HRT and Breast cancer: are all the treatements alike?

Different **progestins**

Route of administration

*In contrast, in this **French study**, where **progesterone or dydrogesterone are used**, **no evidence of increased risk with these formulations was found***

Unequal risks for breast cancer associated with different hormone replacement therapies: results from the E3N cohort study

80.377 postmenopausal women

2.354 breast cancers — Follow-up 8.1 years

Type of HRT	**R.R. of breast cancer**
Estrogen + progesterone	1.00 (0.83-1.22)
Estrogen + dydrogesterone	1.16 (0.94-1.43)
Estrogen alone	1.29 (1.02-1.65)
Estrogen + other progestagens	1.69 (1.50-1.91)

The route of administration of the estrogens did not have a significant effect on the association between HRT use and breast cancer risk

Fournier A et al. Breast Cancer Res Treat 2008

DRUGS IN CONTEXT
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REVIEW

Drugs in Context 2020; 9: 2020-10-1.

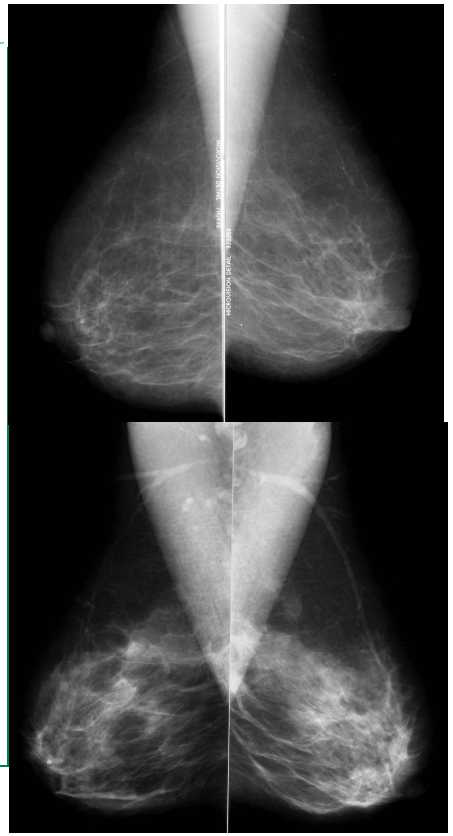
Progestogens as a component of menopausal hormone therapy: the right molecule makes the difference

John C Stevenson MB BS, FRCP, FESC, MFSEM[1], Serge Rozenberg MD, PhD[2], Silvia Maffei MD[3], Christian Egarter Prof Dr Med[4], Petra Stute Prof Dr Med[5], Thomas Römer Prof Dr Med[6]

Different **progestins**

High-density breast tissue

High-density breast tissue is associated with an increased risk of breast cancer.[47,48] Progesterone in combination with estradiol appears less likely than other progestogens to increase mammographic density.[30] Evidence suggesting that breast cancer risk is lower with micronized progesterone or dydrogesterone than with other progestogens[8,26–28] supports their use in women with high breast density concerns. Tibolone has been shown to increase breast density to a lesser extent than estradiol/norethisterone acetate in postmenopausal women during 6 months of treatment.[49]



Tissue-Selective Estrogen Complexes: TSECs

***Rationale** for Development of new class of Tissue-Selective Estrogen Complexes (TSECs)*

TSEC

The partnering of a SERM with one or more estrogens to achieve a preclinical profile based on the blended tissue-selective activities of it components

TSEC
CE 0.45 mg +
Bazedoxifene 20 mg

Available in Italy from 2015

The goal was to combine the established efficacy of estrogens with a SERM to protect against effects of estrogens on the breast and the endometrium

SERMs, Selective Estrogen Receptor Modulators; TSECs, Tissue Selective Estrogen Complexes

Komm BS.A. Reprod Sci.2008 ;15(10):984-92

Overview of the global SMART clinical development program for CE/BZA

Clinical studies conducted worldwide in more than 7500 women[1-5,a]
Studies assessed both CE 0.45 mg/BZA 20 mg and CE 0.625 mg/BZA 20 mg

SMART 1
SMART-1, N=3397
24 months
Menopausal symptoms, BMD and endometrial protection versus placebo

SMART 2
SMART-2, N=318
3 months
VMS
versus placebo

SMART 3
SMART-3, N=652
3 months
VVA
versus placebo

SMART 4
SMART-4, N=1061
1 year Incidence of endometrial hyperplasia and prevention of postmenopausal Osteoporosis versus placebo

SMART 5
SMART-5, N=1843
12 months
Mammographic breast density versus placebo

→ MX density as a surrogate markers for breast cancer risk

SMART, Selective estrogens, Menopause, And Response to Therapy; BMD, bone mineral density.
[a]Includes additional pilot dose-finding study 403.

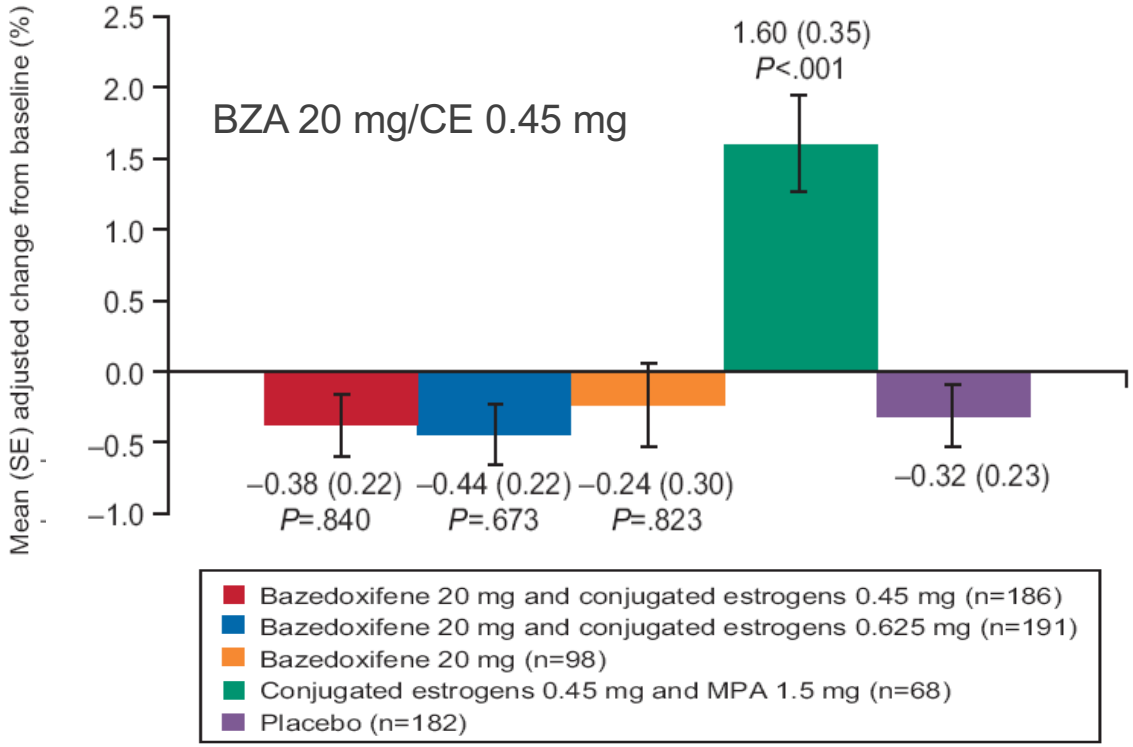
4 treatment groups (N=1061)

BZA 20 mg/CE 0.45 mg	BZA 20 mg/CE 0.625 mg	CE 0.45 mg/MPA 1.5 mg	Placebo

The effects of bazedoxifene on mammographic breast density in postmenopausal women with osteoporosis

Jennifer A. Harvey, MD,[1] Mary K. Holm, MD,[2] Radhika Ranganath, MD,[3] Paul A. Guse, PhD,[3] Edward A. Trott, MD,[3] and Eileen Helzner, MD[3]

Breast Density



Results

-Baseline breast density was low (25.8%-27.6%)
-After 2 years the mean percentage change was low across treatment group
-Fewer women reported breast cysts adr/or fibrocystics breast disease

BZA for 2 years did not affect age related changes in breast density

TOS E CARCINOMA DEL COLON

Colorectal cancer in women: hormone replacement therapy and chemoprevention

E. L. Barnes and M. D. Long

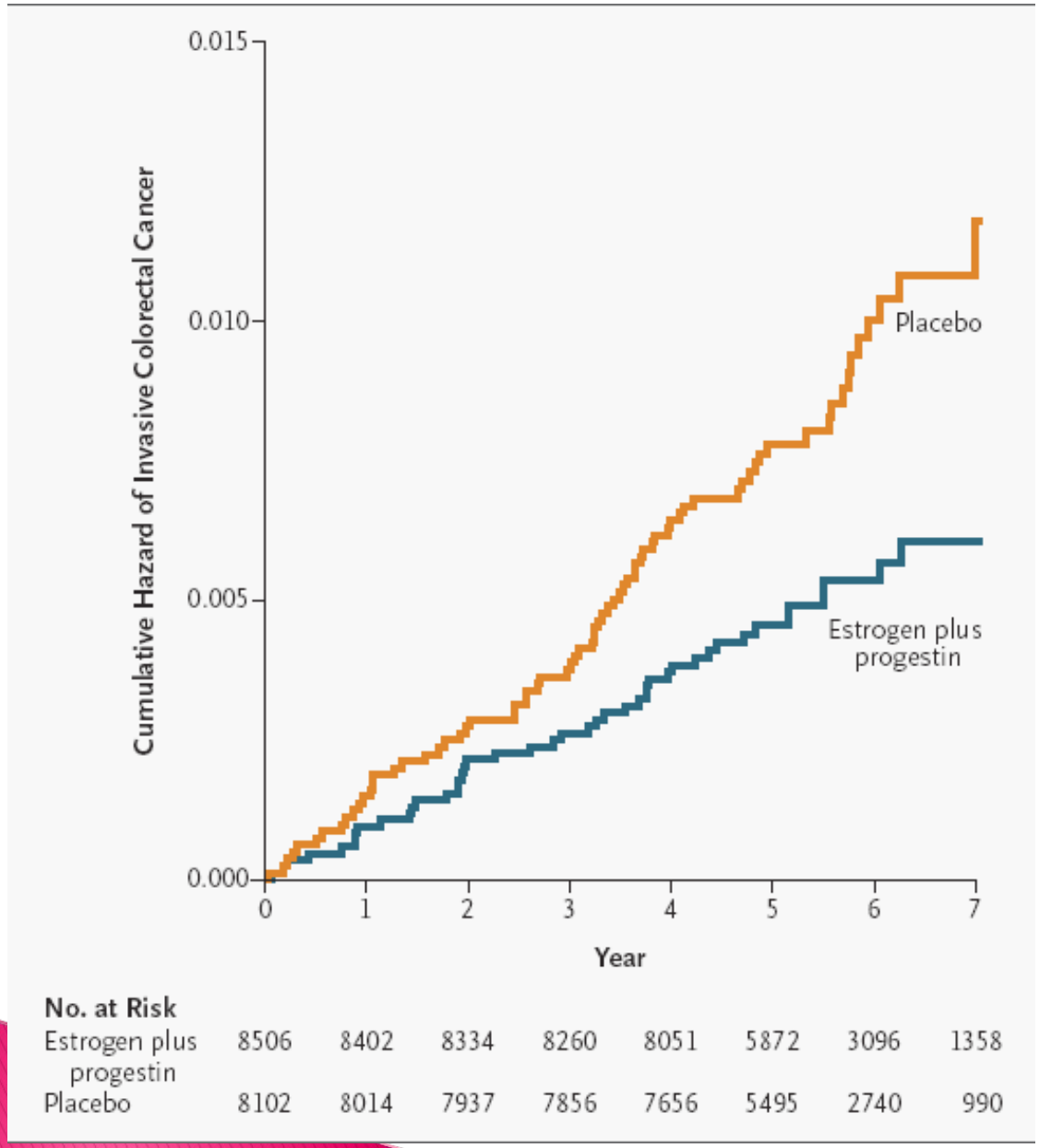
CLIMACTERIC 2012;15:250–255

Table 1 Effect size estimates for reduction of colorectal cancer risk with estrogen and progestin-containing hormone replacement therapy in observational studies since the Women's Health Initiative

Author	*Date*	*Effect estimate*	*95% confidence interval*
Newcomb *et al.*[27]	2007	odds ratio 0.6	0.5–0.9
Delellis Henderson *et al.*[28]	2010	relative risk 0.64	0.51–0.8
Johnson *et al.*[29]	2009	relative risk 0.78	0.60–1.02
Rennert *et al.*[30]	2009	odds ratio 0.67	0.51–0.89
Long *et al.*[31]	2010	odds ratio 0.52	0.38–0.72

A **statistically significant reduction in colorectal cancer risk in current HRT users** with the most significant reduction in risk in those patients who had used HRT **for greater than 5 years**

Cumulative hazard of invasive colorectal cancer according to treatment group



WHI trial

CEE + MPA vs Placebo

HR= 0.56

(95% CI 0.38-0.81)

Chelebowski RT, New Engl J Med 2004

WHI trial - Estrogen only

Outcomes	Hazard ratio	Adjusted 95% CI
Cardiovascular disease		
CHD	0.91	0.72-1.15
Stroke	1.39	0.97-1.99
Venous thromboembolic disease	1.33	0.86-2.08
Cancer		
Invasive breast	0.77	0.57-1.06
Colorectal	**1.08**	**0.63-1.86**
Death	1.08	0.79-1.46
Fractures Hip	0.61	0.33-1.11
Global index	1.01	0.89-1.14

JAMA 2004; 291: 1701-1712

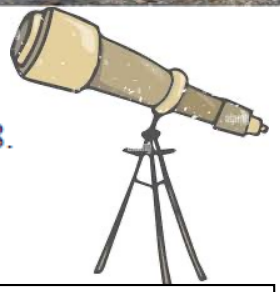
13 years of follow-up of HRT in the **WHI study**

The Women's Health Initiative Hormone Therapy Trials: Update and Overview of Health Outcomes During the Intervention and Post-Stopping Phases

JoAnn E. Manson Dr., MD, DrPH, Dr. Rowan T. Chlebowski, MD, PhD, Dr. Marcia L.

JAMA. 2013 October 2; 310(13): 1353–1368.

[redacted]



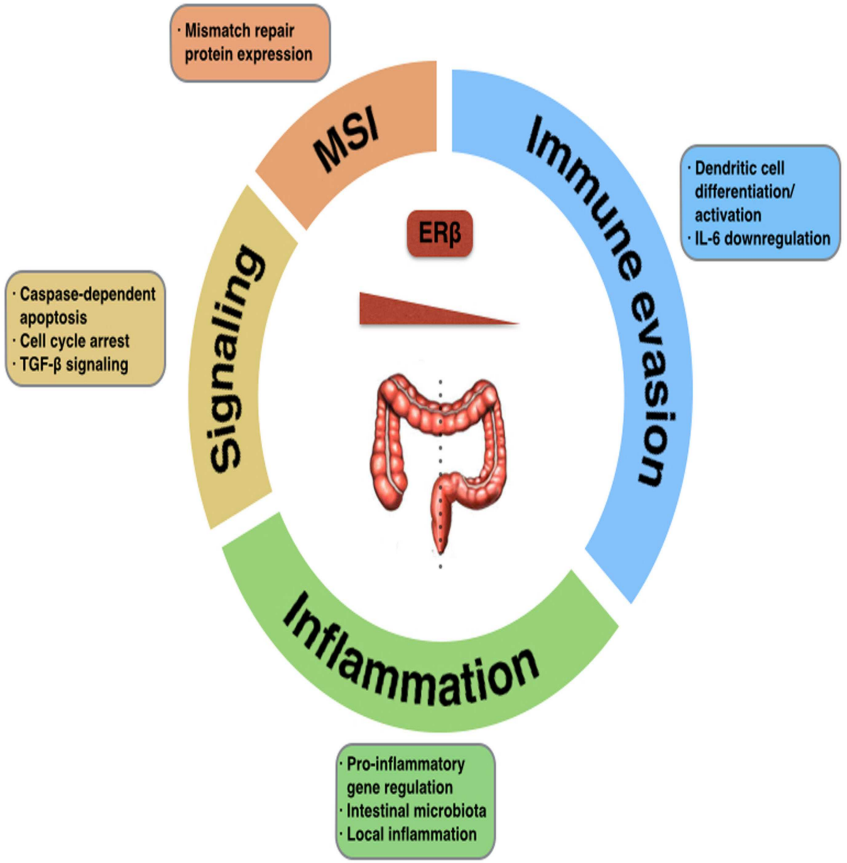
	CEE+MPA Trial						CEE Alone Trial					
Primary Endpoints	**Active N(%*)**	**Placebo N(%*)**	**Diff per 10K pys^**	**HR**	**95%CI**	**P**	**Active N(%*)**	**Placebo N(%*)**	**Diff per 10K pys^**	**HR**	**95%CI**	**P**
Coronary heart disease	487(0.48)	430(0.45)	+3	1.09	(0.96, 1.24)	0.19	363(0.60)	393(0.63)	−4	0.94	(0.82, 1.09)	0.43
Invasive breast cancer	434(0.43)	323(0.34)	+9	1.28	(1.11, 1.48)	<0.001	168(0.28)	216(0.35)	−7	0.79	(0.65, 0.97)	0.02
Other Endpoints in the Global Index												
Stroke	376(0.37)	311(0.32)	+5	1.16	(1.00, 1.35)	0.06	278(0.46)	253(0.41)	+5	1.15	(0.97, 1.37)	0.10
Pulmonary embolism	172(0.17)	128(0.13)	+4	1.26	(1.00, 1.59)	0.05	107(0.17)	96(0.15)	+2	1.15	(0.87, 1.51)	0.34
Colorectal cancer	126(0.12)	150(0.16)	→	0.80	(0.63, 1.01)	0.06	100(0.16)	90(0.14)	→	1.13	(0.85, 1.51)	0.39

In post intervention and cumulative FU: **Post-stopping and cumulative HRs were neutral in both trials**

HRT and Non-gynecologic Tumours: **CRC**

ERβ is the predominant estrogen receptor expressed in both normal and malignant colonic epithelium.

During colon cancer progression, ERβ expression is lost



Estrogens may exert an anti-tumor effect through:

1. selective activation of pro-apoptotic signaling mediated by ERβ,
2. inhibition of inflammatory signals
3. modulation of the tumor microenvironment.

Caiazza, Francesco et al. *Frontiers in oncology* vol. 5 19. 2 Feb. 2015