

Update on HRT

Atlantic Society of Obstetricians
and Gynaecologists
September 23 2005

Recent comprehensive reviews:

ACOG: *Obstet Gynecol.* 2004;104 (Suppl 4):106S-117S.

ASRM Practice Committee 2004: Estrogen and progestin therapy in postmenopausal women: *Fertil Steril* 82 (Suppl 1): 70S-80S.

Update on HRT

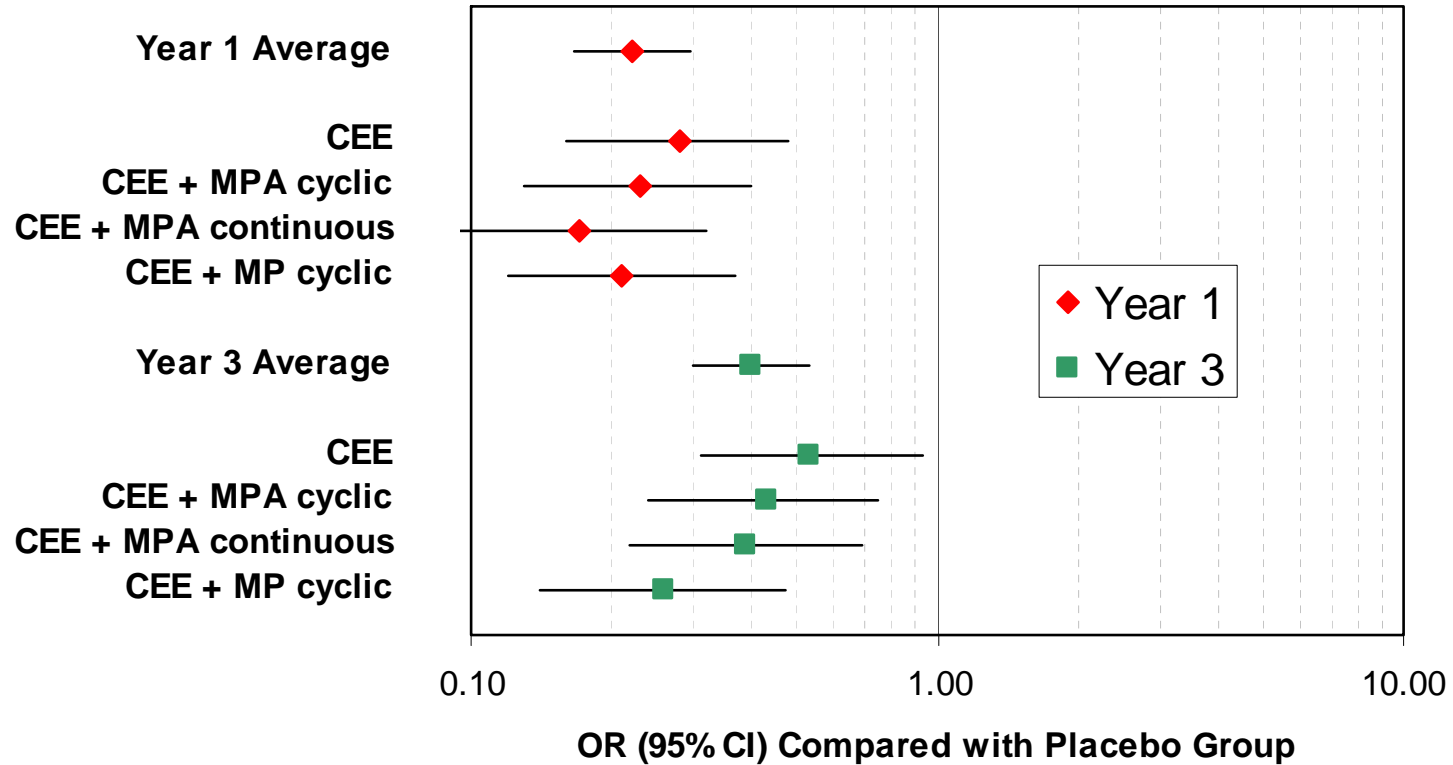
Alternative Treatments

HRT and Heart Disease

HRT and Breast Cancer

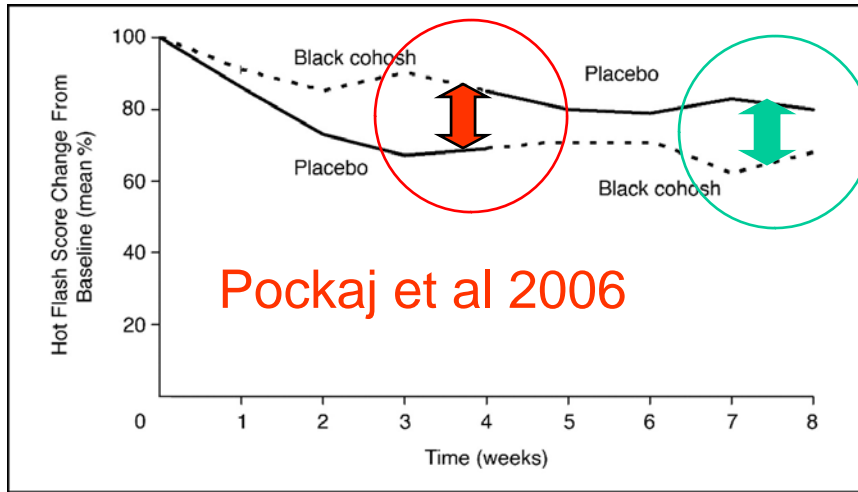
Hormone Therapy and Vasomotor Symptoms

More Severe Vasomotor Symptoms

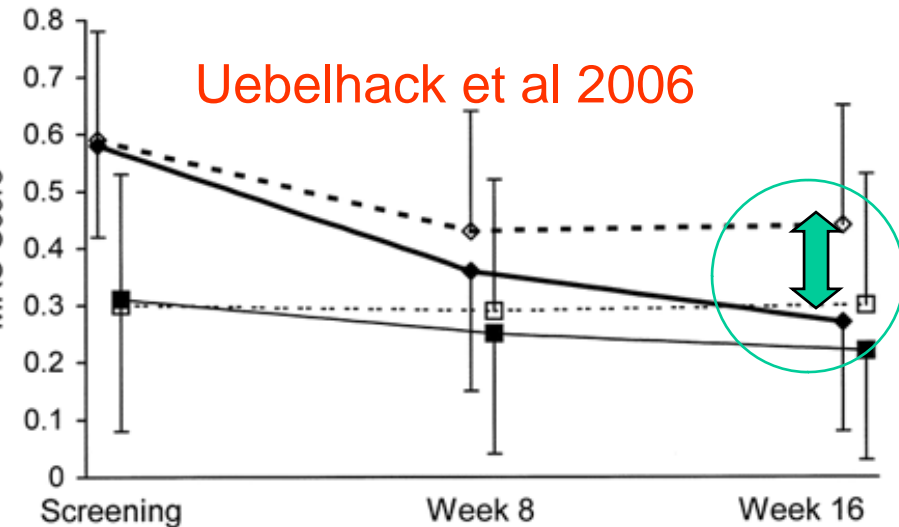
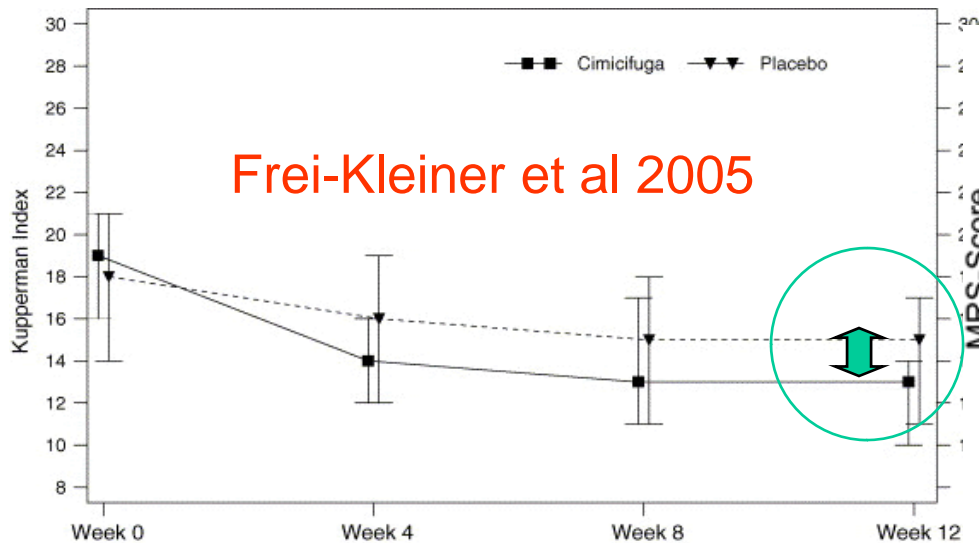
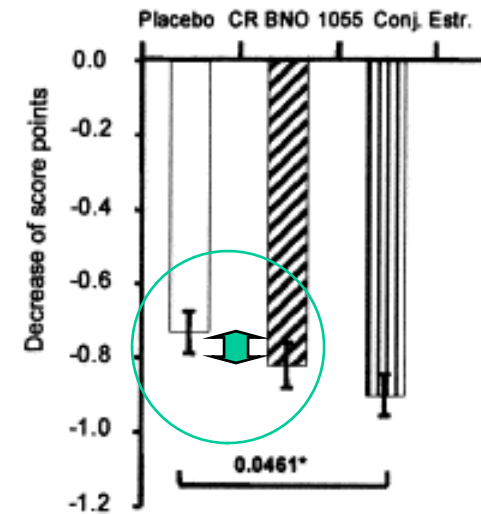


Greendale et al 1998. Symptom relief: results from the Postmenopausal Estrogen/ Progestin Interventions trial. *Obstet Gynecol* 92:962-8.

Black Cohosh: Alternative for Symptoms?



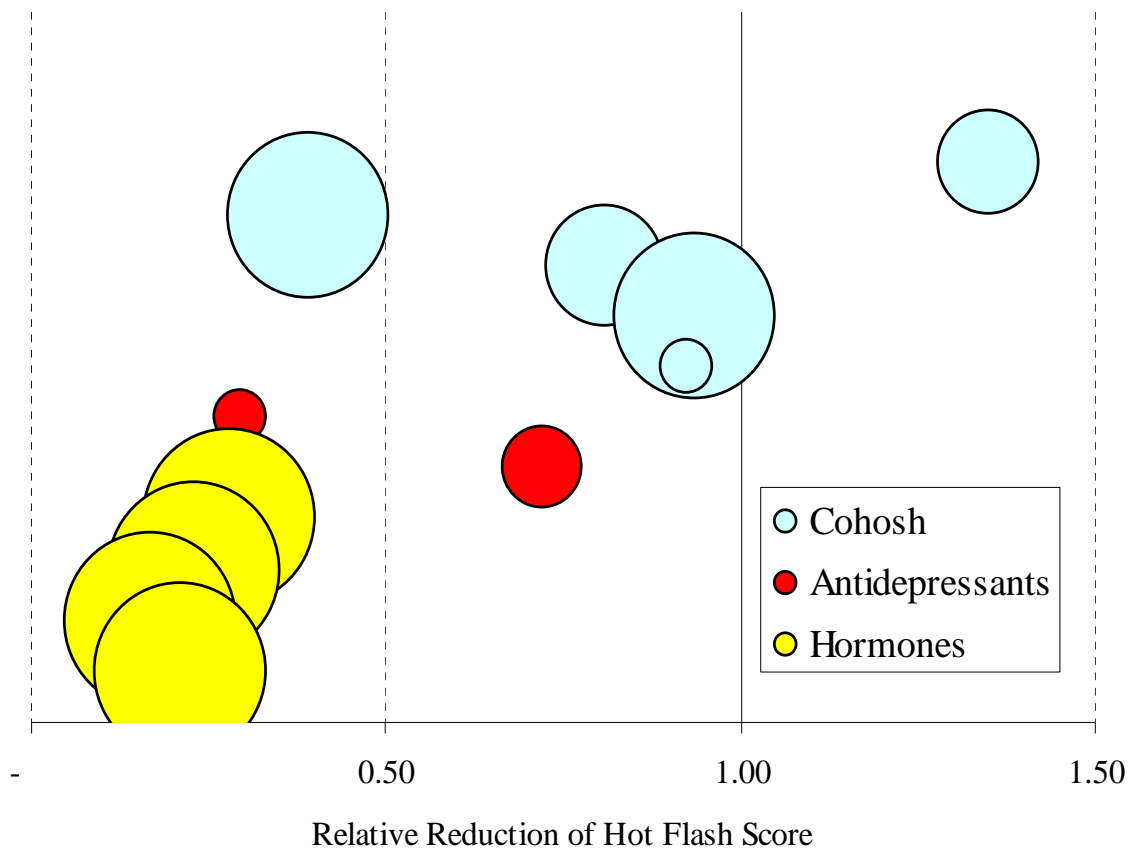
Wuttke et al 2003



Impact of Therapy on Hot Flash Scores

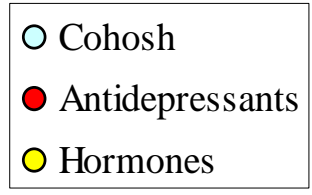
Authors

Pockaj et al 2006
 Uebelhack et al 2006
 Frei-Kleiner et al 2005
 Osmers et al 2005
 Wuttke et al 2003
 Evans et al 2005
 Loprinzi et al 2002
 PEPI CE
 PEPI CE+MPA Seq
 PEPI CE+MPA Cont
 PEPI CE+MP Cont



Relative
Reduction

1.35
 0.39
 0.81
 0.94
 0.93
 0.29
 0.72
 0.28
 0.23
 0.17
 0.21



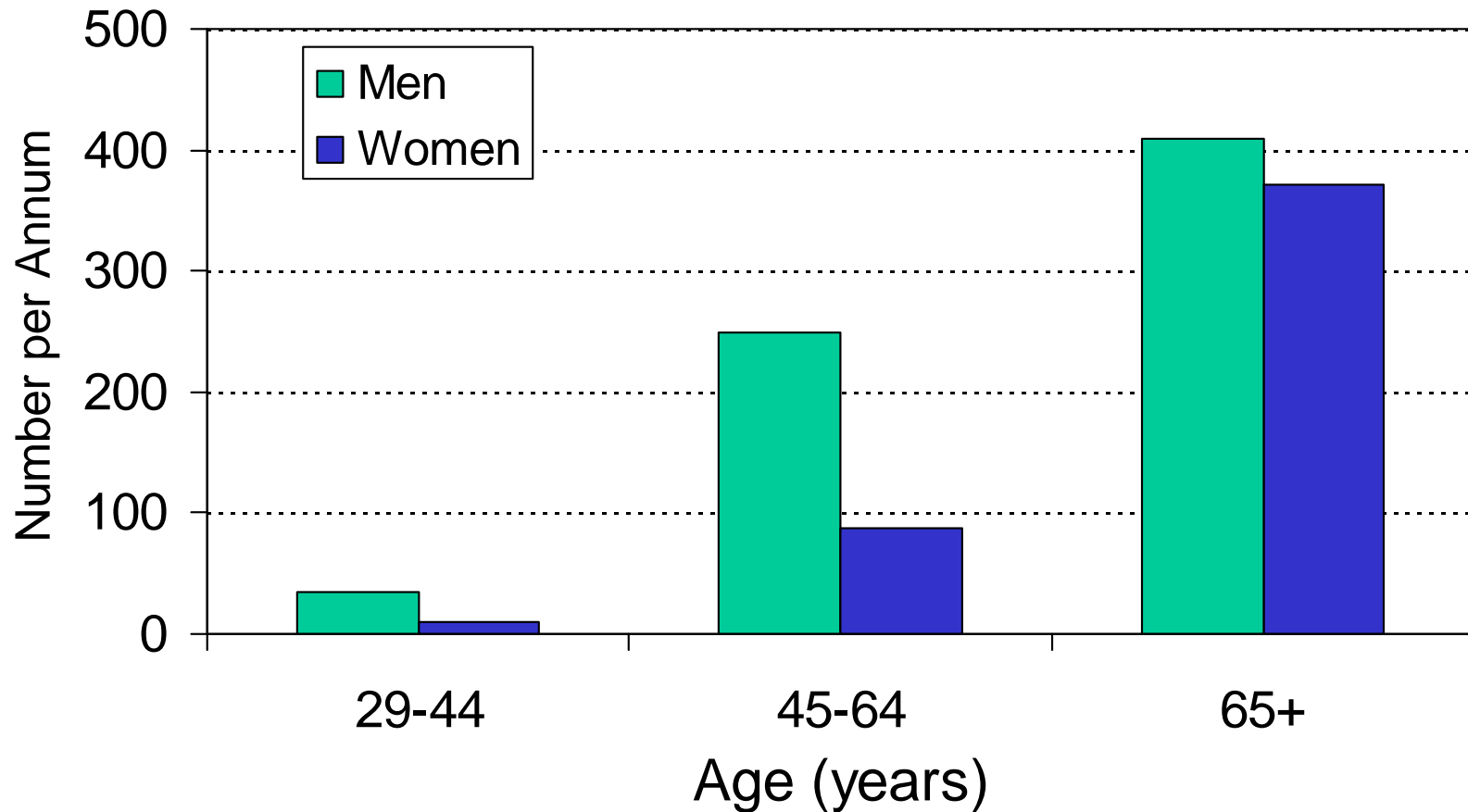
Update on HRT

Alternative Treatments

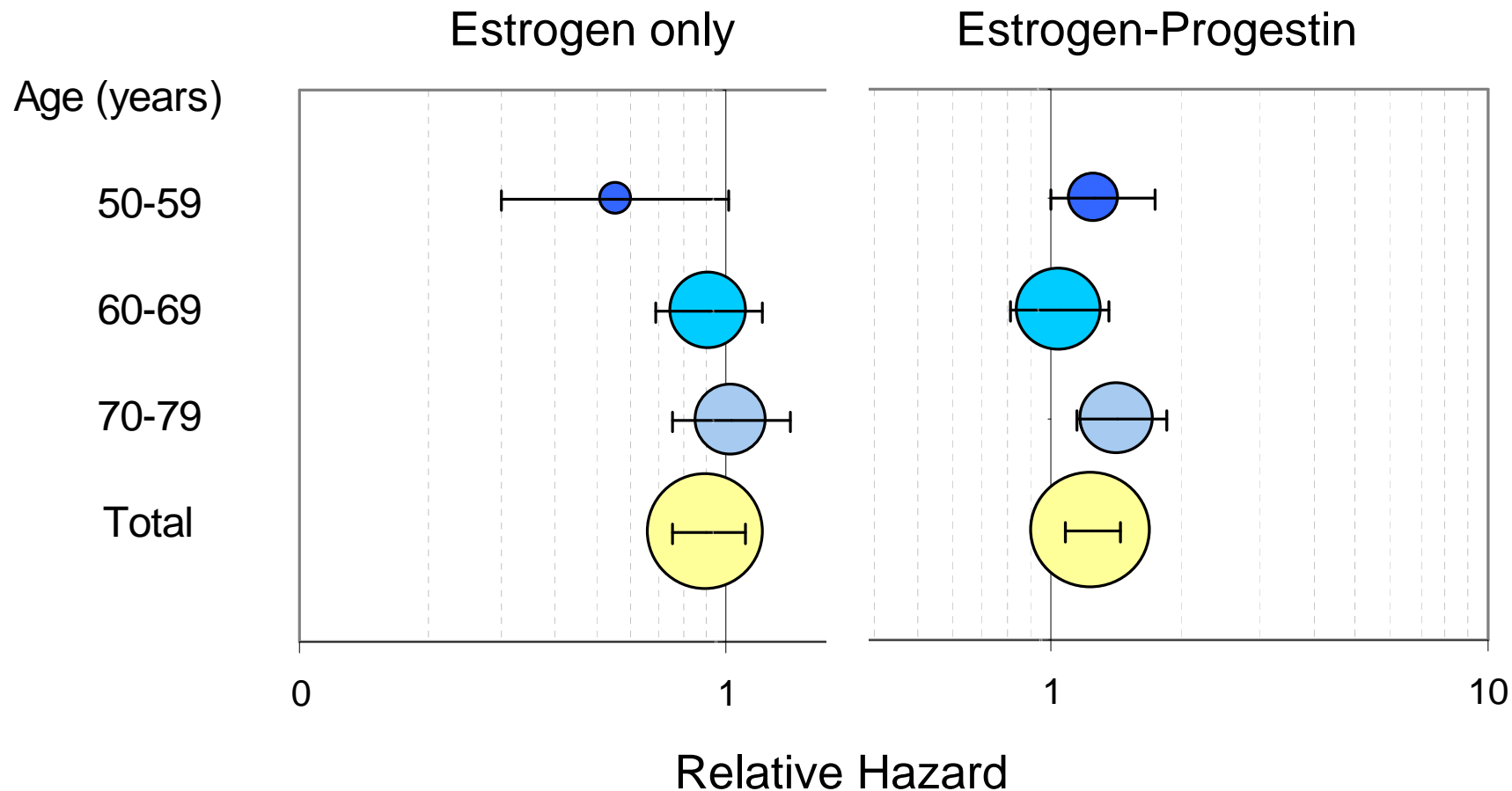
HRT and Heart Disease

HRT and Breast Cancer

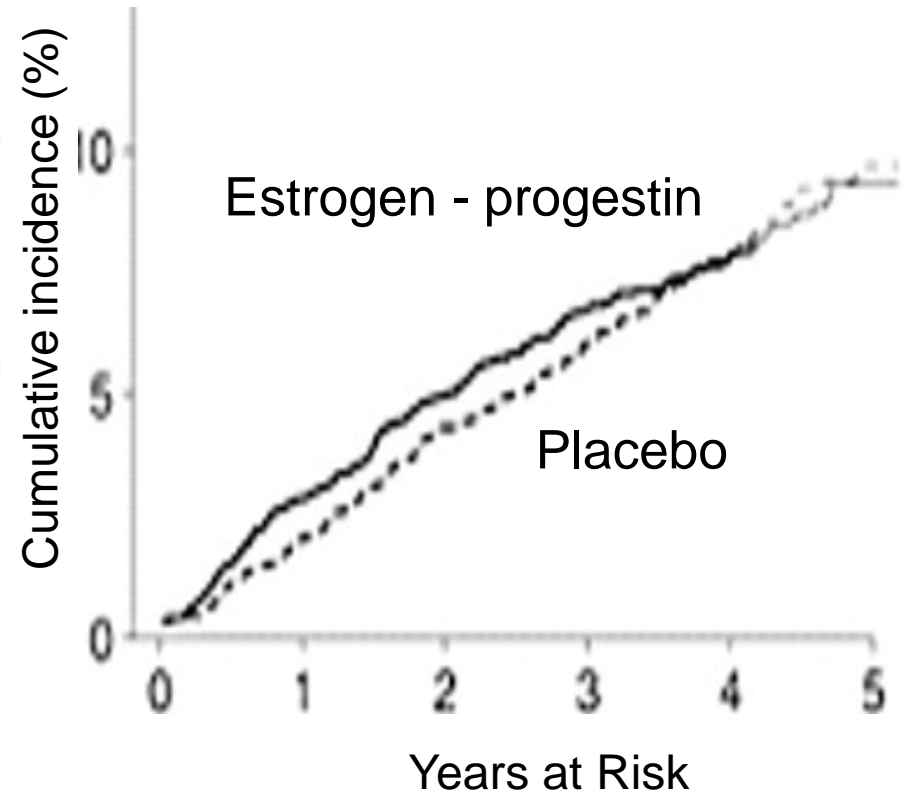
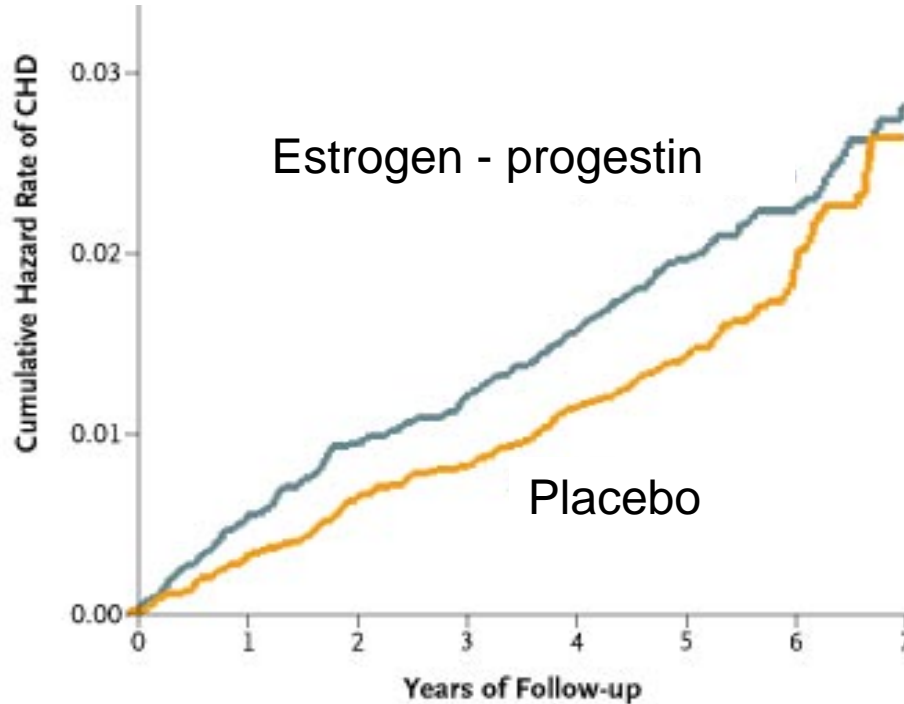
Annual Incidence of First Heart Attack



WHI Hormone Trials: Coronary Heart Disease



WHI and HERS: Time Course of CHD Events

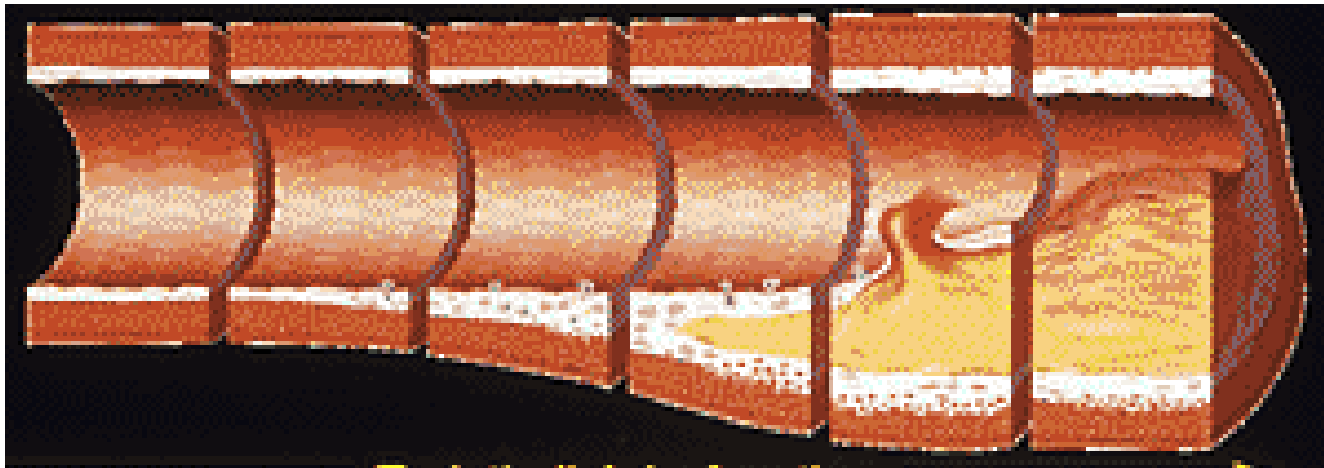


Manson et al. NEJM 2003; 349:523-534.

Hulley et al. JAMA 1998;280:605-613.

Atherosclerosis Timeline

Foam cells Fatty streak Intermediate lesion Atheroma Rupture Fibrous plaque



Growth mainly by lipid accumulation

Thrombosis, hematoma

Estrogen prevents

Estrogen worsens

← Endothelial dysfunction →

A Unified Hypothesis

The complex CHD responses to hormone therapy in recent human trials likely reflect a combination of

1. long-term reduction in plaque formation by estrogen therapy;
2. early erosion/rupture of "vulnerable" coronary plaque by estrogen;
3. more likelihood of clot formation with estrogen.

Phillips & Langer, 2005. Postmenopausal hormone therapy: critical reappraisal and a unified hypothesis. *Fertil Steril* 83:558-566

WHI Estrogen Alone: NNT

Age	Number of Cases (n/year/10,000)		Hazard ratio (95% CI)	P value for interaction
	CEE	Placebo		
50-59	16 (14)	29 (24)	0.56 (0.30, 1.03)	
60-69	87 (54)	98 (59)	0.92 (0.69, 1,23)	0.14
70-79	74 (88)	72 (74)	1.04 (0.75, 1.44)	

Risk difference = (24-14) = 10: NNT = 10,000 / 10 = 1000.

Recommendations on HT and CHD

ASRM Practice Committee

ACOG Task Force

Hormone therapy (estrogen alone or combined therapy) should not be used or continued for primary [or secondary] prevention of coronary heart disease.

Choose alternative health strategies and pharmaceutical agents with established value for prevention of CHD.

ASRM Practice Committee Reports 2004. Estrogen and progestogen therapy in postmenopausal women. Fertil Steril 82 Suppl 1:S70-S80.

ACOG Task Force on Hormone Therapy 2004. Coronary heart disease. Obstet Gynecol 104 supp: 41S-48S.

Update on HRT

Alternative Treatments

HRT and Heart Disease

HRT and Breast Cancer

Breast Cancer Risk in Estrogen RCTs

Hormones reduce BC incidence

Hormones increase BC incidence

Hodis et al, 2001

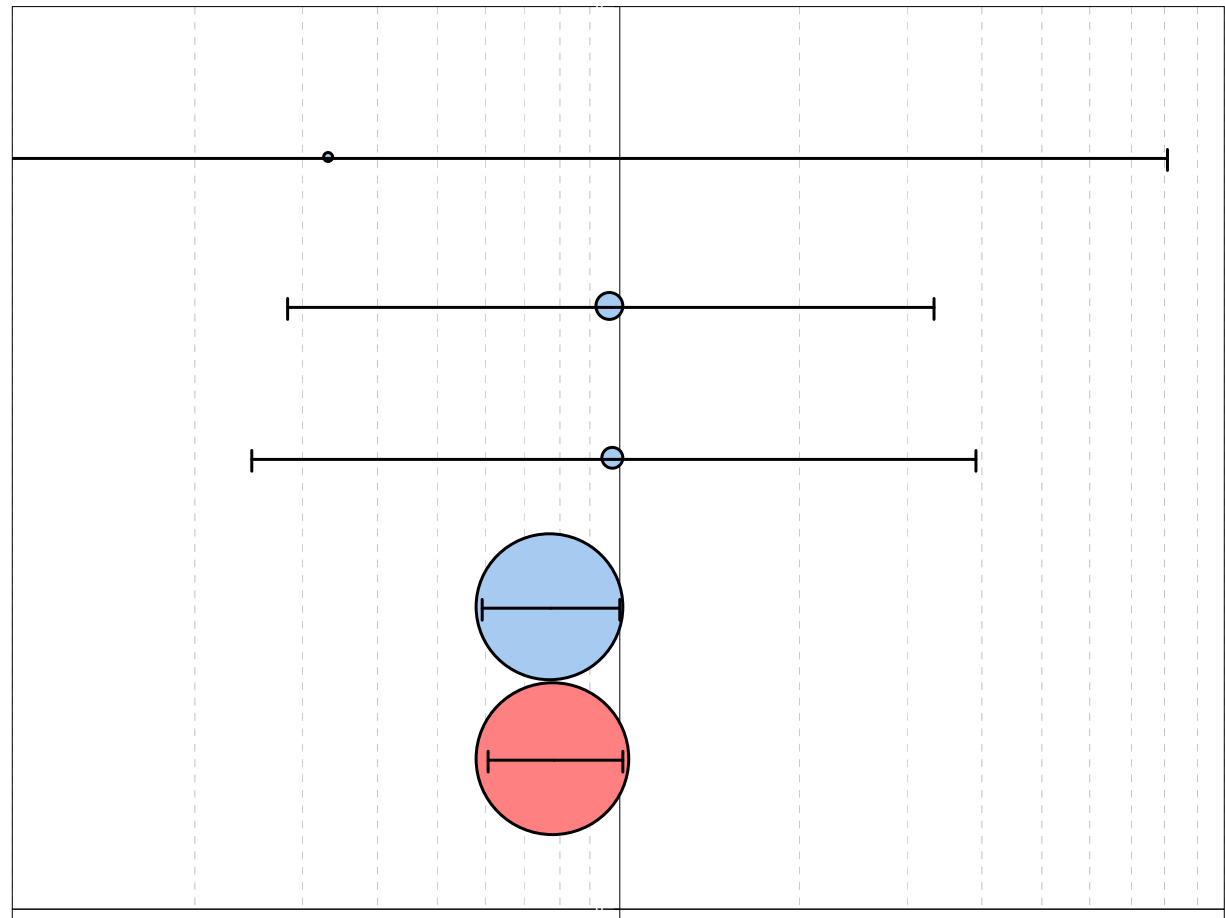
Viscoli et al, 2001

Cherry et al, 2002

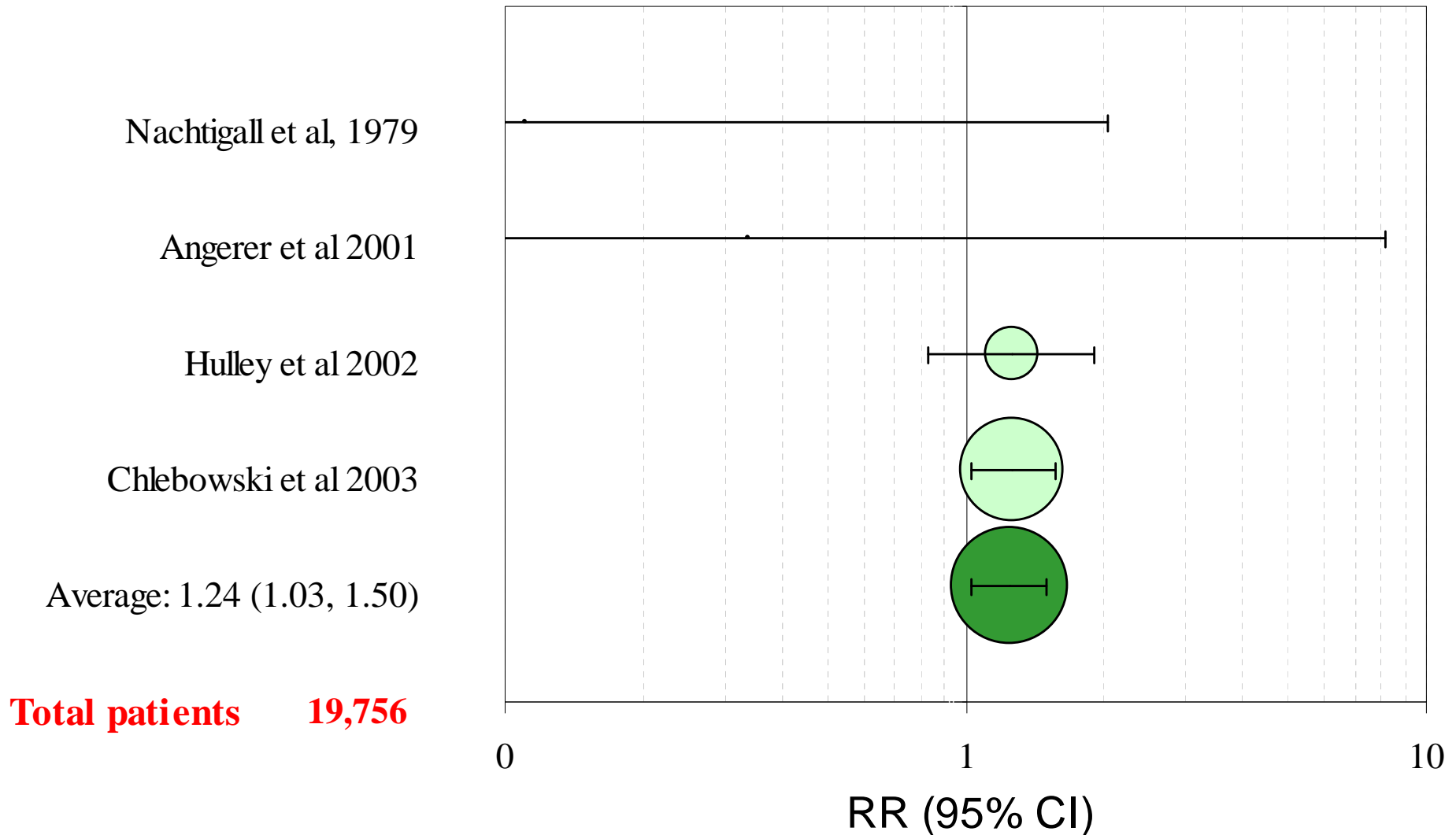
Anderson et al, 2004

Average: 0.79 (0.61, 1.02)

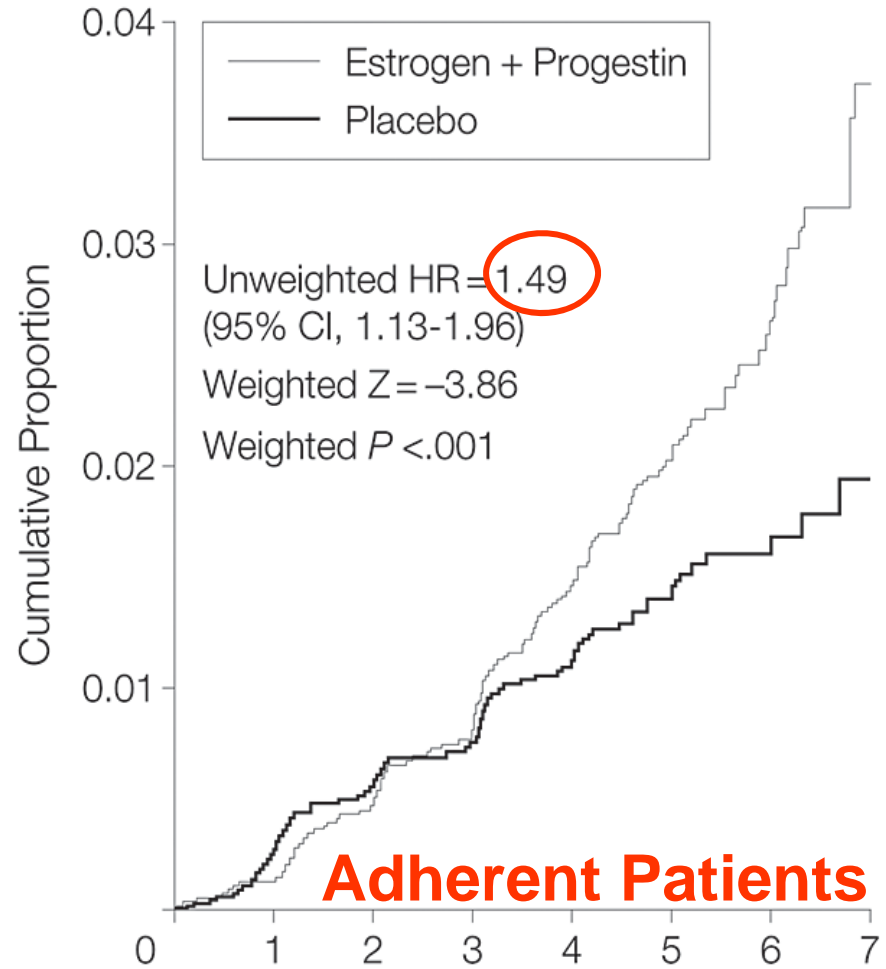
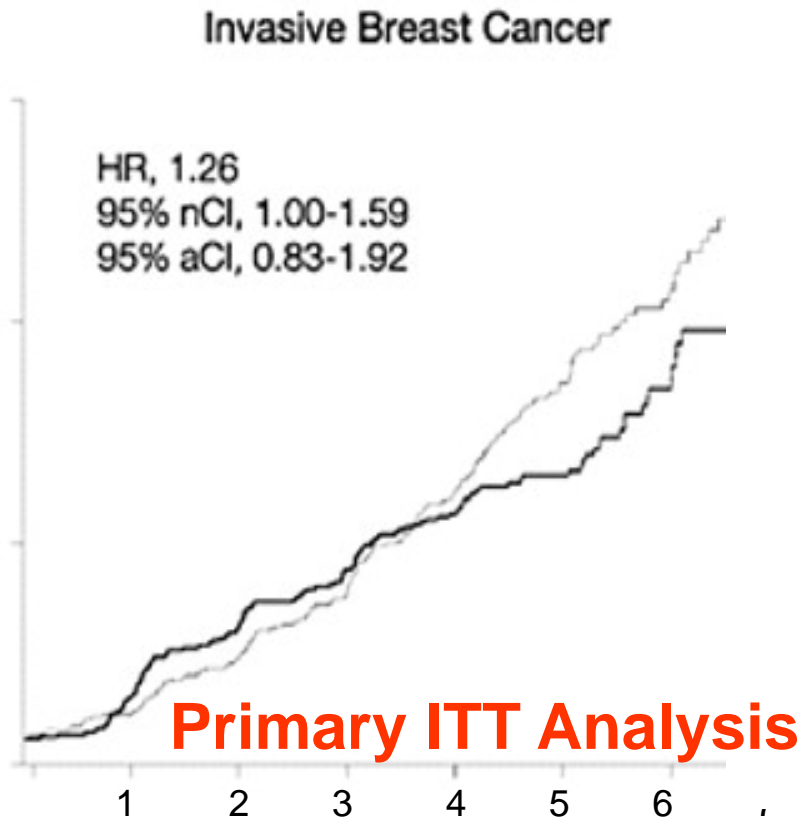
Total patients 12,643



Breast Cancer Risk in EP RCTs



Breast Cancer Rates By Analysis Group



Subjects in Studies of Hormone Use and Breast Cancer

	Exposed Cases	Total Subjects
RCTs	569	32,396
Collaborative Re-analysis, 1997	~6,000	161,116
Epidemiological studies after 1997	15,768	1,850,384

Collins, Blake, Crosignani 2005. Breast cancer risk with postmenopausal hormonal treatment. Hum Reprod Update 11:545-60.

Absolute Breast Cancer Risk

EP risk estimates	Relative risk	New cases per year / 100,000	Cases due to HT
No use*	1	300	
RCTs	1.24	373	73
WHI adherent patients	1.49	447	147
Current use (epi studies)	1.70	510	210

*Ries, Eisner et al 2003. SEER Cancer Statistics Review, 1975-2000.
http://seer.cancer.gov/csr/1975_2000

Prescribing Options

- Hormone type
- Hormone dosage
- Route of administration
- Progestin regimen
(sequential or continuous)

Hormone Types and Breast Cancer Risk

	Studies	Categories	RR
Estrogen	Beral et al, 2003	Equine Es	1.29
		Estradiol	1.24
Progestin	2*	C21	2.14
		C19	2.14

*Beral et al, 2003; Stahlberg et al, 2004. Collins et al Hum Reprod Update 2005.

Hormone Dosage and Breast Cancer Risk

	Studies	Dosage (mg)	RR
Estrogen	2*	≤0.625	1.27
		>0.625	1.25
Progestin	Porch et al 2002	<5	1.54
		5-9	1.30
		10	1.13

*Beral et al, 2003, Porch et al 2002; Collins et al Hum Reprod Update 2005.

Route of Administration and BC Risk

One study reported the breast cancer risk according to the route of administration of estrogen products.

	<i>adjusted RRs</i>
oral	1.32 (1.21 - 1.45)
transdermal	1.24 (1.11 - 1.39)
<u>implanted estrogens</u>	<u>1.65 (1.26 - 2.16)</u>

P = 0.27

*Beral et al 2003. Breast cancer and hormone-replacement therapy in the Million Women Study. Lancet 362:419-27.

Progestin Regimens and Breast Cancer Risk

Analysis	Current Use Summary RR		Q*	P value
	Sequential	Continuous		
Random	1.49	1.87	2.3	0.13
Fixed effects	1.85	1.94	0.89	0.34

*heterogeneity between regimens

Six studies: Beral et al 2003; Chen et al 2002; Li et al 2003; Porch et al 2002; Stahlberg et al 2004; Weiss et al 2002; Collins et al, Hum Reprod Update 2005.

Summary of Prescribing Options

- Type of hormones, the way that they are delivered and the dose have no obvious role in enhancing or modifying the affect on breast cancer risk.
- A continuous regimen could involve 1 more case per 1,000 women per annum than a sequential regimen, but the comparison is not significant.

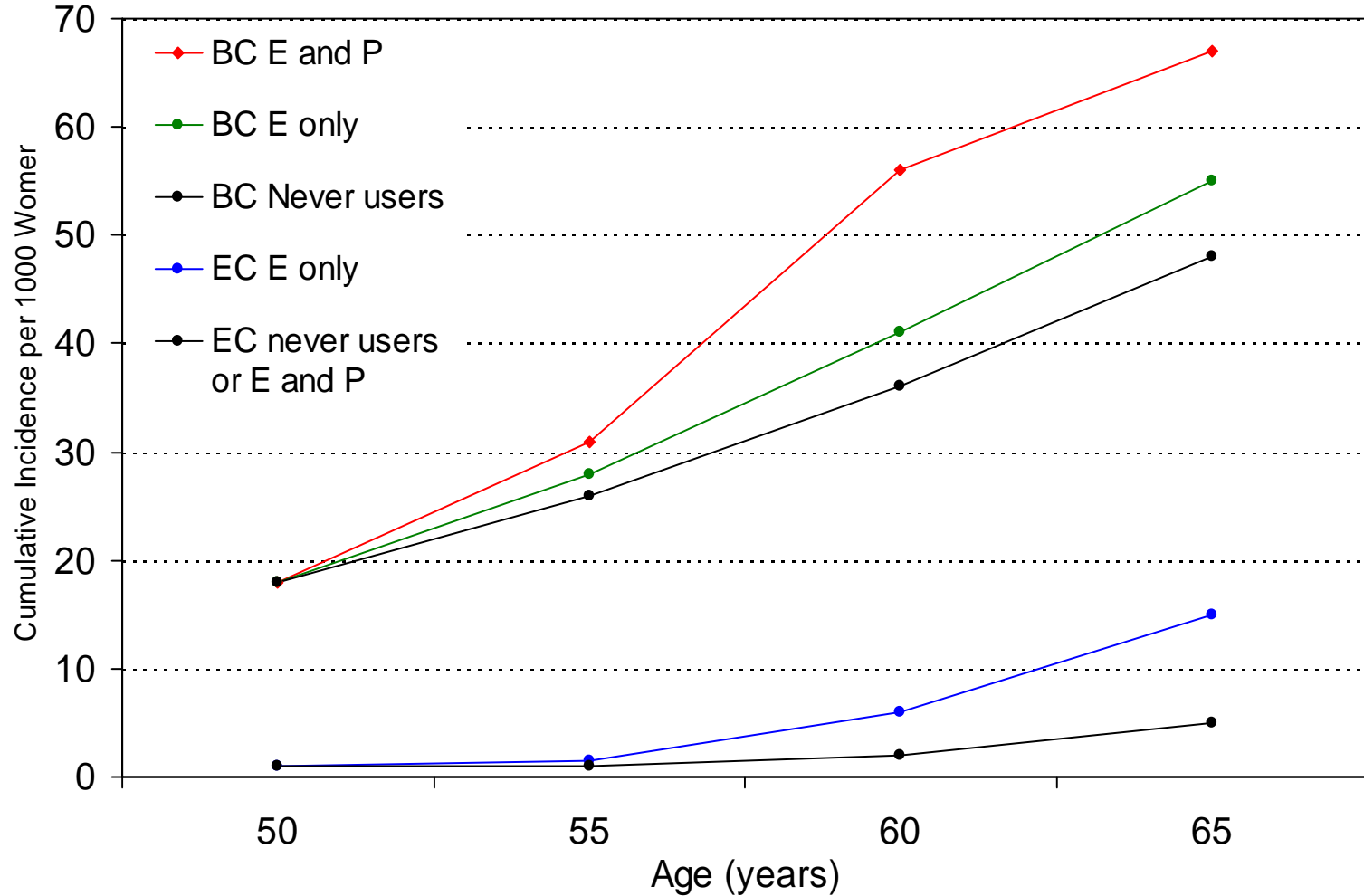
Do Hormone-Associated Tumours have a Better Prognosis?

- In population studies, clinical stage and histological grade are not “better” in hormone-associated tumours.
- Tumours associated with estrogen-progestin use are more likely to be Estrogen receptor-positive.

Summary: Menopausal Hormones and Breast Cancer Risk

1. Risk is increased by EP more than E alone (I, II).
2. Lower risk in RCTs associated with loss of contrast (I,II).
3. EP risk increases over time (I, II).
4. Risks diminish after cessation of exposure (II)

Estrogen and Progestin Effects



The Challenge for Gynecologists

For every 10 endometrial cancers avoided by adding progestin to estrogen, there will be 14 additional breast cancers.

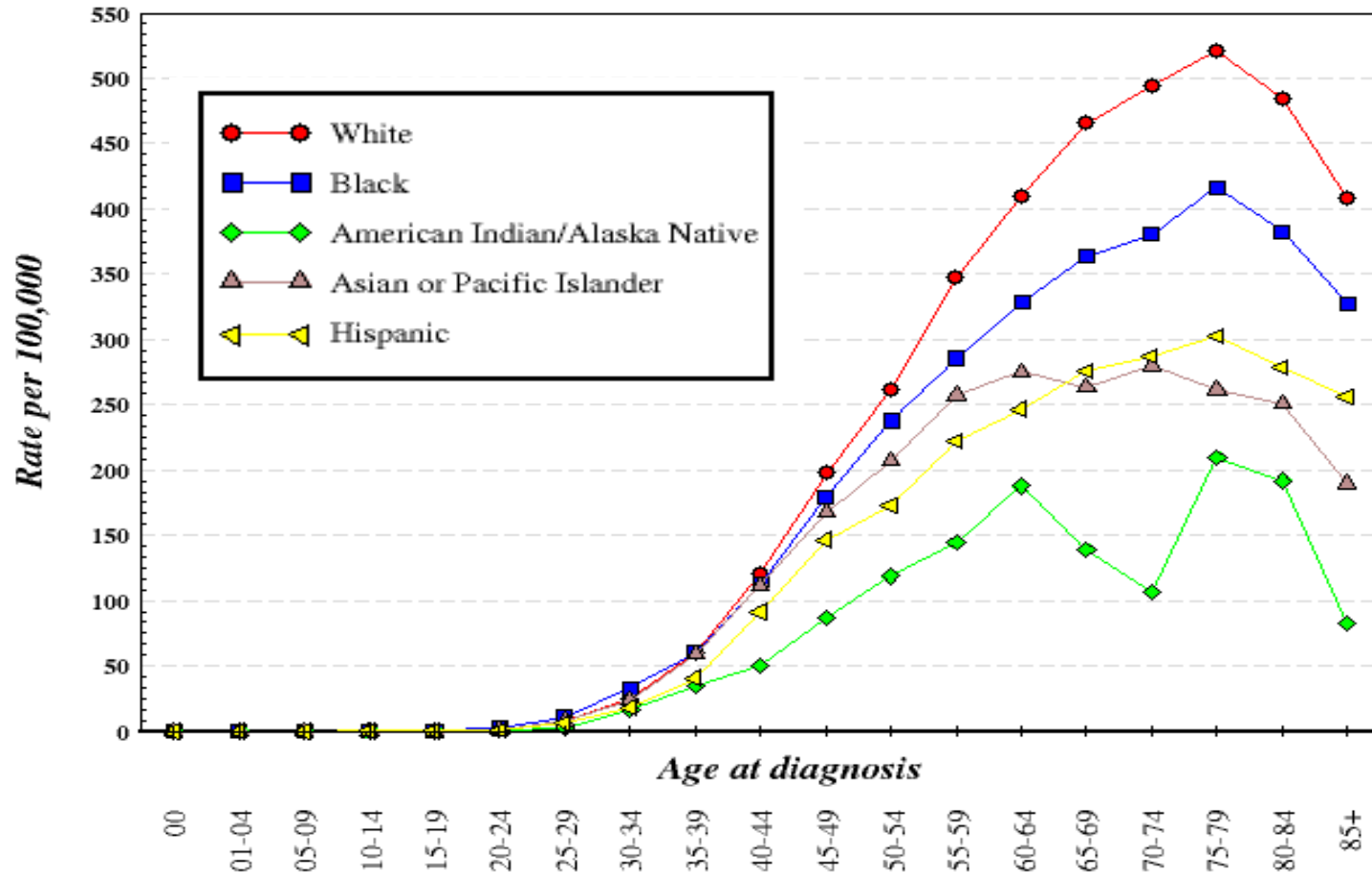
RCTs are needed for prescribing unopposed estrogen safely among women with a uterus

LNG-IUS

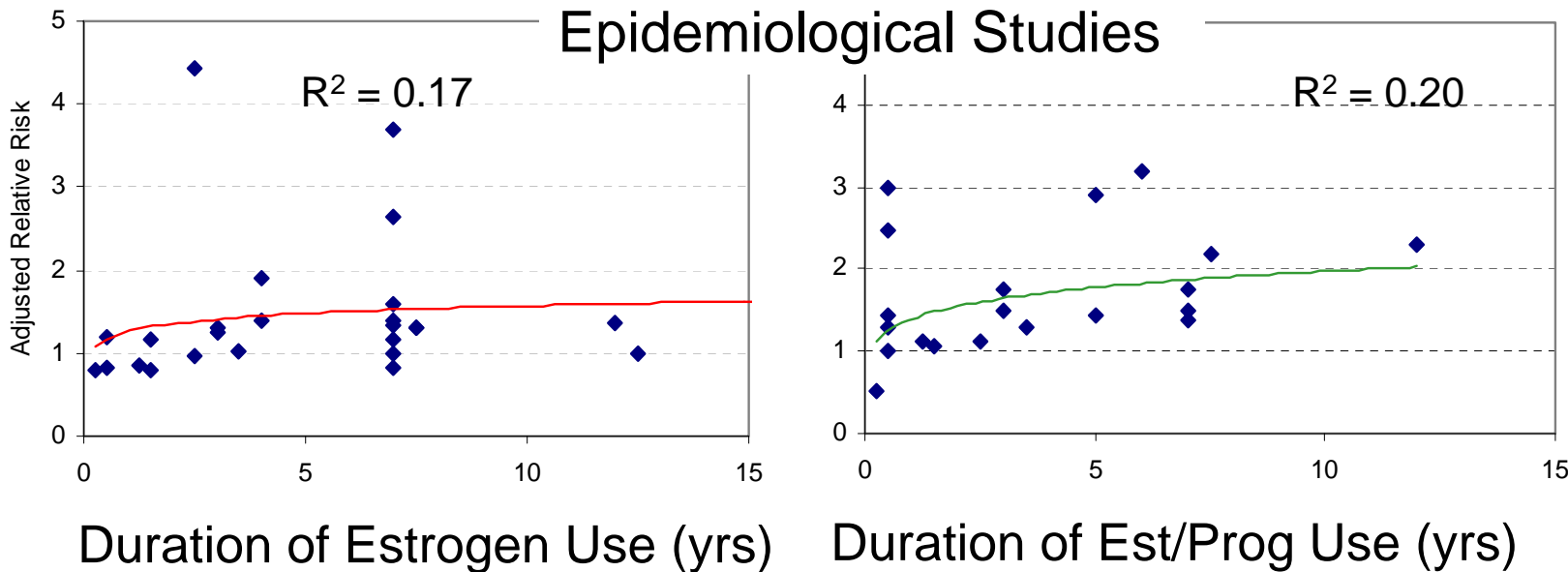
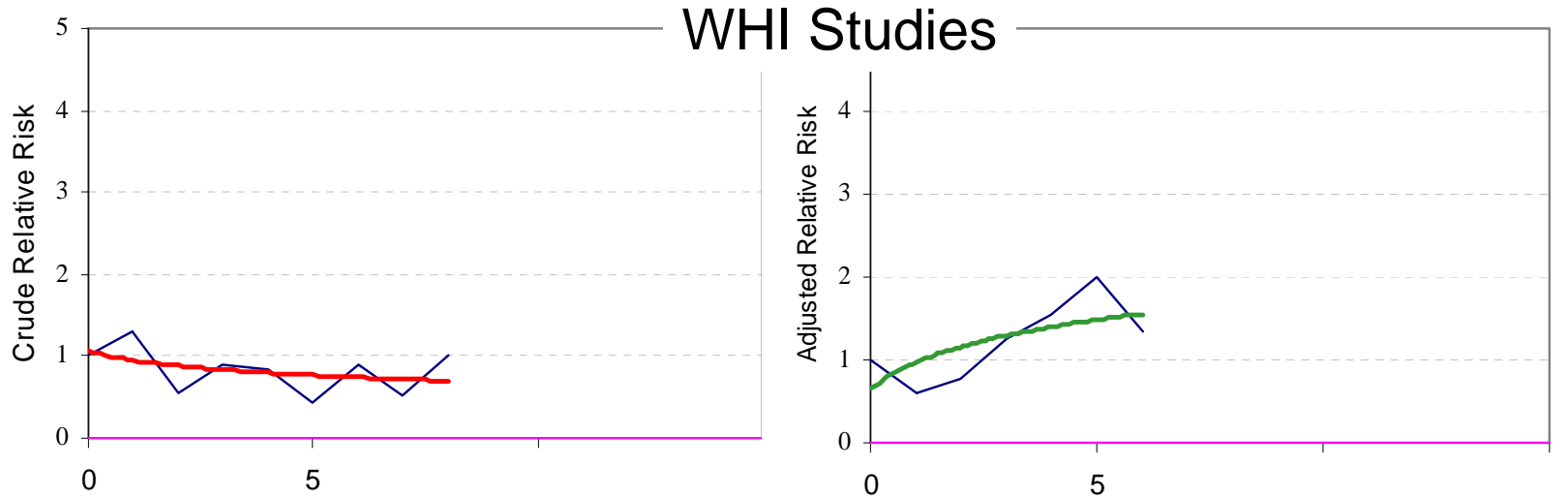
annual endometrial biopsy

endometrial ultrasound follow-up + EB

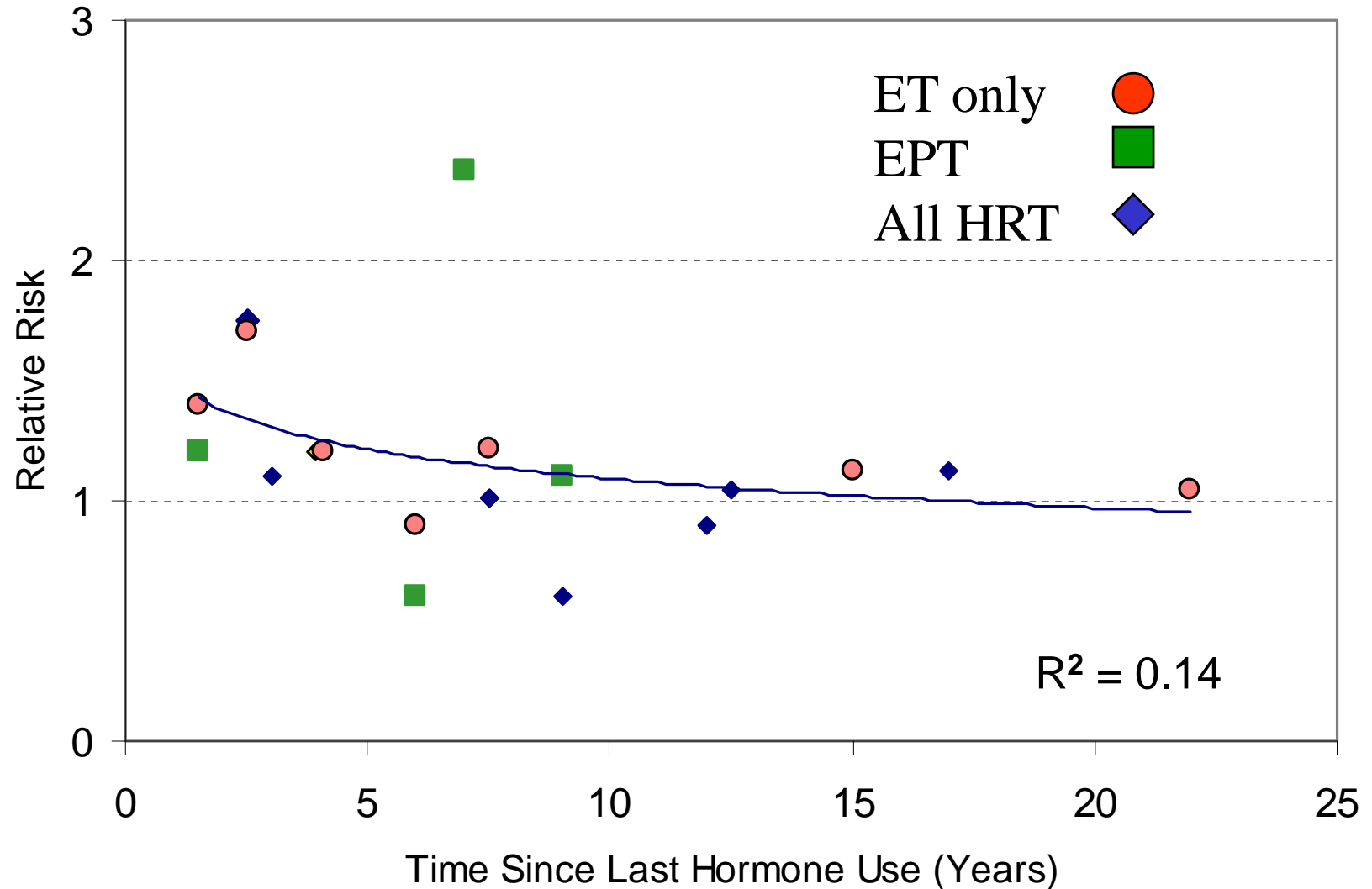
Breast Cancer Incidence by Age



Duration of HT Use



Recency of HT Use and Breast Cancer Risk



Summary of Lobular Breast Cancer

- The hormone-associated risk is two-fold higher for invasive lobular than invasive ductal breast cancer.
- The lobular cancer risk was significantly higher with EP but not with ET.
- The data are based on relatively few cases of lobular cancer.
- Three of seven epidemiological studies are from a single geographic region.