Breast Health During Menopause

"Focus on Breast Cancer Risk using MHT"

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www.menopausesociety.be

Menopause Care: A Comprehensive 2-Day Workshop

Disclosures:

Financial disclosures: None

Conflict of Interest MHT: Breast cancer orientated gynaecologist

The Menopausal Breast,
→(Adding) Oestrogens +/- Progestins
-Breast Cancer Risk & Detection
-Breast Cancer Relapse Risk

This talk:

- **Focus on breast cancer**
  - The peri- and postmenopausal breast
    - Decline in sex-steroids, increase in hormone sensitivity
      - Indirect Evidence : Epidemiology, sex-steroids, SHBG, mammographic density
      - Direct Evidence (RCT): WHI update
  - Breast Cancer Risk of MHT is proven but complex
    - Risk by formulation? Unanswered Q.
    - Risk by other risk factors is proven
      - Age, BMI, Familial Risk, Breast Density
    - Breast follow-up during MHT-use
  - Risk of MHT in patients with prior history of breast cancer

MHT = Menopausal Hormone Therapy

Epidemiology: *Breast, E & P → menopausal transition*

E,P principal hormonal factors
driving adult breast epithelial proliferation

- Menarche & Growth spurt puberty
- Pre-menopause: High E2, P levels
  - Varying (cycle, LNG-IUD) & sustained levels (pregnancy, breast feeding, AC)

- Post-menopause
  - E1 (25-42 pg/ml) most dominant E; E2 (10-25 pg/ml) ; E3 (6 pg/ml)
  - Androgens, IGF-1 (Progestins), polypeptide growth factors, …
    - High [E2, testosterone] increase and High [SHBG] lower breast cancer risk (… but genetic damage is event n°1)

- Menopausal transition
  - Animal models (non Ovx): Reduced ductal length, less branching points
    - Peri-menopause→moderate regression ducts
      - Unresponsive external hormones (sex-steroids in glands).
    - Post-menopause→severe regression ducts; reversible 'E'
      - Hormone hypersensitive also impacting non-epithelial like fibroblasts

A prospective study of endogenous serum hormone concentrations and breast cancer risk in postmenopausal women on the island of Guernsey. Thomas HV et al. BJC 1997; Postmenopausal serum androgen, oestrogens and breast cancer risk: The European prospective investigation into cancer and nutrition. Kaaks R. et al. Endocrine Relat Cancer 2005; Perimenopausal & menopausal mammary glands in a 4-VCD mouse model. Saeki K et al. J Mammary Gland Biol Neoplasia Jul '24

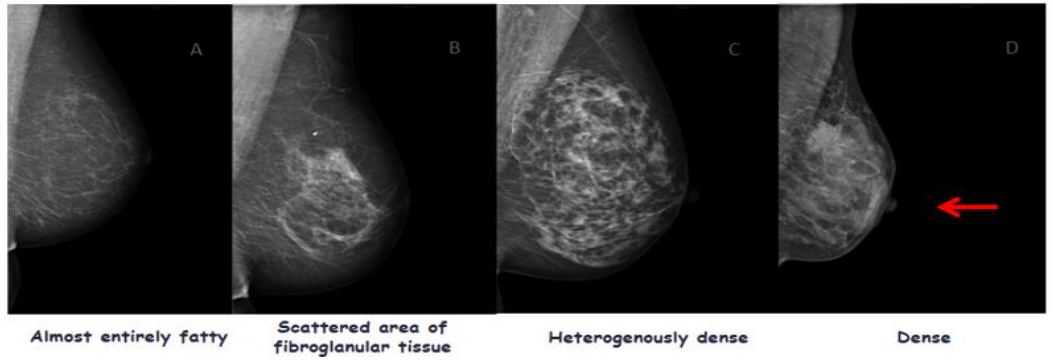
Imaging: Mammogram & DCE-MRI

- Interplay (peri-) Menopause & Mammographic & MR-breast composition
  - Pre-menopause: BD, % BPE ~ timing cycle & BMI
  - Peri-menopause: BD, % BPE lower
  - Menopause: Age ~ BD; BMI & MHT influence ~ % BPE
    - % BPE ~breast cancer risk factor

- Dynamic > Static BD/BPE
  - 48 yrs, perimenop & high br ca risk
    - Patient A →53 yrs menopause
    - Patient B →53 yrs perimenopause

      +/- BD +/- BPE ~breast cancer risk

- A: 25% of glandular tissue
- B: 25 to 50% of glandular tissue
- C: 50 to 75% of glandular tissue
- D: >75% of glandular tissue

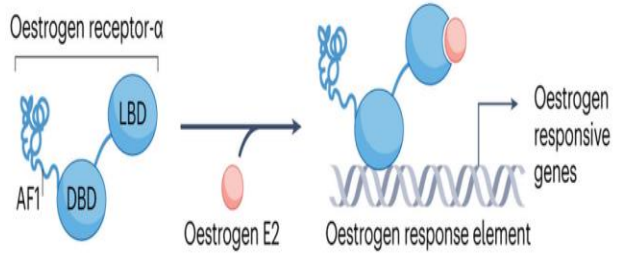


Mammography-Based AI- Breast Cancer Risk Model
Yala A. et al. J Clin Oncol 2021
‘(familial) estrogen sensitivity’
Bone Density ~ Breast Cancer Risk

BD: Mammographic Breast Density
BPE: MR-Background Parenchymal Enhancement (physiologic phenomenon)

MRI background parenchymal enhancement, breast density and serum hormones in postmenopausal women. Brooks et al. int J Cancer 2018. Impact of menopause & age on breast density and background parenchymal enhancement in dynamic contrast-enhanced magnetic resonance imaging. Kuling et al. Feb 2025 Journal of Medical Imaging

***E2 levels**: Breast cancer prevention*



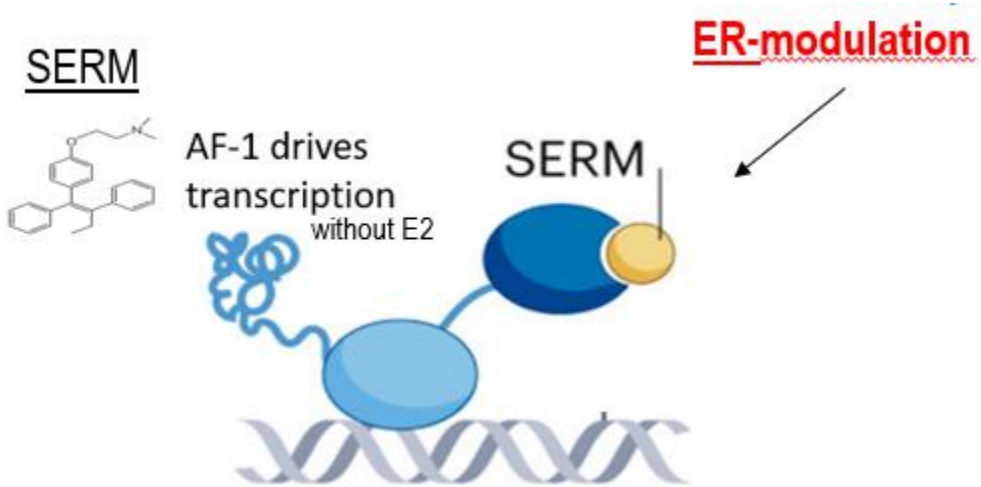
Experiences from RCT

Tamoxifen or Aromatase Inhibitors reduces br ca risk better if

EBCTCG: High qER, PR+ > ER+ PR- lesions

ATAC: AI > Tam if low BMI

POETIC: AI ~ % Ki-67 Postmenopausal plasma [E2]



Royal Marsden BC prevention study: Tamoxifen ~MHT-use

MORE: Raloxifen more efficacious if high E2 levels

IBIS-II: AI most effective in women with higher E2-SHBG ratios

Powles TJ et al. Eur J Cancer 1990; 680-4; Cummings SR et al. JAMA 2002; 216-20; EBCTCG Lancet 2015; 1341-52; Cuzick et al. Lancet Oncol 2024; 25: 108-16; Schuster EF et al. Nat Commun 2023; 14: 4017

ER-levels in normal breast &Risk factors IHC- ER,

- Age: Postmenopausal & older women have higher ER-levels
- Parity: Parous women have less ER and PR-levels than nulliparous women
- Breast Feeding: Breastfeeding was inversely associated ER-levels.
- Alcohol: Higher consumption ~higher levels of ER and PR-levels.
- Height & BMI at age 18: Higher PR-levels
- Ancestry: Higher ER-levels in European women
- Premenopausal BMI >25 vs < 20 kg/m² ~IGF-1R
- MHT: E > EP increases PR-; no effect on ER-levels

NHS : 388 women with benign breast disease (ages 17-67 years). Immunohistochemical staining was performed on tissue microarrays containing **normal breast epithelium** and scored as % epithelial cells that were positively stained.

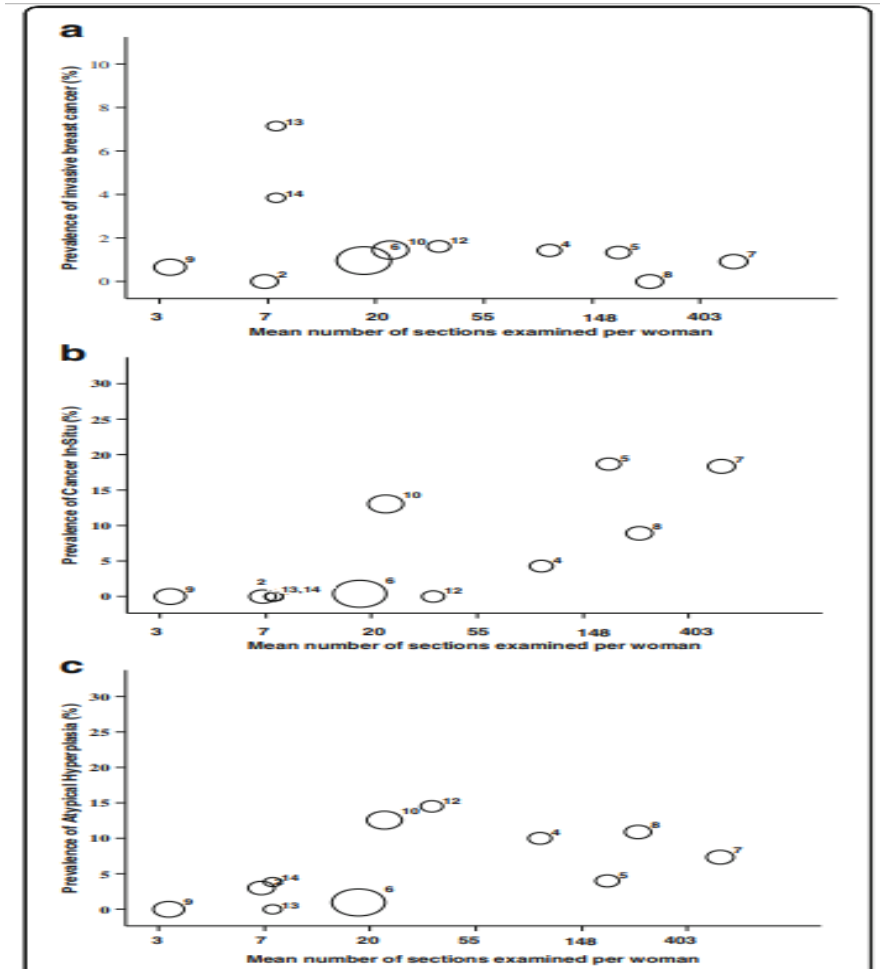
Risk factors associations with hormone receptors and Ki67. H. Oh et al. npj Breast Cancer (2017)

ER & PR abnormal > normal epithelial cells

The prevalence pool of incidential (pre-)cancers

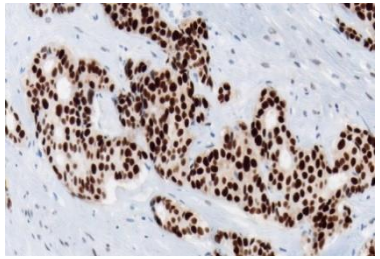
Undiagnosed cancers in autopsy studies (unscreened)

- Prostate cancer
  - 5% at age 30
  - 59% at age 79
- Thyroid cancer
  - 5.7% or 11.2%
- Breast cancer
  - 1.3% invasive
  - 8.9% DCIS

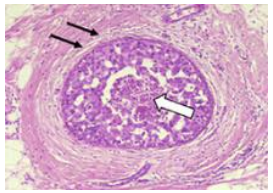


Thomas *et al. BMC Cancer* (2017) 17:808

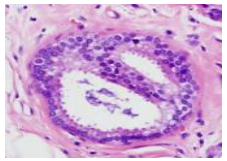
Invasive breast cancer

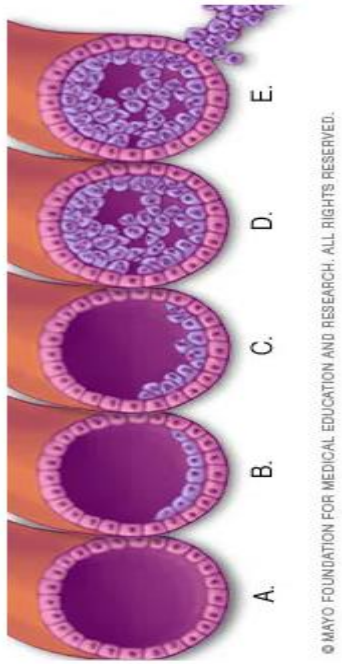


In-situ breast cancer



Atypical hyperplasia





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      - **Indirect Evidence : Epidemiology, sex-steroids, SHBG, density**
      - **Direct Evidence : WHI (update)**
  - Risk of MHT is complex
    - Risk by formulation?
    - Risk by other risk factors
      - Age, BMI, Familial Risk, Breast Density
    - Breast follow-up during MHT-use
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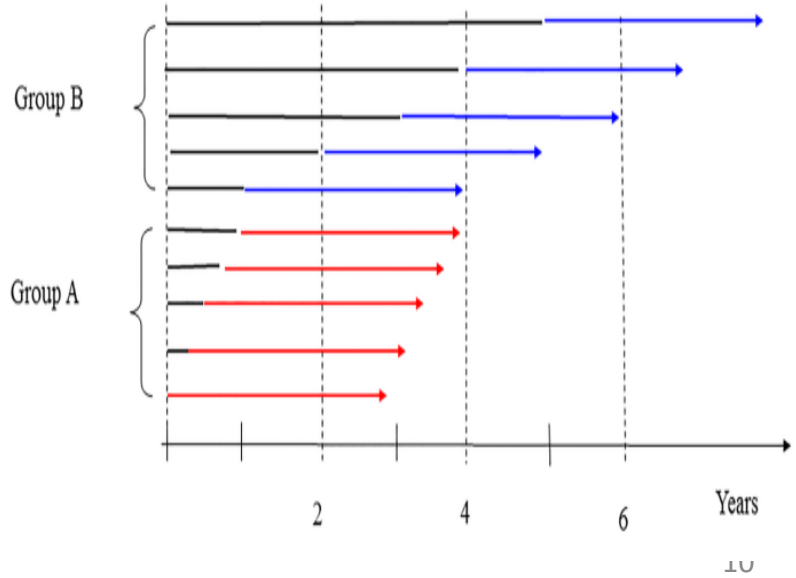
MHT = Menopausal Hormone Therapy

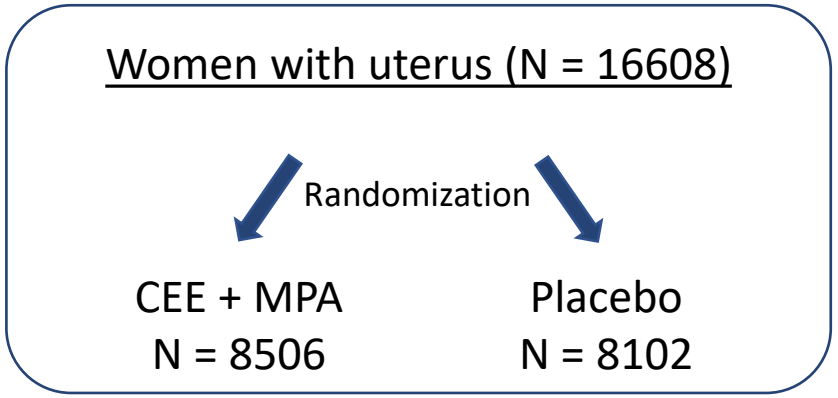
*Breast cancer risk & MHT : **History***

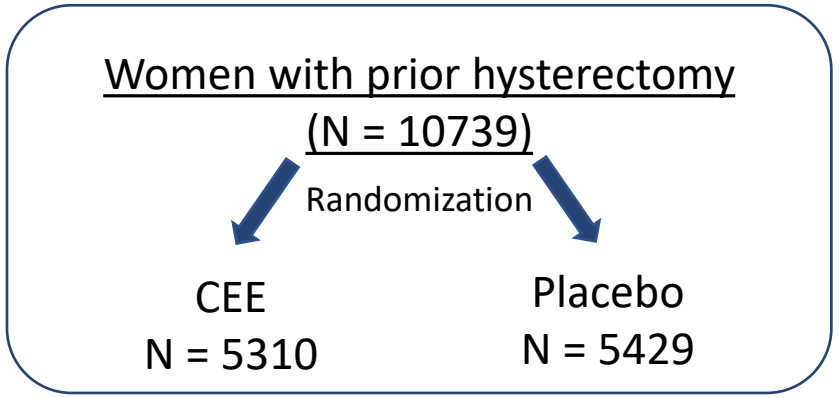
- 1985 – 2000 : Norway/Sweden 50% increased BrCa incidence
- Simultaneously: Use of MHT increased X 5 times
- Influential "observational" studies
  - NHS; MW: MHT E-alone / CHT ~ HR BrCa 1.5 – 2.0
  - Several potential biases
    - baseline risk,
    - time varying effect CHT & BrCa→
    - overdiagnosis by more screening



Benefits and Risks of the Two Hormone-Therapy Formulations
CEE (+ MPA) vs Placebo

WHI 2002: healthy women age 50-79 yrs (average **63** yrs) recruited '93 – '98 USA





Primary outcomes: Prevention of CHD & Invasive Breast Cancer

Both studies stopped early because of MI/Stroke/VTE/BrCa (FDA warning)

Median treatment duration before termination of trial: 5.6 yrs

Median treatment duration before termination of trial: 7.2 yrs

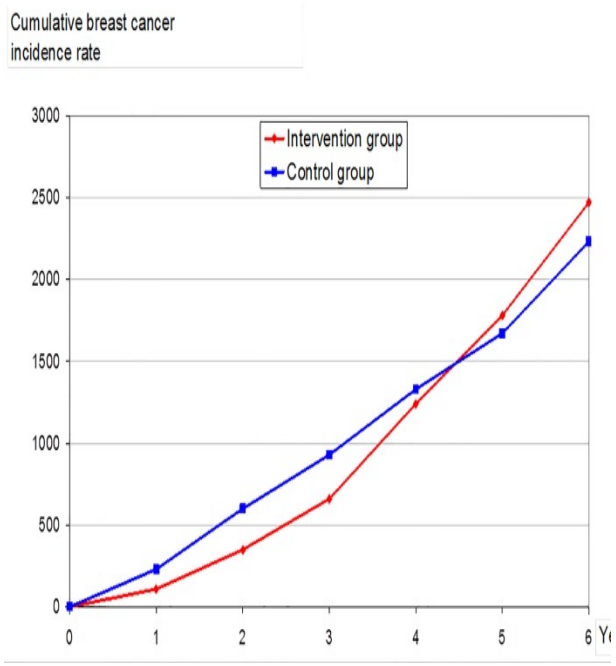
WHI: World Health Initiative; CEE: conjugated equine estrogens; MPA medroxyprogesterone acetate

Manson JE, Chlebowski RT. JAMA 2013; 310:1353-1368.

CHT: Breast cancer risk in WHI (all)

- The randomized WHI trial (CEE + MPA vs placebo/50-79yrs) BrCa HR

  - Combined HT HR:
    - 1.1 no previous use →
    - 1.24 previous use



women in the WHI trial not used CHT prior to randomization

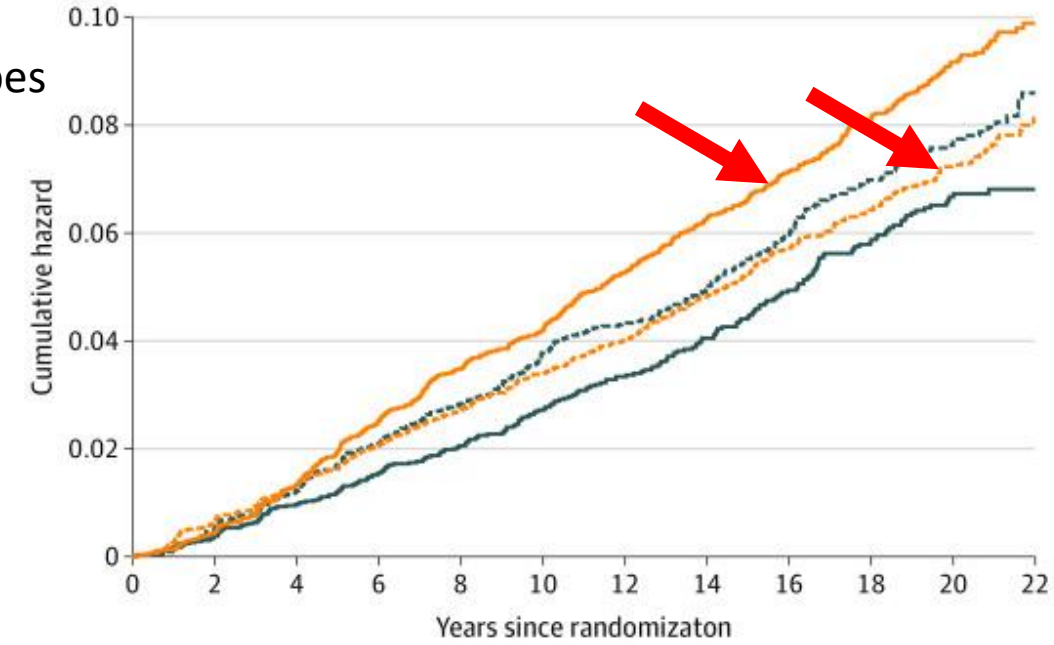
Higher incidence significant > yr 5
Similar histology & grade
Higher stage with LN-pos
At yr 1 : More abnormal mammograms
No significant difference in BCSS

"E + P stimulates breast cancer growth and hinder breast cancer diagnosis"

Association of Menopausal Hormone Therapy With Breast Cancer Incidence and Mortality During Long-term FU WHI Randomized Clinical Trials

1565 BrCa-cases in this report

ER-pos cases; all subtypes



CEE + MPA (conjugated equine estrogen)

Placebo

CEE alone vs placebo: HR, 0.78 (95% CI, 0.65-0.93); *P* = .005
CEE alone
Placebo

MPA vs placebo: HR, 1.28 (95% CI, 1.13-1.45); *P* <.001
CEE + MPA
Placebo

higher breast cancer incidence that persisted for more than a decade after discontinuing use

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

Kaplan-Meier Estimates for the Association of MHT With Invasive Breast Cancer During Cumulative Follow-up

The randomized evidence in WHI is largely for hormone use starting > age 60 yrs!

Chlebowski et al JAMA July 2020

Association of Menopausal Hormone Therapy With Breast Cancer Incidence and Mortality During Long-term FU WHI Randomized Clinical Trials

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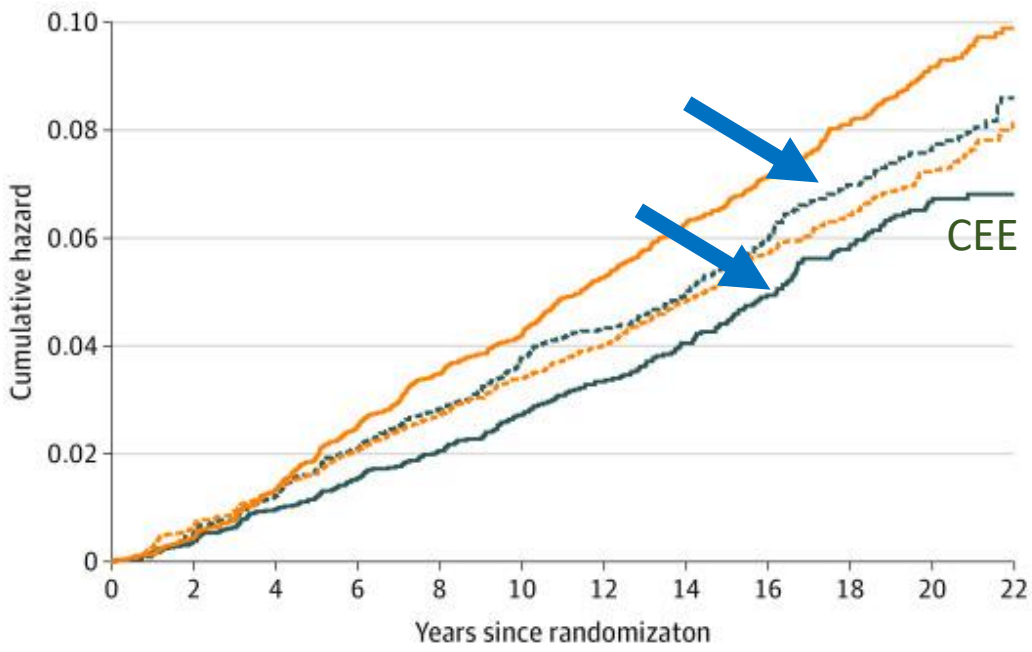

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- Statistically significant **lower** breast cancer incidence
- **No significant difference** in breast cancer **mortality**
- Association with lower breast cancer incidence greater among **women without first degree relative and no previous breast biopsy**
- Association with lower risk strongest for **ER+, PR- cancers**
- Stronger associations with CEE-alone and breast cancer incidence seen for **HER2+ and negative lymph node**

Kaplan-Meier Estimates for the Association of MHT With Invasive Breast Cancer During Cumulative Follow-up

Chlebowski et al JAMA July 2020

WHI Breast Cancer Mortality?

- CEE alone, compared with placebo, among women who had a previous hysterectomy, was significantly associated with lower breast mortality.

- CEE + MPA, compared with placebo, among women who had an intact uterus had no significant difference in breast cancer mortality.

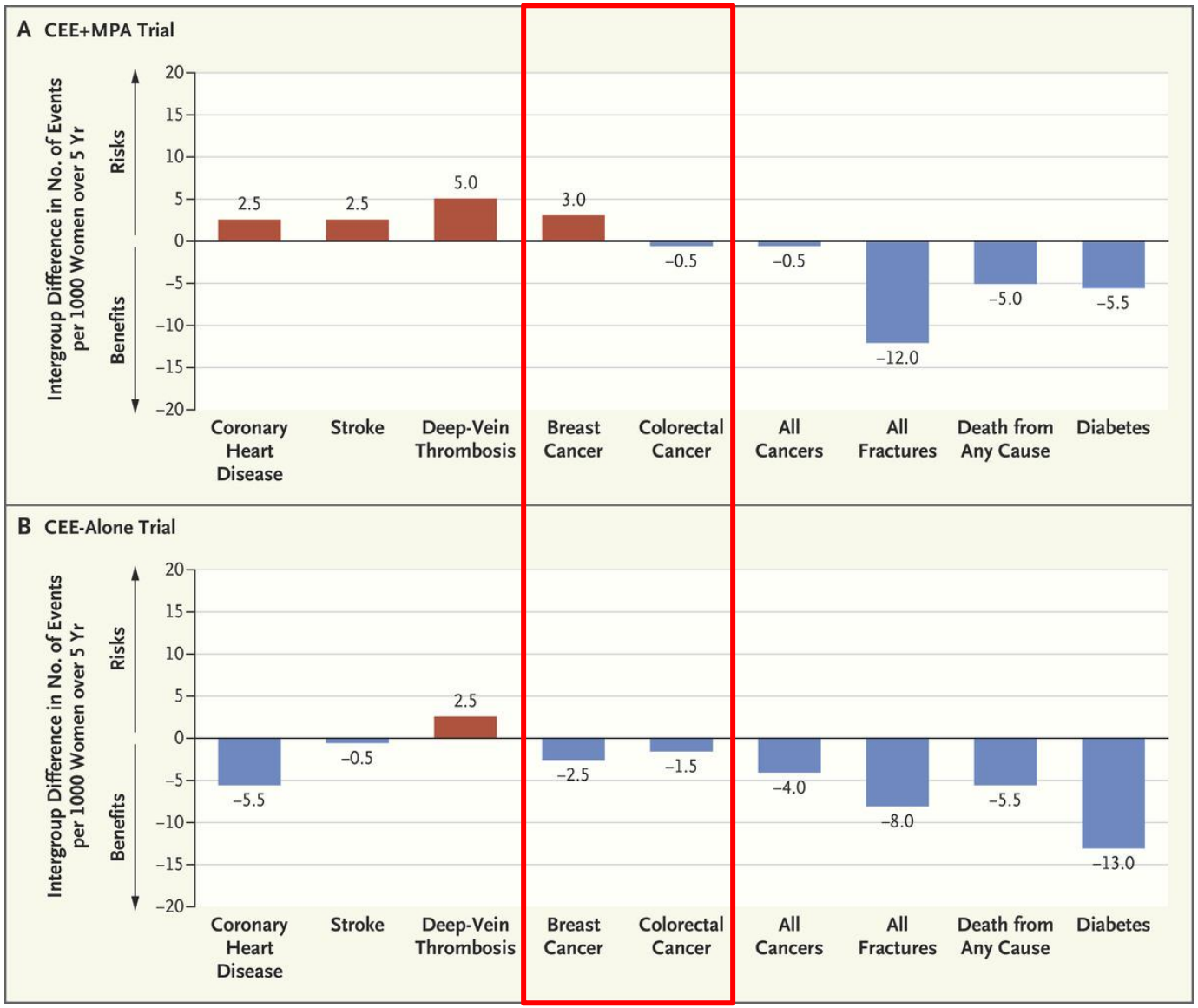
- Chlebowski et al JAMA July 2020

→ Subgroup of WHI

Benefits and Risks of the Two Hormone-Therapy Formulations CEE (+ MPA) versus Placebo: subgroup 50-59yrs of age

CEE + MPA (N = 2837)
vs. Placebo (N = 2683)

CEE (N = 1639)
vs. Placebo (N = 1674)



Combined E-P
+ 0.6 breast cancer
1000 women – year
Without excess mortality

Comparable to
life style affecting risk

E-Alone
- 0.5 breast cancer
1000 women – year
With less mortality

No P after hysterectomy

Manson JE, Kaunitz AM. N Engl J Med 2016;374:803-806.

The NEW ENGLAND JOURNAL of MEDICINE

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MHT = Menopausal Hormone Therapy

Since 2002:

2002: MHT-use dropped by >80%

Parallel breast cancer incidence drop (also in Belgium)

- Link not confirmed in other & longer FU studies

Nowadays: MHT-use anxiety and confusion ! Part due to 'BC-risk'

*New generation of medical graduates lack training & competence in managing menopause

P. Vankrunkelsven et al BCRT 2009;
L. Ameye et al Maturitas 2014

*JE. Manson & AM. Kaunitz in NEJM 2016

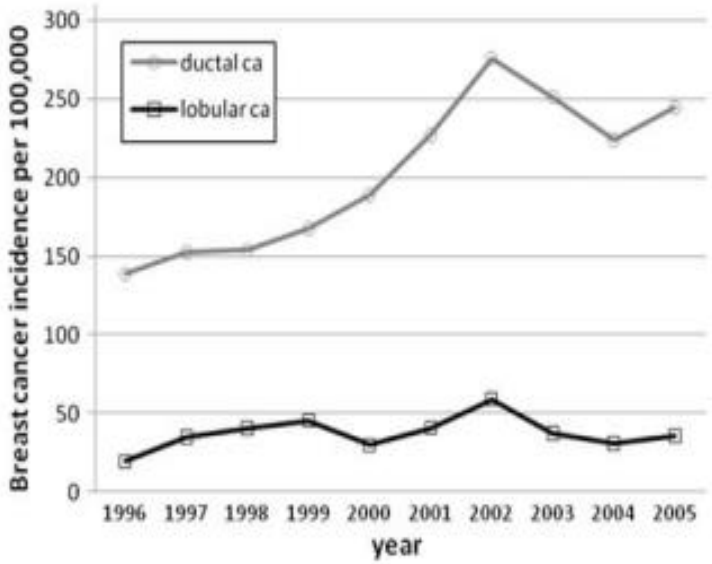


Fig. 2 Annual incidence rates for invasive breast cancer in Limburg 1996–2005 by histological status, the raise and fall of invasive lobular carcinoma is relativity stronger than the one of invasive ductal carcinoma

No report mammography screening rates…
After: Rates up but MST further down

BUT present day → safer hormone formulations — lower doses, transdermal routes of delivery —for treatment of menopausal symptoms, and non-hormonal options including selective serotonin-reuptake inhibitors but non-hormonal options less effective unless…NK3 inhibitors

Put it in its context as 1 of several risk factors: Relative risk of MHT

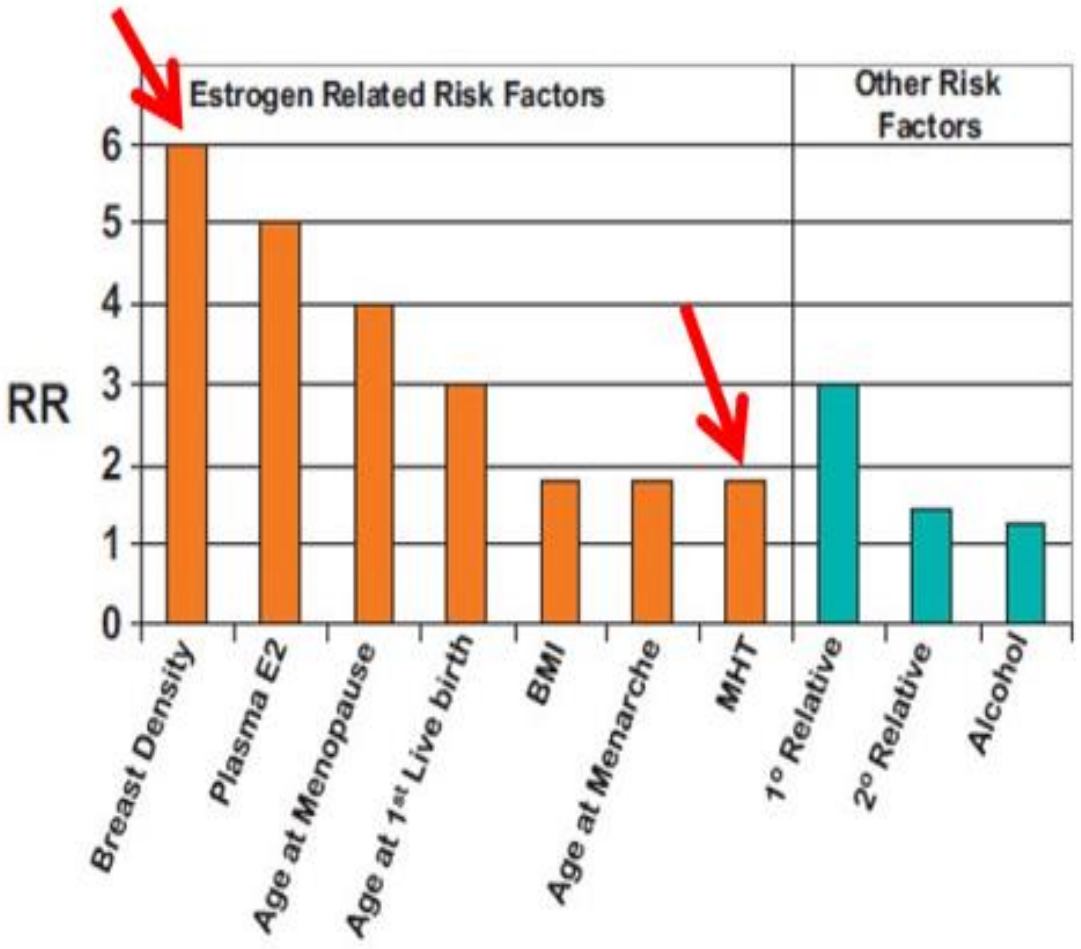
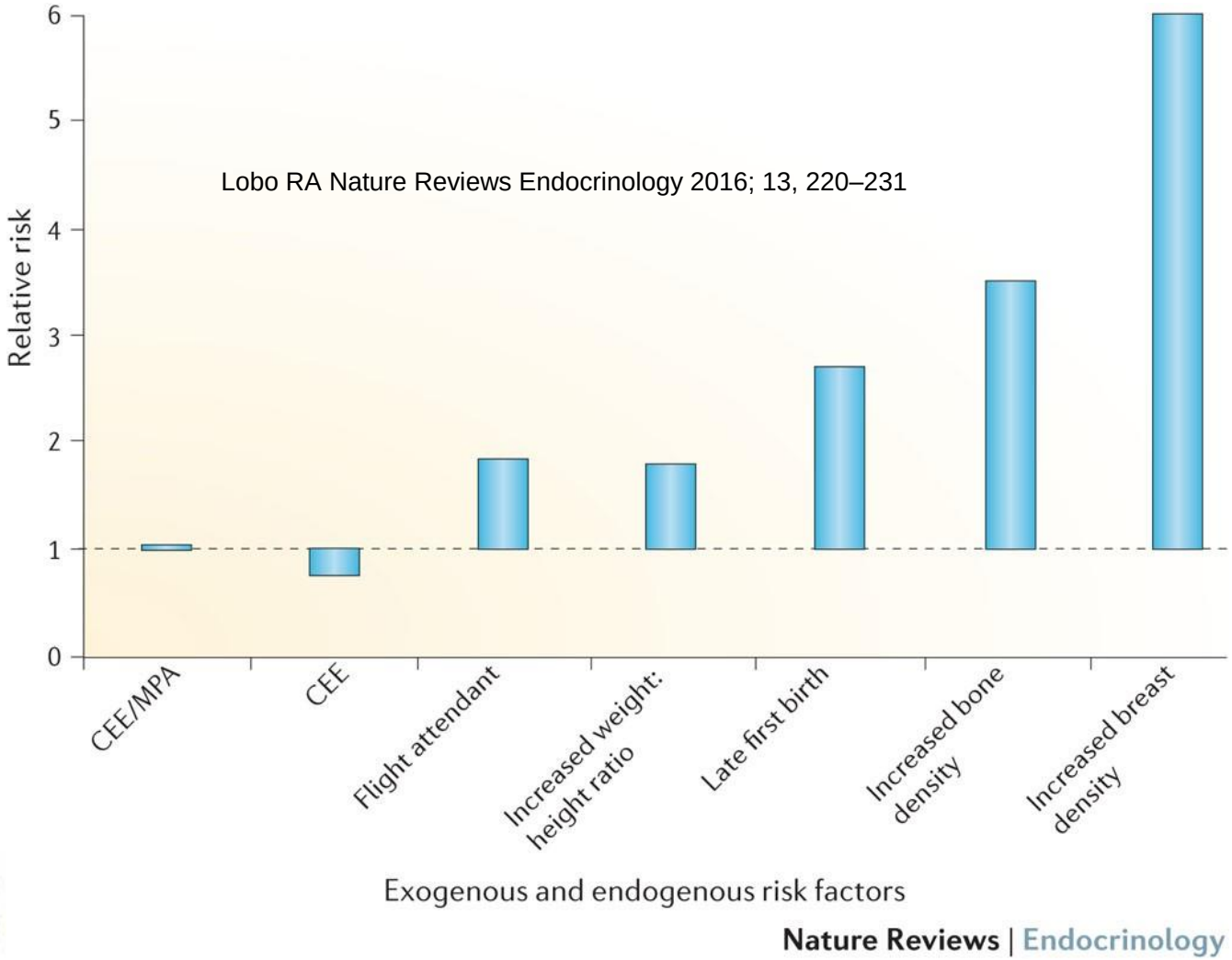


Fig. 1. Estrogen related risk factors for breast cancer. Risk factors for breast cancer related to clinical aspects that are associated with an increased chronic exposure to estradiol and expressed as relative risks (RR).

Figure adapted from the review of E. Amir et al. [83] and published in the article by Yager et al. [16]. Reproduced with the permission of the Endocrine Society.



Familial or genetic risk; Age menarche; menopause; low physical activity; alcohol intake; DES-daughter, mother, previous irradiation;

Elevated breast cancer risk and MHT-use

I.Epidemiological Evidence
II. MHT – BrCa : Several prospective observational studies & 1 RCT

'Influence of MHT & ER-pos breast cancer incidence remains controversial' JAMA 2020

- Incidence of ER+ breast cancer correlates with
  - early menarche
  - late menopause
  - blood estrogen levels
- → High BMI, lower SHBG, more ER-pos breast cancer
- →Exercise lowers ER-pos breast cancer risk

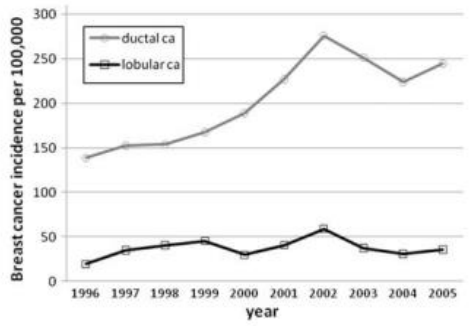


Fig. 2 Annual incidence rates for invasive breast cancer in Limburg 1996–2005 by histological status, the raise and fall of invasive lobular carcinoma is relativity stronger than the one of invasive ductal carcinoma

- Randomized trials have shown that the incidence of ER+ breast cancer is reduced by
  - tamoxifen, raloxifene, lasofoxifene, …
  - aromatase inhibitors
    - Effect = [E2]

2 breast cancer updates

MWS Collaborative Group HFBC

Nested-Case Control study

MWS Collaborative Group HFBC (during and after MHT)

Incident Breast Cancer (mainly) from Prospective Registers (25/59 studies)
Breast Cancer Risk = confirmed: Higher if + P but also 'after stopping MHT'

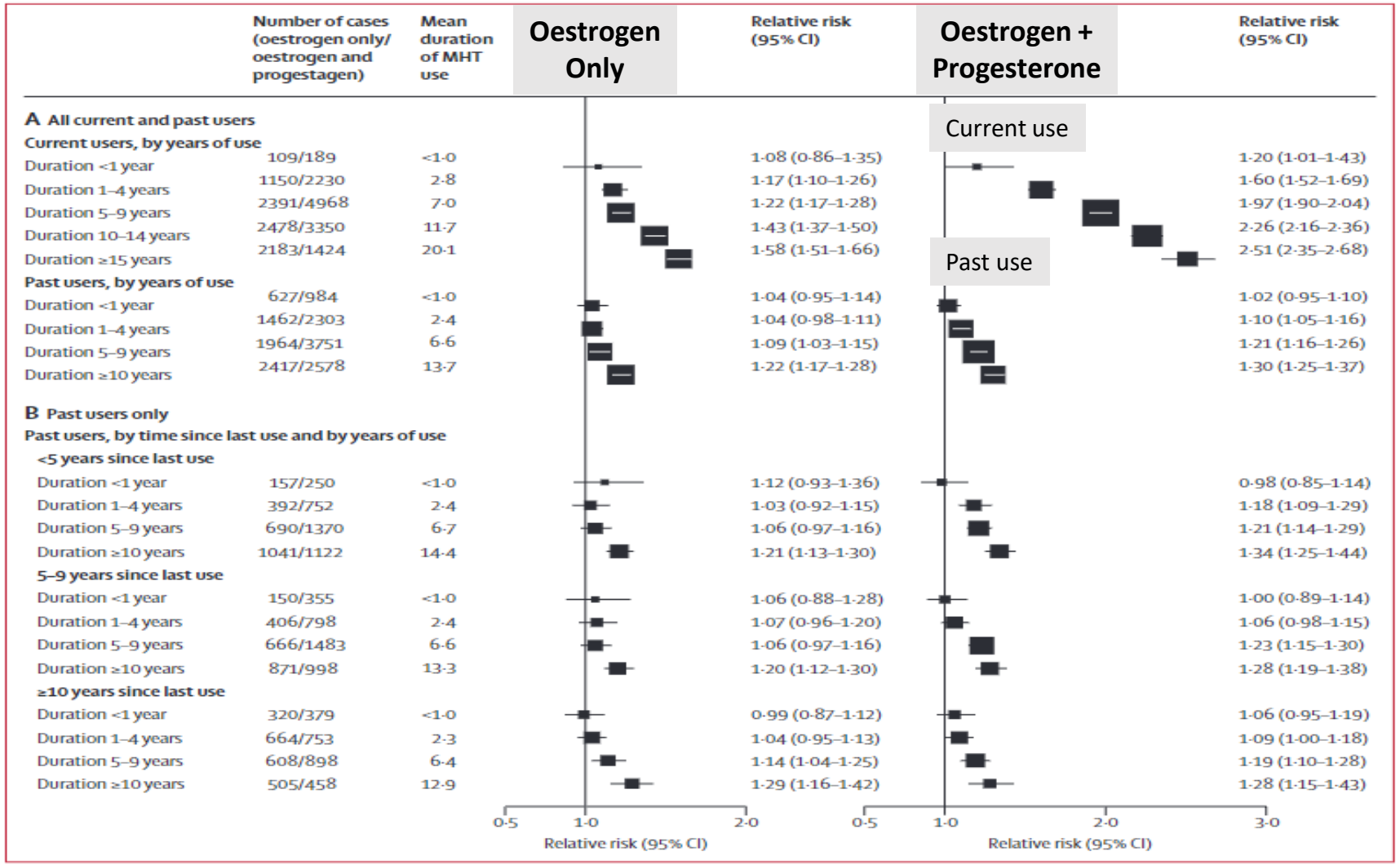


Figure 2: **Type and timing of MHT use in current users and past users**
(A) All current and past users. (B) Past users only, by time since last use of MHT. Fully adjusted relative risks for current versus never users by years of current use, and for past users versus never users by years of use and time since cessation of use (prospective studies). MHT=menopausal hormone therapy.

Prospective follow-up, 108 647 postmenopausal women developed breast cancer at mean age 65 years (SD 7); 55 575 (51%) had used MHT.

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mean MHT duration was 10 yrs (SD 6) in current users and 7 yrs (SD 6) in past users, and mean age was 50 ys (SD 5) at menopause and 50 yrs (SD 6) at starting MHT.

> HRT is an effective treatment for menopause symptoms. But this study found the risk may persist for longer after stopping HRT than we previously thought, so women should think carefully about taking it

Dr Julie Sharp, Cancer Research UK

Breast Cancer Mortality?

MWS Collaborative Group HFBC

Incident Breast Cancer & Breast Cancer Mortality

	Breast cancer deaths/ population at the time of recruitment	Mean number of years of MHT use at recruitment (SD)	Breast cancer mortality rate ratio (95% CI)
Use of MHT reported at recruitment			
Never-user	3523/476 902	0·0	1·00 (ref)
Current user, oestrogen only			
<5 years use	231/31 996	2·4 (1·4)	1·15 (1·01–1·32)
≥5 years use	661/79 833	9·6 (4·3)	1·35 (1·24–1·47)
Current user, oestrogen and progestagen			
<5 years use	557/65 188	2·3 (1·4)	1·39 (1·27–1·53)
≥5 years use	905/86 282	8·4 (3·2)	1·64 (1·52–1·76)
Past user			
<5 years use	816/119 475	1·1 (1·3)	0·99 (0·91–1·06)
≥5 years use	393/47 516	8·0 (3·1)	1·24 (1·12–1·38)

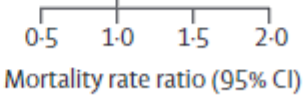

Figure: **20-year breast cancer mortality rate ratio in relation to MHT use at the time of recruitment into the Million Women Study[2]**

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Contrasts with WHI data

Breast Cancer Risk by baseline BMI

Incident Breast Cancer (mainly) from Prospective Registers by BMI during 10 years

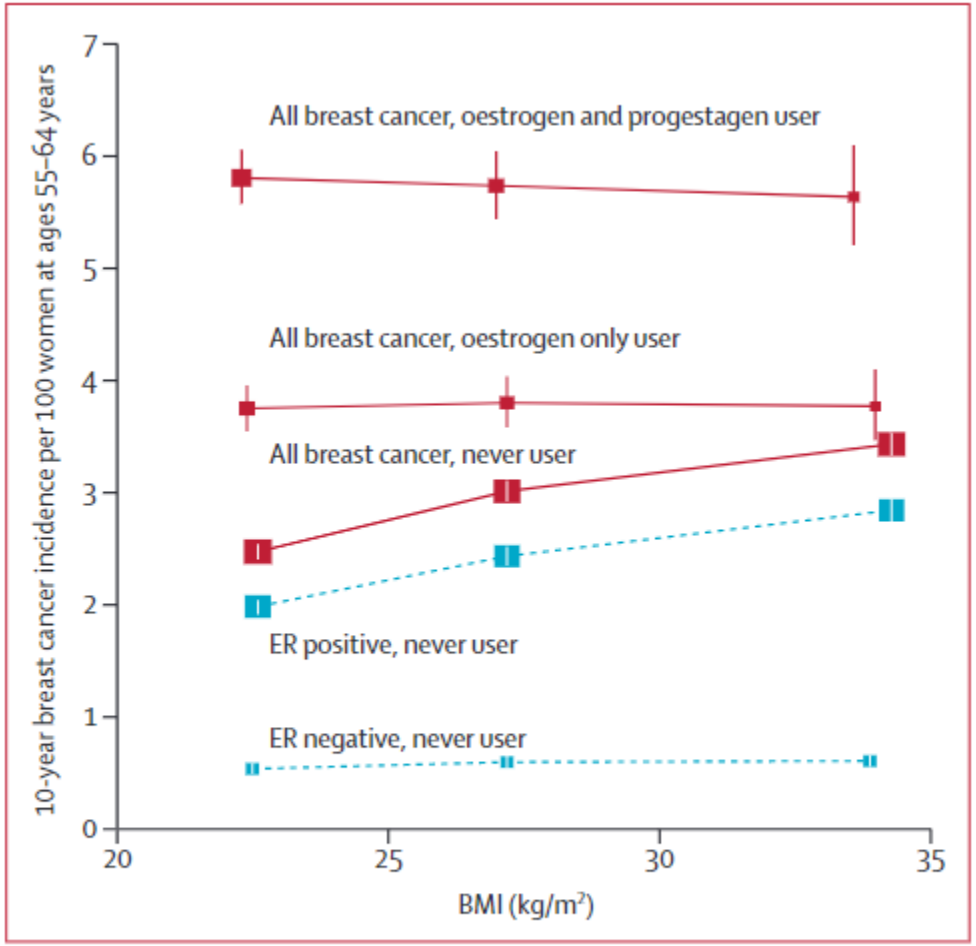

Figure 6: **Relevance of BMI to the absolute 10 year breast cancer incidence rate per 100 women at ages 55–64 years in never users and in current users of MHT**

10 yrs BrCa risk +/- 3% if average BMI and no MHT-use

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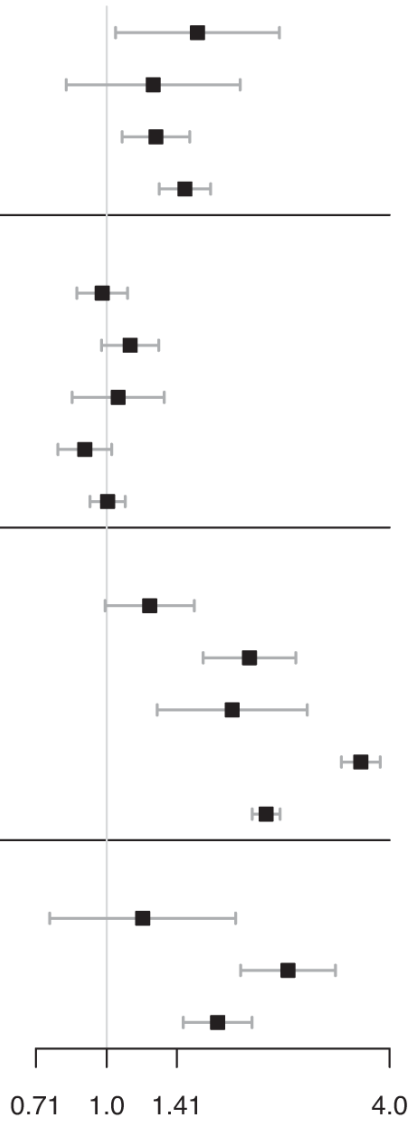
Population based cohort study of 1,3 million women in Norway

	Cases	HR (95% CI)
Oral ET		
<1 year	28	1.56 (1.04–2.33)
1–4.9 years	24	1.26 (0.82–1.92)
≥ 5 years	162	1.27 (1.08–1.50)
Unknown duration	289	1.47 (1.29–1.66)
Vaginal ET		
<1 year	281	0.98 (0.86–1.11)
1–2.9 years	225	1.12 (0.98–1.29)
3–4.9 years	85	1.06 (0.84–1.33)
≥ 5 years	252	0.90 (0.79–1.02)
Unknown duration	603	1.00 (0.92–1.10)
Oral oestrogen-NETA		
<1 year	92	1.23 (0.99–1.54)
1–2.9 years	92	2.01 (1.60–2.53)
3–4.9 years	34	1.85 (1.28–2.67)
≥ 5 years	613	3.47 (3.16–3.82)
Unknown duration	1141	2.18 (2.04–2.34)
Oral tibolone		
<4.9 years	21	1.19 (0.76–1.88)
≥ 5 years	91	2.43 (1.93–3.07)
Unknown duration	165	1.72 (1.46–2.04)



Median follow-up 12,7 years

- Long duration (≥5y) of any type of oral MHT associated with increase in risk
- Combination MHT associated with increased risk

- Risk increase was strongest for luminal A breast tumors
- Vaginal estrogen therapy not associated with breast cancer risk

Støer et al BJC May 2024

Role of Progestogens: Are they All the Same?

Probably the most important finding is that compared to the synthetic progestogens medroxyprogesterone acetate, norethisterone and levonorgestrel, combined preparations containing dydrogesterone were associated with a lower risk of diagnosis, which supports a growing body of observational evidence with similar findings.

Vinogradova's group et al BMJ 2022

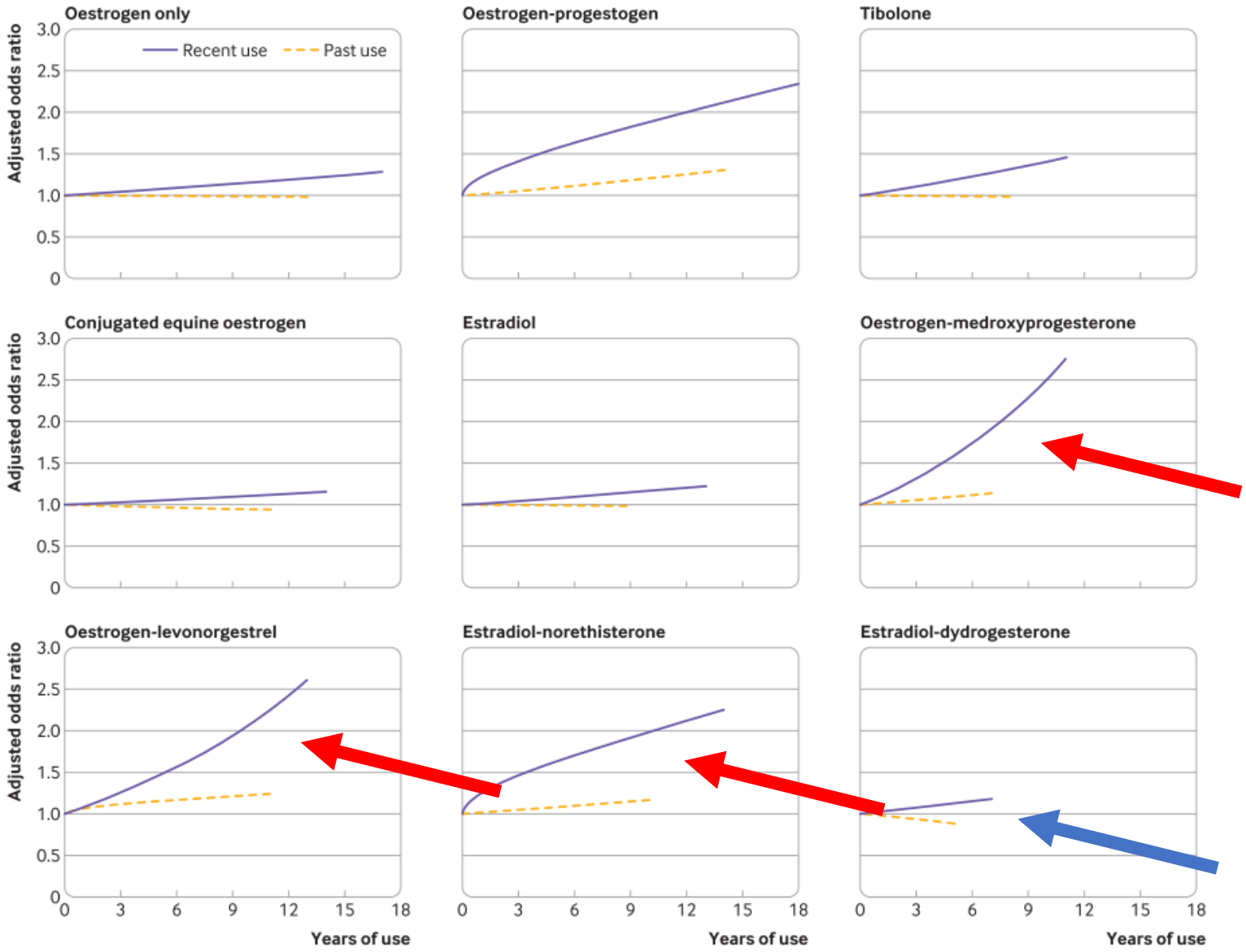


Fig 4 | Adjusted odds ratios for different durations of recent and past exposures to hormone replacement therapies in association with breast cancer risk. Odds ratios are with reference to never users and adjusted for smoking status, alcohol consumption, Townsend fifth (QResearch only), body mass index, ethnicity, history of other cancers, oophorectomy or hysterectomy, records of early and late menopause, menopausal symptoms, mammography or scans, family history, comorbidities, other drugs, and years of data. Cases are matched to controls by age, general practice, and index date. Model includes fractional polynomial terms for recent use of oestrogen-progestogen (power 0.5), estradiol-norethisterone (power 0.5), past use of oestrogen-levonorgestrel (power 0.5), and linear terms (1) for all other exposures

Vinogradova' group et al BMJ 2022

Progesterone is the principal hormonal factor driving adult mammary/breast epithelial proliferation and is E-dependent

NHS : More BrCa risk among postmenopausal wme on POP HRT (RR 2.24, 95% CI 1.26-3.98)

Micronized progesterone, used along with estrogen HRT, was not significantly associated with an increased risk of breast cancer when used up to 5 years (HR 1.13, 95% CI 0.99-1.29).

The use of estrogens and progestins and the risk of breast cancer in postmenopausal women. Colditz GA et al. NEJM 1995
Risk of breast cancer after stopping MHT in the E3N cohort Fournier A et al. BCRT 2014 Progesterone action in normal mouse mammary gland. Wang S. et al. Endocrinology 1990

Guidelines on Hormone Therapy from Professional Societies including duration. 'Menopausal Symptoms'

Table 2. Guidelines on Hormone Therapy from Professional Societies.*

Aspect of Treatment	ACOG*	NAMS*	AACE and ACE	Endocrine Society*	U.S. Preventive Services Task Force
Indication	Menopausal symptoms	Menopausal symptoms	Menopausal symptoms	Menopausal symptoms	Menopausal symptoms, primary ovarian insufficiency, and surgical menopause not addressed
Risk calculation before initiation	None specifically recommended; individualize on basis of risk:benefit ratio	Consideration of age and time from menopause onset recommended; initiate if patient <60 yr of age or within 10 yr after onset of menopause	Consideration of age, time from menopause onset, lipid profile, smoking history, risk of CVD disease recommended	Assessment of risk of CVD and breast cancer recommended, with therapy avoided if is risk high	Neither evaluated nor recommended
Dosing considerations	Lowest effective dose for shortest period needed to relieve symptoms and minimize risks of therapy	Lowest effective dose of appropriate drug, with consideration of route and duration	Lowest dose needed to relieve symptoms and protect bone	Shared decision making to determine formulation, dose, and route	Not addressed
Duration of use	Based on risk–benefit analysis, with recommendation against routine discontinuation in patient ≥65 yr of age	Extended for vasomotor symptoms, bone loss, or quality of life after attempt at stopping; add if benefits are greater than risks	Recommended for ≤5 yr; longer-term use controversial; reduce dose if continuing	Shortest total duration for treatment goals and risk assessment	Not recommended
Recommendation for prevention of chronic disease (CVD, osteoporosis, and diabetes)	Not recommended for CHD or osteoporosis prevention	Not recommended for CHD prevention; supportive of osteoporosis prevention if other therapies not indicated	Not recommended for prevention of CHD or diabetes; supportive of prevention of osteoporosis in selected women	Not recommended for prevention of CVD, osteoporosis, or dementia	Not recommended for primary or secondary prevention of chronic disease
Recommendation of timing of therapy	Data suggest possible benefit in prevention of CVD when initiated close to menopause	Data suggest possible benefit in prevention of CVD when initiated close to menopause	Data suggest reduced risk of CVD when initiated close to menopause		
Recommendation for transdermal therapy	Less risk than oral therapy if elevated risk of VTE	Less risk than oral therapy if elevated risk of VTE; minimized risk of CVD and stroke seen as women age	Less risk than oral therapy if elevated risk of VTE, hypertension, hypertriglyceridemia, or cholelithiasis	Less risk than oral therapy if elevated risk of VTE, metabolic syndrome, obesity, or hypertension	Not recommended
Recommendation for vaginal therapy for genitourinary syndrome in women at risk for breast cancer	Involvement of oncologist recommended if history of breast cancer	Low dose recommended, in conjunction with involvement of oncologist if history of breast or uterine cancer	Use of vaginal therapies not addressed	Shared approach to decision making with oncologist	Genitourinary syndrome of menopause not addressed

After BrCa →

* Women with premature menopause or primary ovarian insufficiency are encouraged to use hormone therapy at least until they reach the average age for the onset of menopause. The American Association of Clinical Endocrinologists (AACE),[47] the American College of Endocrinology (ACE),[47] the American College of Obstetricians and Gynecologists (ACOG),[27] the North American Menopause Society (NAMS),[4] and the Endocrine Society[34] advise against the use of compounded hormone therapy that has not been approved by the FDA. These groups also generally advise against the use of hormone therapy in women with a history of breast cancer. ACOG guidelines were developed in 2014 and reaffirmed in 2016, the NAMS guidelines were developed in 2017, the AACE and ACE guidelines were updated in 2017, and the Endocrine Society guidelines were developed in 2015. The U.S. Preventive Services Task Force final recommendations[48] were released in 2017. See Table S4 in the Supplementary Appendix for selected international professional guidelines on hormone therapy.CHD denotes coronary heart disease, CVD cardiovascular disease, and VTE venous thromboembolism.

The NEW ENGLAND JOURNAL of MEDICINE

JV Pinkerton. N Engl J Med 2020;382:446-455.

Accepted Manuscript

British Journal of General Practice

Breast cancer risk assessment for prescription of Menopausal Hormone Therapy in women who have a family history of breast cancer

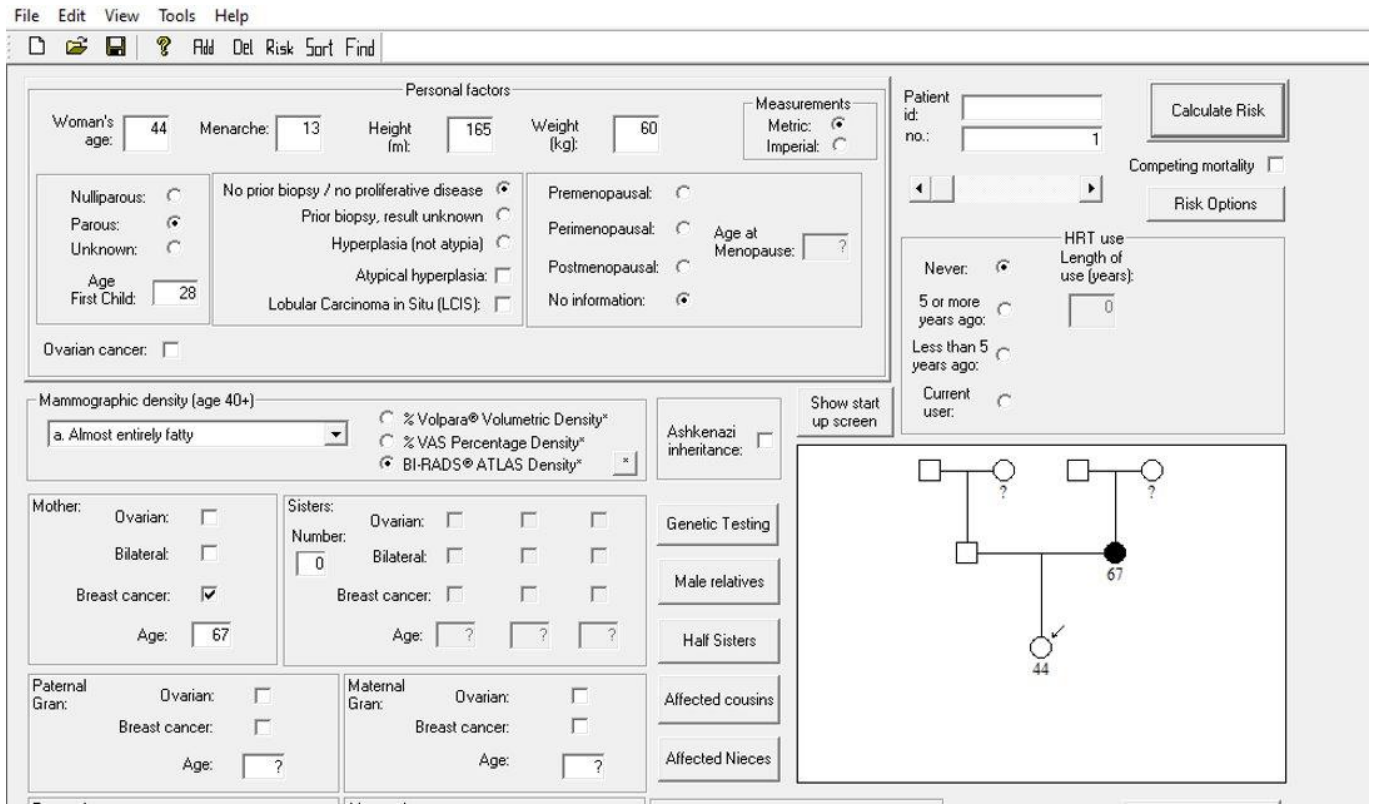
Catherine Huntley … Clare Turnbull BJGP 2024

	MHT Type	Current age	51.0	52.0	53.0	54.0	55.0	60.0	65.0	70.0	75.0	80.0	Likelihood of developing breast cancer age 50-80. One in:	Likelihood of developing breast cancer age 50-80 attributable to MHT. One in:
		Population risk	**0.3%**	**0.5%**	**0.8%**	**1.0%**	**1.3%**	**2.8%**	**4.4%**	**6.3%**	**8.1%**	**9.9%**	10.1	
Average woman	None	No MHT	**0.2%**	**0.5%**	**0.7%**	**1.0%**	**1.2%**	**2.7%**	**4.3%**	**6.2%**	**8.0%**	**9.8%**	10.2	
	Oestrogen only	MHT used age 50.0-51.0	0.3%	0.6%	0.8%	1.1%	1.3%	2.9%	4.6%	6.6%	8.4%	10.2%	9.8	256
		MHT used age 50.0-55.0	0.3%	0.6%	0.9%	1.3%	1.5%	3.1%	4.9%	6.9%	8.7%	10.5%	9.5	148
		MHT used age 50.0-60.0	0.3%	0.6%	0.9%	1.3%	1.5%	3.3%	5.1%	7.3%	9.0%	10.8%	9.2	98
	Combined - all types	MHT used age 50.0-51.0	0.3%	0.5%	0.7%	1.1%	1.3%	2.9%	4.6%	6.6%	8.4%	10.2%	9.8	256
		MHT used age 50.0-55.0	0.3%	0.8%	1.1%	1.6%	1.9%	3.7%	5.5%	7.7%	9.5%	11.3%	8.9	67
		MHT used age 50.0-60.0	0.3%	0.8%	1.1%	1.6%	1.9%	4.8%	6.9%	9.4%	11.2%	12.9%	7.7	32
Strong Family History (Two affected FDR age 50)	None	No MHT	**0.7%**	**1.3%**	**2.0%**	**2.7%**	**3.4%**	**7.0%**	**10.6%**	**14.2%**	**17.1%**	**19.6%**	5.1	
	Oestrogen only	MHT used age 50.0-51.0	0.9%	1.6%	2.3%	3.0%	3.8%	7.6%	11.4%	15.1%	18.0%	20.5%	4.9	114
		MHT used age 50.0-55.0	0.9%	1.7%	2.6%	3.4%	4.3%	8.2%	12.0%	15.8%	18.7%	21.1%	4.7	66
		MHT used age 50.0-60.0	0.9%	1.7%	2.6%	3.4%	4.3%	8.6%	12.6%	16.6%	19.4%	21.8%	4.6	45
	Combined - all types	MHT used age 50.0-51.0	0.9%	1.4%	2.1%	2.9%	3.6%	7.4%	11.2%	15.0%	18.0%	20.5%	4.9	114
		MHT used age 50.0-55.0	1.1%	2.1%	3.2%	4.3%	5.4%	9.5%	13.6%	17.7%	20.5%	22.9%	4.4	30
		MHT used age 50.0-60.0	1.1%	2.1%	3.2%	4.3%	5.4%	12.2%	16.8%	21.3%	23.9%	26.2%	3.8	15

Individual breast cancer risk estimation, incorporation of the specific individual details of family history, genetic testing, breast density, BMI and other factors is required for which the IBIS (Tyrer-Cuzick) tool allows incorporation of both past and proposed future MHT usage whilst the CanRisk (BOADICEA) interactive tool considers past and current MHT usage only

Use calculators

- For Breast cancer: Eg. IBIS-risk calculator (Tyrer-Cuzick)



Breast cancer cutoffs for counseling before recommending MHT

Risk category*	5-year NCI or IBIS breast cancer risk assessment (%)	Suggested approach
Low	<1.67	MHT ok
Intermediate	1.67 to 5	Caution¶
High	>5	Avoid

Used to advise on anti-E for BrCa-prevention

This talk:

- **Focus on breast cancer**
  - The peri- and postmenopausal breast
    - Decline in sex-steroids, increase in hormone sensitivity
      - Indirect Evidence : Epidemiology, sex-steroids, SHBG, mammographic density
      - Direct Evidence (RCT): WHI update
  - **Breast Cancer Risk of MHT is proven but complex**
    - Risk by formulation? Unanswered Q.
    - Risk by other risk factors is proven
      - Age, BMI, Familial Risk, Breast Density
    - **Breast follow-up during MHT-use**
  - Risk of MHT in patients with prior history of breast cancer

MHT = Menopausal Hormone Therapy

Once on MHT

- Explain impact of life style (obesity, alcohol, daily exercise)
- Screening for breast cancer ~population based
  - Explain pro's and con's
- If other risk factors like dense breast
  - Adjust introducing US or more frequent screening
  - Regimen with less effect on breast density (lower dose, TSEC)

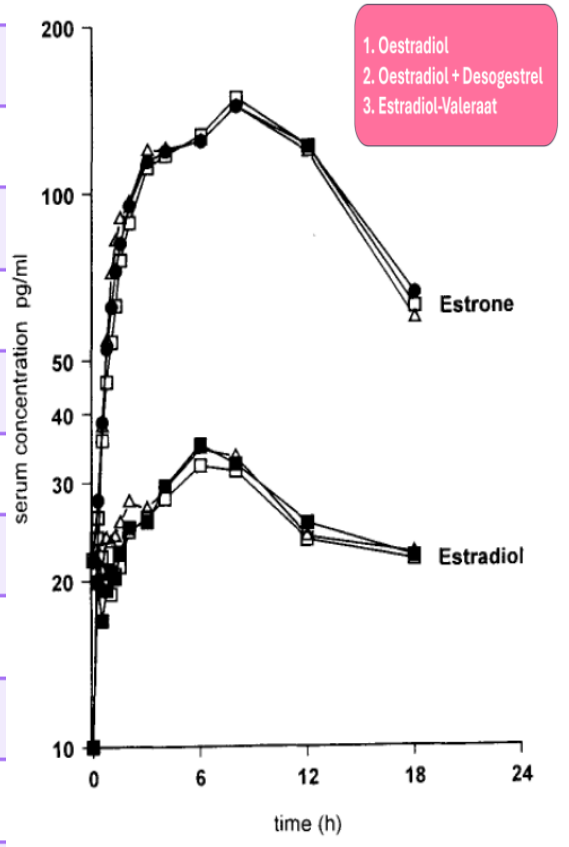
Many remaining questions

- What is the safest MHT-formulation.
- What is the safest MHT-duration?

- Transdermal
- Continuous-Sequential
- Bio-Identical - Natural

BIO-IDENTIEKE HORMONEN?

	Per os	Transdermaal
E2 - mono	Estrofem, Zumenon	Dermestril, Feminova, Lenzetto, Oestrogel, Systen
E2V - mono	Progynova	
E3 - mono	Aacifemine	
E2 + DNG	Velbiene, Laclimella	
E2 + DRSP	Klimedix, Angeliq	
E2 + DYD	Femoston	
E2 + NETA	Activelle, Kliogest, Trisequens	
E2 + P	Bijuva	
E2 + LNG		(Feminova Plus)
Tibolon	Heria, Livial, Sempreluna	
CEE + BZA	Duavive	
P	Progebel, Utrogestan	
DYD	Duphaston	



Bron:© Sander Dumont, gebaseerd op Bcfi.be

Original Research

Menopausal Hormone Therapy Formulation and Breast Cancer Risk

Haim A. Abenhaim, MD, MPH, Samy Suissa, PhD, Laurent Azoulay, PhD, Andrea R. Spence, PhD, Nicholas Czuzoj-Shulman, MMA, and Togas Tulandi, MD MHCM

OBSTETRICS & GYNECOLOGY

Table 3. Hormone Use Among Women With Breast Cancer and Women in the Control Group, Restricted to Ages 50–60 Years

Type of Hormone	Control Group (n=143,070)	Case Group (n=14,307)	Crude OR (95% CI)	Adjusted OR (95% CI)
Ever menopausal HT*	26,639(18.6)	2,874 (20.1)	1.19 (1.16–1.23)	1.10 (1.07–1.13)
Estrogen†				
No estrogen	119,219 (83.3)	11,742 (82.1)	1.0 (Ref)	1.0 (Ref)
Bioidentical	9,788 (6.8)	1,072 (7.5)	1.18 (1.13–1.23)	1.03 (0.98–1.08)
Animal-derived	10,151 (7.1)	1,114 (7.8)	1.20 (1.16–1.25)	0.99 (0.95–1.04)
Both	3,912 (2.7)	379 (2.7)	1.13 (1.05–1.20)	0.94 (0.88–1.01)
Progestogen‡				
No progestogen	133,049 (93.0)	13,162 (92.0)	1.0 (Ref)	1.0 (Ref)
Bioidentical	72 (0.1)	10 (0.1)	0.98 (0.54–1.77)	0.98 (0.54–1.77)
Synthetic	9,941 (7.0)	1,134 (7.9)	1.34 (1.28–1.39)	1.28 (1.21–1.34)
Both	8 (0.01)	1 (0.01)	1.36 (0.31–5.93)	1.31 (0.30–5.73)

OR, odds ratio; HT, hormone therapy; Ref, referent.
Data are n (%) unless otherwise specified.
* Adjusted for age, body mass index, smoking status, alcohol consumption, hysterectomy, oophorectomy, history of endometrial cancer, history of family breast cancer, and oral contraceptive use.
† Adjusted for exposure to progestogen therapy and age, body mass index, smoking status, alcohol consumption, hysterectomy, oophorectomy, history of endometrial cancer, history of family breast cancer, and oral contraceptive use.
‡ Adjusted for exposure to estrogen therapy and age, body mass index, smoking status, alcohol consumption, hysterectomy, oophorectomy, history of endometrial cancer, history of family breast cancer, and oral contraceptive use.

Obstetrics & Gynecology 139 (6) :p 1103-1110, June 2022.

MHT works best if ~ Guidelines BMS

→Multi-symptoms:

- < 10 yrs from menopause (<60 y) at MHT start
- no previous VTE, stroke, heart disease
- not if very high IBIS brca risk (ACR-A mammo)

→If 1 symptom : vaginal dryness/dyspareunia

"Behavioral interventions"

Lubricants/Moisturizers , Local E;
Hot Flashes: OCT (Serelys) – oxybutinine; low dose paroxetine

This talk:

- **Focus on breast cancer**
  - The peri- and postmenopausal breast
    - Decline in sex-steroids, increase in hormone sensitivity
      - Indirect Evidence : Epidemiology, sex-steroids, SHBG, mammographic density
      - Direct Evidence (RCT): WHI update
  - Breast Cancer Risk of MHT is proven but complex
    - Risk by formulation? Unanswered Q.
    - Risk by other risk factors is proven
      - Age, BMI, Familial Risk, Breast Density
    - Breast follow-up during MHT-use
  - **Risk of MHT in patients with prior history of breast cancer**

MHT = Menopausal Hormone Therapy

What after breast cancer?

- Breast cancer survivors suffer more from menopausal symptoms
  - Vaso-motor; sexual; cognitive dysfunction; arthralgia; bone, …
- 4 RCTs meta-analysis (n = 4050 pts).
  - 2022 pts: HRT (estrogen/progestogen combination or tibolone) and 2023 Ctrl (placebo or no HRT). Increased BC-risk (HR 1.46, 95% CI 1.12-1.91, p = 0.006); ER-pos (HR 1.8, 95% CI 1.15-2.82, p = 0.010) & ER-neg (HR 1.19, 95% CI 0.80-1.77, p = 0.390) (F. Poggio et al. BCRT 2022)
- Vaginal Estrogen Treatment (VET):
- *No BrCa: VET not associated with BC-risk
- * BrCa: Several cohort studies and nested case – control studies

- Old studies, few patients, small follow-up
- Vaginal absorption studies: Controversial data
- Most recent JNCI 2022 study by Cold et al. CAVE if oral AI-use

UZ Leuven Policy: Breast cancer patients

OCT (supplements, phyto, bio-, herbs ‘menohop’)
Non hormonal drugs for hot flashes (clonidine, gabapentin)
-SSRI (venlafaxine, not frequently used)
-Oxybutinine (cave cognition)
-NK1/3R-antagonist
-Q-122 Lancet 2022

‘modulation of oestrogen-responsive neurons in the hypothalamus’
LFT (Veoza); Elinazetant

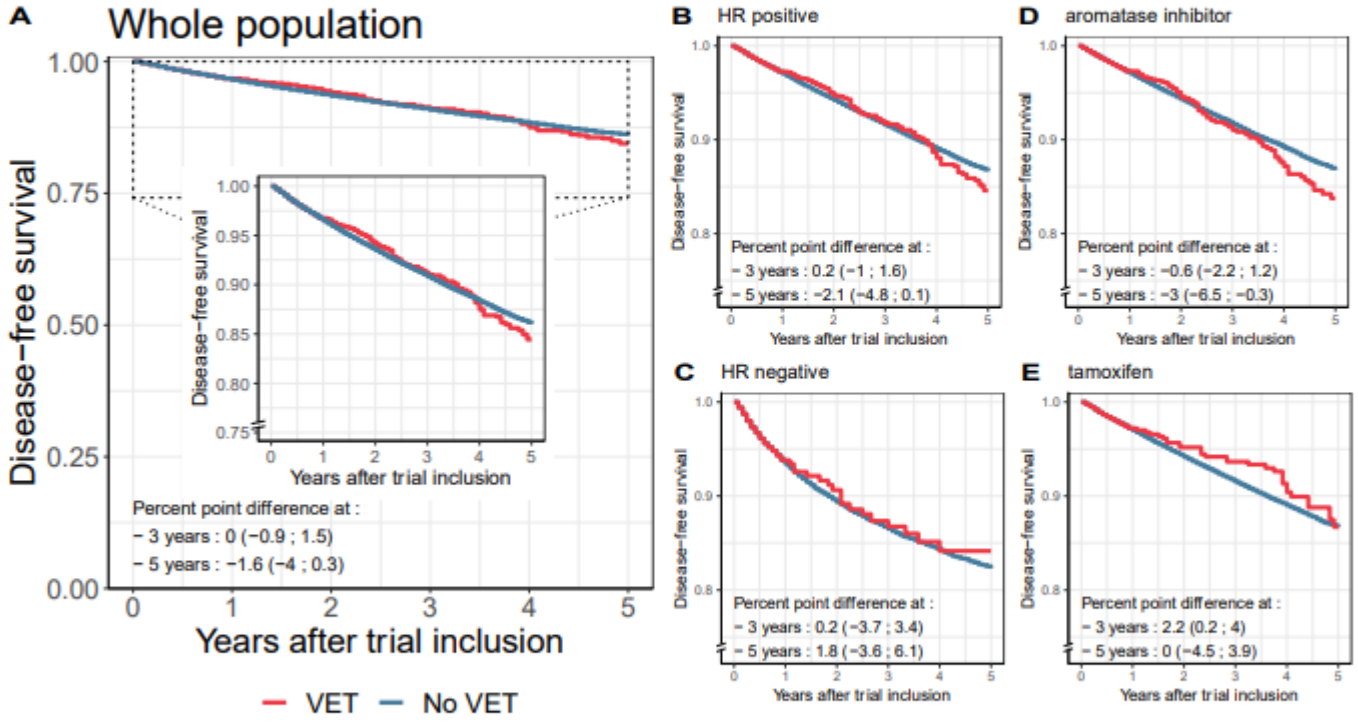
MHT only if non-hormonal alternatives fail (tibolone?)
Vaginal ET: Fine (E2, E3 (1st choice?), DHEA)

RESULTS

Among 134,942 unique patients, 1739 started vaginal estrogen therapy
56%, promestriene; 34%, estriol; and 10%, both.

Disease-free survival (DFS) curves for the whole population and per subgroup

- No effect in the whole population
- But there is heterogeneity:
  - **Decrease of 3 percent points in DFS at five years** (95% CI -6.5 to -0.3) **in patients currently treated with AI.**
  - No decrease in patients currently treated with tamoxifen, or with *HR*-negative tumor.



2024 ESMO BREAST CANCER

⇨ But, unclear how many events were registered and if there were corrections for any unbalanced patient or tumor characteristics. Other studies show no impact of use of VET on BC mortality in AI users

CONCLUSION

Menopausal Hormone Therapy (MHT) in 2024 Focus on Breast Cancer

"Risk and Recurrence"

Symptoms of the menopause can be severe in many women. HRT alleviates these symptoms and can be life-changing.

- Use MHT to treat menopausal symptoms unless contra-indication
- MHT for prevention of chronic diseases?
- Lowest dose and shortest possible duration (<5yrs); transdermal/oral
- MHT is linked with breast cancer risk; other risk factors also play
- Inform the woman about risk-benefit in absolute figures (IBIS calculator)

Discussion

- MHT is most efficient therapy for menopausal vasomotor symptoms
- Increase in risk of breast cancer remains controversial, unanswered Q. but small risk is relatively greater than risk reduction of colon, endometrial cancer
- Relative risk of MHT for development of breast cancer lower in comparison to other risk factors like sedentary life, abdominal fat, alcohol
- Small increase in absolute risk needs to be weighed against all positive effects of MHT
- Clear communication on positive effects and risks of MHT with patients is of uttermost importance, especially if other risk factors
- Ideal topic for further RCT (like low-dose LNG-IUD + TD/Oral E2)