

**Data Analysis I:**  
Results of the Women's Health Initiative  
Randomized Trial of Estrogen plus Progestin

.....  
Garnet Anderson, PhD  
WHI Clinical Coordinating Center  
Fred Hutchinson Cancer Research  
Center



---

---

---

---

---

---

---

---

**WHI Estrogen+Progestin Trial**

**....Background circa 1992**

- Suspected benefits of hormones:
  - ↓ risk of CHD
  - ↓ risk of fracture
  - ↓ risk of colorectal cancer
- Suspected risks of hormones:
  - Possible ↑ risk of breast cancer
  - ↑ risk of VTE/PE



---

---

---

---

---

---

---

---



---

---

---

---

---

---

---

---

# WHI Estrogen+Progestin Trial Specific Aims.....

- To test whether E+P
  - reduces the incidence of CHD and other CVD
  - reduces the incidence of hip fractures and other osteoporotic fractures
  - increases the risk of breast cancer
- To determine the balance of risks and benefits of estrogen+progestin on the overall health of postmenopausal women



---

---

---

---

---

---

---

---

# Women's Health Initiative Trial of Estrogen + Progestin

.....  
Methods

---

---

---

---

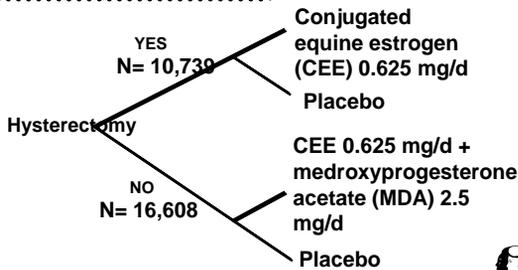
---

---

---

---

# WHI Hormone Program Design



---

---

---

---

---

---

---

---

Risks and benefits of estrogen plus progestin in healthy menopausal women:  
Principal Results from the Women's Health Initiative randomized controlled trial

JAMA 2002;288:321-333

---

---

---

---

---

---

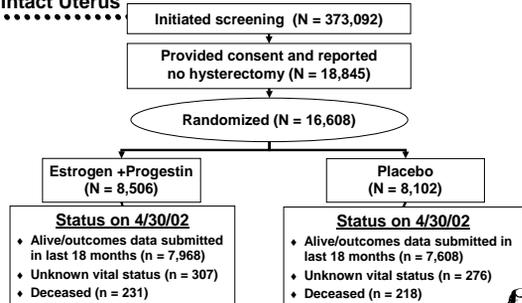
---

---

---

---

Profile of the Women's Health Initiative Randomized Trial of Estrogen Plus Progestin in Women With an Intact Uterus




---

---

---

---

---

---

---

---

---

---

Baseline Characteristics of E+P Participants by Randomization Assignment

	Estrogen + Progestin			Placebo			P-value
	N	Mean	SD	N	Mean	SD	
Age (yrs) at screening	8506	63.2	7.1	8102	63.3	7.1	0.39
BMI (kg/m <sup>2</sup> )	8470	28.5	5.8	8050	28.5	5.9	0.66
Systolic BP (mm Hg)	8506	127.6	17.6	8102	127.8	17.5	0.51
Diastolic BP (mm Hg)	8506	75.6	9.1	8102	75.8	9.1	0.31

---

---

---

---

---

---

---

---

---

---

### Baseline Characteristics of E+P Participants by Randomization Assignment

	Estrogen + Progestin		Placebo		P-value
	N	%	N	%	
<b>Ethnicity</b>					0.33
White	7140	83.9	6805	84.0	
Black	549	6.5	575	7.1	
Hispanic	472	5.5	416	5.1	
American Indian	26	0.3	30	0.4	
Asian/Pacific Islander	194	2.3	169	2.1	
Unknown	125	1.5	107	1.3	




---

---

---

---

---

---

---

---

---

---

### Baseline Characteristics of E+P Participants by Randomization Assignment

	Estrogen + Progestin		Placebo		P-value
	N	%	N	%	
Treated diabetes	374	4.4	360	4.4	0.88
Treated for hypertension or BP $\geq$ 140/90	3039	35.7	2429	36.4	0.37
High cholesterol requiring pills	944	12.5	962	12.9	0.50
Statin use	590	6.9	548	6.8	0.66
Aspirin ( $\geq$ 80mg) use	1623	19.1	1631	20.1	0.09




---

---

---

---

---

---

---

---

---

---

### Baseline Characteristics of E+P Participants by Randomization Assignment

	Estrogen + Progestin		Placebo		P-value
	N	%	N	%	
History of MI	139	1.6	157	1.9	0.14
History of angina	238	2.8	234	2.9	0.73
History of CABG/PTCA	95	1.1	120	1.5	0.04
History of stroke	61	0.7	77	1.0	0.10
History of DVT or PE	79	0.9	62	0.8	0.25




---

---

---

---

---

---

---

---

---

---

## Baseline Characteristics of E+P Participants by Randomization Assignment

	Estrogen + Progestin		Placebo		P-value
	N	%	N	%	
<b>Hormone use</b>					0.49
Never	6280	73.9	6024	74.4	
Past	1674	19.7	1588	19.6	
Current	548	6.4	487	6.0	
<b>Duration of prior hormone use (years)</b>					0.25
<5	1538	69.1	1467	70.6	
5 - 10	426	19.1	357	17.2	
10+	262	11.8	253	12.2	




---

---

---

---

---

---

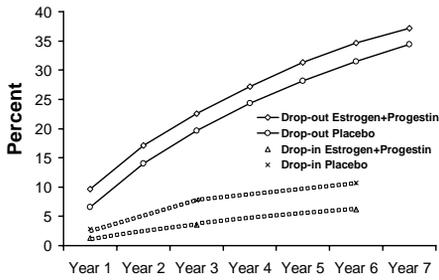
---

---

---

---

## Cumulative Drop-out and Drop-in Rates by Randomization Assignment and Follow-up Time




---

---

---

---

---

---

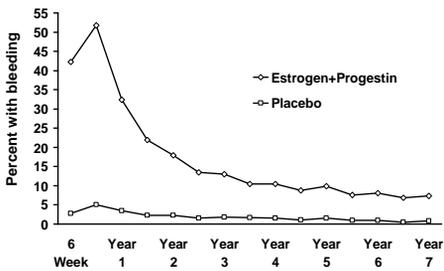
---

---

---

---

## Reports of Bleeding by Randomization Assignment




---

---

---

---

---

---

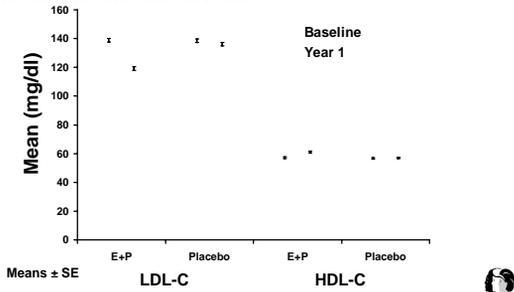
---

---

---

---

## Blood Specimen Analysis for E+P Participants




---

---

---

---

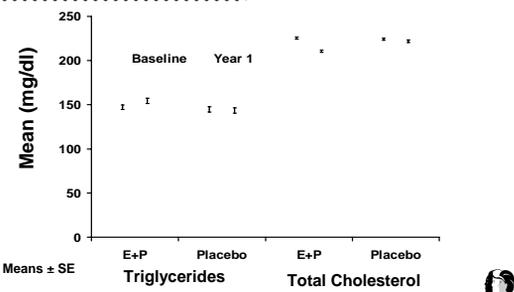
---

---

---

---

## Blood Specimen Analysis for E+P Participants




---

---

---

---

---

---

---

---

## Data Analysis Plan

Analyses of clinical event rates based on a weighted logrank test

$$Z = \sum w_i(O_i - E_i)$$

With weights defined for each endpoint to reflect the anticipated lag-time to full intervention effect

---

---

---

---

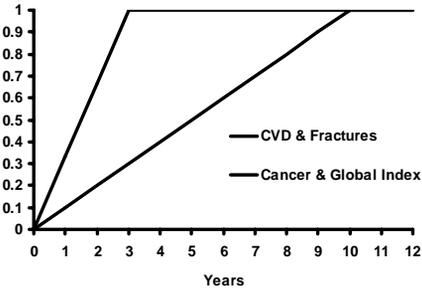
---

---

---

---

### Weights by time since randomization for the logrank statistic



---

---

---

---

---

---

---

---

### Data Analysis Plan

- Primary endpoint
  - Monitored with O'Brien-Fleming (OBF) stopping boundaries
    - for benefit, with 1-sided 0.025 level test
    - for harm, with 1-sided 0.05 test and Bonferroni correction for multiple endpoints
- Primary adverse effect
  - Monitored with 1-sided 0.05 level OBF boundary

---

---

---

---

---

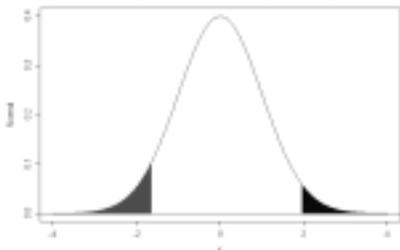
---

---

---

### Levels of statistical evidence

$\Pr(X < -1.645) = 0.05$  and  $\Pr(X > 1.96) = 0.025$



---

---

---

---

---

---

---

---

# Data Analysis Plan

- All other specified endpoints
  - Monitored for harm with OBF, with Bonferroni correction for multiple endpoints
- Global Index—considered supportive of overall
  - Benefit, if statistic were greater than an upper 0.05-level OBF
  - Harm, if statistic were smaller than  $Z=-1$

---

---

---

---

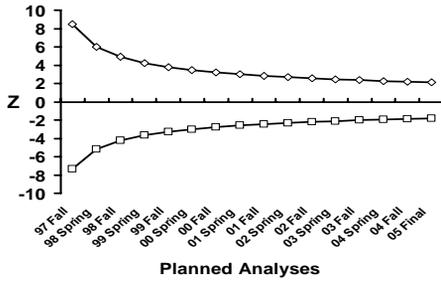
---

---

---

---

## OBF boundaries for primary beneficial effect (CHD) and for primary adverse effect (breast cancer)




---

---

---

---

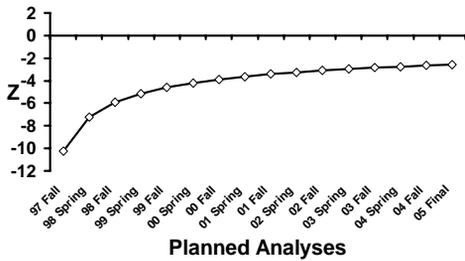
---

---

---

---

## OBF lower limit for secondary adverse outcomes (CHD, Hip Fractures, PE, Colorectal Cancer, Endometrial Cancer, DOC)




---

---

---

---

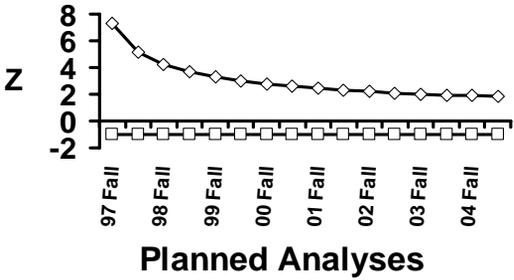
---

---

---

---

Boundaries for evidence of support from the global index for benefit or harm



---

---

---

---

---

---

---

---

Early stopping of the E+P trial

- May 31, 2002—With data from an average of 5.2 years of follow-up, the WHI Data and Safety Monitoring Board recommended that the E+P trial be stopped early based on:
  - Breast cancer statistic exceeding the pre-specified adverse effect boundary
  - Global index of overall effects supporting overall harm, as defined in the monitoring plan

---

---

---

---

---

---

---

---

Reporting the E+P results

- NHLBI accepted decision on May 31
- Paper submitted to JAMA on June 5
  - based on locally adjudicated outcome data
  - Outcomes data available through April 30, 2003
- Paper published
  - July 9 on the web
  - July 19 in JAMA

---

---

---

---

---

---

---

---

## Issues arising in reporting principal results...

- Estimation versus hypothesis testing
- Weighted versus unweighted analyses
- Accounting for asymmetry in assessing benefits and harms
- Acknowledgement of multiple testing
  - over time
  - across endpoints

---

---

---

---

---

---

---

---

---

---




---

---

---

---

---

---

---

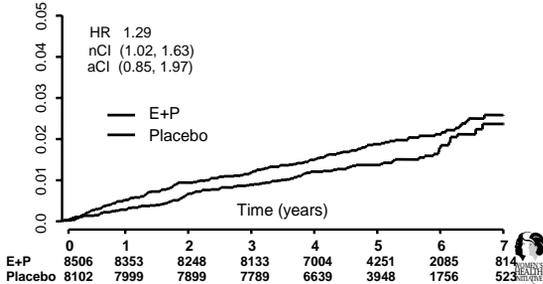
---

---

---

## Kaplan-Meier Estimates of Cumulative Hazards for CHD

The number of women at risk are presented below the horizontal axis for each treatment arm.




---

---

---

---

---

---

---

---

---

---

### Clinical Outcomes (Annualized Percentage) by Randomization Assignment

#### CHD

	Estrogen + Progestin		Placebo		Ratio
Year 1	43	(0.51%)	23	(0.29%)	1.78
Year 2	36	(0.43%)	30	(0.38%)	1.15
Year 3	20	(0.24%)	18	(0.23%)	1.06
Year 4	25	(0.32%)	24	(0.32%)	0.99
Year 5	23	(0.39%)	9	(0.16%)	2.38
Year 6	17	(0.33%)	18	(0.42%)	0.78

Z-value for trend **-1.19**




---

---

---

---

---

---

---

---

---

---

### Clinical Outcomes (Annualized Percentage) by Randomization Assignment

	Estrogen + Progestin		Hazard Ratio	95% CI	
		Placebo		Nominal	Adjusted*
CHD †	164	122	1.29	(1.02, 1.63)	(0.85, 1.97)
	(0.37%)	(0.30%)			
CHD Death	33	26	1.18	(0.70, 1.97)	(0.47, 2.98)
	(0.07%)	(0.06%)			
Non-fatal MI	133	96	1.32	(1.02, 1.72)	(0.82, 2.13)
	(0.30%)	(0.23%)			
CABG / PTCA	183	171	1.04	(0.84, 1.28)	(0.71, 1.51)
	(0.42%)	(0.41%)			

\* Adjusted for multiple comparisons across time (OBF procedures). A Bonferroni adjustment for 7 outcomes was applied to all outcomes other than CHD, Breast Cancer and the global Index.

† CHD includes acute MI requiring hospitalization, silent MI determined from serial electrocardiograms and coronary deaths. There were 8 silent MIs.




---

---

---

---

---

---

---

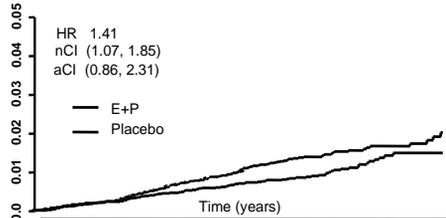
---

---

---

### Kaplan-Meier Estimates of Cumulative Hazards for Stroke

The number of women at risk are presented below the horizontal axis for each treatment arm.



	0	1	2	3	4	5	6	7
E+P	8506	8375	8277	8155	7032	4272	2088	814
Placebo	8102	8005	7912	7804	6659	3960	1760	524




---

---

---

---

---

---

---

---

---

---

Clinical Outcomes (Annualized Percentage)  
by Randomization Assignment

**Stroke**

	Estrogen + Progestin		Placebo		Ratio
Year 1	17	(0.20%)	17	(0.21%)	0.95
Year 2	27	(0.32%)	15	(0.19%)	1.72
Year 3	30	(0.36%)	16	(0.20%)	1.79
Year 4	25	(0.32%)	14	(0.19%)	1.70
Year 5	16	(0.27%)	8	(0.14%)	1.87
Year 6	12	(0.23%)	15	(0.35%)	0.66

Z-value for trend -0.51




---

---

---

---

---

---

---

---

---

---

Clinical Outcomes (Annualized Percentage)  
by Randomization Assignment

	Estrogen + Progestin	Placebo	Hazard Ratio	95% CI	
				Nominal	Adjusted
Stroke	127 (0.29%)	85 (0.21%)	1.41	(1.07,1.85)	(0.86,2.31)
Fatal stroke	16 (0.04%)	13 (0.03%)	1.20	(0.58,2.50)	(0.32,4.49)
Non-fatal stroke	94 (0.21%)	59 (0.14%)	1.50	(1.08,2.08)	(0.83,2.70)

Interim results: Data accumulated through April 30, 2002




---

---

---

---

---

---

---

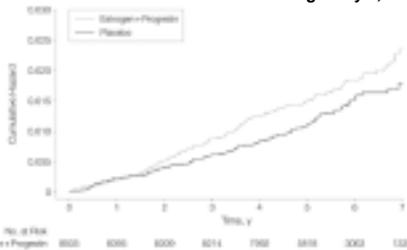
---

---

---

Kaplan-Meier estimates of cumulative hazard  
for stroke by randomization assignment

Data through July 7, 2002



Smoller, Hendrix, Limacher, Heiss, Kooperberg, Baird, et al. Effect of Estrogen Plus Progestin on Stroke in Postmenopausal Women: the Women's Health Initiative. JAMA 2003;289:2673-2684.

---

---

---

---

---

---

---

---

---

---

## Final Clinical Outcomes (Annualized Percentage) by Randomization Assignment

Data through July 7, 2002

	Estrogen + Progestin	Placebo	Hazard Ratio	Nominal 95% CI
<b>All Stroke</b>	151 (0.31%)	107 (0.24%)	1.31	(1.02,1.68)
Ischemic	125 (0.26%)	81 (0.18%)	1.44	(1.09,1.90)
Hemorrhagic	18 (0.04%)	20 (0.04%)	0.82	(0.43,1.56)

Smoller, Hendrix, Limacher, Heiss, Kooperberg, Baird, et al. Effect of Estrogen Plus Progestin on Stroke in Postmenopausal Women: the Women's Health Initiative. *JAMA* 2003;289:2673-2684.




---

---

---

---

---

---

---

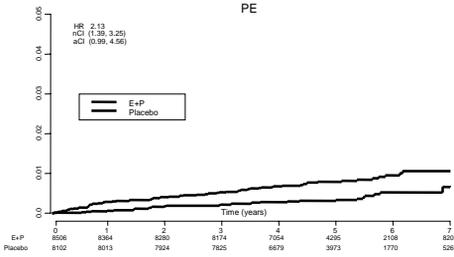
---

---

---

## Kaplan-Meier Estimates of Cumulative Hazards for PE

The number of women at risk are presented below the horizontal axis for each treatment arm.




---

---

---

---

---

---

---

---

---

---

## Clinical Outcomes (Annualized Percentage) by Randomization Assignment

95% CI

	Estrogen + Progestin	Placebo	Hazard Ratio	Nominal	Adjusted
<b>VTE†</b>	151 (0.34%)	67 (0.16%)	2.11	(1.58,2.82)	(1.26,3.55)
<b>DVT†</b>	115 (0.26%)	52 (0.13%)	2.07	(1.49,2.87)	(1.14,3.74)
<b>PE†</b>	70 (0.16%)	31 (0.08%)	2.13	(1.39,3.25)	(0.99,4.56)

† VTE, venous thromboembolic disease; DVT, deep vein thrombosis; PE, pulmonary embolism




---

---

---

---

---

---

---

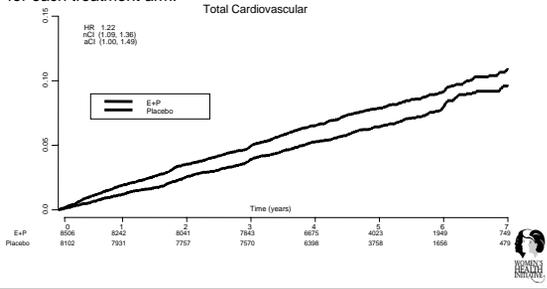
---

---

---

## Kaplan-Meier Estimates of Cumulative Hazards for Total CVD

The number of women at risk are presented below the horizontal axis for each treatment arm.




---

---

---

---

---

---

---

---

---

---

## Clinical Outcomes (Annualized Percentage) by Randomization Assignment

	Estrogen + Progestin	Placebo	Hazard Ratio	95% CI	
				Nominal	Adjusted
Total CVD	694 (1.57%)	546 (1.32%)	1.22	(1.09, 1.36)	(1.00, 1.49)




---

---

---

---

---

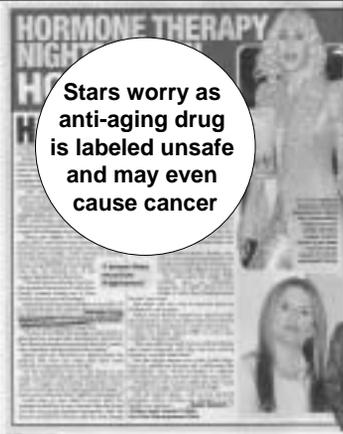
---

---

---

---

---



**Stars worry as anti-aging drug is labeled unsafe and may even cause cancer**

---

---

---

---

---

---

---

---

---

---

## Clinical Outcomes (Annualized Percentage) by Randomization Assignment

	Estrogen + Progestin	Placebo	Hazard Ratio	95% CI	
				Nominal	Adjusted
<b>Invasive breast cancer</b>	<b>166</b> <b>(0.38%)</b>	<b>124</b> <b>(0.30%)</b>	<b>1.26</b>	<b>(1.00,1.59)</b>	<b>(0.83,1.92)</b>
Endometrial cancer	22 (0.05%)	25 (0.06%)	0.83	(0.47,1.47)	(0.29,2.32)
Colorectal cancer	45 (0.10%)	67 (0.16%)	0.63	(0.43,0.92)	(0.32,1.24)
Total cancer	502 (1.14%)	458 (1.11%)	1.03	(0.90,1.17)	(0.86,1.22)




---

---

---

---

---

---

---

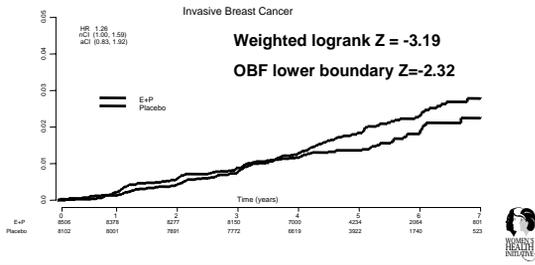
---

---

---

## Kaplan-Meier Estimates of Cumulative Hazards for Breast Cancer

The number of women at risk are presented below the horizontal axis for each treatment arm.




---

---

---

---

---

---

---

---

---

---

## Clinical Outcomes (Annualized Percentage) by Randomization Assignment

### Invasive breast cancer

	Estrogen + Progestin	Placebo	Ratio
Year 1	11 (0.13%)	17 (0.21%)	17
Year 2	26 (0.31%)	30 (0.38%)	30
Year 3	28 (0.34%)	23 (0.29%)	23
Year 4	40 (0.50%)	22 (0.29%)	22
Year 5	34 (0.57%)	12 (0.22%)	12
Year 6	27 (0.53%)	20 (0.47%)	20

Z-value for trend 2.56




---

---

---

---

---

---

---

---

---

---




---

---

---

---

---

---

---

---

**Breast Cancer Outcome (Annualized Percentages)  
by Prior Postmenopausal Hormone Use**

	Estrogen + Progestin	Placebo	Hazard Ratio	95% Nominal CI
Years of Prior Use				
Never used	114 (0.35%)	102 (0.33%)	1.06	(0.81,1.38)
<5	32 (0.39%)	15 (0.20%)	2.13	(1.15,3.94)
5 - <10	11 (0.49%)	2 (0.11%)	4.61	(1.01,21.02)
≥10	9 (0.69%)	5 (0.40%)	1.81	(0.60,5.43)




---

---

---

---

---

---

---

---

**Final Clinical Outcomes (Annualized Percentage) by  
Randomization Assignment**

Data through July 7, 2002

	Estrogen + Progestin	Placebo	Hazard Ratio	Weighted P-values
Invasive breast cancer	199 (0.41%)	150 (0.33%)	1.24	0.003
In situ breast cancer	47 (0.10%)	37 (0.08%)	1.18	0.086
Total breast cancer	245 (0.54%)	185 (0.41%)	1.24	0.0004

Nominal 95% CI: (1.01,1.54); Adjusted 95% CI (0.97,1.59)

Chlebowski, Hendrix, Langer, Stefanick, Gass, Cyr, et al. Estrogen plus progestin influence on breast cancer and mammography in healthy postmenopausal women in the Women's Health Initiative randomized trial. JAMA 2003;289.




---

---

---

---

---

---

---

---

### Breast cancer tumor size by randomization assignment

Data through July 7, 2002

	Estrogen+Progestin		Placebo		p-value
Tumor size, cm	170	1.7(1.1)	128	1.5(0.9)	0.038
Tumor size	<u>N</u>	<u>%</u>	<u>N</u>	<u>%</u>	0.504
No primary mass	0	0.0	1	0.7	
Microscopic foci	8	4.3	9	6.4	
< 0.5 cm	18	9.7	17	12.1	
0.5 – 1 cm	45	24.2	36	25.5	
1 – 2 cm	73	39.2	56	39.7	
2 – 5 cm	37	19.9	21	14.9	
> 5 cm	5	2.7	1	0.7	
Missing	13	6.5	9	6.0	0.84

Chlebowski, et al. JAMA (2003)




---

---

---

---

---

---

---

---

---

---

### Positive lymph nodes in breast cancer cases by randomization assignment

Data through July 7, 2002

	Estrogen+Progestin		Placebo		p-value
Women with lymph nodes examined	191	10.3(7.9)	143	10.9(7.8)	0.52
Number of + nodes					0.08
None	129	74.1	112	84.2	
1 – 3	36	20.7	15	11.3	
4+	9	5.2	6	4.5	
Missing	25	12.6	17	11.3	0.73

Chlebowski, et al. JAMA (2003)




---

---

---

---

---

---

---

---

---

---

### SEER stage of breast cancer cases by randomization assignment

Data through July 7, 2002

	Estrogen+Progestin		Placebo		p-value
SEER stage					0.048
Localized	144	74.6	124	82.7	
Regional	47	24.4	21	14.0	
Metastatic	2	1.0	3	2.0	
Missing	6	3.0	2	1.3	0.47

Chlebowski, et al. JAMA (2003)




---

---

---

---

---

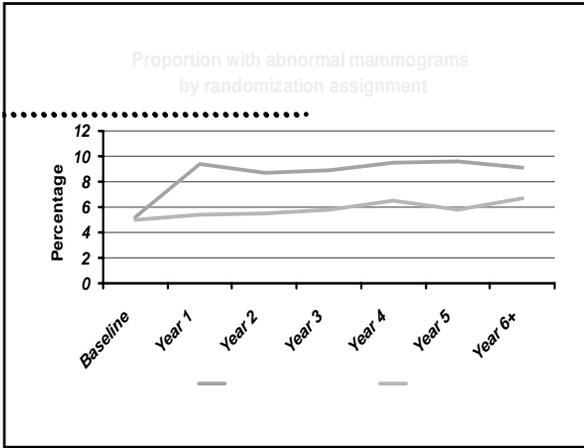
---

---

---

---

---




---

---

---

---

---

---

---

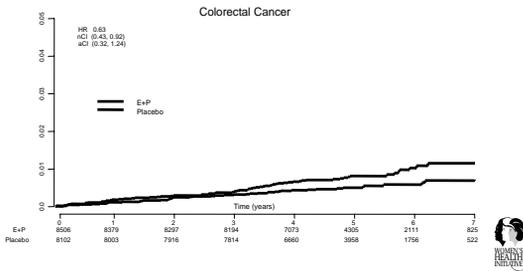
---

---

---

### Kaplan-Meier Estimates of Cumulative Hazards for Colorectal Cancer

The number of women at risk are presented below the horizontal axis for each treatment arm.




---

---

---

---

---

---

---

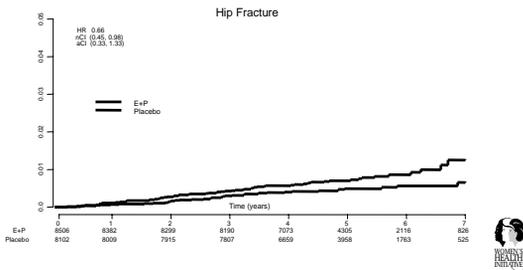
---

---

---

### Kaplan-Meier Estimates of Cumulative Hazards for Hip Fracture

The number of women at risk are presented below the horizontal axis for each treatment arm.




---

---

---

---

---

---

---

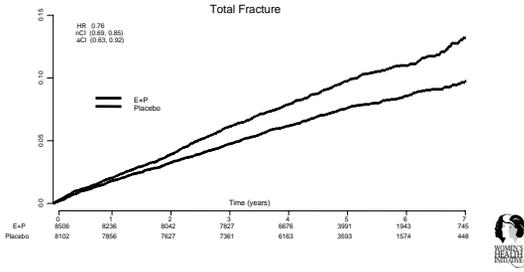
---

---

---

## Kaplan-Meier Estimates of Cumulative Hazards for Total Fractures

The number of women at risk are presented below the horizontal axis for each treatment arm.




---

---

---

---

---

---

---

---

---

---

## Clinical Outcomes (Annualized Percentage) by Randomization Assignment

	Estrogen +		Hazard Ratio	95% CI	
	Progestin	Placebo		Nominal	Adjusted
Hip fracture	44 (0.10%)	62 (0.15%)	0.66	(0.45,0.98)	(0.33,1.33)
Vertebral fracture	41 (0.09%)	60 (0.15%)	0.66	(0.44,0.98)	(0.32,1.34)
Other osteoporotic fracture†	579 (1.31%)	701 (1.70%)	0.77	(0.69,0.86)	(0.63,0.94)
Total fracture	650 (1.47%)	788 (1.91%)	0.76	(0.69,0.85)	(0.63,0.92)

† Other osteoporotic fractures include all fractures other than chest/sternum, skull/face, fingers, toes and cervical vertebrae, and hip and vertebral fractures (reported separately).




---

---

---

---

---

---

---

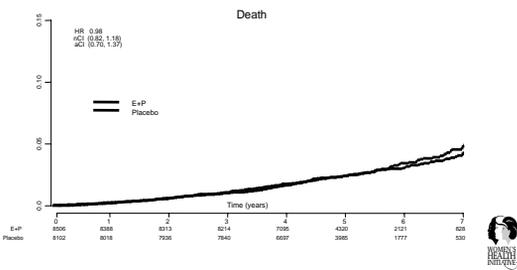
---

---

---

## Kaplan-Meier Estimates of Cumulative Hazards for Death

The number of women at risk are presented below the horizontal axis for each treatment arm.




---

---

---

---

---

---

---

---

---

---

## Causes of Death (Annualized Percentages) by Randomization Assignment

	Estrogen + Progestin	Placebo
Number randomized	8506	8102
Mean follow-up time (months)	62.2	61.2
Total deaths	231	(0.52%)
Adjudicated deaths	215	(0.49%)
Cardiovascular	65	(0.15%)
Breast cancer	3	(0.01%)
Other cancer	104	(0.24%)
Other known cause	34	(0.08%)
Unknown cause	9	(0.02%)




---

---

---

---

---

---

---

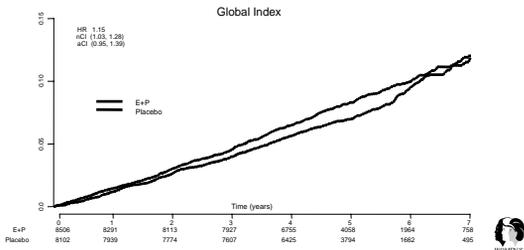
---

---

---

## Kaplan-Meier Estimates of Cumulative Hazards for the Global Index

The number of women at risk are presented below the horizontal axis for each treatment arm.




---

---

---

---

---

---

---

---

---

---

## Clinical Outcomes (Annualized Percentage) by Randomization Assignment

	Estrogen + Progestin	Placebo	Hazard Ratio	95% CI	
				Nominal	Adjusted
Death from other causes	165 (0.37%)	166 (0.40%)	0.92	(0.74, 1.14)	(0.62, 1.35)
Total death	231 (0.52%)	218 (0.53%)	0.98	(0.82, 1.18)	(0.70, 1.37)
<b>Global index †</b>	<b>751 (1.70%)</b>	<b>623 (1.51%)</b>	<b>1.15</b>	<b>(1.03, 1.28)</b>	<b>(0.95, 1.39)</b>

† Global index is the first event for each participant from among the following types: CHD; stroke; PE; breast cancer; endometrial cancer; colorectal cancer; hip fracture; and death from other causes




---

---

---

---

---

---

---

---

---

---

## Attributable Risk Summary

- Excess risk per 10,000 person-years on E+P
  - 7 more women with CHD
  - 8 more women with stroke
  - 8 more women with PE
  - 8 more women with breast cancer
- Risk reduction per 10,000 person-years on E+P
  - 6 fewer women with colorectal cancer
  - 5 fewer women hip fractures
- Summary: 19 additional women with monitored events per 10,000 person-years on E+P

---

---

---

---

---

---

---

---

## Women's Health Initiative Trial of Estrogen + Progestin

### Summary

---

---

---

---

---

---

---

---

## WHI Estrogen+Progestin Trial Summary

- Treatment with estrogen plus progestin for up to 5 years is not beneficial overall.
- There is early harm for CHD, continuing harm for stroke and VTE, and increasing harm for breast cancer.
- This risk-benefit profile is not consistent with a viable intervention for primary prevention of chronic diseases in postmenopausal women.

---

---

---

---

---

---

---

---

## Aftermath of the publication

.....  
Critiques and Response

---

---

---

---

---

---

---

---

## WHI studied the wrong women:

.....  
They were too old—this is not how hormones are used in practice.  
They had pre-existing disease.  
They were too fat.

---

---

---

---

---

---

---

---

## Clinical Outcomes (Annualized Percentage) by Randomization Assignment

### CHD

	Estrogen + Progestin	Placebo	Ratio
Age			
50 - 59	33 (0.21%)	19 (0.13%)	1.67
60 - 69	68 (0.35%)	51 (0.28%)	1.26
70 - 79	63 (0.71%)	52 (0.60%)	1.18



---

---

---

---

---

---

---

---

Clinical Outcomes (Annualized Percentage)  
by Randomization Assignment

**Stroke**

	Estrogen + Progestin	Placebo	Ratio
Age			
50 - 59	19 (0.12%)	11 (0.08%)	1.57
60 - 69	54 (0.27%)	36 (0.20%)	1.40
70 - 79	54 (0.61%)	38 (0.44%)	1.35




---

---

---

---

---

---

---

---

Clinical Outcomes (Annualized Percentage)  
by Randomization Assignment

**VTE**

	Estrogen + Progestin	Placebo	Ratio
Age			
50 - 59	28 (0.18%)	9 (0.06%)	2.87
60 - 69	71 (0.36%)	35 (0.19%)	1.90
70 - 79	52 (0.58%)	23 (0.27%)	2.18




---

---

---

---

---

---

---

---

Clinical Outcomes (Annualized Percentage)  
by Randomization Assignment

**Global Index**

	Estrogen + Progestin	Placebo	Ratio
Age			
50 - 59	142 (0.92%)	115 (0.80%)	1.16
60 - 69	339 (1.72%)	271 (1.48%)	1.18
70 - 79	270 (3.03%)	237 (2.76%)	1.10




---

---

---

---

---

---

---

---

CHD Outcomes (Annualized Percentages) by  
Self-Reported History of CHD Related Conditions

	Estrogen + Progestin	Placebo	Hazard Ratio	95% Nominal CI
No prior MI or CABG/PTCA	145 (0.34%)	106 (0.26%)	1.28	(1.00,1.65)
Prior MI or CABG/PTCA	19 (2.08%)	16 (1.60%)	1.28	(0.64,2.56)




---

---

---

---

---

---

---

---

The trial was flawed.

- .....
- Too many women were unblinded.
- Too many women dropped out.

---

---

---

---

---

---

---

---

Effect of non-adherence to  
interventions

- Cross-contamination dilutes the differences between groups
  - Lack of adherence to active intervention tends to reduce the intervention’s impact on diseases, both positive and negative
  - Exposure of control arm to active intervention introduces the effects into the comparison group

---

---

---

---

---

---

---

---

## Considering adherence in analyses

.....

- Intent-to-treat analysis must always be the basis of primary analyses
- Should not assume lack of adherence is uncorrelated with events
- Sensitivity analyses may give some hint of the impact of non-adherence

---

---

---

---

---

---

---

---

## Types of sensitivity analyses

.....

- “Per Protocol”—censoring data after individuals become non-adherent
  - Preserves original randomization assignment
  - Stops counting events when there is no intervention
  - May reduce power
  - May need to consider carry-over effect

---

---

---

---

---

---

---

---

## Types of sensitivity analyses

.....

- “As Treated”—changes the treatment arm of the individual as that person changes exposure
  - Assigns follow-up time and events to the current exposure
  - Retains all events
  - May be complicated by lag-time and carry-over effects
  - Does not respect the randomization

---

---

---

---

---

---

---

---

## “Per protocol” sensitivity analysis of selected outcomes in the E+P trial\*

	Hazard Ratio	95% Nominal CI
CHD	1.51	(1.13,2.01)
Stroke	1.67	(1.17,2.40)
VTE	3.29	(2.25,4.82)
Invasive breast cancer	1.49	(1.10,2.02)

\* Censored 6 months after becoming non-adherent (using <80%, or stopping pills)



---

---

---

---

---

---

---

---

The trial was stopped too early.

.....  
Nothing was significant.  
Longer follow-up is needed.

---

---

---

---

---

---

---

---

## Statistical considerations in reporting WHI results

- Monitoring analyses based on more sophisticated (weighted) statistics
- Presentation provided unweighted hazard ratios and confidence intervals because
  - Familiar
  - Quantitative estimate of effect sizes

---

---

---

---

---

---

---

---

## Statistical considerations in reporting WHI results

- Nominal confidence intervals were shown because
  - Familiar
  - Interpretable individually as having 95% chance of covering the true hazard ratio
  - Can be compared to other studies
  - Have a probability > 5% of rejecting the null hypothesis of no treatment effects on any disease examined

---

---

---

---

---

---

---

---

## Statistical considerations in reporting WHI results

- Adjusted confidence intervals were shown to
  - Control overall error rate
  - Interpretable as having a 95% chance of covering the true hazard ratios for all of these endpoints
  - Provide a view of the data closer to that used by the DMSB
  - Are quite conservative

---

---

---

---

---

---

---

---

## Considerations in presenting results

- Transparency of results
- Clinical relevance
- Guidance of
  - the protocol-specified analysis plan
  - the formal monitoring plan
- Avoid over-interpretation
- Respect the DSMB perspective

---

---

---

---

---

---

---

---



---

---

---

---

---

---

---

---