Hormone therapy and breast cancer
- 10 Years after WHI -

고려의대 산부인과학교실

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HISTORY: HT and Breast cancer (BC)

Table 1. Estrogen and breast cancer: findings from selected studies

Year	First author (reference)	Study design	Finding
1896	Beatson (1)	Case report	Oophorectomy associated with breast cancer regressions
1968	Feinleib (2)	Cohort analysis	Oophorectomy associated with lower breast cancer risk
1970	MacMahon (3)	International collaborative study	Age at first birth related to breast cancer risk
1973	McGuire (4)	Summary, findings from clinical correlative studies	Estrogen receptor quantitative status correlated with clinical breast cancer response to hormone-directed therapy
1976	Hoover (5)	Incidence rate in cohort vs rate in general population	Exogenous estrogen alone associated with higher breast cancer risk
1980	Ross (6)	Case–control analysis	Exogenous estrogen associated with higher breast cancer risk
1983	Pike (7)	Analysis	Model of endogenous hormonal risk factors with breast cancer
1989	Bergkvist (8)	Cohort analysis	Exogenous estrogen alone and exogenous estrogen plus progestin both associated with higher breast cancer risk
1995	Colditz (9)	Cohort analysis	Exogenous estrogen alone and exogenous estrogen plus progestin both associated with higher breast cancer risk
1997	Collaborative Group on Hormonal Factors in Breast Cancer (10)	Collaborative reanalysis of 51 case–control studies	Hormone therapy (80% exogenous estrogen alone) associated with higher breast cancer risk
2003	Beral (11)	Cohort analysis with mammography at entry	Exogenous estrogen alone and exogenous estrogen plus progestin both associated with higher breast cancer risk. Trend for higher breast cancer mortality in estrogen plus progestin users

Nurses' Health Study (1995)

- **725,550 person-years of follow-up, 1978-1992**

  1935 women diagnosed BC

Table 1. Type of Hormone Currently Used by Postmenopausal Women and Relative Risk of Breast Cancer in the Nurses' Health Study, 1978 to 1992.

Hormone	Cases of Breast Cancer*	Person-Years of Follow-up	Relative Risk Adjusted for Age at Menopause and Type of Menopause	Multivariate Adjusted Relative Risk (95% CI)†
None	923	344,942	1.0	1.0
Conjugated estrogens alone	270	89,427	1.36	1.32 (1.14–1.54)
Other estrogens	53	16,202	1.37	1.28 (0.97–1.71)
Estrogen plus progestin	111	28,946	1.50	1.41 (1.15–1.74)
Progestins alone	12	1,983	2.40	2.24 (1.26–3.98)
Estrogen plus testosterone	4	810	1.78	1.64 (0.53–5.09)

ET : RR 1.32 (1.14-1.54)

EPT : RR 1.41 (1.15-1.74)

Colditz et al., NEJM 1995

Table 2. Duration of Current and Past Postmenopausal Hormone Therapy and Relative Risk of Breast Cancer in the Nurses' Health Study, 1976 to 1992.

Hormone Use	Cases of Breast Cancer	Person-Years of Follow-up	Adjusted Relative Risk (95% CI)*
None	972	374,197	1.0
Current			
1–23 Mo	82	31,966	1.14 (0.91–1.45)
24–59 Mo	140	49,672	1.20 (0.99–1.44)
60–119 Mo	150	44,112	1.46 (1.22–1.74)
≥120 Mo	141	37,454	1.46 (1.20–1.76)
Past			
1–23 Mo	193	81,047	0.90 (0.77–1.05)
24–59 Mo	120	54,046	0.86 (0.71–1.05)
60–119 Mo	89	34,952	1.00 (0.80–1.26)
≥120 Mo	48	18,104	1.03 (0.76–1.41)

- **Duration of 5 yrs use:** Increase of BC risk

→ limited to the period of use of HRT

- More pronounced risk in women aged > 55 yrs

Colditz et al., NEJM 1995

Unopposed ET & BC risk
Nurses' Health Study

ET Use and Duration, y	All	
	Cases	Risk
Never	226	1.00
Current		
<5	99	0.96 (0.75-1.22)
5-9.9	145	0.90 (0.73-1.12)
10-14.9	190	1.06 (0.87-1.30)
15-19.9	129	1.18 (0.95-1.48)
≥20	145	1.42 (1.13-1.77)
P for trend for current use		<.001

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Chen et al., JAMA 2006

COLLABORATIVE ANALYSIS

Meta-analysis of 51 epidemiologic studies

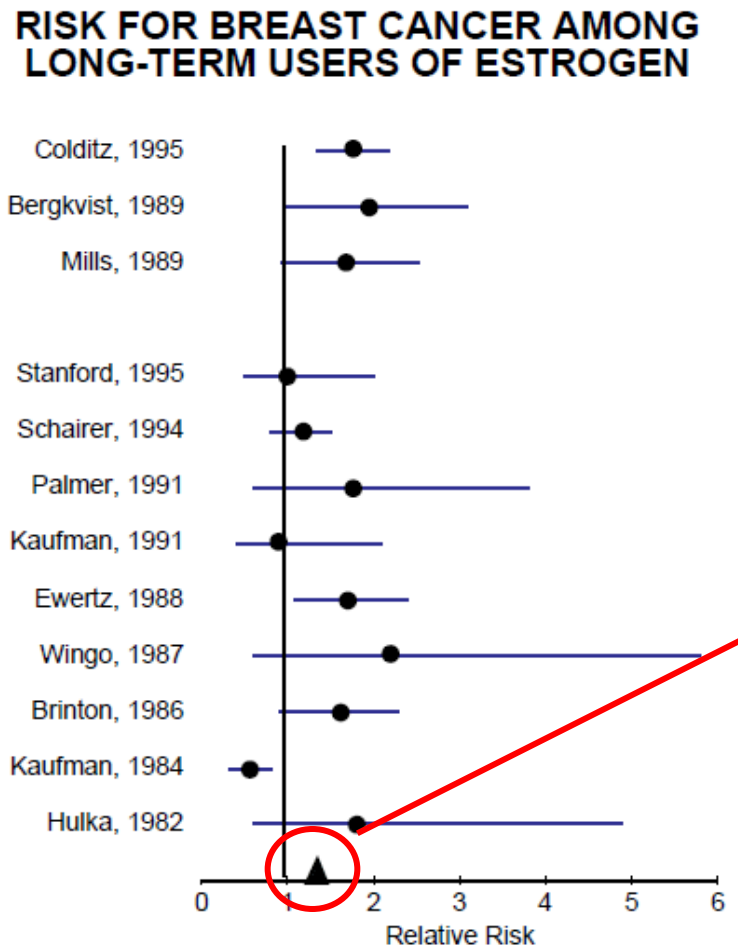
52,705 women with BC/ 108,411 women without BC

- Increased RR of BC with HRT, with a significant trend toward increasing risk with time.
  - The risk reached statistical significance at 5 yrs returned to that of non-users within 4 yrs of cessation.
- The risk for BC: larger with EPT than with ET.

Collaborative Group. Lancet 1997

ESTROGEN ALONE

: Meta-analysis of 8 observational studies and 3 cohort studies (1998)



RR : 1.32 95% CI 1.16-1.51

Barret-Connor et al., Annu Rev Public Health 1998

OVERVIEW: OBSERVATION STUDIES (~ 2003)

Author	ET(RR)	EPT(RR)
Schairer et al. (USA) [20] cohort, 46335 women	1.20 (1.00–1.40)	1.40 (1.10–1.80)
Ross et al. (USA) [11] case-control, 1897 cases	1.06 (0.97–1.15)[a]	1.24 (1.07–1.45)[a]
Moorman et al. (USA) [12] case-control, 397 cases	0.80 (0.50–1.20)	0.70 (0.40–1.10)
Chen et al. (USA) [13] case-control, 705 cases	1.17 (0.85–1.60)	1.49 (1.04–2.12)
Newcomb et al. (USA) [19] case-control, 5298 cases	1.23 (1.09–1.39)	1.43 (1.18–1.74)
Porch et al. (USA) [14] cohort, 17835 women	0.96 (0.65–1.42)	1.37 (1.05–1.78)
Weiss et al. (USA) [15] case-control, 1870 cases	0.84 (0.67–1.06)	1.22 (0.99–1.50)
Kerlikowske et al. (USA) [43] cohort, 374465 women	0.92 (0.84–1.00)[b]	1.49 (1.36–1.63)[b]
Li et al. (USA) [16] case-control, 975 cases	1.00 (0.70–1.30)	1.90 (1.40–2.60)
Million Women Study (UK) [18] cohort, 828923 wom	1.30 (1.21–1.40)	2.00 (1.88–2.12)
Magnusson et al. (Sweden) [38] case-control, 2563 cas	1.94 (1.47–2.55)	1.63 (1.37–1.94)
	2.70 (1.47-4.96)[c]	2.95 (1.84–4.72)[c]
Olsson et al. (Sweden) [17] cohort, 28378 women	0.71 (0.40–1.26)	1.22 (0.74–2.00)[d]
		2.45 (1.61-3.71)[e]
Stahlberg et al. (Denmark) [39] cohort, 10874 women	1.96 (1.16–3.35)	2.70 (1.96–3.73)
Bakken et al. (Norway) [139] cohort, 31451 women	1.80 (1.10–1.90)	2.50 (1.90–3.20)

[a] Per 5 years.
[b] >5 years of use.
[c] >10 years of use.
[d] Sequential therapy.
[e] Continuous-combined therapy.

Campagnoli et al., J Steroid Biochem 2005

Concept before 2002: HT & BC

Combined estrogen plus progestin use

- Estrogen plus progestin increases breast cancer risk

Estrogen-alone use

- Estrogen alone increases breast cancer risk but may require longer duration exposure than combined estrogen plus progestin for an effect

*Hormone therapy**

- Breast cancer associated with hormone therapy are mainly hormone receptor–positive cancers
- Breast cancers associated with hormone therapy are diagnosed at earlier stage
- Breast cancers associated with hormone therapy have a favorable prognosis

Chlebowski et al., J Natl Cancer Inst. 2012

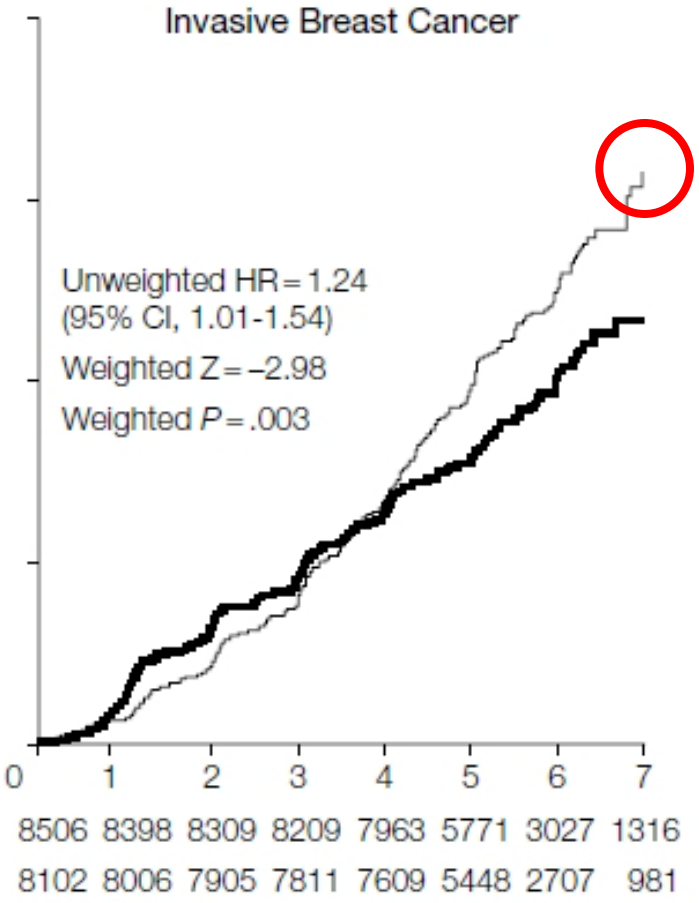
WHI study - 2002

- National Insititutes of Health (NIH)-sponsored multi-outcome study
- 16,608 recruited from 40 US centers in 1993 ~1998
- EPT (CEE 0.625 mg + MPA 2.5 mg) & CEE only

- One billion USD costs for the trial

EPT arm (5.6 yrs follow-up)

16,608 PM women (50~79 yrs)



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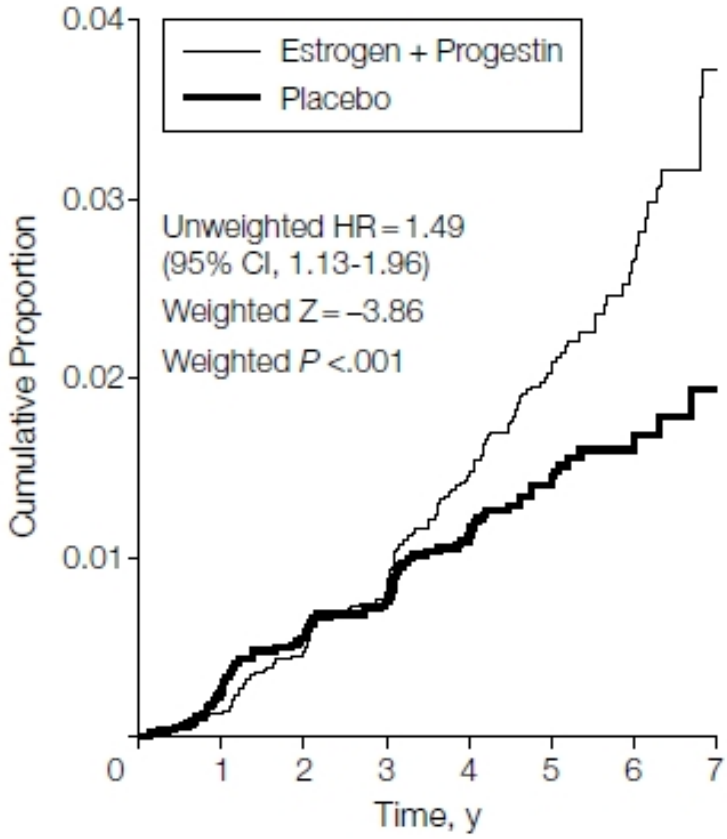
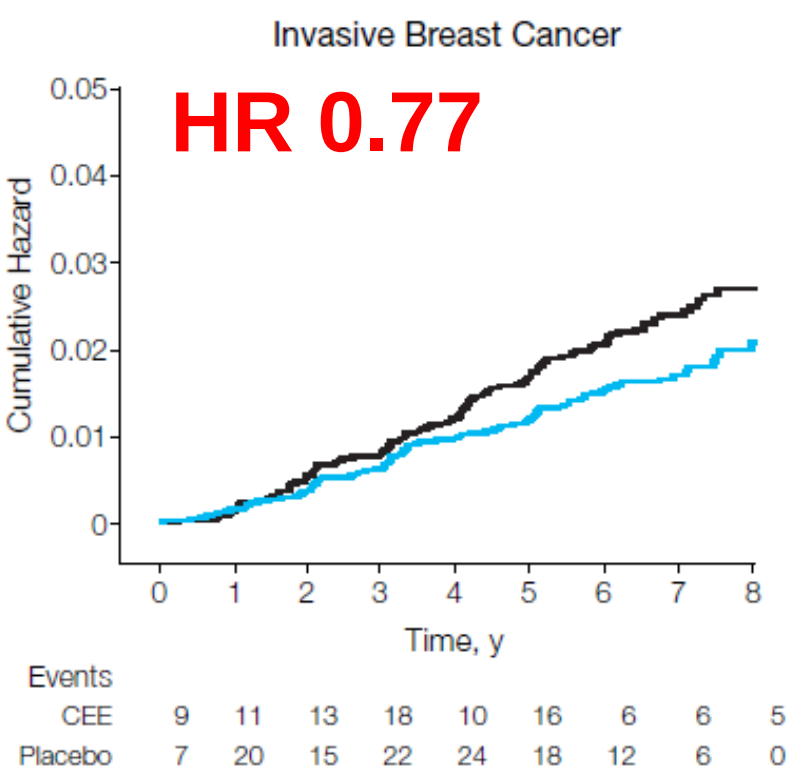


Chlebowski et al., JAMA 2003

ET arm (7.1 yrs follow-up)

10,739 PM women



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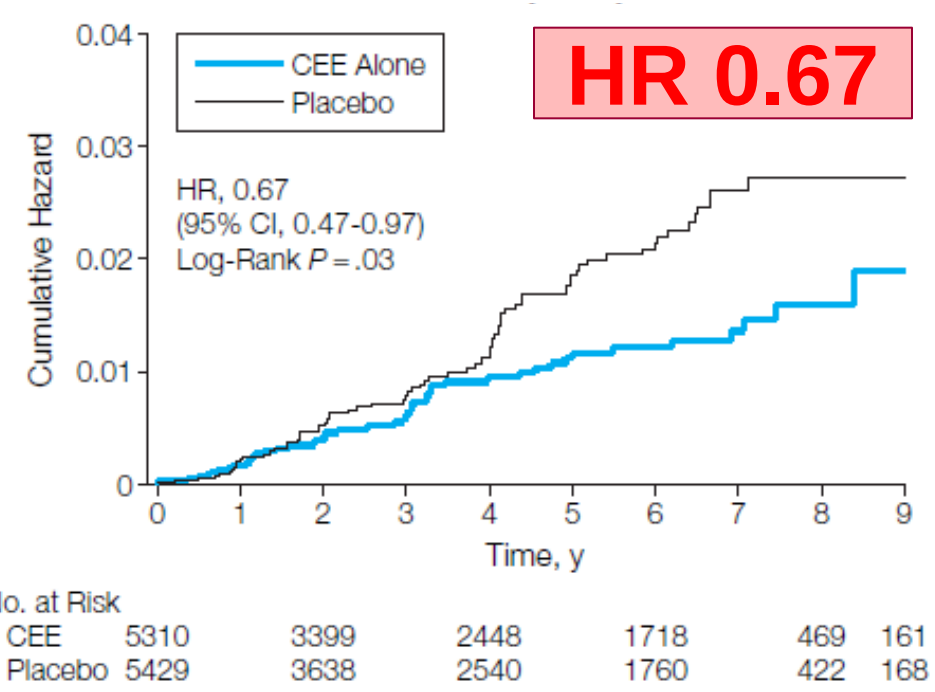

Anderson et al., JAMA 2004 & Stefanick et al., JAMA 2006

WHAT'S THE IMPACT OF WHI TRIAL ?

ET alone does not increase BC risk

Pontential effects of Progestogen (type, dose, formulation)

"DURATION", "Gap time"

EXTENSION / RE-ANALYSIS

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Estrogen Plus Progestin and Breast Cancer Incidence and Mortality in Postmenopausal Women

Rowan T. Chlebowski, MD, PhD
Garnet L. Anderson, PhD
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Lewis H. Kuller, MD
JoAnn E. Manson, MD, DrPH
Marcia L. Stefanick, PhD
Judith Ockene, MD
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Karen C. Johnson, MD, MPH
Jean Wactawski-Wende, PhD
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Context In the Women's Health Initiative randomized, placebo-controlled trial of estrogen plus progestin, after a mean intervention time of 5.6 (SD, 1.3) years (range, 3.7-8.6 years) and a mean follow-up of 7.9 (SD, 1.4) years, breast cancer incidence was increased among women who received combined hormone therapy. Breast cancer mortality among participants in the trial has not been previously reported.

Objective To determine the effects of therapy with estrogen plus progestin on cumulative breast cancer incidence and mortality after a total mean follow-up of 11.0 (SD, 2.7) years, through August 14, 2009.

Design, Setting, and Participants A total of 16 608 postmenopausal women aged 50 to 79 years with no prior hysterectomy from 40 US clinical centers were randomly assigned to receive combined conjugated equine estrogens, 0.625 mg/d, plus medroxyprogesterone acetate, 2.5 mg/d, or placebo pill. After the original trial completion date (March 31, 2005), reconsent was required for continued follow-up for breast cancer incidence and was obtained from 12 788 (83%) of the surviving participants.

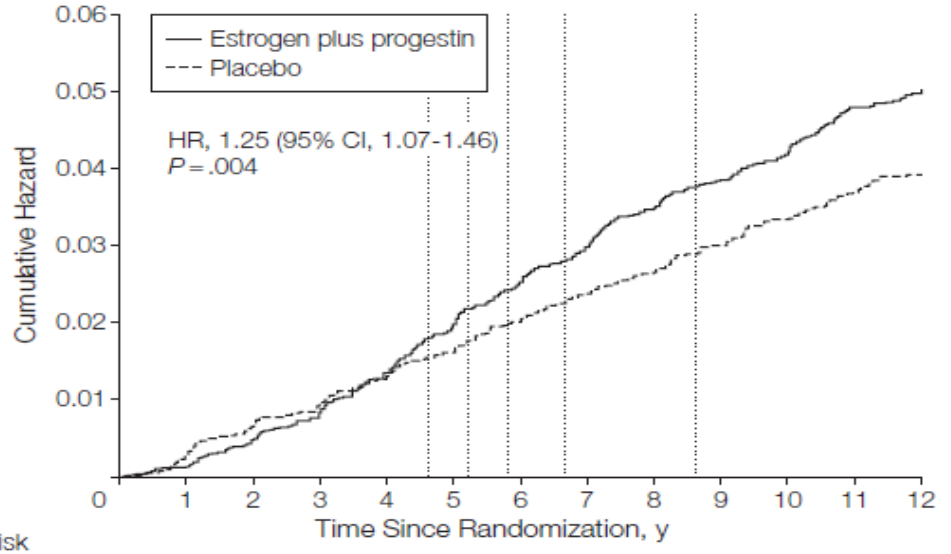
Main Outcome Measures Invasive breast cancer incidence and breast cancer mortality.

Chlebowski et al, JAMA 2010

EPT: BC incidence

- **HR 1.25 (95% CI: 1.07-1.46)**
  Positive LN: HR 1.78 (95% CI: 1.23-2.58)

Incidence of Invasive Breast Cancer in the WHI Clinical Trial



No. at risk							
Estrogen plus progestin	8506	8329	8109	7796	7009	6189	2914
Placebo	8102	7914	7721	7466	6692	5889	2648

E+P 385 cases [0.42%/yr]

Placebo 293 cases [0.34% /yr]

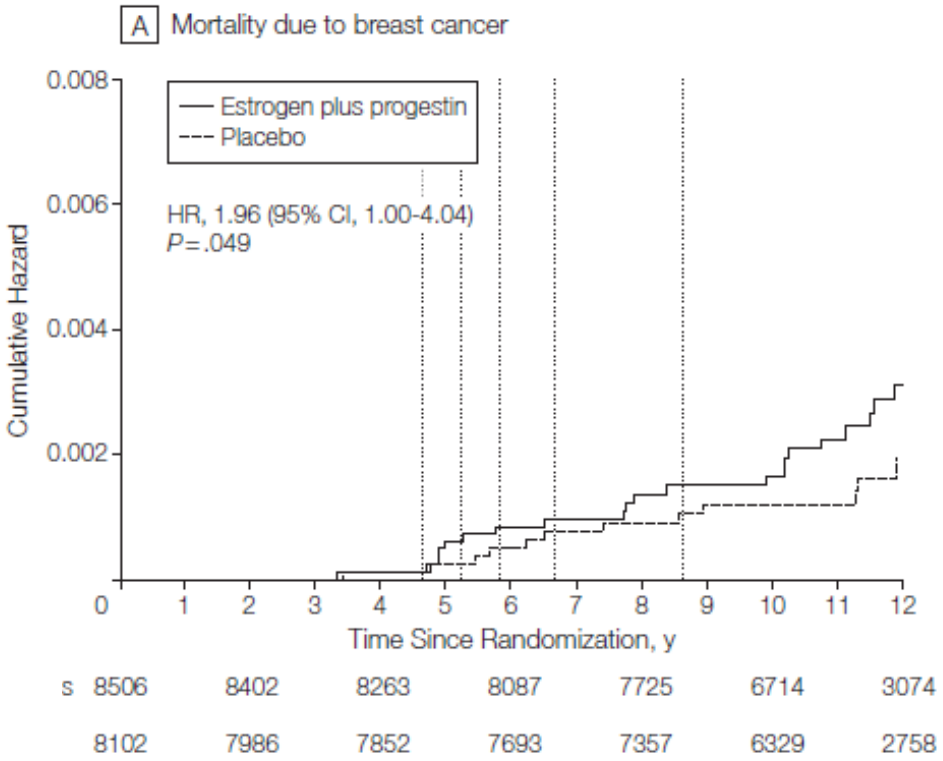
8/ 10,000 person-year

Chlebowski et al, JAMA 2010

EPT: Mortality after BC

- **Death after BC: HR 1.96 (95% CI: 1.00 - 4.04)**

All cause mortality after BC: HR 1.57 (95% CI: 1.01-2.48)



1.3/ 10,000 person-year

E+P 25 deaths [0.03% / yr]

Placebo 12 deaths [0.01% / yr]
(2.6 vs 1.3 per 10,000 women / yr)

Chlebowski et al, JAMA 2010

Estrogen Plus Progestin and Breast Cancer Incidence and Mortality in the Women's Health Initiative Observational Study

Rowan T. Chlebowski, JoAnn E. Manson, Garnet L. Anderson, Jane A. Cauley, Aaron K. Aragaki, Marcia L. Stefanick, Dorothy S. Lane, Karen C. Johnson, Jean Wactawski-Wende, Chu Chen, Lihong Qi, Shagufta Yasmeen, Polly A. Newcomb, Ross L. Prentice

Manuscript received August 27, 2012; revised January 20, 2013; accepted February 13, 2013.

Correspondence to: Rowan T. Chlebowski, MD, PhD, Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, 1124W Carson St, Torrance, CA, 90502 (e-mail: rowanchlebowski@gmail.com).

Background In the Women's Health Initiative (WHI) randomized trial, estrogen plus progestin increased both breast cancer incidence and mortality. In contrast, most observational studies associate estrogen plus progestin with favorable prognosis breast cancers. To address differences, a cohort of WHI observational study participants with characteristics similar to the WHI clinical trial was studied.

Methods We identified 41 449 postmenopausal women with no prior hysterectomy and mammogram negative within 2 years who were either not hormone users (n = 25 328) or estrogen and progestin users (n = 16 121). Multivariable-adjusted Cox proportional hazard regression was used to calculate hazard ratios (HRs) with 95% confidence intervals (CI). All statistical tests were two-sided.

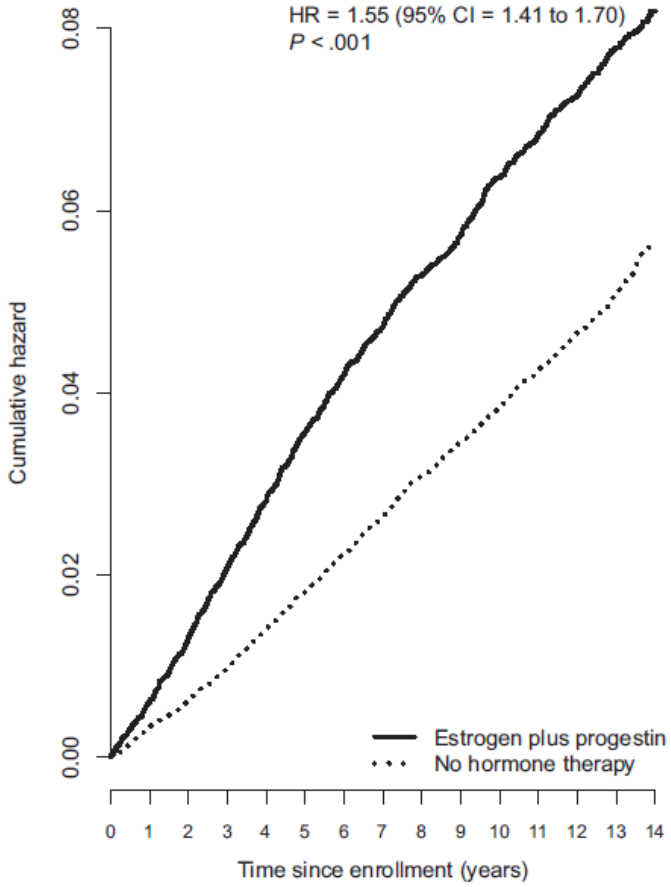
Results After a mean of 11.3 (SD = 3.1) years, with 2236 breast cancers, incidence was higher in estrogen plus progestin users than in nonusers (0.60% vs 0.42%, annualized rate, respectively; HR = 1.55, 95% CI = 1.41 to 1.70, $P < .001$). Women initiating hormone therapy closer to menopause had higher breast cancer risk with linear diminishing influence as time from menopause increased ($P < .001$). Survival after breast cancer, measured from diagnosis, was similar in combined hormone therapy users and nonusers (HR = 1.03, 95% CI = 0.79 to 1.35). On a population basis, there were somewhat more deaths from breast cancer, measured from cohort entry (HR = 1.32, 95% CI = 0.90 to 1.93, $P = .15$), and more all-cause deaths after breast cancer (HR = 1.65, 95% CI = 1.29 to 2.12, $P < .001$) in estrogen plus progestin users than in nonusers.

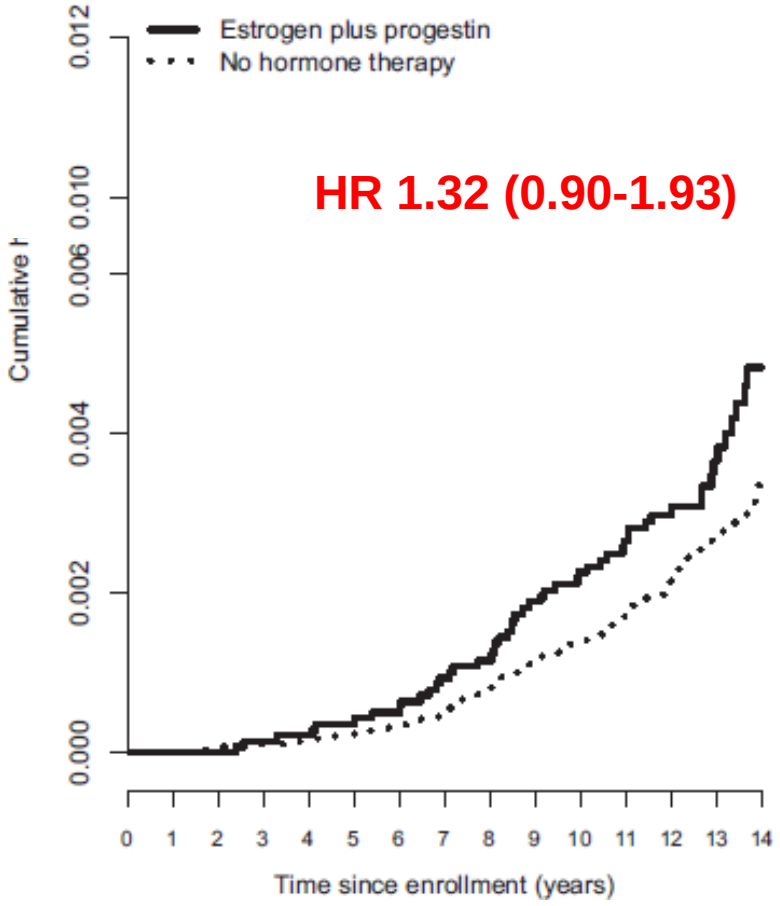
Conclusions Consistent with WHI randomized trial findings, estrogen plus progestin use is associated with increased breast cancer incidence. Because prognosis after diagnosis on combined hormone therapy is similar to that of nonusers, increased breast cancer mortality can be expected.

Chlebowski et al, J Natl Cancer Inst. 2013

EPT: Mortality after BC

HR 1.55 (0.6% vs. 0.42%)
Prior EPT users (5.3 yrs)





Chlebowski et al, J Natl Cancer Inst. 2013

Conjugated equine oestrogen and breast cancer incidence and mortality in postmenopausal women with hysterectomy: extended follow-up of the Women's Health Initiative randomised placebo-controlled trial

Garnet L Anderson, Rowan T Chlebowski, Aaron K Aragaki, Lewis H Kuller, JoAnn E Manson, Margery Gass, Elizabeth Bluhm, Stephanie Connelly, F Allan Hubbell, Dorothy Lane, Lisa Martin, Judith Ockene, Thomas Rohan, Robert Schenken, Jean Wactawski-Wende

- 7645 women of 9786 living participants enrolled in WHI-ET arm
- Extended follow-up to Aug, 2009
- Mean follow-up of **11.8 yrs**

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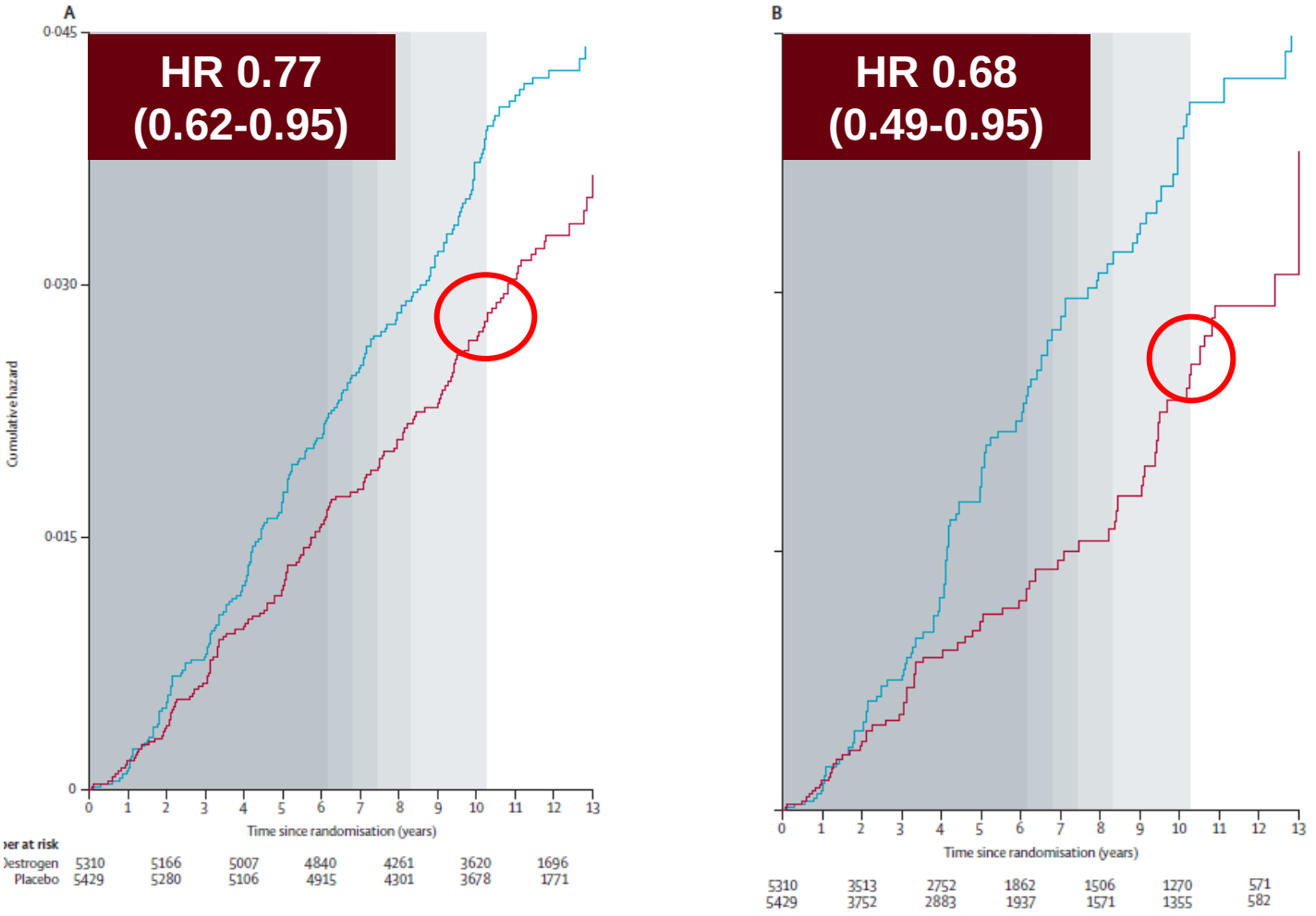
Lancet Oncol. 2012

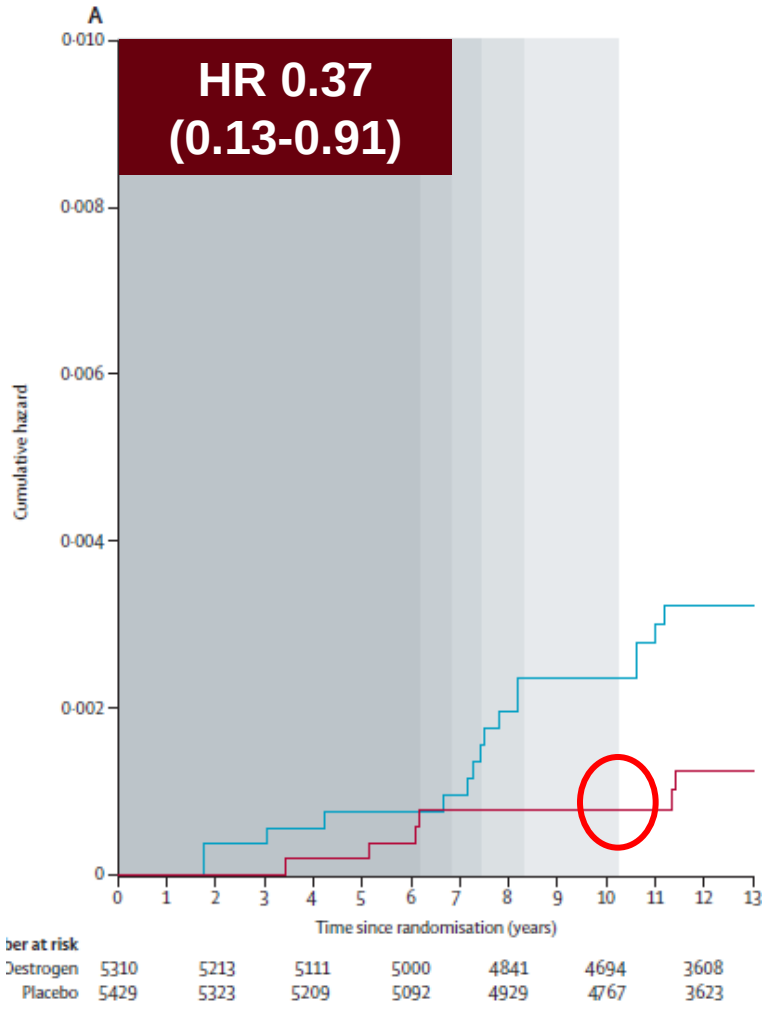
ET: cumulative HR for BC

Adherence-adjusted

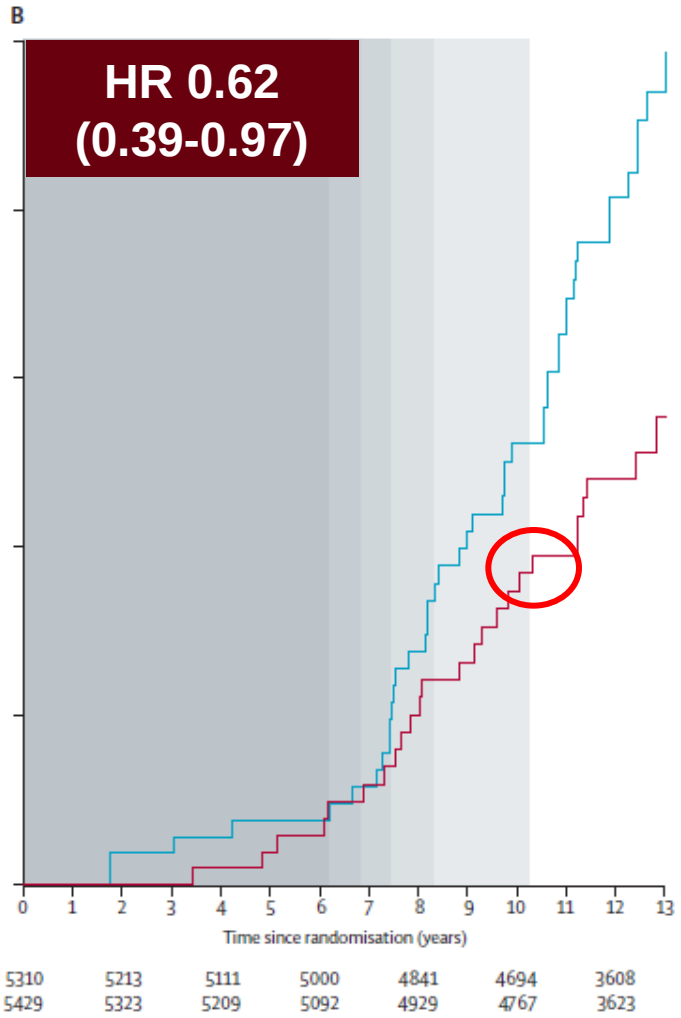


Lancet Oncol. 2012

BC death



All cause mortality



Lancet Oncol. 2012

EFFECT OF HT ON BC RISK
- WHI / EXTENSION TRIALS -

- **EPT increase the risk of BC and mortality**

- **ET did not increase the BC risk, rather decrease the risk of the BC at least for 7 years-use**

POTENTIAL FACTORS

- PRIOR Hx. OF HT
- GAP TIME (YEARS SINCE MENOPAUSE)
- BODY SIZE (BMI)
- ROUTE & TYPE OF HT

Prior hormone therapy and breast cancer risk in the Women's Health Initiative randomized trial of estrogen plus progestin

Garnet L. Anderson [a,*], Rowan T. Chlebowski [b], Jacques E. Rossouw [c],

- **Sub-group analysis of 16,608 women in EPT arm**

Estrogen plus progestin effects on invasive breast cancer (annualized %) by prior hormone therapy use

ADJUSTED

	E+P		Placebo		Unadjusted			Adjusted		
	N	%	*N*	%	Hazard ratio	95% CI	*p*-Value†	Hazard ratio	95% CI	*p*-Value†
Overall	199	0.41	150	0.33	1.24	(1.02, 1.50)		1.20	(0.94, 1.53)	
Prior PHT use										
No	141	0.40	121	0.36	1.09	(0.86, 1.39)	0.037	1.02	(0.77, 1.36)	0.027
Yes (any)	58	0.46	29	0.25	1.85	(1.18, 2.90)		1.96	(1.17, 3.27)	
Type of prior HT use										
Estrogen alone only	22	0.54	14	0.37	1.47	(0.75, 2.89)	0.120	1.73	(0.88, 3.40)	0.042
Combined E+P use only	28	0.37	13	0.19	1.91	(0.99, 3.71)		1.92	(1.07, 3.44)	
Other	8	0.73	2	0.19	4.41	(0.92, 21.0)		3.22	(1.30, 7.99)	

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Anderson et al, Maturitas 2006

Duration of prior EP use

	E+P		Placebo		Unadjusted			Adjusted*		
	N	%	*N*	%	Hazard ratio	95% CI	*p*-Value†	Hazard ratio	95% CI	*p*-Value†
Duration of prior E+P use (years)										
<2	11	0.35	6	0.20	1.63	(0.60, 4.43)	0.231	1.86	(0.73, 4.73)	0.084
2+	17	0.38	7	0.18	2.14	(0.88, 5.19)		2.61	(1.18, 5.78)	
Recency of prior E+P use (years)										
Current	8	0.31	2	0.09	2.78	(0.56, 13.8)	0.106	2.36	(0.93, 6.00)	0.215
≤5	13	0.41	8	0.27	1.51	(0.62, 3.67)		2.47	(1.05, 5.83)	
5+	7	0.39	3	0.17	2.62	(0.67, 10.3)		1.96	(0.67, 5.74)	

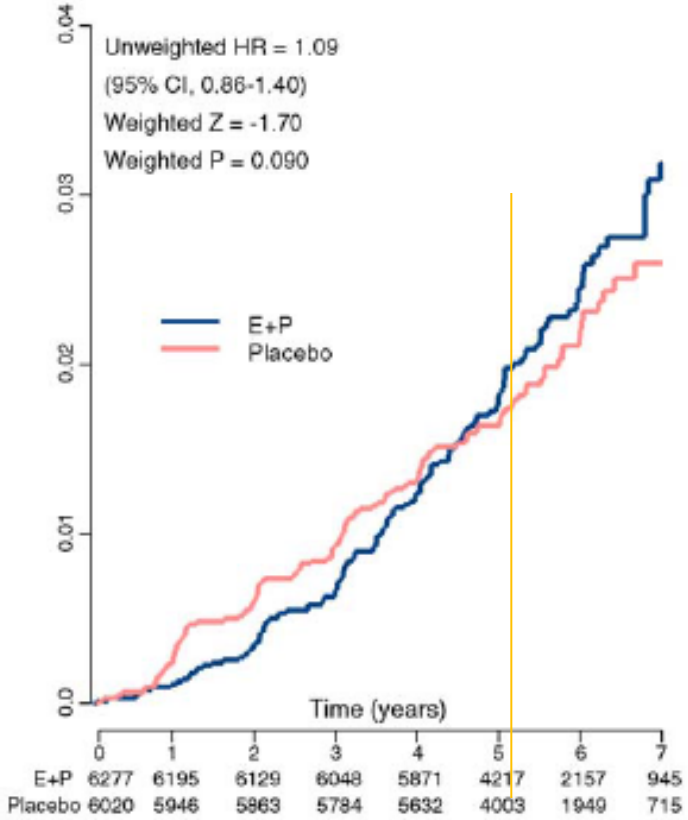
- Prior EPT use > 2 yrs: HR 2.61 (1.18 - 5.78)

  Prior use of EPT within 5 yrs: HR 2.47 (1.05 -5.83)

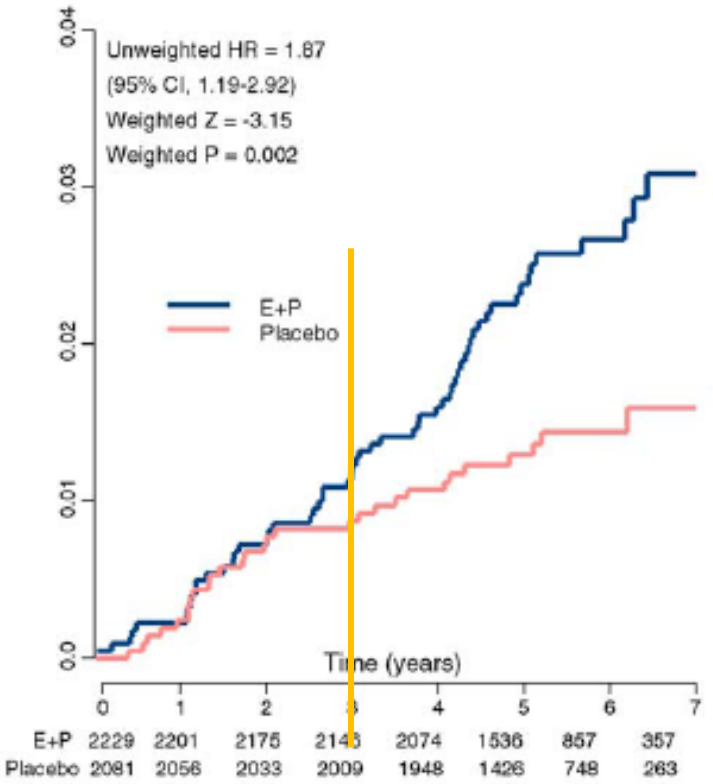
Anderson et al, Maturitas 2006

Cumulative incidence of BC
Prior use of HT

No prior use



Prior use

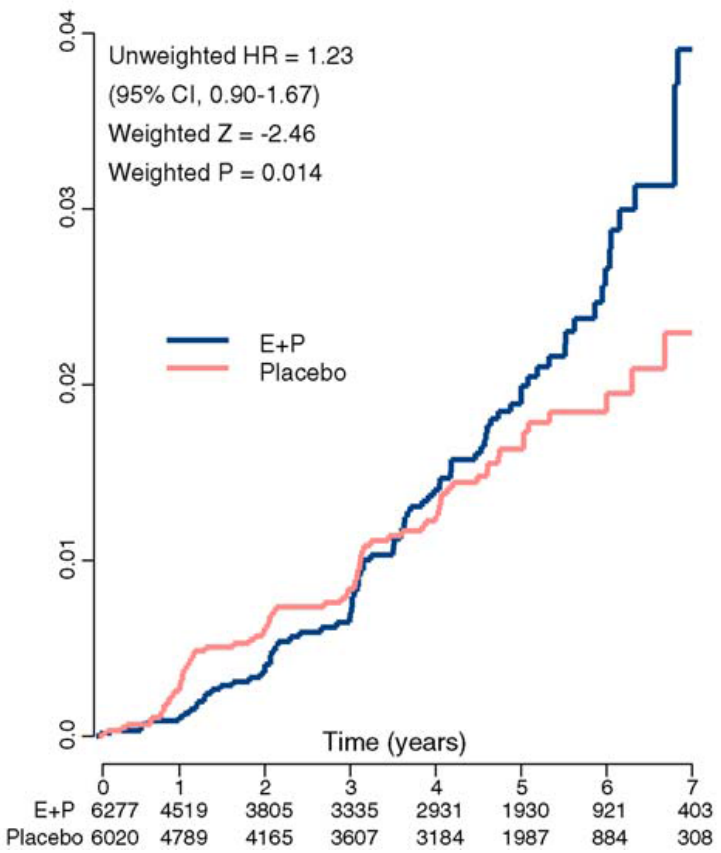


Anderson et al, Maturitas 2006

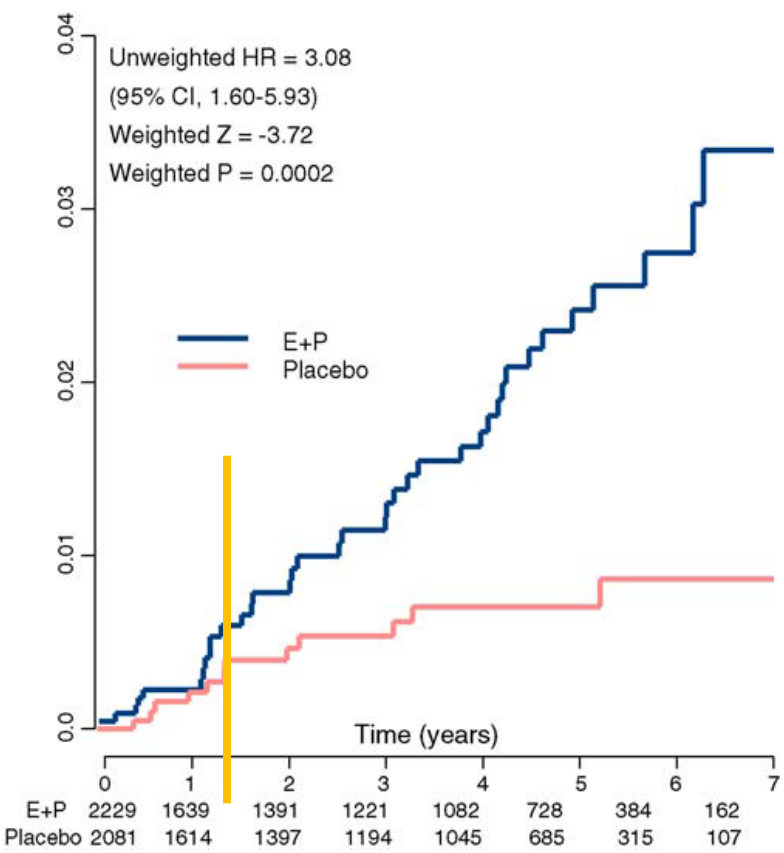
Cumulative incidence of BC

Prior use of HT – adherence adjusted

No prior use



Prior use



Anderson et al, Maturitas 2006

Breast Cancer Risk in Relation to the Interval Between Menopause and Starting Hormone Therapy

Valerie Beral, Gillian Reeves, Diana Bull, Jane Green for the Million Women Study Collaborators

- 1.3 million women recruited from 1996 to 2001

  → participants were resurveyed

- **Updated information**

  : Menopause and use of HT over time

  More PM women (828,923 → 1,129,025)

  HT ever user (53% → 55%)

  More BC cases due to extended f/up (7,140 → 15,759)

Beral et al., J Natl Cancer Inst. 2011

Million Women Study (MWS)

Prospective, resurveyed

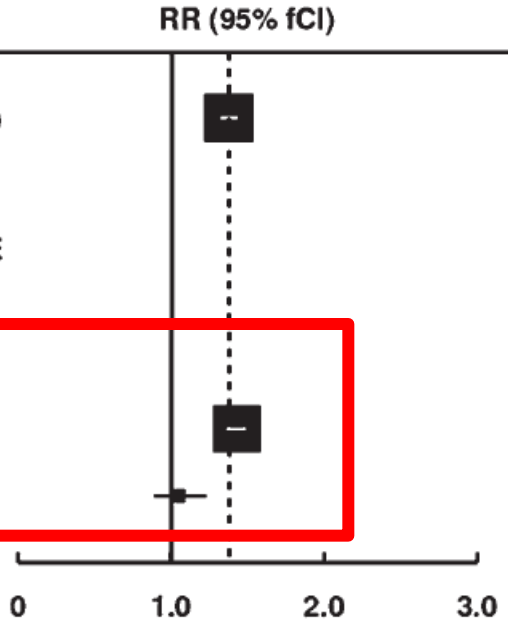
Last reported use of hormone therapy	Years of hormone therapy use*	No. Cases†/ Population (1000s)	RR (95% fCI)
Never user	-	6127/513.3	1.00 (0.97 to 1.03)
Past user	3.7	2525/221.1	1.08 (1.04 to 1.12)
Current user	7.2	7107/394.7	1.68 (1.64 to 1.72)
Estrogen-only	8.0	2131/151.0	1.38 (1.32 to 1.44)
Estrogen + progestin	6.8	4292/200.6	1.96 (1.90 to 2.02)
Tibolone	7.0	383/23.7	1.38 (1.25 to 1.52)
Other/unknown	7.4	301/19.3	1.55 (1.38 to 1.73)

Beral et al., J Natl Cancer Inst. 2011

MWS: GAP TIME

Estrogen alone

	Years of hormone therapy use*	No. Cases†	RR (95% fCI)
ALL CURRENT USERS OF HORMONE THERAPY	8.0	2131	1.38 (1.32 to 1.44)
BY AGE AT FIRST USE, DURATION OF USE AND TIME BETWEEN MENOPAUSE AND FIRST USE			
Time between menopause and first hormone therapy use			
Less than 5 years	8.3	1924	1.43 (1.36 to 1.49)
5 years or longer	5.7	151	1.05 (0.89 to 1.23)



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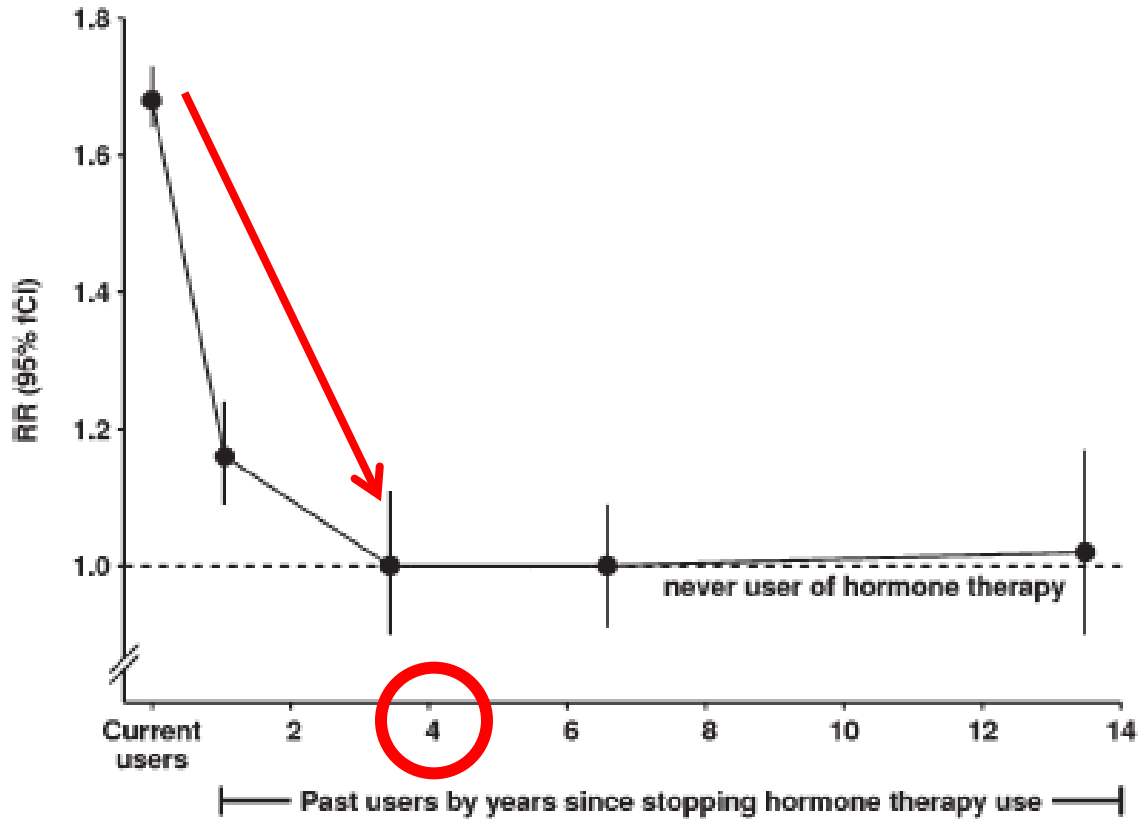
Beral et al. Am J Epidemiol 2008.

BC RISK CHANGE BY STOPPING HT



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Beral et al. Am J Epidemiol 2008.

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Advance Access publication April 29, 2008

Original Contribution

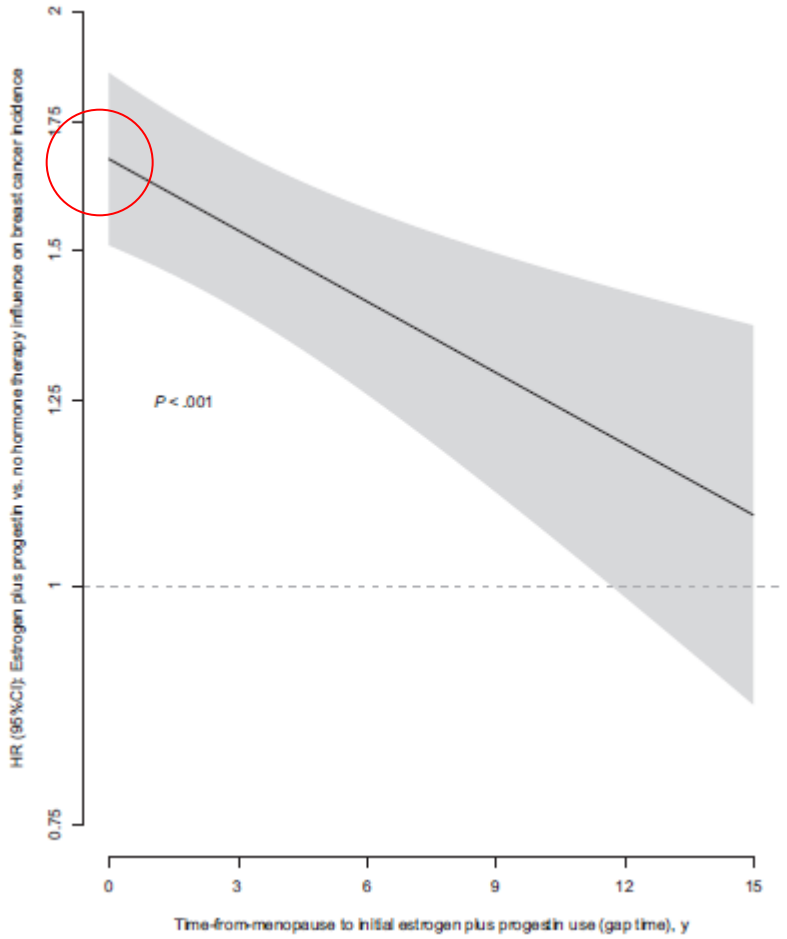
Conjugated Equine Estrogens and Breast Cancer Risk in the Women's Health Initiative Clinical Trial and Observational Study

	Gap time (years)†				HR* for interaction with gap time (<5 vs. ≥5 years) (*p* value)‡
	<5		≥5		
	HR	95% CI*	HR	95% CI	
No prior hormone therapy§	1.77	1.07, 2.93	0.99	0.74, 1.31	0.02
Prior hormone therapy§	2.06	1.30, 3.27	1.30	0.57, 2.99	
HR for interaction with prior hormone therapy (no vs. yes) (*p* value)¶			0.53		

Prentice RL, et al. Am J Epidemiol 2008.

GAP TIME: WHI-Observational Study

Zero gap time
HR 1.68
(1.52-1.86)



In EPT duration < 5 years…

- Gap time < 5 yrs

  HR 1.45 (1.13-1.88)

- Gap time ≥ 5 yrs

  HR 1.19 (0.92- 1.55)

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Chlebowski RT, et al. J Natl Cancer Inst 2013.

BC risk according to BMI factor

Table 3. Breast Cancer Risk by Duration of ET Use Stratified by BMI*

ET Use and Duration, y	BMI <25		BMI ≥25	
	Cases	Risk	Cases	Risk
Never	78	1.00	148	1.00
Current				
<5	45	1.03 (0.69-1.52)	54	0.96 (0.69-1.33)
5-9.9	78	1.17 (0.84-1.62)	66	0.74 (0.55-1.00)
10-14.9	94	1.18 (0.86-1.62)	94	0.97 (0.74-1.28)
15-19.9	66	1.36 (0.97-1.92)	63	1.11 (0.82-1.51)
≥20	80	1.77 (1.26-2.48)	65	1.25 (0.91-1.71)

From Nurses Health Studies/ Chen et al. Arch Intern Med. 2006

- **BMI significantly interacted with EPT and BC**

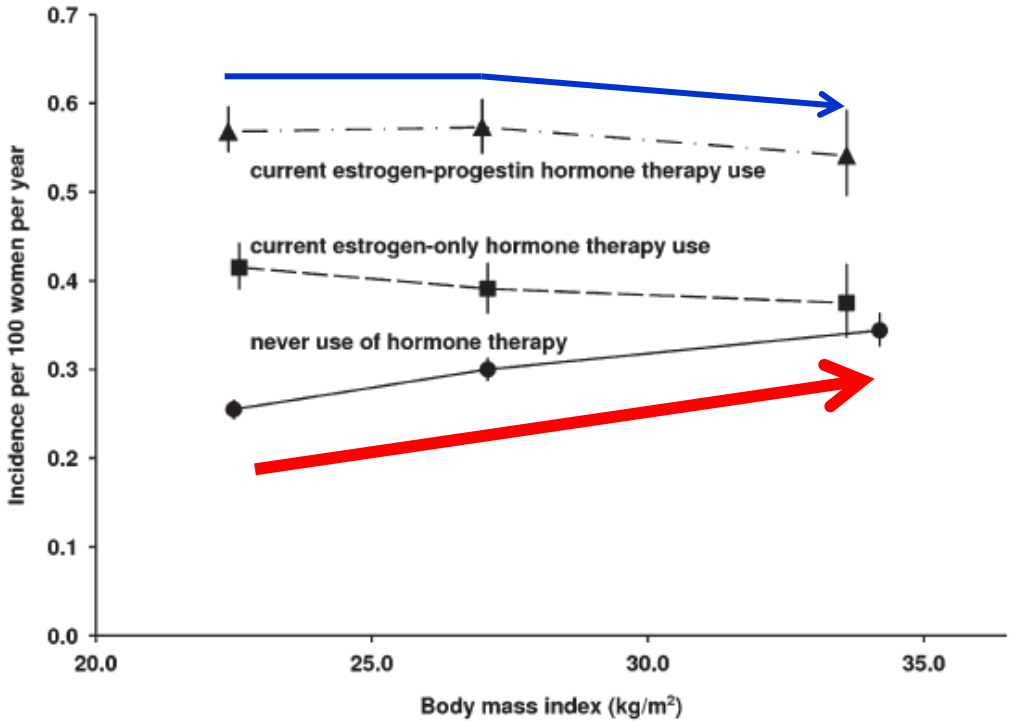
BMI < 25 : HR 1.70 (1.48-1.95)

25 ~30 : HR 1.50 (1.29-1.75)

≥ 30 : HR 1.34 (1.11-1.62)

WHI observational studies / Chlebowski et al. JAMA. 2013

BMI and BC risk: MWS

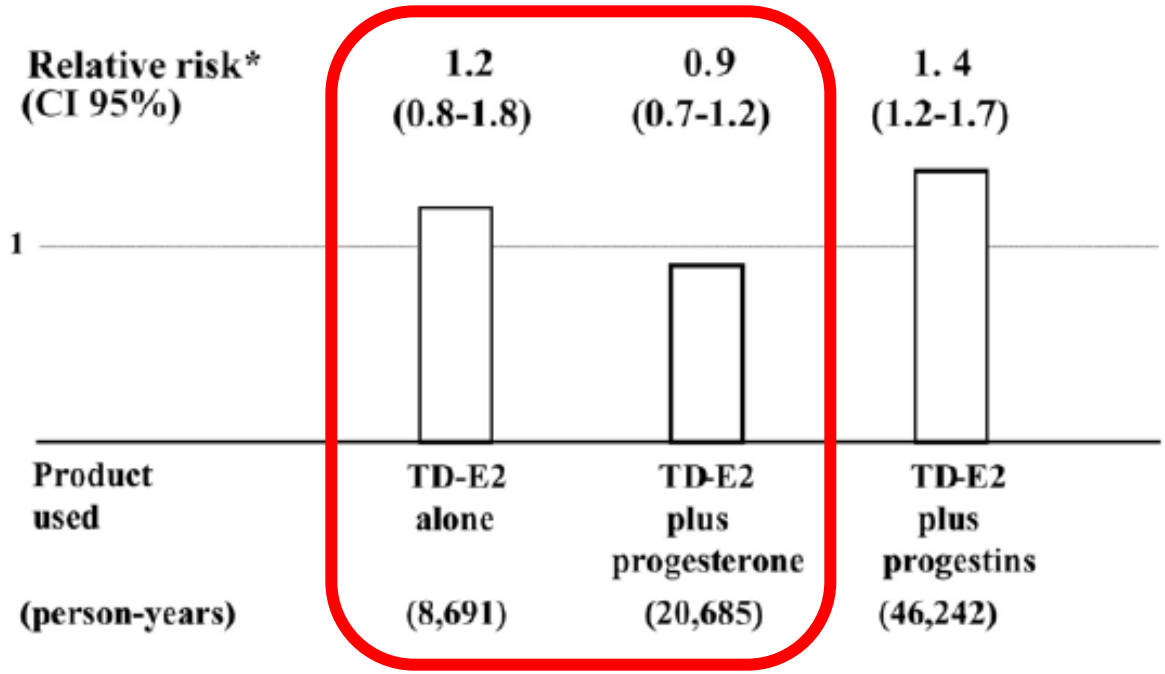


- HT would change women's net exposure to sex hormones to a greater extent among leaner women than obese women.

Beral et al. J Natl Can I. 2013

FORMULATION OF E and P

E3N – French cohort (N = 54,548 PM)



- Routes of estrogen
- Natural progesterone *vs.* synthetic progestins

Fournier et al., Int J Cancer 2005

Current concept (2012): HT & BC

Combined estrogen plus progestin use

- Estrogen plus progestin increases breast cancer risk and the effect on risk may be greater in women who initiate therapy closer to menopause†
- Estrogen plus progestin broadly increases breast cancer risk with the increase in risk not limited to hormone receptor–positive cancers†
- Estrogen plus progestin interferes with breast cancer mammographic detection resulting in cancers diagnosed at more advanced stage†
- Estrogen plus progestin increases breast cancer mortality†

Estrogen-alone use

- Estrogen alone reduces breast cancer risk†
- Estrogen alone does not substantially interfere with breast cancer detection by mammography†

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Chlebowski et al., J Natl Cancer Inst. 2012

SUMMARY (1): EPT on BC risk

- **Many observational studies and a RCT**
  : EPT increased the risk of BC and mortality
  - *Different risk according to prior HT, GAP time, Body size, progestogen type ...*

- Young women initiating standard dose for the first time at the onset of menopause do not have an increased risk of BC for at least 5 years
  (absolute increased risk for 5 yrs - 0.67%)

Lobo al, J Clin Endocrin Metab. 2013

SUMMARY (2): ET on BC risk

- **Observational data ≠ WHI trial**
  - ET alone does not increase the risk of BC

    Reduce the risk and mortality due to BC

    (11.8 yrs follow-up extenision trial)
  - BC risk did not increase for at least 15 years