaster	25 µg Estradiol + 125 µg NETA/Tag	Novartis Pharma
Sequidot	Pflaster	50 µg Estradiol + 140 µg NETA/Tag 50 µg Estradiol + 250 µg NETA/Tag	Novartis Pharma
Systen Conti TTS	Pflaster	50 µg Estradiol + 170 µg NETA/Tag	Janssen Cilag

5. Estrogen Mono Präparate			transdermal
5.1 Gele			
Divigel	Gel	0,5 – 1,5 mg Estradiol/Tag	Orion Pharma
Oestrogel	Gel	1,5 (– 3) mg Estradiol/Tag	Vifor
Sandrena	Gel	0,5 – 1,5 mg Estradiol/Tag	Essex Chemie
5.2 Pflaster			
Climara 50	Pflaster	50 µg Estradiol/Tag	Bayer/Schering
Estradot TTS	Pflaster	25/-37,5/-50/-75/-100 µg Estradiol/Tag	Novartis Pharma
Estramon	Pflaster	25/-50/-100 µg Estradiol/Tag	Sandoz
Systen	Pflaster	25/-50/-75 µg Estradiol/Tag	Janssen Cilag

6. Estrogene + Androgene			Injektion
Gynodian Depot	Fertigspritze		Bayer/Schering

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4. Estrogene + Gestagene			transdermal
4.1 Zyklische Präparate			
Estracomb TTS	Pflaster	50 µg Estradiol + 250 µg NETA/Tag	Novartis Pharma
Systen Sequi TTS	Pflaster	50 µg Estradiol + 170 µg NETA/Tag	Janssen Cilag
4.2 Kontinuierlich kombinierte Präparate			
Estalis	Pflaster	50 µg Estradiol + 140 µg NETA/Tag 50 µg Estradiol + 250 µg NETA/Tag	Novartis Pharma
Estragest TTS	Pflaster	25 µg Estradiol + 125 µg NETA/Tag	Novartis Pharma
Sequidot	Pflaster	50 µg Estradiol + 140 µg NETA/Tag 50 µg Estradiol + 250 µg NETA/Tag	Novartis Pharma
Systen Conti TTS	Pflaster	50 µg Estradiol + 170 µg NETA/Tag	Janssen Cilag

5. Estrogen Mono Präparate			transdermal
5.1 Gele			
Divigel	Gel	0,5 – 1,5 mg Estradiol/Tag	Orion Pharma
Oestrogel	Gel	1,5 (– 3) mg Estradiol/Tag	Vifor
Sandrena	Gel	0,5 – 1,5 mg Estradiol/Tag	Essex Chemie
5.2 Pflaster			
Climara 50	Pflaster	50 µg Estradiol/Tag	Bayer/Schering
Estradot TTS	Pflaster	25/-37,5/-50/-75/-100 µg Estradiol/Tag	Novartis Pharma
Estramon	Pflaster	25/-50/-100 µg Estradiol/Tag	Sandoz
Systen	Pflaster	25/-50/-75 µg Estradiol/Tag	Janssen Cilag

6. Estrogene + Androgene			Injektion
Gynodian Depot	Fertigspritze		Bayer/Schering

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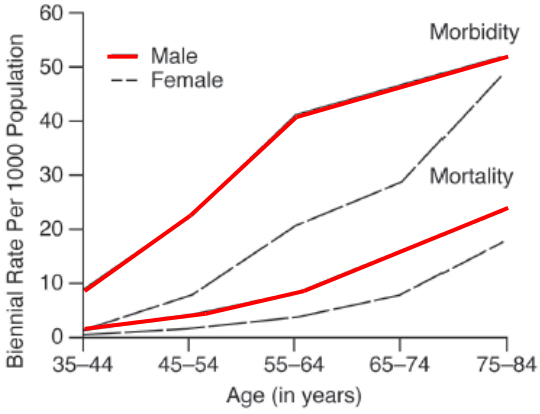
Hot flashes are for real!!!



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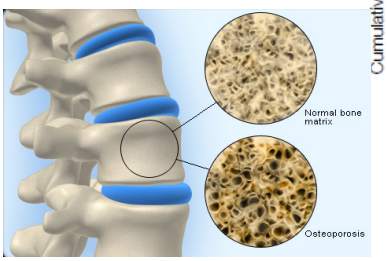
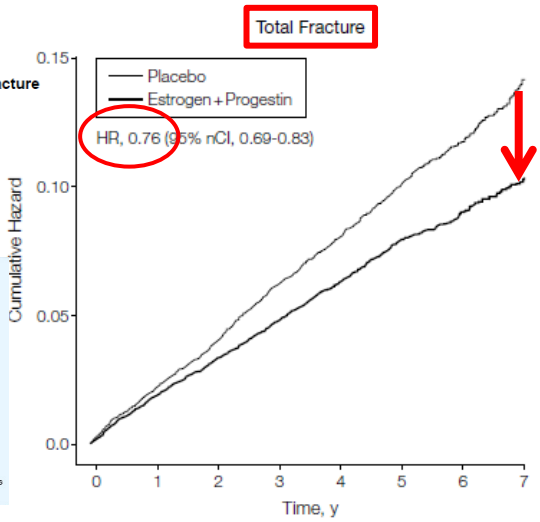
Effects of Estrogen Plus Progestin on Risk of Fracture and Bone Mineral Density: The Women's Health Initiative Randomized Trial

Jane A. Cauley; John Robbins; Zhao Chen; et al.

JAMA. 2003;290(13):1729-1738 (doi:10.1001/jama.290.13.1729)





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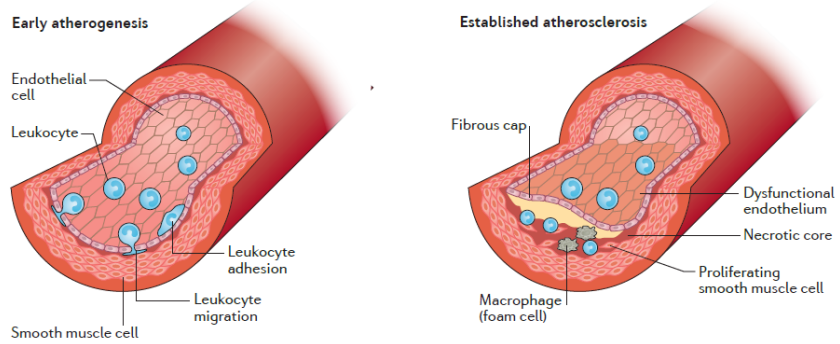

Beneficial effects of HRT

- ↑ Vasodilation
  - ↑ Nitric oxide levels
  - ↓ Endothelin levels
  - ↑ COX2 levels
- ↓ Inflammatory activation
  - ↑ Nitric oxide levels
  - ↓ CAM levels
  - ↓ MCP1 and TNF levels
- ↓ Lesion progression
  - ↑ Nitric oxide levels
  - ↓ Inflammatory cell adhesion
  - ↓ LDL cholesterol oxidation/binding
  - ↓ Platelet activation
  - ↓ VSMC proliferation

Altered biology of HRT

- ↓ ER expression, function
- ↓ Vasodilation
- ↑ Inflammatory activation
- ↑ Plaque instability
  - ↑ MMP levels
  - ↑ Neovascularization

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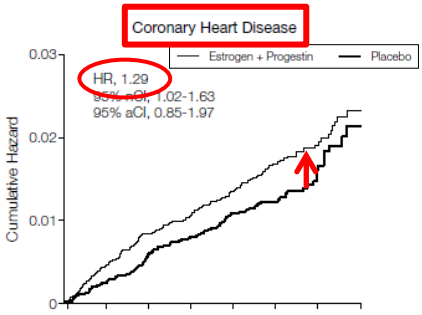
Pflegekongress 2021: Menopausebeschwerden

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

Writing Group for the Women's Health Initiative Investigators

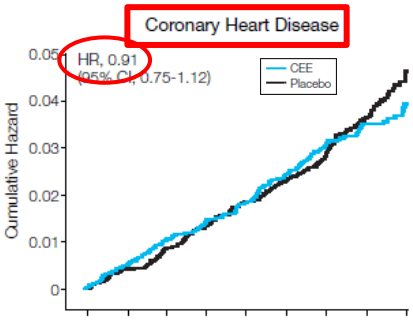
JAMA. 2002;288(3):321-333 (doi:10.1001/jama.288.3.321)



Effects of Conjugated Equine Estrogen in Postmenopausal Women With Hysterectomy: The Women's Health Initiative Randomized Controlled Trial

The Women's Health Initiative Steering Committee

JAMA. 2004;291(14):1701-1712 (doi:10.1001/jama.291.14.1701)



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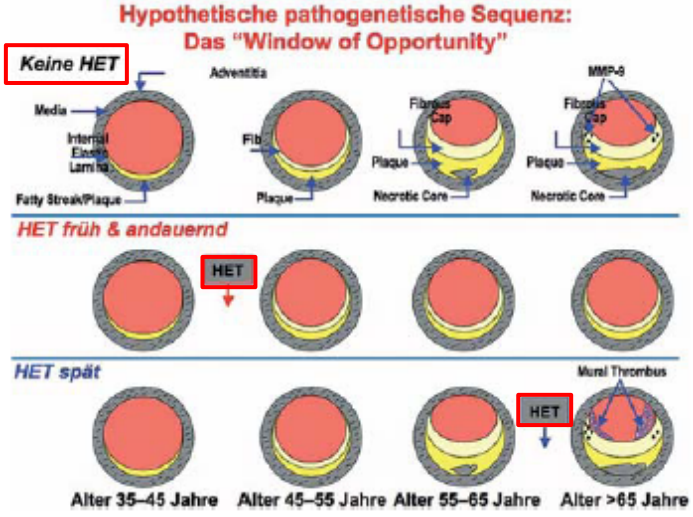
Theorie des „günstigen Fensters“



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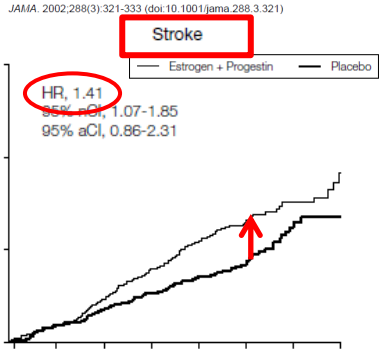

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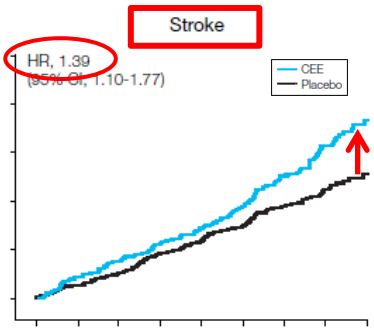
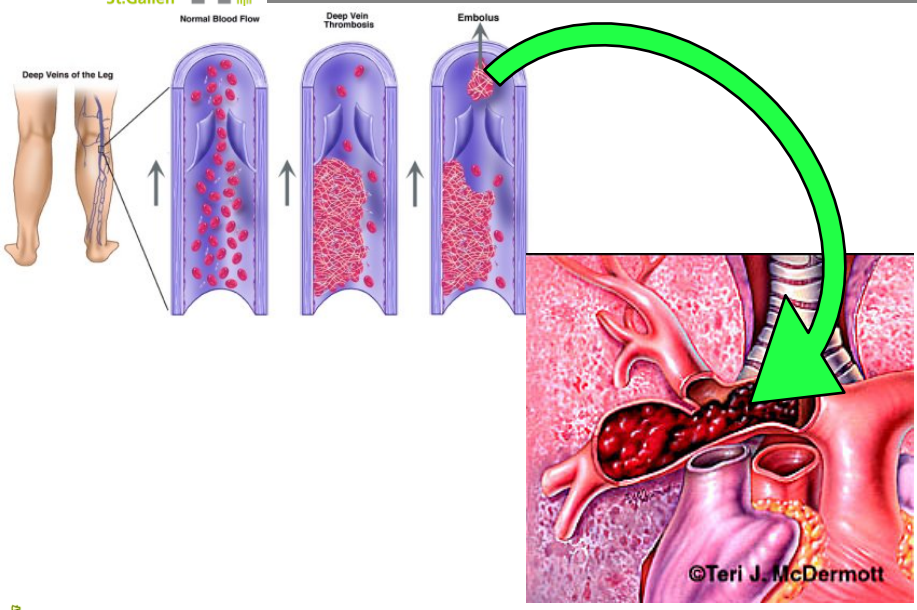


Pflegekongress 2021: Menopausebeschwerden



Pflegekongress 2021: Menopausebeschwerden

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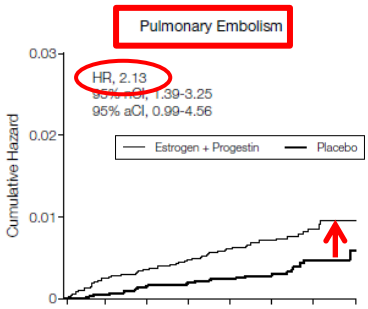

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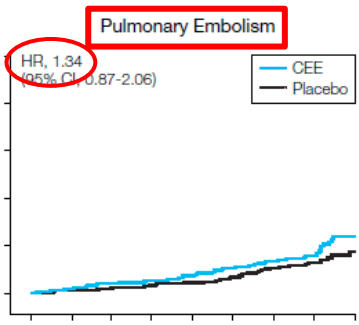
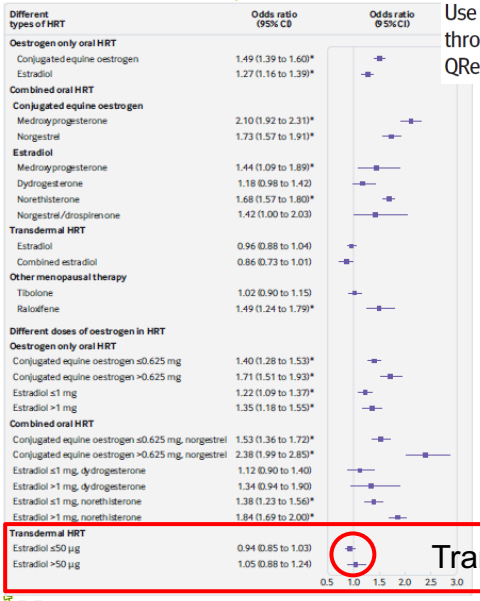


Pflegekongress 2021: Menopausebeschwerden

Use of hormone replacement therapy and risk of venous thromboembolism: nested case-control studies using the QResearch and CPRD databases



BMJ 2019;364:k4810

Transdermale HRT scheint sicher

Kantonsspital St.Gallen

Pflegekongress 2021: Menopausebeschwerden

TABLE 1. Risk Factors Associated With the Development of Breast Cancer

Risk Factor	Relative Risk	95% Confidence Interval (CI)*	References
Conjugated equine estrogen	0.77	0.59–1.01	34
Birth weight	1.09†	2.00–17.00	35
Fish intake	1.14	1.03–1.26	36
Premarin/Progestin	1.24	1.01–1.54	37
Premarin/Progestin	1.26	1.00–1.59	25
French fries (1 additional serving per week)	1.27	1.12–1.44	38
Grapefruit	1.3	1.06–1.58	39
Night shift work	1.51	1.36–1.68	40, 41
Flight attendant (Finnish)	1.87	1.15–2.23	42, 43
Dutch famine‡	2.01	0.92–4.41	44
Antibiotic use§	2.07	1.48–2.89	45
Flight attendant (Icelandic)	4.1	1.70–8.50	46
Electric blanket use¶	4.9	1.50–15.6	47
Tobacco smoking and lung cancer	26.07	6.58–103.3	48

Hormone Replacement Therapy: Real Concerns and False Alarms.
Bluming, Avrum; Tavris, Carol

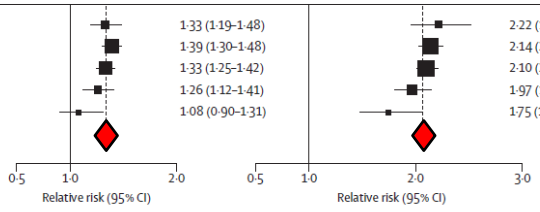
Cancer Journal. 15(2):93-104, March/April 2009.
DOI: 10.1097/PPO.0b013e31819e332a

Hornung René
Kantonsspital St.Gallen – ein Unternehmen, drei Spitäler. St.Gallen Rorschach Flawil
Kantonsspital St.Gallen

Type and timing of menopausal hormone therapy and breast cancer risk: individual participant meta-analysis of the worldwide epidemiological evidence

Lancet 2019; 394: 1159–68

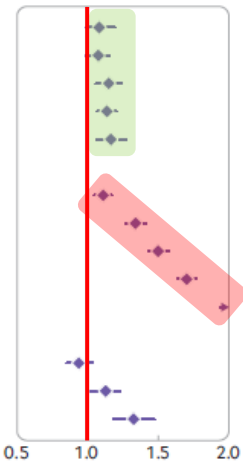
	Number of cases (oestrogen only/ oestrogen and progestagen)	Mean age at menopause	Mean duration of MHT use	Oestrogen only: Relative risk (95% CI)	Oestrogen and progestagen: Relative risk (95% CI)
40–44 years	437/359	42·9	10·7	1·33 (1·19–1·48)	2·22 (1·96–2·52)
45–49 years	1279/2017	47·4	9·3	1·39 (1·30–1·48)	2·14 (2·03–2·26)
50–54 years	1261/2727	50·9	8·8	1·33 (1·25–1·42)	2·10 (2·01–2·21)
55–59 years	372/741	52·0	8·3	1·26 (1·12–1·41)	1·97 (1·81–2·15)
60–69 years	135/203	51·5	7·9	1·08 (0·90–1·31)	1·75 (1·48–2·06)



Use of hormone replacement therapy and risk of breast cancer: nested case-control studies using the QResearch and CPRD databases

BMJ 2020;371:m3873

	Recent use: No of cases	Mean duration	Odds ratio (95% CI)	Odds ratio (95% CI)
Oestrogen only				
<1 year	629	0.5		1.09 (1.00 to 1.19)
1-2 years	962	2.0		1.08 (1.00 to 1.16)
3-4 years	940	4.0		1.15 (1.07 to 1.24)
5-9 years	1665	7.3		1.14 (1.08 to 1.21)
≥10 years	781	13.0		1.17 (1.08 to 1.27)
Oestrogen-progestogen				
<1 year	1911	0.5		1.11 (1.06 to 1.17)
1-2 years	2945	2.0		1.34 (1.28 to 1.40)
3-4 years	2671	4.0		1.50 (1.43 to 1.57)
5-9 years	4537	7.2		1.70 (1.64 to 1.76)
≥10 years	1841	12.9		2.05 (1.94 to 2.17)
Tibolone				
<1 year	656	0.4		0.95 (0.87 to 1.03)
1-4 years	779	2.7		1.13 (1.04 to 1.23)
≥5 years	460	8.0		1.33 (1.20 to 1.48)

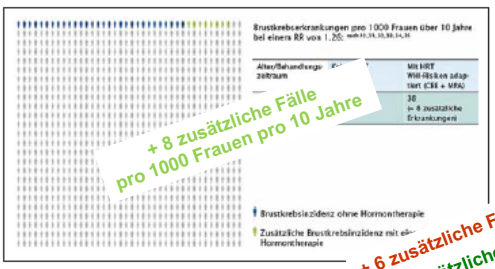


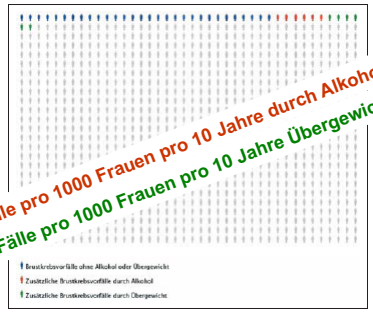
HRT und Risiko Mammakarzinom

- Östrogen erhöht Risiko leicht
- Östrogen-Gestagen erhöhen das Risiko zeitabhängig

Mamma-Ca-Risiko und HRT

- Risiko Mammakarzinom durch langdauerenden HRT
- Risiko Mammakarzinom durch Lebenswandel
  - Adipositas und Alkoholkonsum





Mamma-Ca-Risiko und HRT

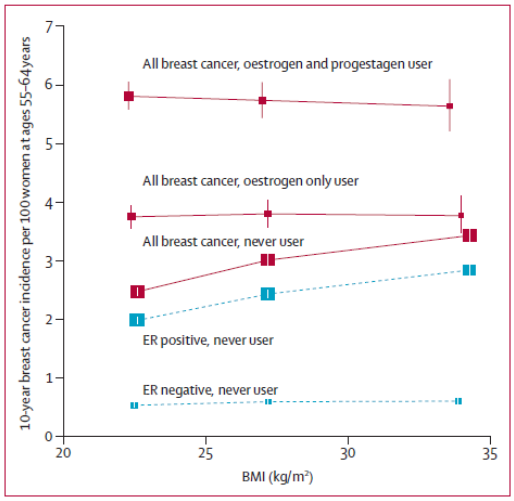
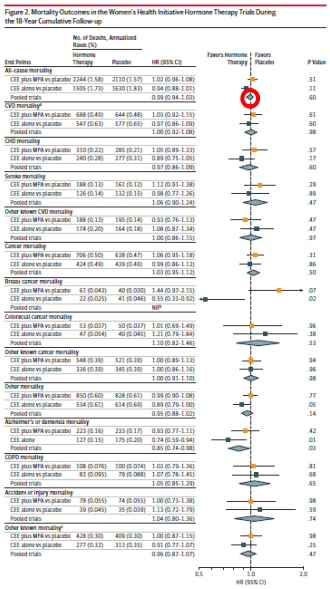


Figure 6: Relevance of BMI to the absolute 10 year breast cancer incidence rate per 100 women at ages 55–64 years in never users and in current users of MHT

Lancet 2019; 394: 1159–68



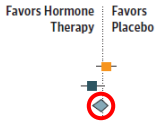
Menopausal Hormone Therapy and Long-term All-Cause and Cause-Specific Mortality

The Women's Health Initiative Randomized Trials

JAMA September 12, 2017 Volume 318, Number 10

Figure 2. Mortality Outcomes in the Women's Health Initiative Hormone Therapy Trials During the 18-Year Cumulative Follow-up

End Points	No. of Deaths, Annualized Rates (%): Hormone Therapy	Placebo	HR (95% CI)
All-cause mortality			
CEE plus MPA vs placebo	2244 (1.58)	2110 (1.57)	1.02 (0.96-1.08)
CEE alone vs placebo	1505 (1.73)	1630 (1.83)	0.94 (0.88-1.01)
Pooled trials			0.99 (0.94-1.03)



Relevanz für die Praxis

- Indikation der HRT:
  klimakterische und urogenitale Beschwerden und Primärprevention der **Osteoporose**
- bei Beginn < 60 LJ überwiegt der Nutzen
  (auch hinsichtlich der Primärprävention für Herzinfarkt, Diabetes mellitus und Kolonkarzinom) ***(„window of opportunity“)***
- Beginn > 60 LJ nur ausnahmsweise
- Erhöhtes Insultrisiko bei Beginn > 60 Jahre und vorbestehendem Hypertonus

Relevanz für die Praxis

- Risiko für Thromboembolien kann stark gesenkt werden durch ***transdermale*** **HRT**
- Über das Risiko, dass ein vorbestehendes **Mammakarzinom** - v.a. durch eine kombinierte HRT - stimuliert werden kann, muss aufgeklärt werden, unter Vergleich mit anderen z.T. erheblicheren Risikofaktoren

Fragen?