Hormone Replacement Therapy

Reevaluation of Benefits and Risks

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謝燦堂副院長

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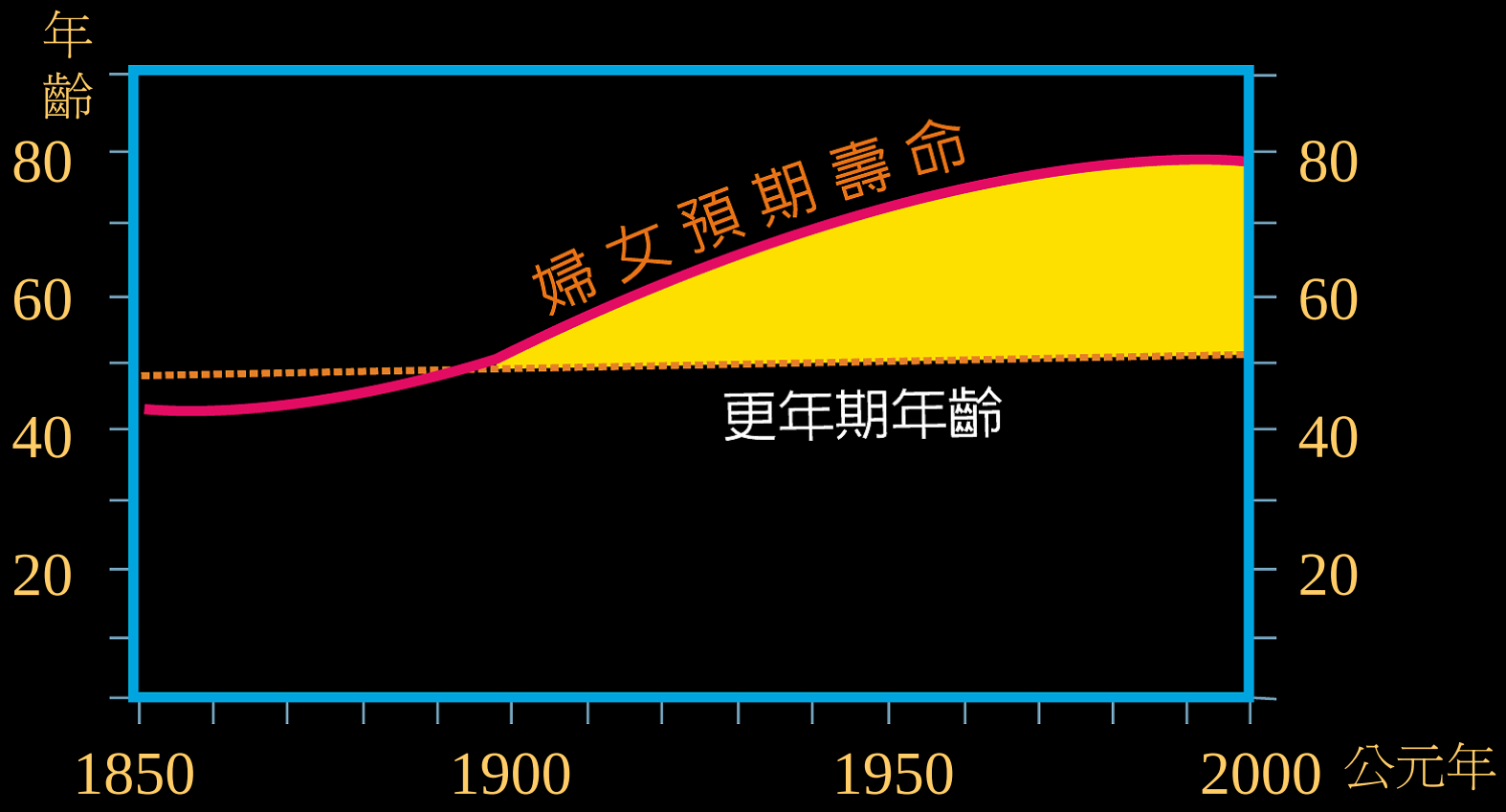
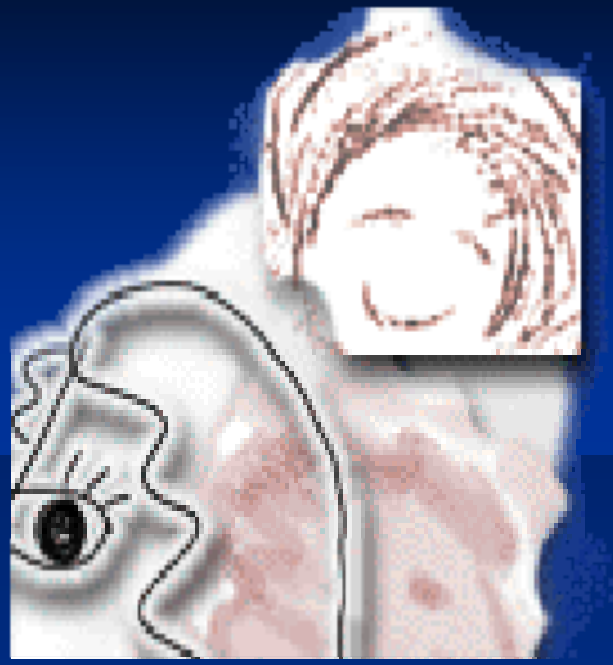
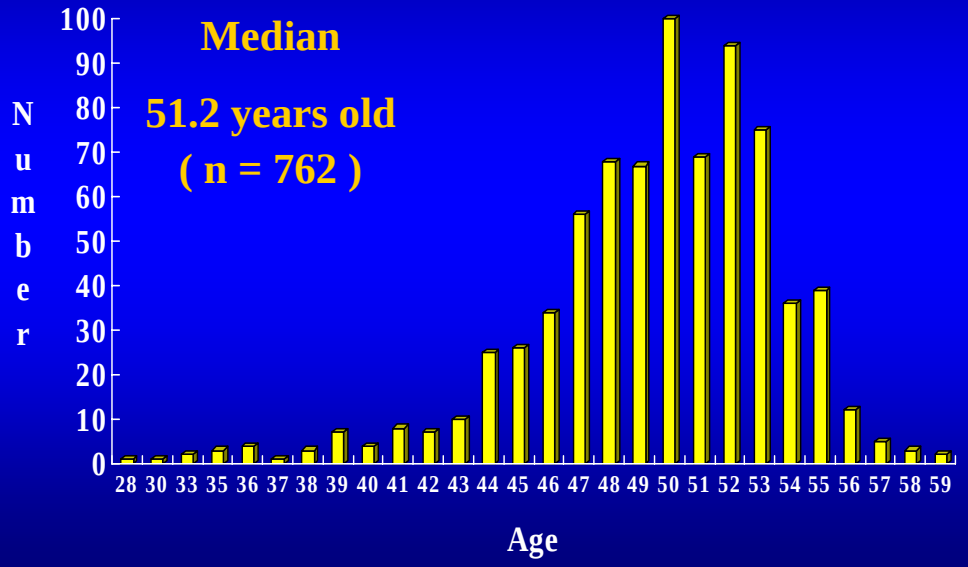
INTRODUCTION

女性的平均壽命 (79.3歲)

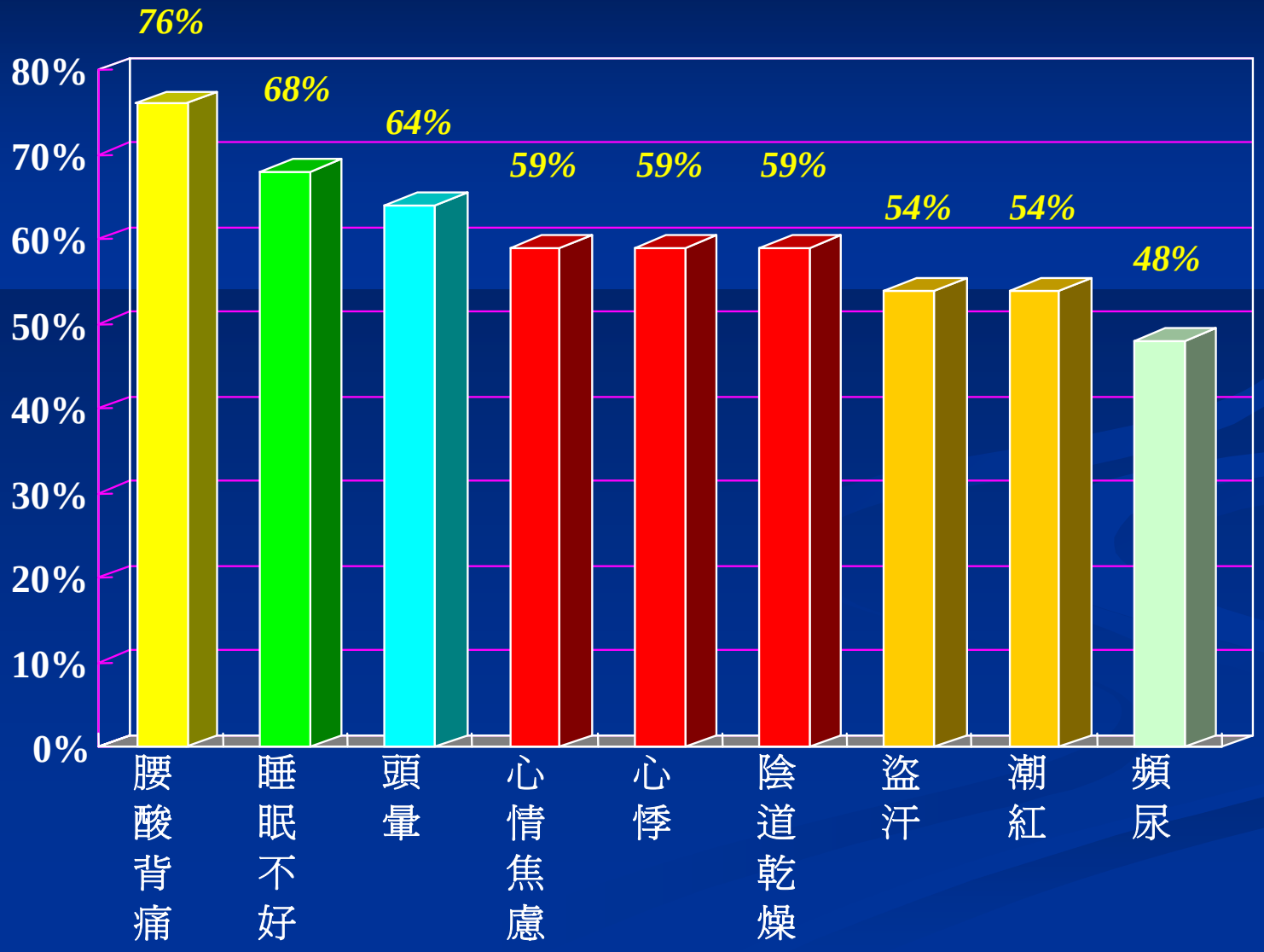




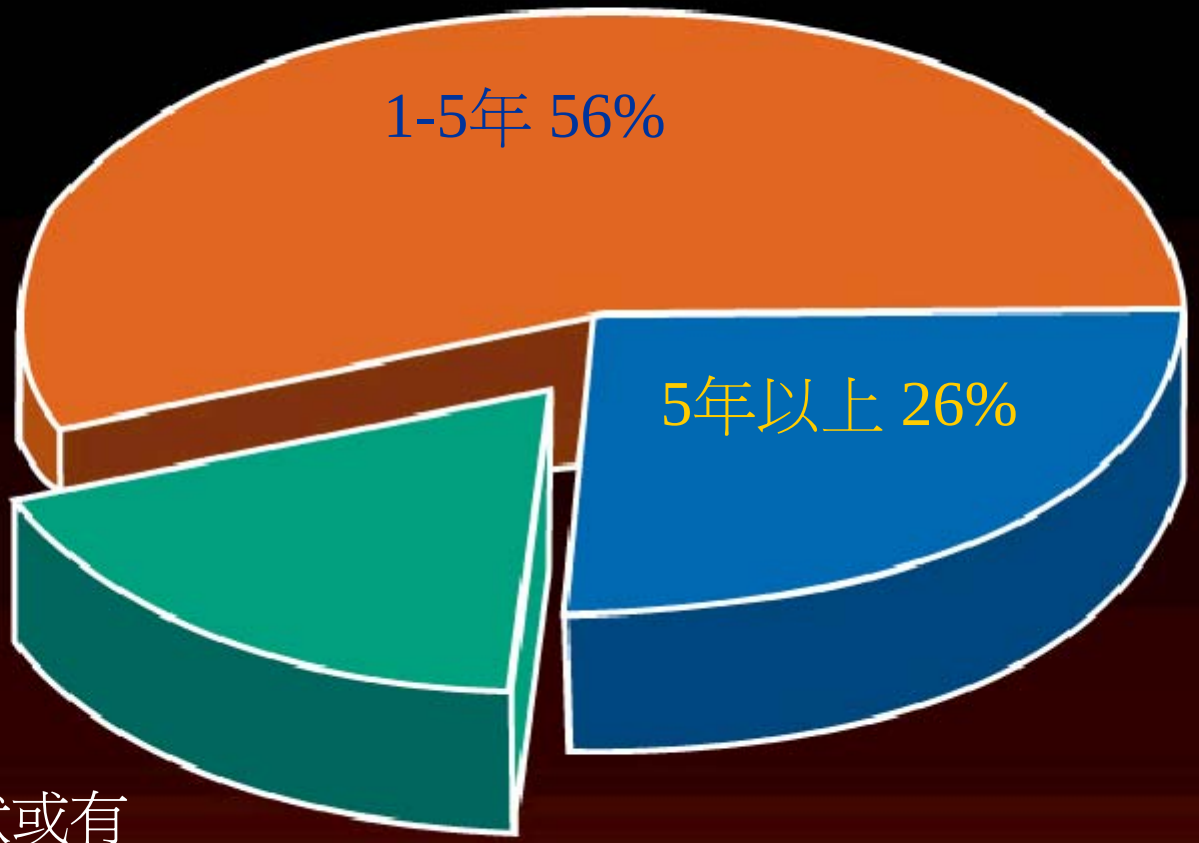
Age of Menopause in Taiwan



更年期症狀


80%
70%
60%
50%
40%
30%
20%
10%
0%
76%
68%
64%
59%
59%
59%
54%
54%
48%
腰酸背痛
睡眠不好
頭暈
心情焦慮
心悸
陰道乾燥
盜汗
潮紅
頻尿

婦女有更年期症狀的平均年數



沒有症狀或有
症狀但不超過一年 18%

參考資料：Mckinlay and Jetterys Br J.
Prov 800 Med 1974:28:108-115

- For over half a century hormonal replacement therapy (HRT) has been accepted as the standard of care for postmenopausal symptoms and many other illnesses associated with and following the menopause.

- Despite decades of accumulated observational evidence, the balance of risks and benefits for hormone use in healthy postmenopausal women remains uncertain.

Risk & Benefits of DRT in Postmenopausal Women

RISKS	UNCERTAIN IMPACT	BENEFITS
Endometrial cancer	Primary prevention of CHD	Relief of vasomotor symptoms
Venous thromboembolism	Cognitive decline of dementia	Increase in bone density
Gallbladder disease		
Breast cancer		
Early increase in CV events in women with CHD		

American Journal of OBSTETRICS AND GYNECOLOGY

Current perspectives on benefits and risks of hormone replacement therapy--- Review

[The Hormone Continuum: Accrual of Women's Health Benefits]

Volume 185(2) Supplement

August 2001

pp. S13-S23

- Prevention of osteoporosis
- Release vasomotor symptoms
- **Protection against cardiovascular disease**
- Prevention of colorectal cancer
- Slowing of the progress of Alzheimer's disease
- **Increase the risk of breast cancer**

- Benefits associated with therapy far outweigh any slight increase in breast cancer risk.

Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women: Principle Results from the Women's Health Initiative (WHI) Randomized Controlled Trial

JAMA Volume 288(3), P321-333,
17 July 2002

荷爾蒙療法 應定期追蹤

連續使用四年以上 必須進一步進行利益風險評估

媒體：自由時報　版面：15 自由廣場　日期：2002/07/13

停經後婦女荷爾蒙替代療法何去何從？

謝炎堯

美國國家衛生研究院發表由其主導的前瞻性停經後婦女荷爾蒙替代療法試驗結果，比較使用和不使用荷爾蒙替代療法各一萬名婦女中，使用者比不使用者，得乳癌的病人多八人，心臟病多七人，中風多八人，下肢和肺臟血栓栓塞多十八人，雖然具有學術性的統計意義，可是對病人的人生意義又是如何？

婦女停經是因爲老化導致卵巢功能衰退，雌激素和黃體素兩種女性荷爾蒙的分泌量減少，引起身體交感神經陷入不穩定狀態，出現臉部灼熱潮紅、冒汗、情緒不穩定、睡眠障礙和憂鬱等更年期症候群症狀。同時全身生理和新陳代謝產生變化，長久以後，骨骼骨質密度減少，骨質疏鬆逐漸進行，至七、八十歲時，常發生脊椎骨和四肢骨折，同時女性生殖器官和膀胱脫退化萎縮，容易感染細菌和黴菌，發生陰道炎和膀胱炎，陰道乾燥，從事房事時，痛苦不堪，從而避免性行爲，可能發生家庭危機。

我國女性平均壽命七十九歲，生理停經年齡在四十五歲至五十五歲之間，所以婦女停經後平均尚有約三十歲的壽命，必須珍惜維持良好的健康狀態。依據世界衛生組織的定義，健康不只是無病，而是肉體無病、精神愉快、家庭圓滿、社交正常和工作稱職。醫師給停經後婦女施行荷爾蒙替代療法，就是要補充老化的衰退卵巢功能，維護停經後婦女的健康。

要解讀美國國家衛生研究院的臨床試驗報告，不要因爲上述差異，不加思索，立即停止一切荷爾蒙替代療法。正確的態度，應該思考是經由荷爾蒙替代療法，阻止或緩解老化的生理衰退和新陳代謝變化，而產生上述的罹病率差異，所以是維持健康和抗衰老所付出的代價。

婦女個人擁有思考能力和自由意志，應自我評估個人家族遺傳背景和健康狀態，和醫師研商討論，決定是否要接受荷爾蒙替代療法。

乳癌、血管粥狀硬化心血管疾病（包括中風和心臟病）以及靜脈血栓栓塞症，有明顯的家族遺傳傾向，已經切除子宮的婦女，沒有子宮體癌（請注意不是子宮頸癌）的顧慮，不需要服用黃體素，單獨服用雌激素，危險性降低，另當別論，此研究報告不適用於這一群婦女。

對是否接受荷爾蒙替代療法，應考慮個人的需要，對預期的可爲老化導致卵巢功能衰退，雌激素和黃體素兩種女性荷爾蒙替代療法，上述停經後的症狀，一定會出現，只是出現的快慢和症狀的輕重的差異而已，當然也要看能活多久。接受荷爾蒙替代療法，罹患乳癌的危險只是高出萬分之八，心臟病高出萬分之八，下肢和肺臟靜脈血栓栓塞症高出萬分之十八。靜脈血栓栓塞症的發生率，中國人和白人，有明顯的種族差異，中國人的罹病率遠低於白人，所以危險性不如白人高。

某些醫師建議改用所謂「植物性女性荷爾蒙（phytoestrogen）」，或服用choxifene（Evista）。所謂「植物性女性荷爾蒙」，只是植物所含有的類固醇，被抽取製成飲食添加物（dietary supplement），沒有正規的醫學文獻證明它具有和藥品雌激素同等的生理作用和療效。

Raloxifene（Evista）和細胞膜的雌激素受器結合，調節雌激素受器的功能，抑制停經後的骨質流失，能防止骨質疏鬆，對乳房和子宮似無作用，所以比較安全，但是也只是對防止骨質疏鬆有效而已，同時要注意臨床研究觀察期間只有三年，在現階段，仍然無法確認有效防止十年以後的骨質疏鬆，而且此藥也有增加下肢和肺臟靜脈血栓塞的危險。

處置治療是人類的創作，難免有學派、主觀判斷及經驗的偏差，不容易取得放諸四海皆準的共識，請停經後的婦女，愼重思考何去何從。（作者謝炎堯／和信治癌中心醫院副院長）

國內三學會：繼續使用荷爾蒙療法

針對美醫界致癌報告 更年期、婦癌、骨質疏鬆醫學會發表聯合聲明 認其實利大於弊

PREMPRO LAWSUITS

Get Legal Help Here

Get Legal Help

Hormone Replacement Therapy

Women's Health Initiative Study

PREMPRO Dangerous Side Effects

Potential Lawsuits

Hormone Replacement Therapy
(HRT)
Reevaluation

Benefits ?


解讀
Women's Health
Initiative Study
研究方法

WHI

- The Women's Health Initiative is a large and complex clinical investigation of strategies for the prevention and control of some of the most common causes of morbidity and mortality among *postmenopausal women*, including *cancer, cardiovascular disease, and osteoporotic fractures.*

- Clinical trial
  - Hormone replacement therapy
  - Calcium & vitamin D supplementation
  - Low-fat eating pattern
- Observation study

Main Outcomes Measures

- Global index
  - Summarizing the balance of risks and benefits
    - CHD
    - Breast cancer
    - Stroke
    - Pulmonary embolism
    - Endometrial cancer
    - Colorectal cancer
    - Hip fracture
    - Death to other cause

- Primary adverse outcome
  - Prevention of coronary heart disease (CHD)
  - Invasive breast cancer

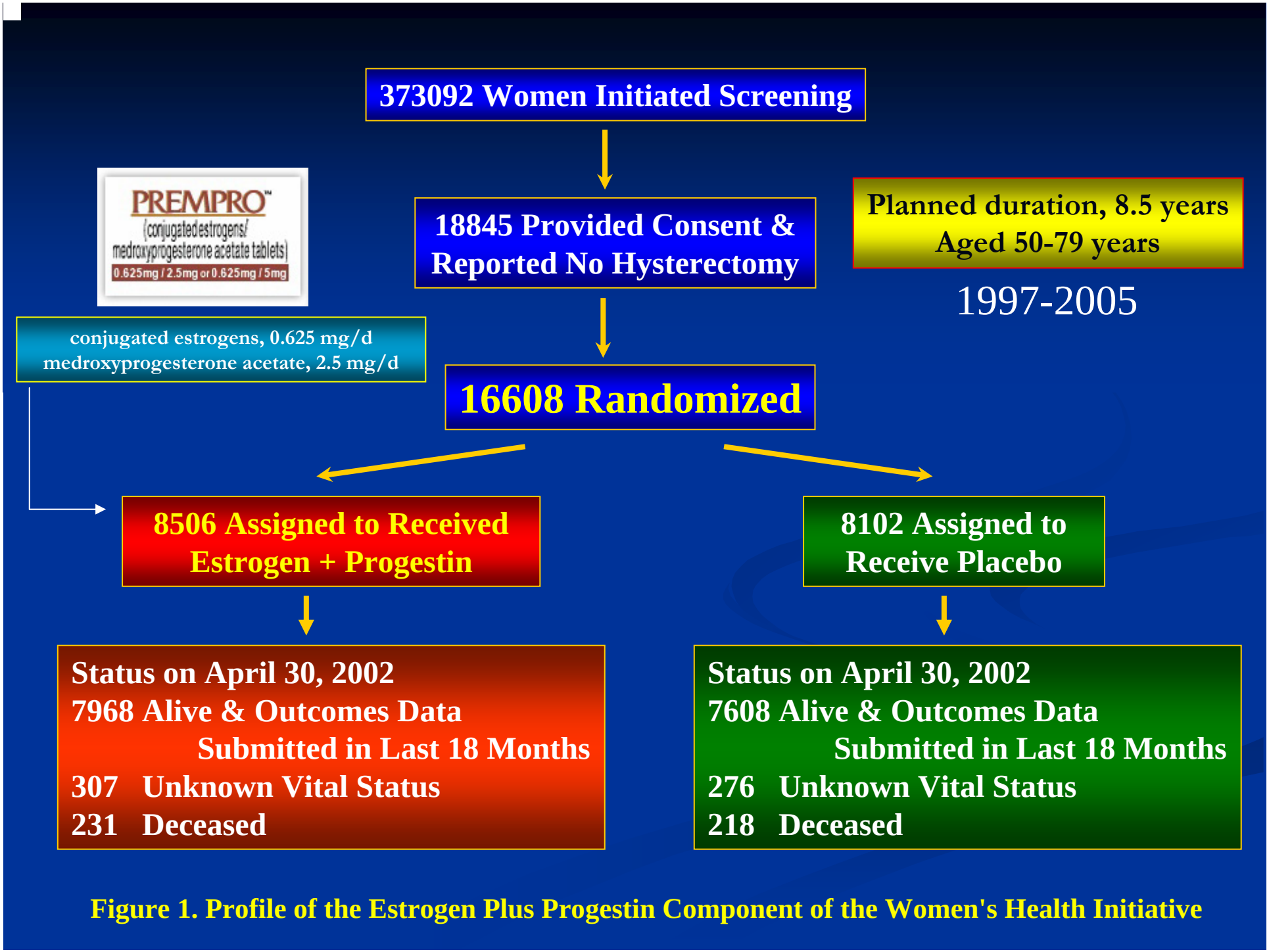


Figure 1. Profile of the Estrogen Plus Progestin Component of the Women's Health Initiative

Data Safety Monitoring Board (DSMB)

Risks

Breast cancer
CHD
Stroke
Pulmonary embolism

outweigh

Benefits

Hip fracture
Colorectal cancer

Early stopping of the estrogen plus progestin component of the trial (5.2 years)

The estrogen-alone portion of the study was not terminated because there is no evidence that the risks of ERT exceed its benefits.

解讀
Women's Health Initiative Study
結果

Baseline Characteristics of the Women's Health Initiative Estrogen Plus Progestin Trial Participants

Characteristics	Estrogen + Progestin (n = 8506)	Placebo (n = 8102)	*P* Value†
Age at screening, mean (SD), y	63.2 (7.1)	63.3 (7.1)	.39
Age group at screening, y			
50-59	2839 (33.4)	2683 (33.1)	.80
60-69	3853 (45.3)	3657 (45.1)	
70-79	1814 (21.3)	1762 (21.7)	
Race/ethnicity			
White	7140 (83.9)	6805 (84.0)	.33
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)	
Hormone use			
Never	6280 (73.9)	6024 (74.4)	.49
Past	1674 (19.7)	1588 (19.6)	
Current‡	548 (6.4)	487 (6.0)	
Duration of prior hormone use, y			
<5	1538 (69.1)	1467 (70.6)	.25
5-10	426 (19.1)	357 (17.2)	
≥10	262 (11.8)	253 (12.2)	

Baseline Characteristics of the Women's Health Initiative Estrogen Plus Progestin Trial Participants

Characteristics	Estrogen + Progestin (n = 8506)	Placebo (n = 8102)	*P* Value†
Body mass index, mean (SD), kg/m²§	28.5 (5.8)	28.5 (5.9)	.66
Body mass index, kg/m²			
<25	2579 (30.4)	2479 (30.8)	.89
25-29	2992 (35.3)	2834 (35.2)	
≥30	2899 (34.2)	2737 (34.0)	
Systolic BP, mean (SD), mm Hg	127.6 (17.6)	127.8 (17.5)	.51
Diastolic BP, mean (SD), mm Hg	75.6 (9.1)	75.8 (9.1)	.31
Smoking			
Never	4178 (49.6)	3999 (50.0)	.85
Past	3362 (39.9)	3157 (39.5)	
Current	880 (10.5)	838 (10.5)	
Parity			
Never pregnant/no term pregnancy	856 (10.1)	832 (10.3)	.67
≥1 term pregnancy	7609 (89.9)	7233 (89.7)	
Age at first birth, y‖			
<20	1122 (16.4)	1114 (17.4)	.11
20-29	4985 (73.0)	4685 (73.0)	
≥30	723 (10.6)	621 (9.7)	

Baseline Characteristics of the Women's Health Initiative Estrogen Plus Progestin Trial Participants

Characteristics	Estrogen + Progestin (n = 8506)	Placebo (n = 8102)	*P* Value†
Treated for diabetes	374 (4.4)	360 (4.4)	.88
Treated for hypertension or BP ≥140/90 mm Hg	3039 (35.7)	2949 (36.4)	.37
Elevated cholesterol levels requiring medication	944 (12.5)	962 (12.9)	.50
Statin use at baseline¶	590 (6.9)	548 (6.8)	.66
Aspirin use (≥80 mg/d) at baseline	1623 (19.1)	1631 (20.1)	.09
History of myocardial infarction	139 (1.6)	157 (1.9)	.14
History of angina	238 (2.8)	234 (2.9)	.73
History of CABG/PTCA	95 (1.1)	120 (1.5)	.04
History of stroke	61 (0.7)	77 (1.0)	.10
History of DVT or PE	79 (0.9)	62 (0.8)	.25
Female relative had breast cancer	1286 (16.0)	1175 (15.3)	.28
Fracture at age ≥55 y	1031 (13.5)	1029 (13.6)	.87

Clinical Outcomes by Randomization Assignment

Outcomes	Estrogen+Progestin (n=8506)	Placebo (n=8102)	Hazard Ratio (HR)
Follow-Up Time, Mean (SD), Mo	62.2	61.2	
Coronary Heart Disease (CHD)	164	122	1.29
Stroke	127	85	1.41
Pulmonary Embolism	70	31	2.13
Breast Cancer	166	124	1.26
Colorectal Cancer	45	67	0.63
Endometrial Cancer	22	25	0.83
Hip fracture	44	62	0.66
Death due to Other Causes	165	166	0.92

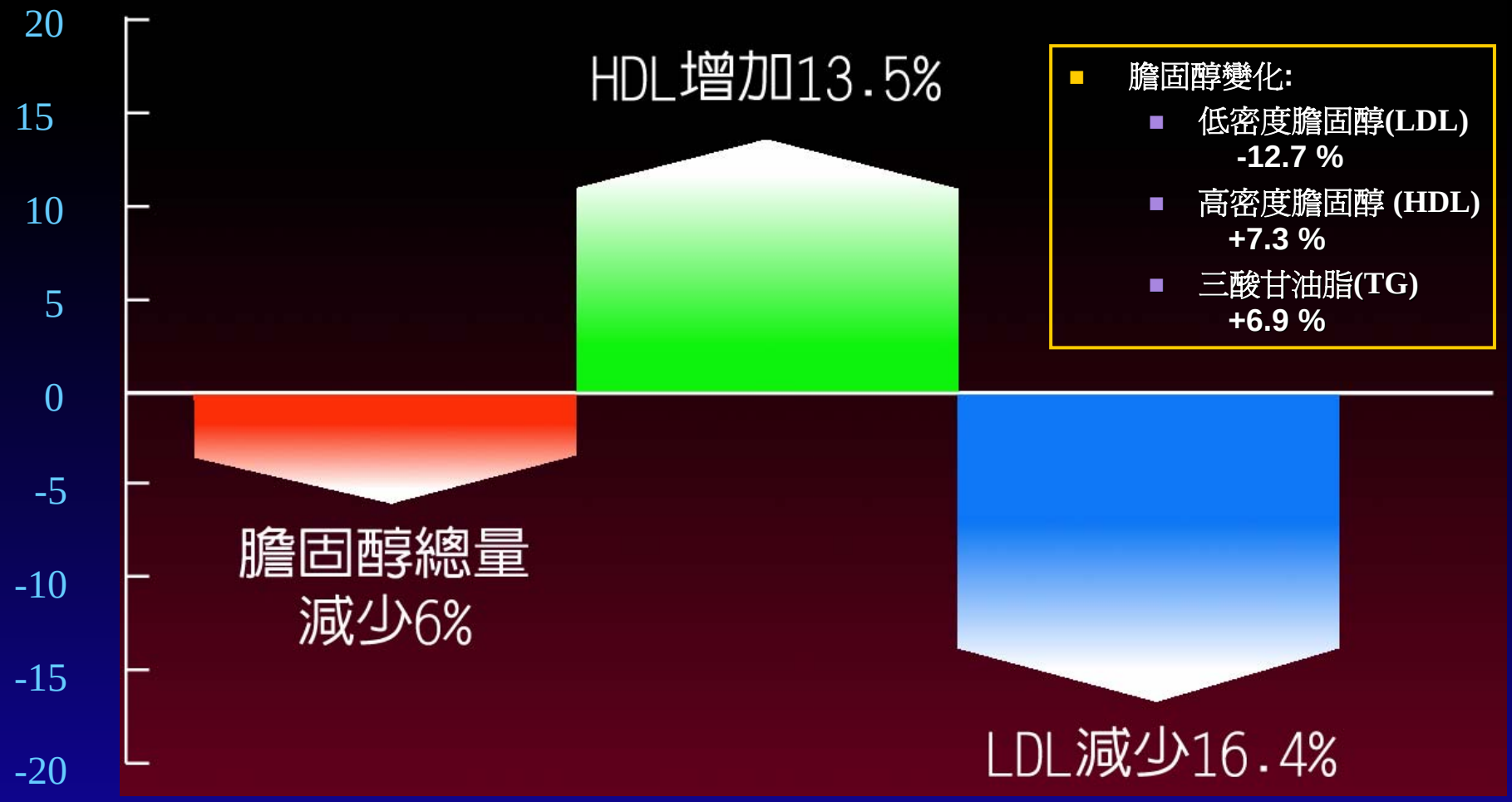
Hazard Ratio for Composite Outcomes

Outcomes	Estrogen+Progestin (n=8506)	Placebo (n=8102)	Hazard Ratio (HR)
Total Cardiovascular Diseases	694	546	1.22
Total Cancer	502	458	1.03
Combined Fracture	650	788	0.76
Total Mortality	231	218	0.98
Global Index	751	623	1.15

Absolute Risks *per 10,000* Women/year Attributable to Estrogen Plus Progestin

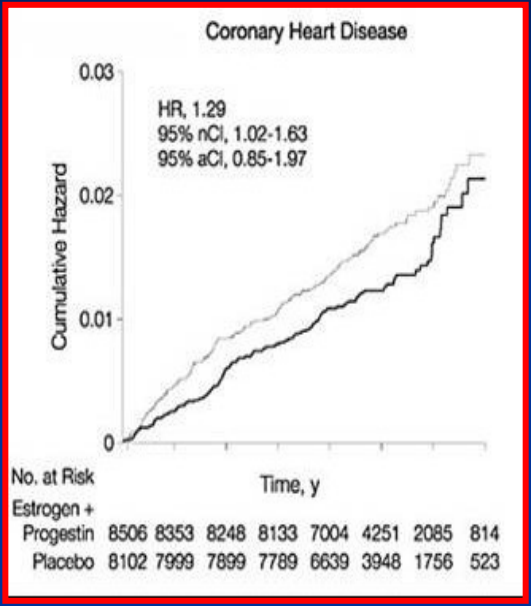
Prempro Side Effects:			
Disease Rates for Women on Estrogen Plus Progestin (E+P) or Placebo			
Disease	E+P	Placebo	
CHD	37	30	7
Pulmonary Embolism	16	8	8
Strokes	29	21	8
Breast Cancer	38	30	8
Colorectal Cancer	10	16	-6
Hip Fractures	10	15	-5
Endometrial Cancer	5	6	-1
Absolute Excess Risk in the Global Index			19

停經後婦女接受一年HRT後血脂測量值的平均變化

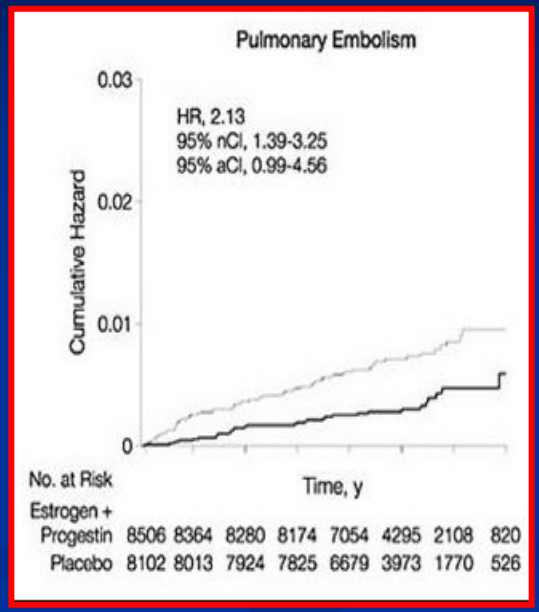


參考資料：**Barnes RB et al. Obstet Gynecol 66:216,1985.**

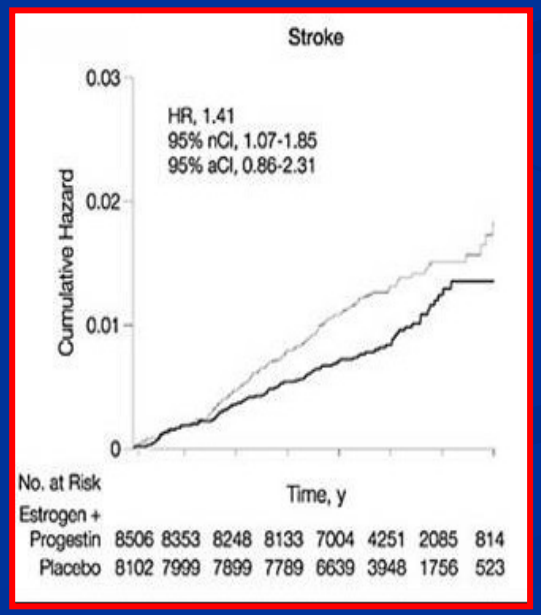
Cumulative Hazards for Select Clinical Outcomes



Diverging between 1 and 2 years after randomization, and this difference persists beyond the fifth year

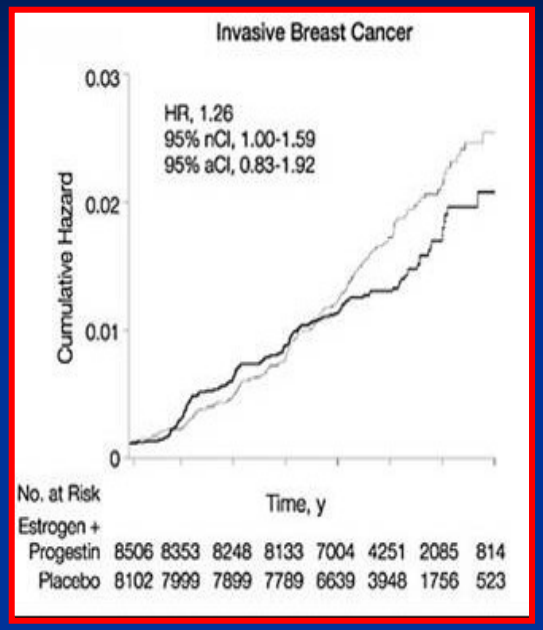


The difference began to develop soon after randomization. These curves provide little evidence of convergence through 6 years of follow-up

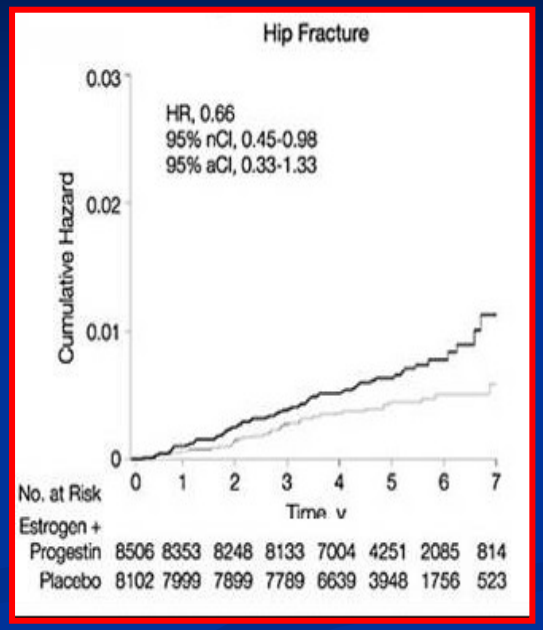


Separating soon after randomization and showing continuing adverse effects throughout the observation period

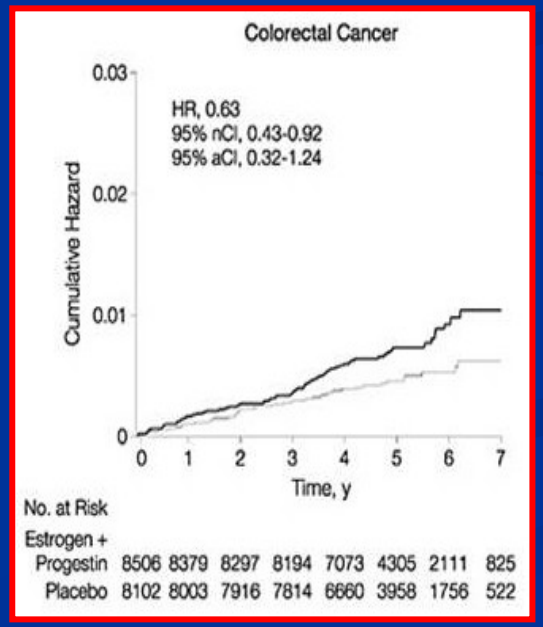
Cumulative Hazards for Select Clinical Outcomes



Benefit begins at 3 years



The cumulative hazard functions are comparable through the first 4 years, at which point the curve for estrogen plus progestin begins to rise more rapidly than that for placebo

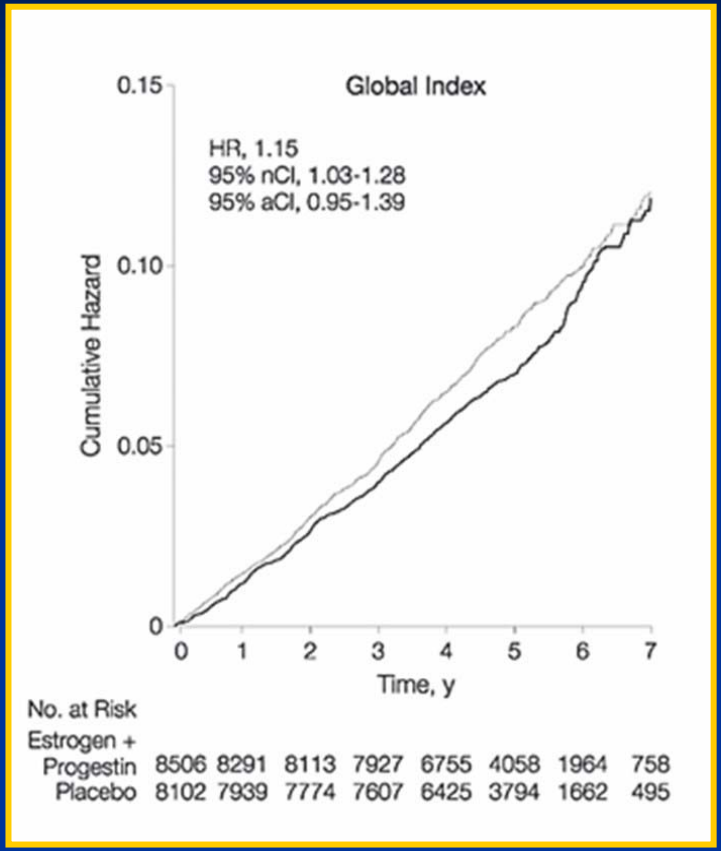


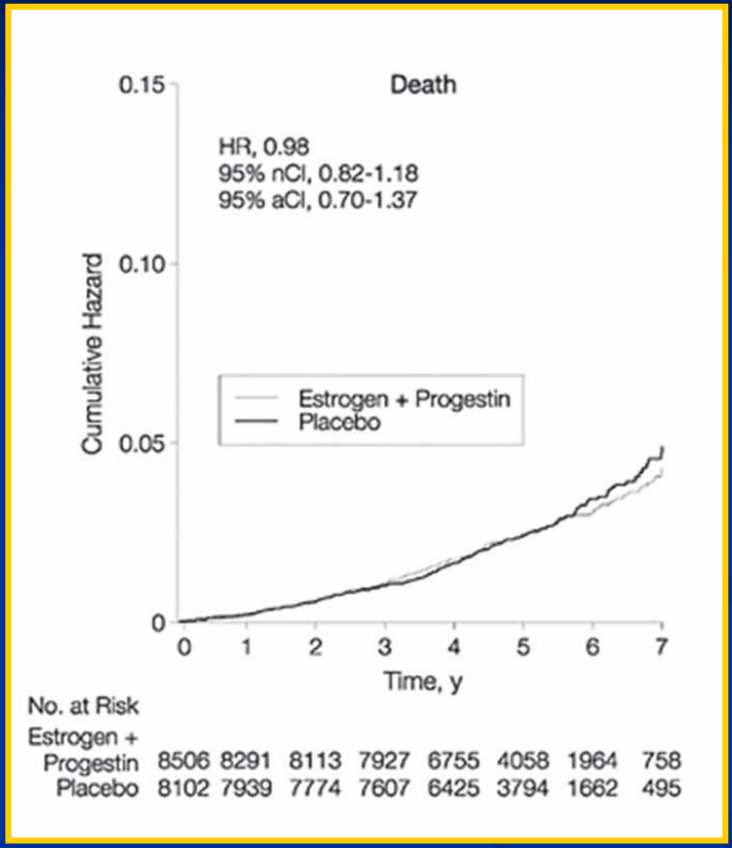
Increasing cumulative benefit over time

Causes of Death by Randomization Assignment

	No. (Annualized %)	
	Estrogen + Progestin (n = 8506)	Placebo (n = 8102)
Total deaths	231 (0.52)	218 (0.53)
Adjudicated deaths	215 (0.49)	201 (0.49)
Cardiovascular	65 (0.15)	55 (0.13)
Breast cancer	3 (0.01)	2 (<0.01)
Other cancer	104 (0.24)	86 (0.21)
Other known cause	34 (0.08)	41 (0.10)
Unknown cause	9 (0.02)	17 (0.04)

Cumulative Hazards for Global Index and Death



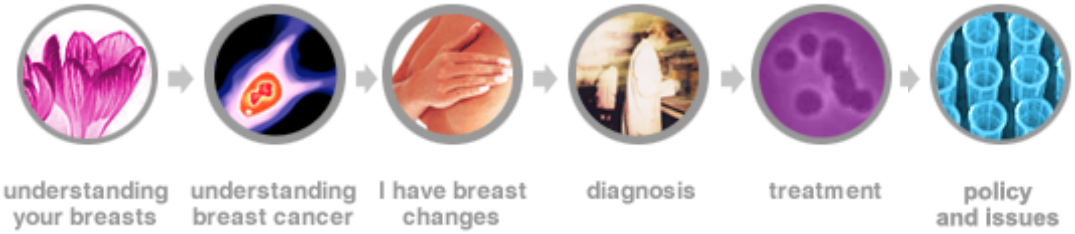


A gradual increase in adverse effects compared with benefits for estrogen plus progestin through year 5

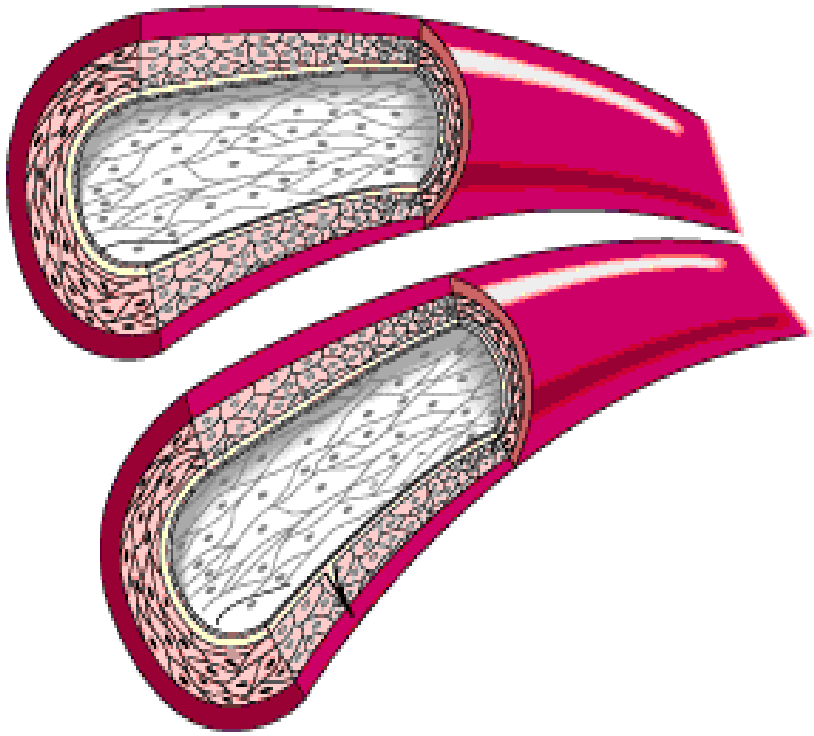
Total mortality rates are indistinguishable between estrogen plus progestin and placebo.

COMMENTS

疾病	冠狀動脈疾病	中風	乳癌	肺栓塞	直腸癌	髖部骨折	子宮內膜癌
相對風險	1.29	1.41	1.26	2.13	0.63	0.66	0.83
每一萬名婦女中所增加的*絕對風險*	7	8	8	8			
每一萬名婦女中所增加的*絕對效益*					6	5	1



- 此研究是以相對危險性 (relative Risk) 報告，但是當應用於臨床時應轉換爲絕對危險性 (absolute risk)，而對個別婦女而言，絕對危險性仍是相當低。

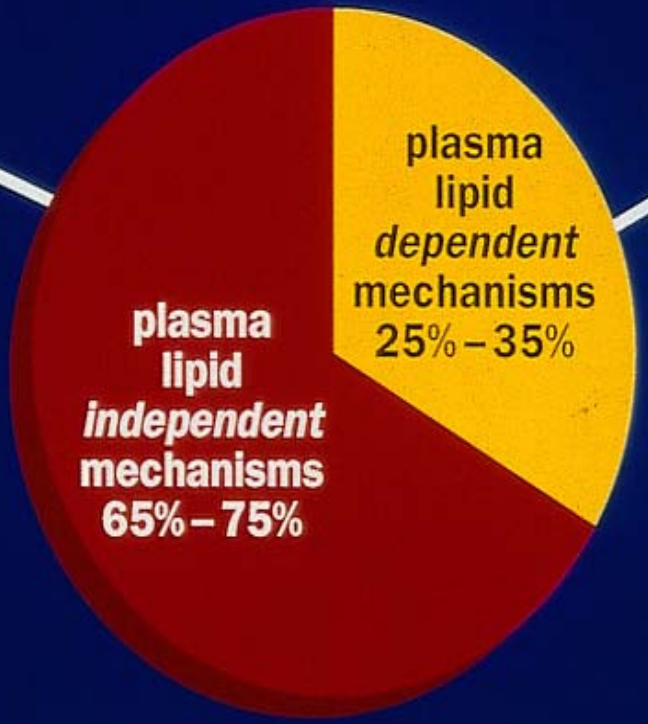


CARDIOVASCULAR DISEASES

ERT/HRT Mechanisms of Cardioprotection and Impact on Mortality

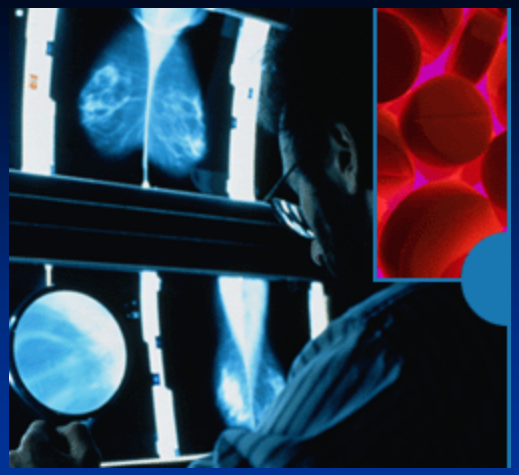
CHD mortality ↓ 50%

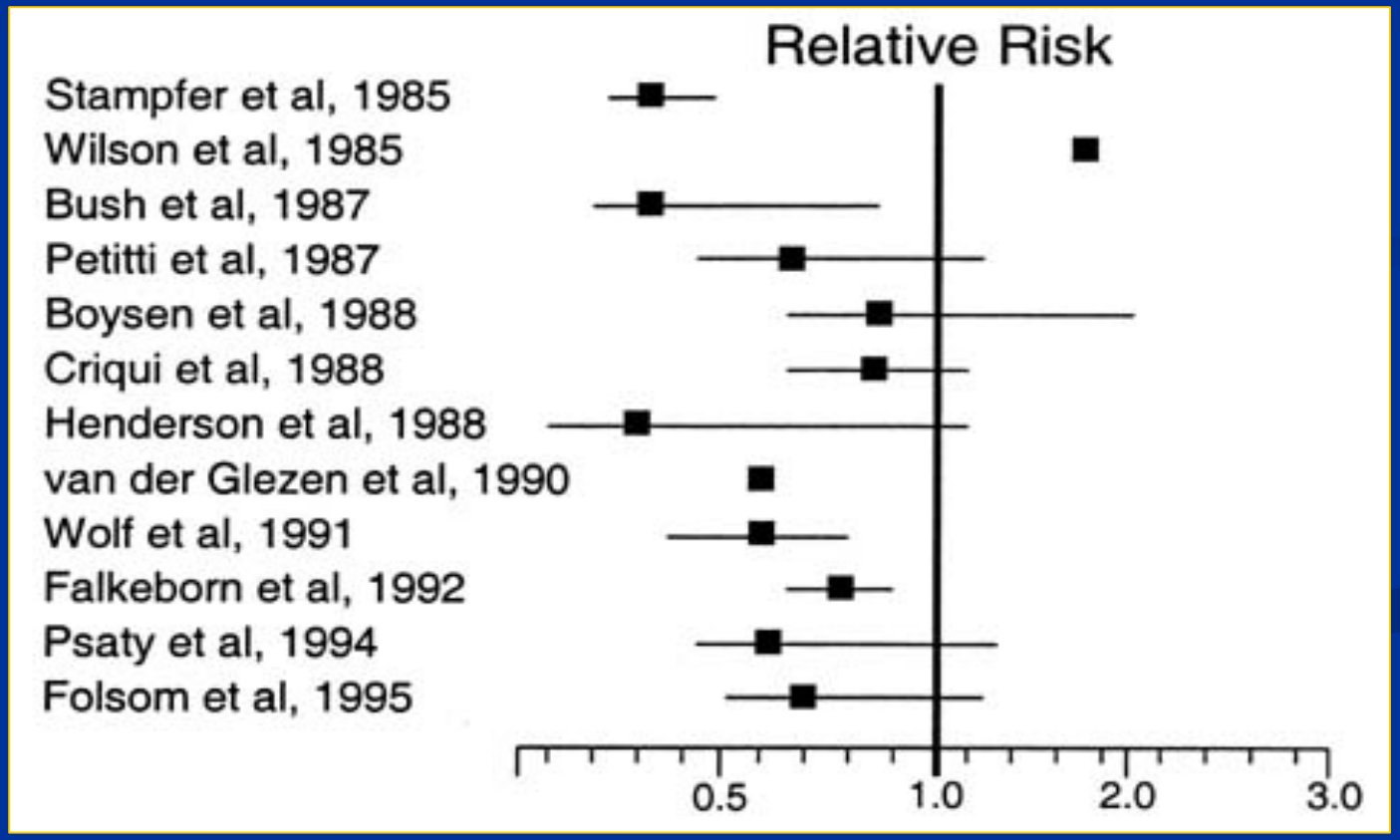
↑Endothelial effects
↑Insulin sensitivity
↑Vascular dilatation
↓Coagulation factors
↓Coronary artery LDL uptake



↑HDL
↓LDL
↓Lp (a)
↓LDL oxidation

Clarkson et al. *Estrogens and Antiestrogens*. 1997;chap 8.Lippincott-Raven.




Relative Risk
Stampfer et al, 1985
Wilson et al, 1985
Bush et al, 1987
Petitti et al, 1987
Boysen et al, 1988
Criqui et al, 1988
Henderson et al, 1988
van der Glezen et al, 1990
Wolf et al, 1991
Falkeborn et al, 1992
Psaty et al, 1994
Folsom et al, 1995
0.5
1.0
2.0
3.0

Randomized Trial of Estrogen Plus Progestin for *Secondary Prevention* of Coronary Heart Disease

Outcomes	Treatment Group: Estrogen-Progestin (n=1380)	Treatment Group: Placebo (n=1383)	RH (95% CI)	*P* Value
Primary CHD events†	172	176	0.99 (0.80-1.22)	.91
CHD death	71	58	1.24 (0.87-1.75)	.23
Nonfatal MI	116	129	0.91 (0.71-1.17)	.46
Venus thromboembolic event				
Deep vein thrombosis	25	8	3.18 (1.43-7.04)	.004
Pulmonary embolism	11	4	2.79 (0.89-8.75)	.08
Any thromboembolic event	34	12	2.89 (1.50-5.58)	.002
Gallbladder disease	84	62	1.38 (1.00-1.92)	.05

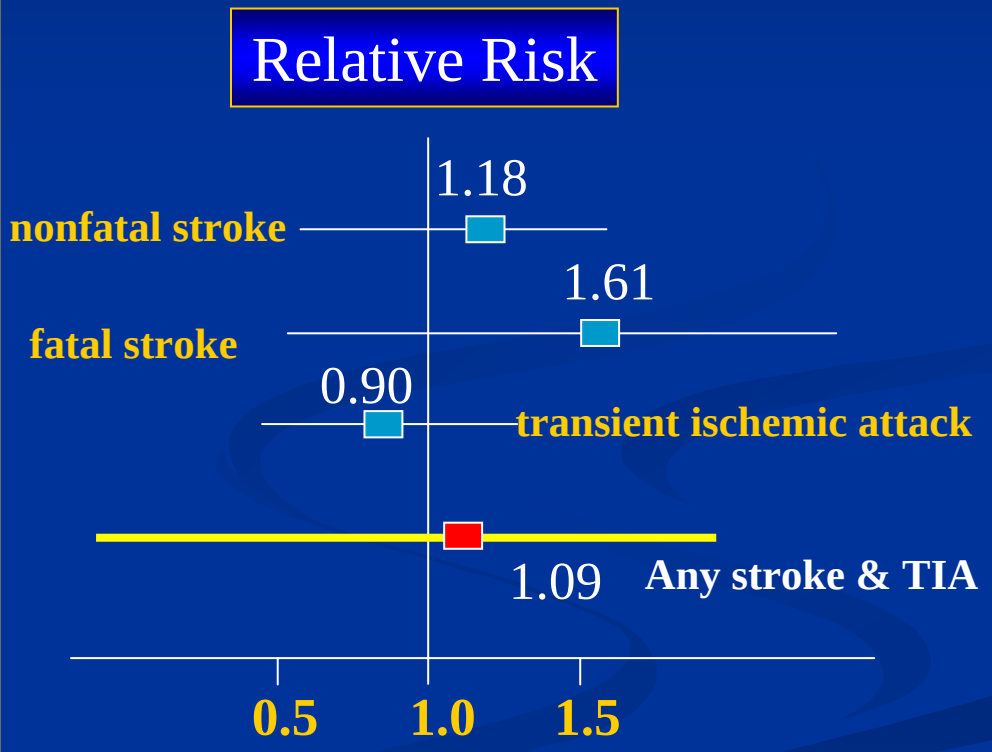
- The treatment group *did not reduce* the overall rate of CHD events in postmenopausal women with *established coronary disease*.
- The treatment *did increase* the rate of thromboembolic events and gallbladder disease.

- **We do not recommend starting this treatment for the purpose of secondary prevention of CHD.**

JAMA, 280(7), 19 August 1998, P605-613

Postmenopausal Hormone Therapy and Risk of Stroke (HERS)

- Postmenopausal women (n=2763)
  - Healthy: 2614
  - Stroke (above 1): 149
  - 2763 women were randomly assigned to take conjugated estrogen plus progestin or placebo.
- The results provide the *HRT was not protective against stroke* in the cohort of postmenopausal women with CHD.



Circulation, 2001, 103(5), P.638-642

Relative risk of Venous Thromboembolism According to Duration of ERT/HRT Use

Study	*Duration (y)*	*Relative risk*	*95% CI*
Jick et al[52]	<1	6.7	1.5-30.8
	1-5	2.8	0.6-11.7
	>5	4.4	1.0-12.2
	Unknown	2.2	0.5-9.4
Daly et al[53]	<1	6.7	2.1-21.3
	1-3	4.4	1.6-11.9
	3-5	1.8	0.6-7.8
	>5	2.1	0.8-6.1

- Venous thromboembolism is increased approximately *3-fold to 4-fold* among current users of ERT/HRT.
- The increase in risk is greatest during *the first year of ERT/HRT use* and decreases with longer use.

American Journal of Obstetrics and Gynecology 185(2) Supplement, August 2000, pp S13-S23

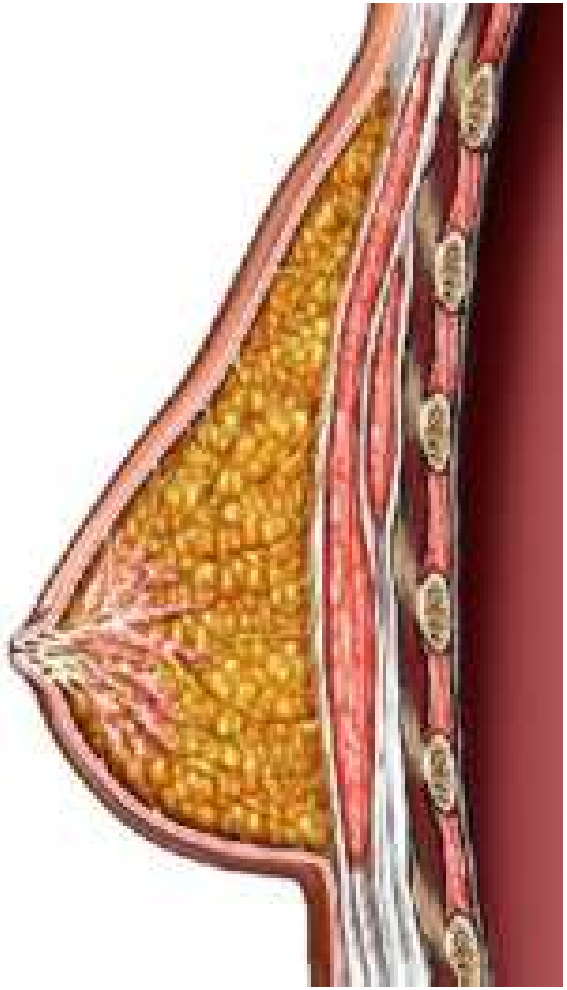
HRT and Progression of Intima-Media Thickness in Carotid artery

TABLE 3. Ultrasound Outcome Measures: Absolute Change From Baseline After 48 Weeks*: Intention-To-Treat and Valid Case Analysis

Carotid Arteries	No HRT	HRT 1	HRT 2
n (intention-to-treat)	93	86	85
Mean maximum IMT, mm	0.02±0.05	0.03±0.05	0.03±0.05
Single maximum IMT, mm	0.04±0.13	0.04±0.13	0.04±0.12
Mean intima-media area, mm^2	0.26±1.20	0.22±0.74	0.21±0.66

- **With the estrogen replacement for atherosclerosis trial, the treatment group did not inhibit progression of atherosclerosis.**

Arteriosclerosis Thromb Vasc Biol. 2001;21:262–268



BREAST CNACER

Clinical Questions Regarding Breast Cancer and Hormone Replacement

- Does HRT alter breast cancer incidence and type (noninvasive or invasive)?
- What is the effect of progestin-containing regimens?
- Does a positive family history alter the effect of HRT on risk?
- What is the survival rate of women with HRT-associated breast cancer?

Median year of diagnosis	Study	HRT ever-use Cases/Controls	HRT never-use Cases/Controls	O-E	var(O-E)	Relative risk of breast cancer in ever-users vs never-users RR and 99% CI*	RR (SE)*
Prospective studies							
1985	Canadian NBSS[28]	205/954	243/976	0.5	72.6		1.01 (0.118)
1985	Schairer[36]	341/1418	370/1422	-3.4	100.5		0.97 (0.098)
1986	Nurses' Health[39]	618/2442	714/3084	38.6	208.3		1.20 (0.076)
1988	Netherlands Cohort[44]	30/125	306/1076	-0.4	17.5		0.98 (0.236)
1991	Iowa Women's Health[40]	355/1338	178/702	12.1	66.9		1.20 (0.134)
	Other[3,5,9,12,15,19,20,22,47,48]	427/1521	240/887	-7.8	16.4		0.62 (0.196)
All prospective studies		**1976/7798**	**2051/8147**	**39.5**	**482.2**		**1.09 (0.047)**
Case-control with population controls							
1976	Brinton[2]	808/932	714/869	12.8	152.3		1.09 (0.085)
1981	CASH[13]	437/542	335/420	13.4	74.9		1.20 (0.127)
1981	Hislop[7]	86/84	275/282	2.8	19.2		1.15 (0.245)
1983	Bain[21]	39/86	226/458	3.0	10.8		1.33 (0.352)
1983	Ewertz[14]	136/109	400/414	8.0	26.7		1.35 (0.226)
1984	Long Island[33]	157/122	519/547	12.7	31.9		1.49 (0.218)
1988	4 State Study[43]	604/720	1892/2297	23.1	143.7		1.17 (0.090)
1989	Yang/Gallagher[31]	132/148	269/277	5.7	22.2		1.29 (0.242)
1989	Stanford[45]	117/134	149/161	-5.0	17.6		0.75 (0.208)
	Other[1,8,10,18,23,29,30,35,37,38]	297/485	783/1155	-1.7	41.4		0.96 (0.152)
All case-control studies with population controls		**2813/3362**	**5562/6880**	**74.7**	**540.7**		**1.15 (0.046)**
Case-control with hospital controls							
1974	Morabia[32]	80/144	104/178	3.5	10.1		1.41 (0.376)
1982	Vessey[4,11]	47/51	369/411	2.0	10.2		1.21 (0.345)
1987	La Vecchia[27]	119/64	1496/1386	14.3	27.9		1.67 (0.247)
1990	Katsouyanni[42]	42/70	404/770	1.8	12.0		1.16 (0.312)
1992	Franceschi[41]	151/132	1265/1379	14.4	45.6		1.37 (0.174)
	Other[6,16,17,24,25,34,46]	254/727	1216/4417	1.3	49.9		1.03 (0.143)
All case-control studies with hospital controls		**693/1188**	**4854/8541**	**37.3**	**155.7**		**1.27 (0.091)**
All studies		**5482/12348**	**12467/23568**	**151.5**	**1178.6**		**1.14 (0.031)**

Summary of Hormonal Action on Breast Cells

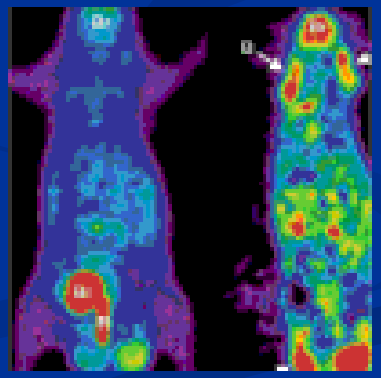
Estrogen	Progesterone
▪ Stimulate ductal growth ▪ Proliferative effect	▪ Stimulates alveolar growth ▪ Both proliferative and anti-proliferative effects
▪ Highest during follicular phase ▪ Increase estrogen and progesterone receptors ▪ *Increased growth factor production*	▪ Highest during luteal phase ▪ Decreased estrogen and progesterone receptors ▪ *Induce differentiation*

myc
ras
fos

Type of Hormone Currently Used by Postmenopausal Women and Relative Risk of Breast Cancer

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)

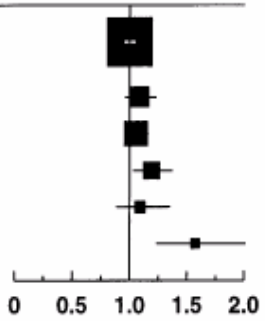
- Per annual increase in breast cancer
  - Estrogen alone: 1.7%
  - Estrogen plus all progestin: 5.4%
    - Estrogen with *cyclic progestin*: 7.6%
    - Estrogen with *continuous progestin*: 1.8%



JAMA. 2000;283:485-91
Lancet. 1997;350:1047-1059

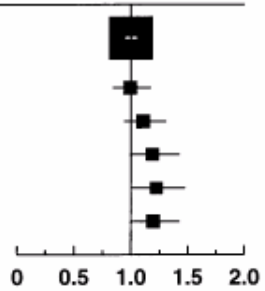
a: By duration of use (years)

	Cases/Controls	RR (FSE)*	RR and 99% FCI*
Never-user	12467/23568	1.00 (0.020)	
<1	1154/2546	1.09 (0.050)	
1-4	1660/3999	1.05 (0.039)	
5-9	813/1912	1.19 (0.061)	
10-14	386/867	1.09 (0.087)	
≥15	337/584	1.58 (0.121)	



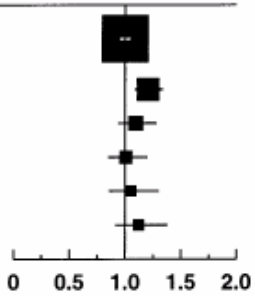
b: By time since first use (years)

	Cases/Controls	RR (FSE)*	RR and 99% FCI*
Never-user	12467/23568	1.00 (0.021)	
<5	932/1646	0.99 (0.065)	
5-9	876/1439	1.11 (0.068)	
10-14	710/1188	1.19 (0.077)	
15-19	548/1026	1.22 (0.081)	
≥20	640/1297	1.20 (0.075)	



c: By time since last use (years)

	Cases/Controls	RR (FSE)*	RR and 99% FCI*
Never-user	12467/23568	1.00 (0.019)	
Current	1796/3814	1.21 (0.044)	
1-4	702/1660	1.10 (0.063)	
5-9	500/1239	1.01 (0.068)	
10-14	346/821	1.05 (0.084)	
≥15	416/729	1.12 (0.084)	



- **Relative risk of breast cancer**
  - **Average (have used): 1.14**
  - **HRT for 5 years or longer: 1.35**
- **No increased risk with HRT use for 4 years or less**
- **Average risk : *2.3%/year***
- **Delaying menopause:**
  - **Increases by a factor : 1.028 *2.8%/year***
- **Five or more years after cessation of HRT use**
  - ***No significant excess of breast cancer***

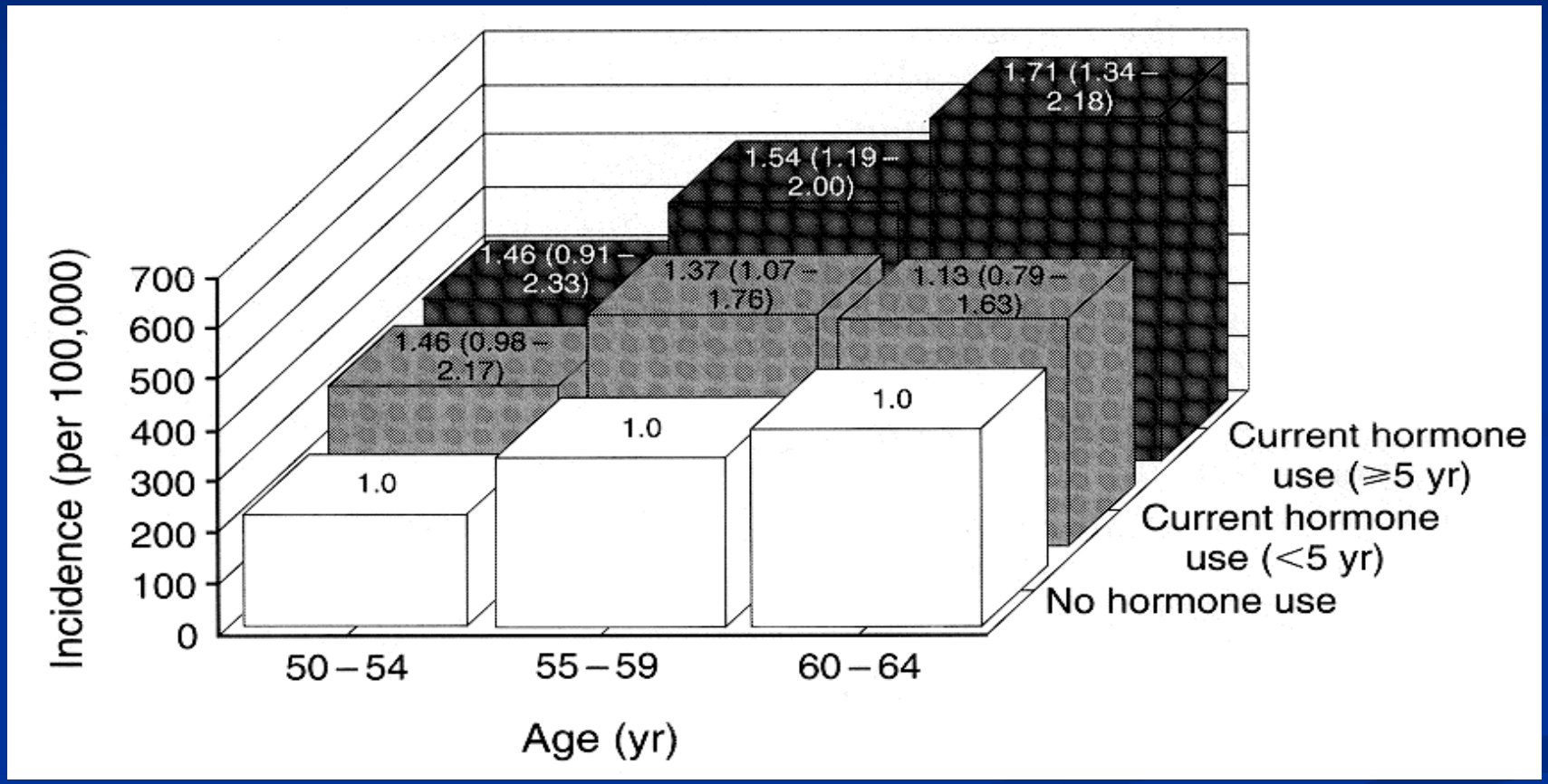
Lancet. 1997;350:1047-1059

Breast Cancer and Hormone Replacement Therapy: Results From the Reanalysis of Epidemiologic Studies by The Collaborative Group On Hormonal Factors in Breast Cancer

Time on HRT	Breast Cancers Diagnosed During 20 Years Between the Ages of 50-70 Years	Extra Breast Cancers
Never	45/1000	--
Used 5 years	47/1000	2/1000
Used 10 years	51/1000	6/1000
Used 15 years	57/1000	12/1000

Lancet. 1997;350:1047-1059

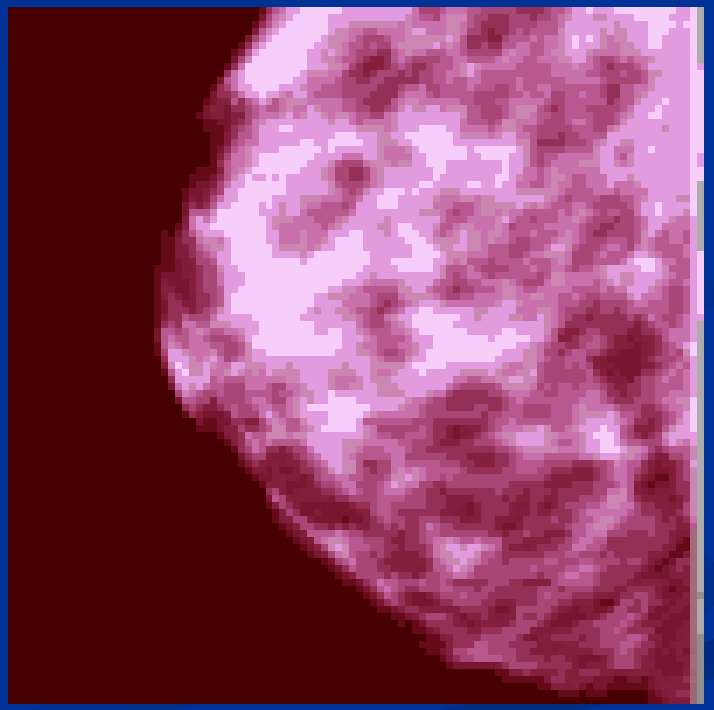
Incidence and Relative Risk of Breast Cancer According to Age and the Duration of Current Postmenopausal Hormone Therapy



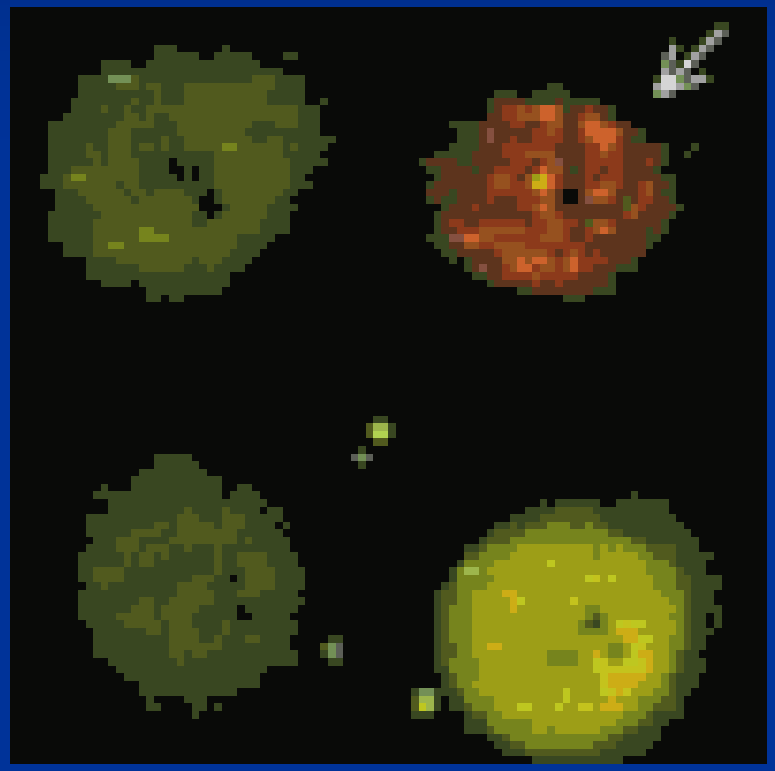
New England Journal of Medicine 1995;332:1589–1593.

The Impact of HRT on Breast Cancer Risk in Women with a Positive Family History

- For the breast cancer risk in women with a positive family history
  - A positive family history ***did not increase*** the risk of breast cancer among HRT users.
    (*JAMA 1999; 281:2091-7*)

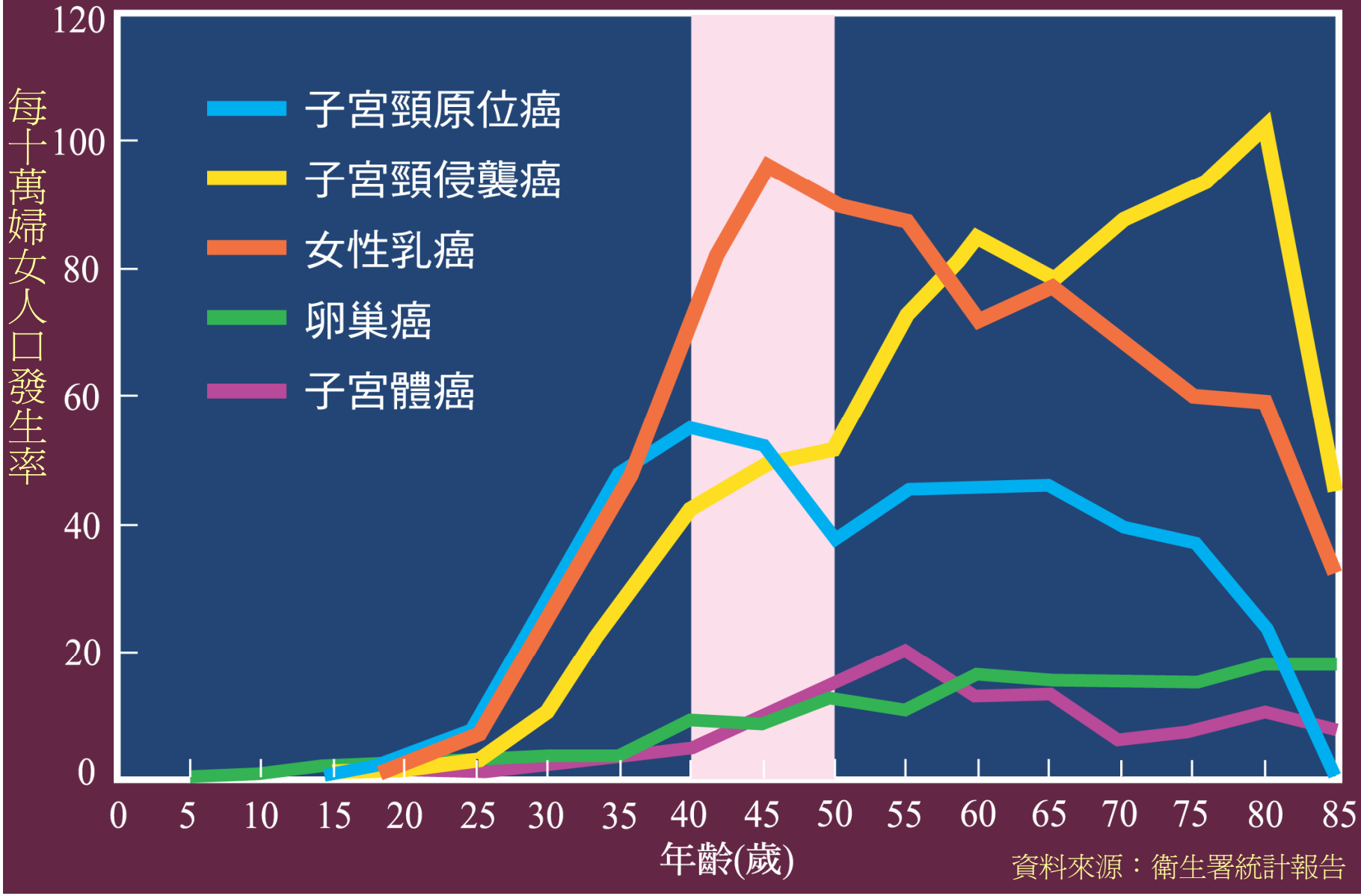


Hormone replacement therapy and Histology of Breast cancer

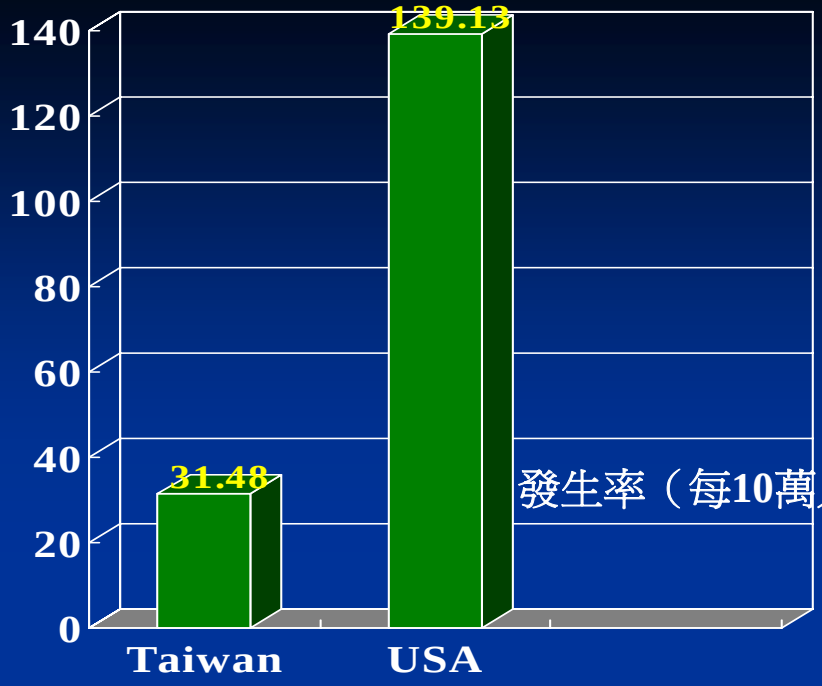


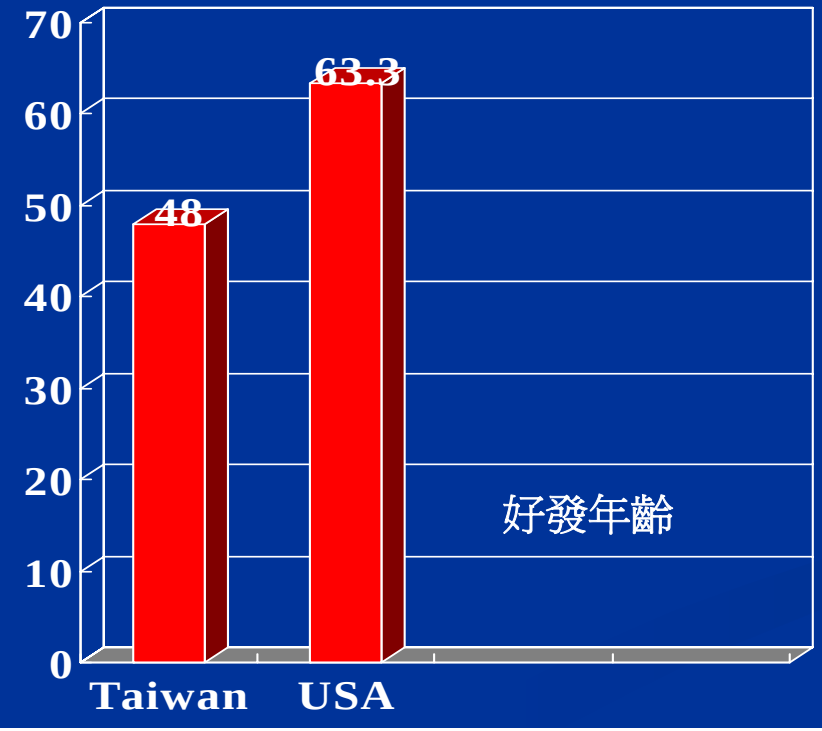
- Women using ERT/HRT who develop breast cancer are more likely to have ***localized disease*** rather than to have disease that has spread to the axillary nodes.
- The lobular histological type accounts for 5% to 10% of all breast cancer cases and the ***ductal type*** accounts for 80% to 85% of cases. (***JAMA 1999; 281:2091-7***)

1997台灣女性癌症年齡別發生率



資料來源：衛生署統計報告





■衛生署癌症登記年報及美國國家癌症研究院的統計數字顯示，國內乳癌發生率每十萬人爲三十一點四八人，美國乳癌發生率每十萬人爲一三九點一三人，比台灣高出3到4倍。

■美國婦女乳癌的發生在五十歲以後明顯增加，六十到六十五歲爲發生高峰，台灣婦女的發生高峰則在四十八歲。

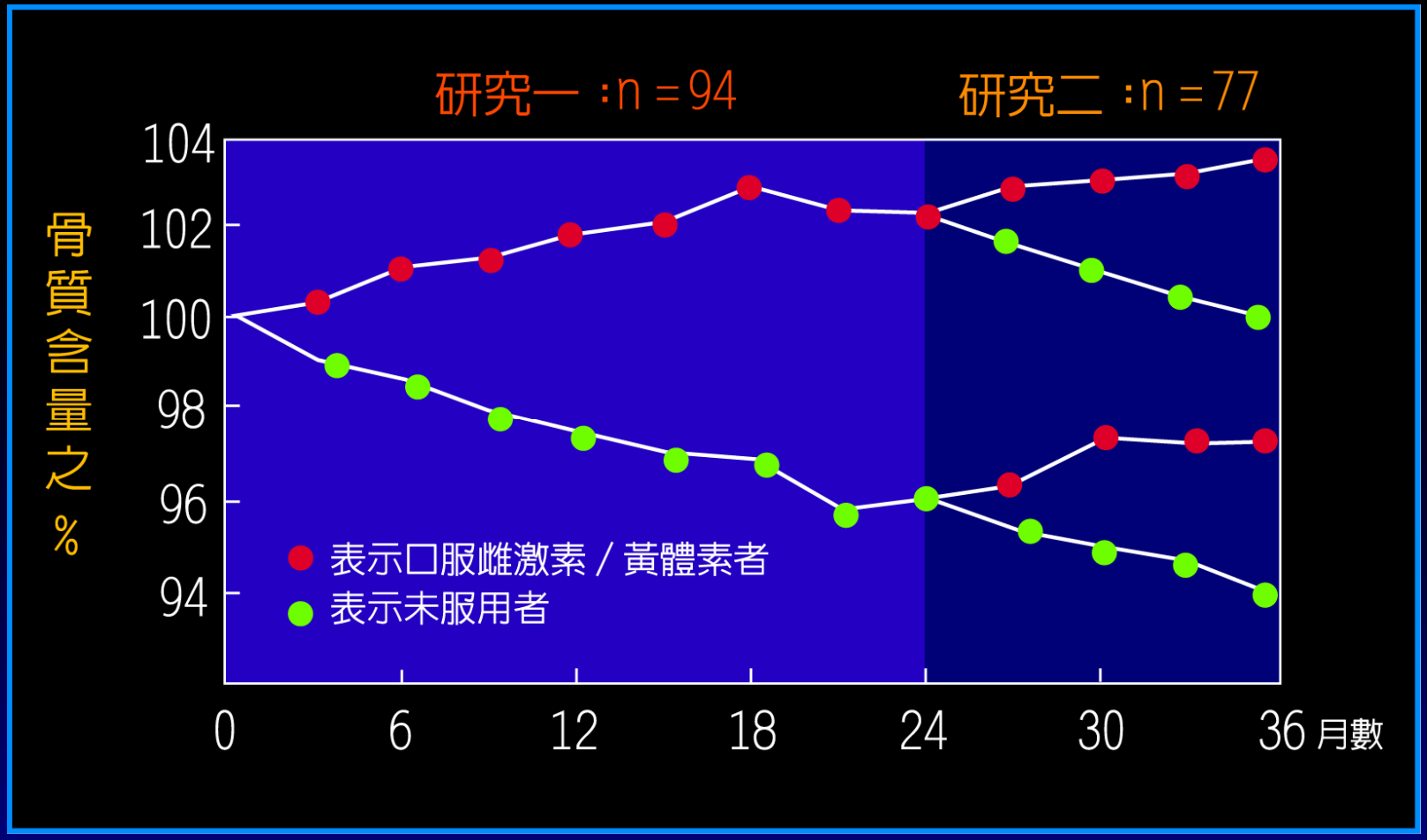
針對美國婦女更年期荷爾蒙替代療法的研究結論未必適用於台灣婦女。

OSTEOPOROSIS

Estimated Female Deaths

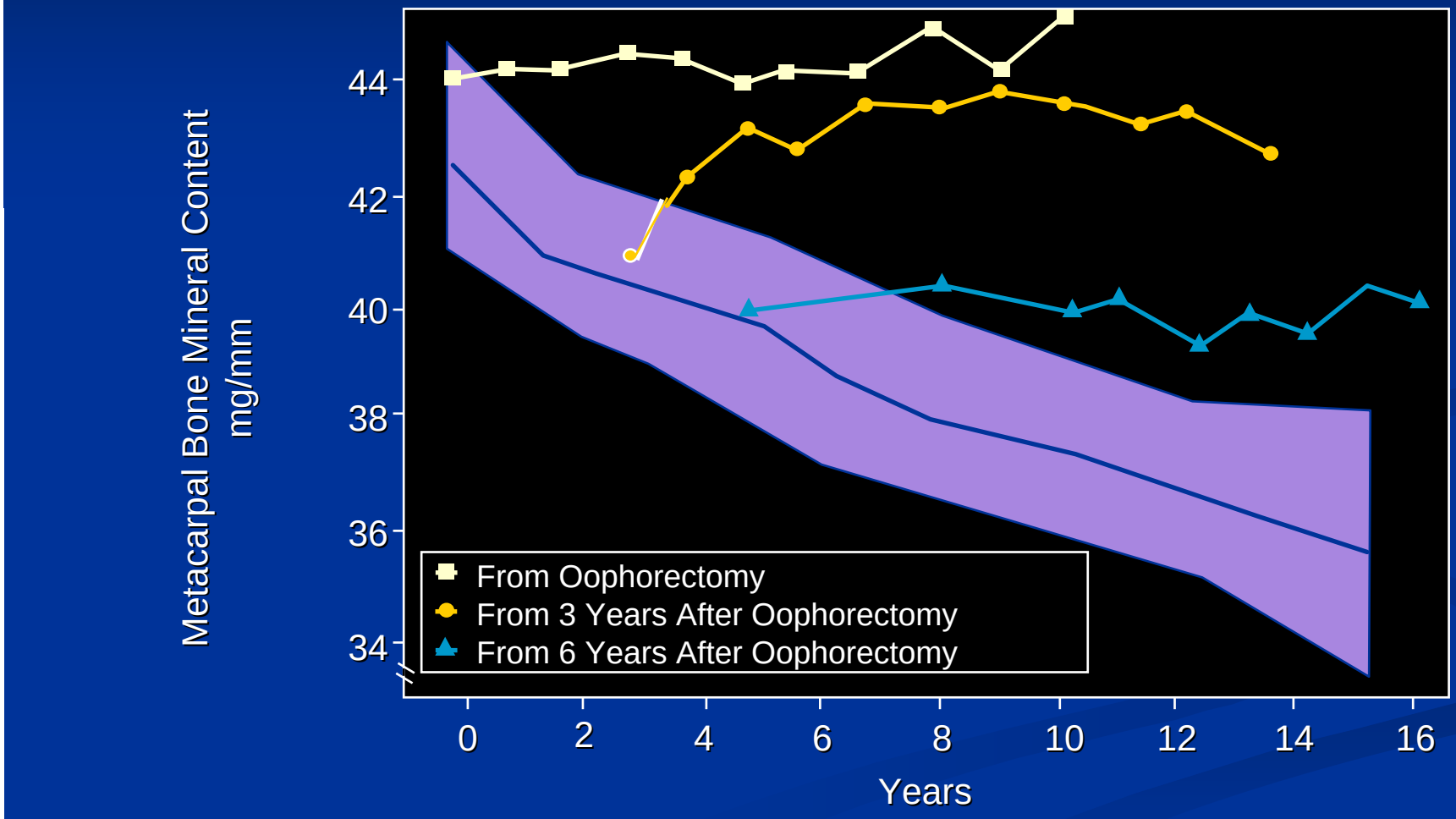
	New	Mortality	
	Cases/year	Cases No.	Per 100,000
Endometrial cancer	3700	2,900	2.6
Osteoporotic fracture	700,000	30,000	27.2
Breast cancer	119,000	38,400	34.8
Lung cancer	46,000	38,600	35.0

荷爾蒙補充療法能預防骨質的流失



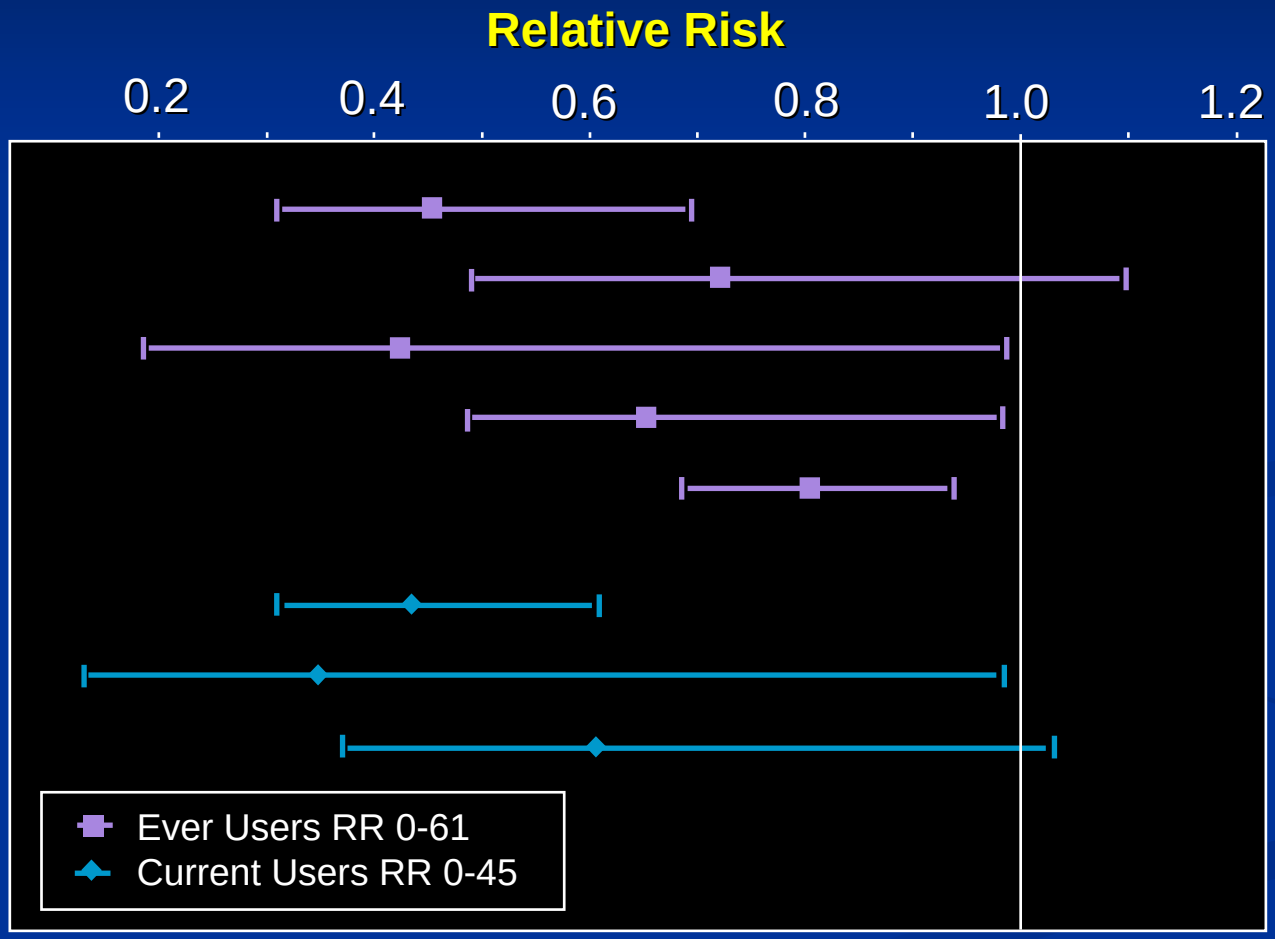
參考資料：**Christiansen C et al. Lancet 1981:1:459**

Effects of Delay of ERT Treatment on Bone Loss



Clin Obstet Gynecol, 1987; 30: 847.

Preventive Effect of ERT/HRT on Hip Fracture



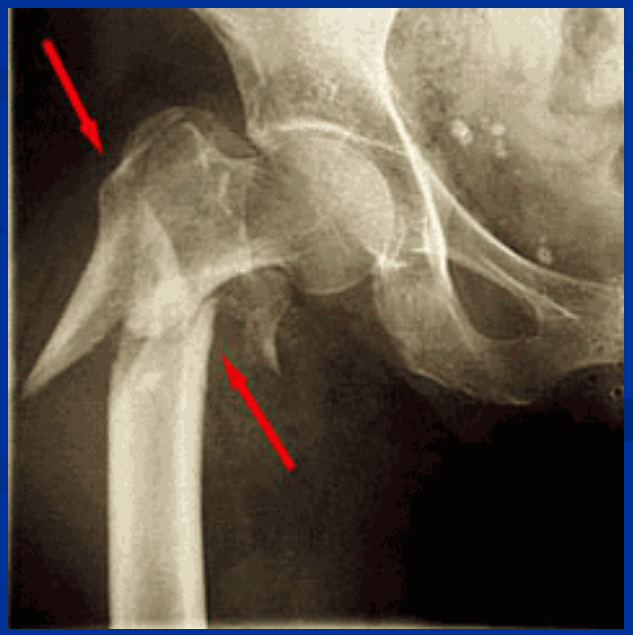
Weiss, 1980
Johnson, 1981
Paganini-Hill, 1981
Kiel, 1987
Naessen, 1990

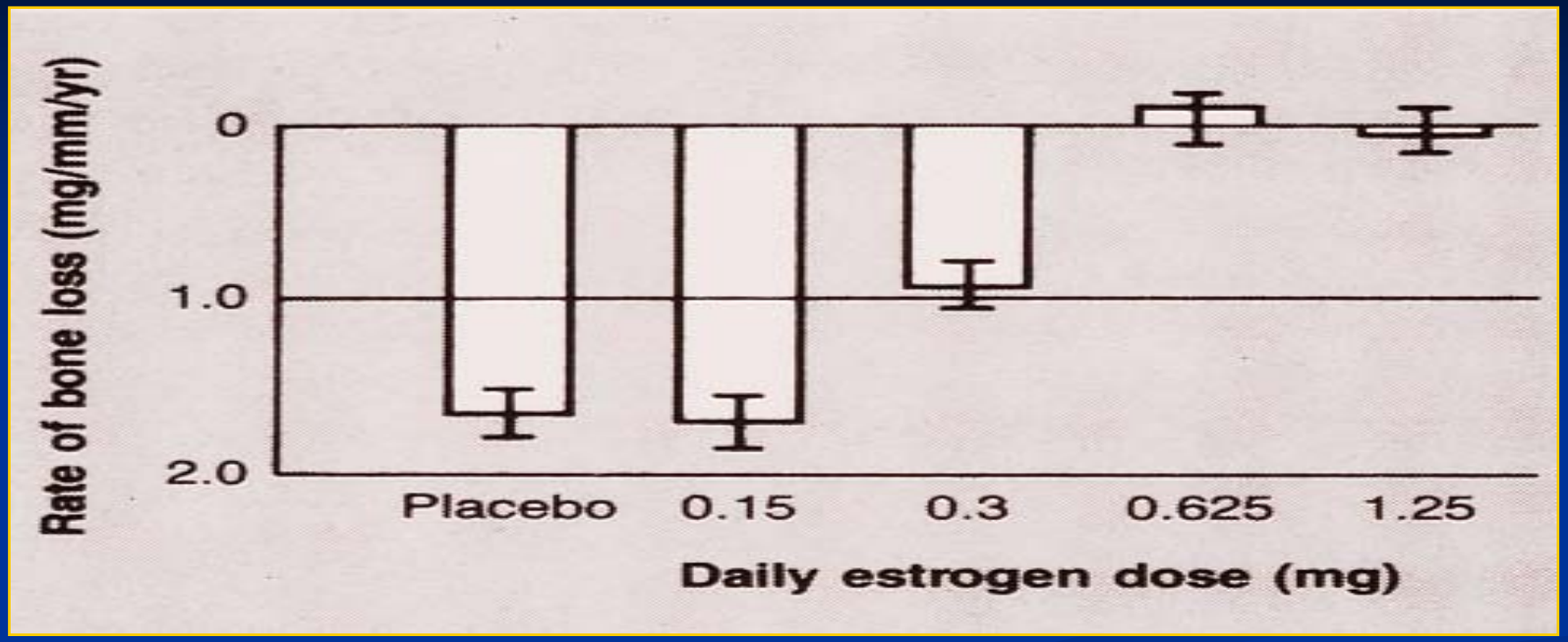
Weiss, 1980
Kiel, 1987
Cauley, 1995

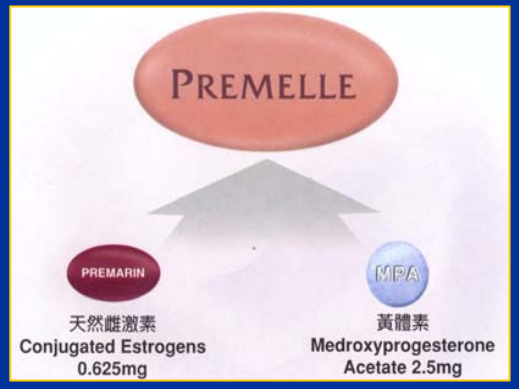
Adapted from Gallagher. In: Marcus et al, Eds. Osteoporosis, San Diego, CA: Academic Press;1996:Chap 63.

Daily Estrogen Dose Reported to Arrest Bone Loss

Estrogen	*Dose*	*Study*
Conjugated estrogens	0.3 to 0.625 mg	Recker et al, 1999[16]
Esterified estrogen	0.3 mg	Genant et al, 1997[17]
Estrone sulfate	0.625 mg	Genant et al, 1990[18]
17β-Estradiol	0.5 to 1.0 mg	Ettinger et al, 1992[13]
Transdermal estradiol	0.025 mg	Evans and Davie, 1996[19]
Ethinyl estradiol	5 to 10 µg	Speroff et al, 1996[20]





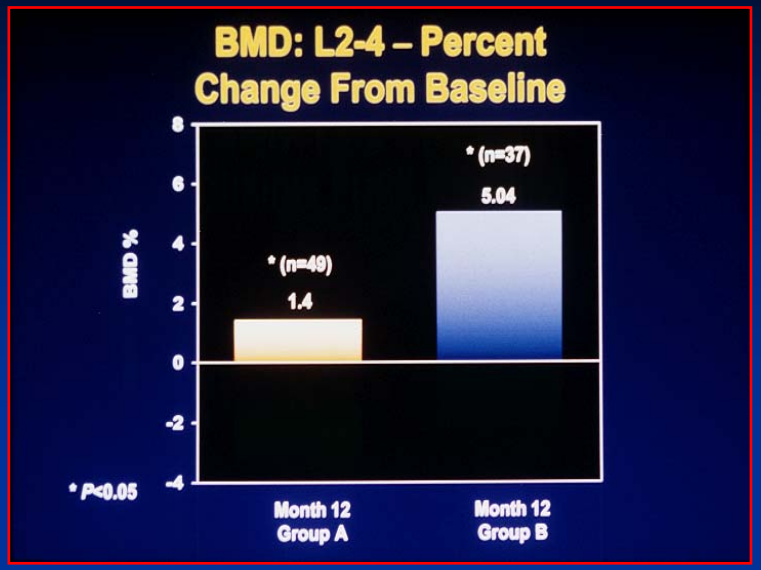


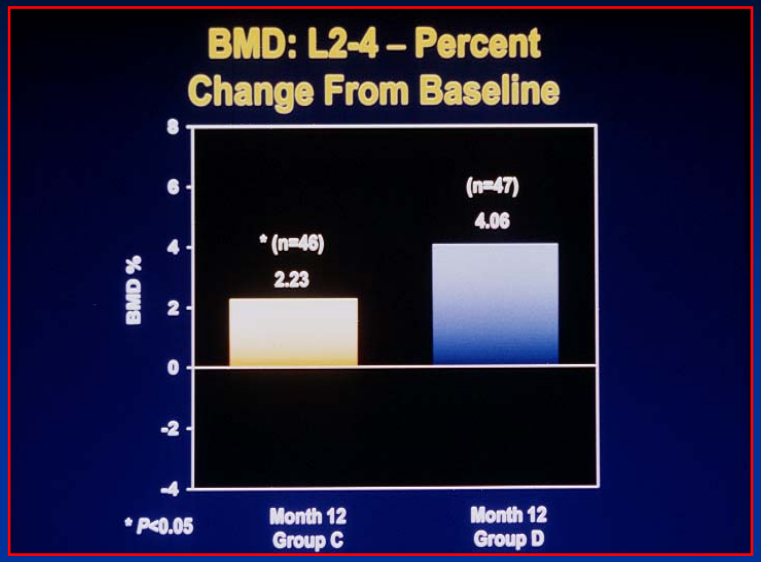
Doses of less than 0.625 mg/day of conjugated estrogen *were not* able to halt bone loss. Doses of 1.25 mg/day *had not* increased benefit over those of 0.625 mg/day.

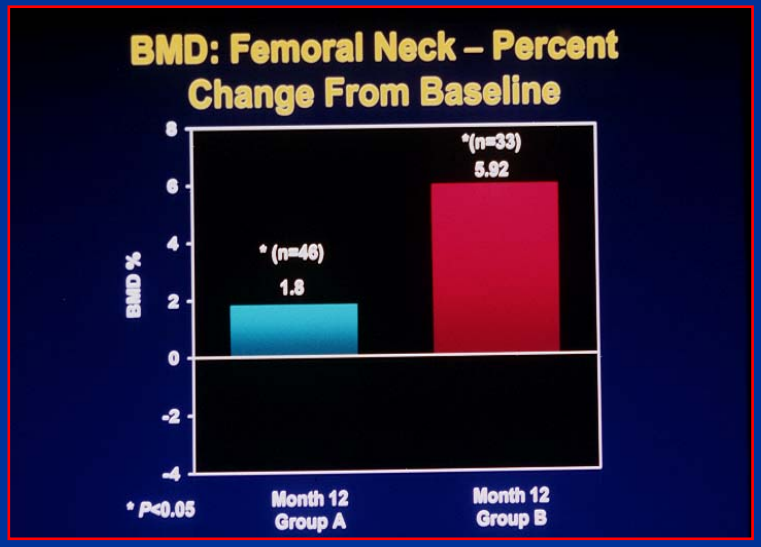
Multi- Center Trial on HRT in Taiwan

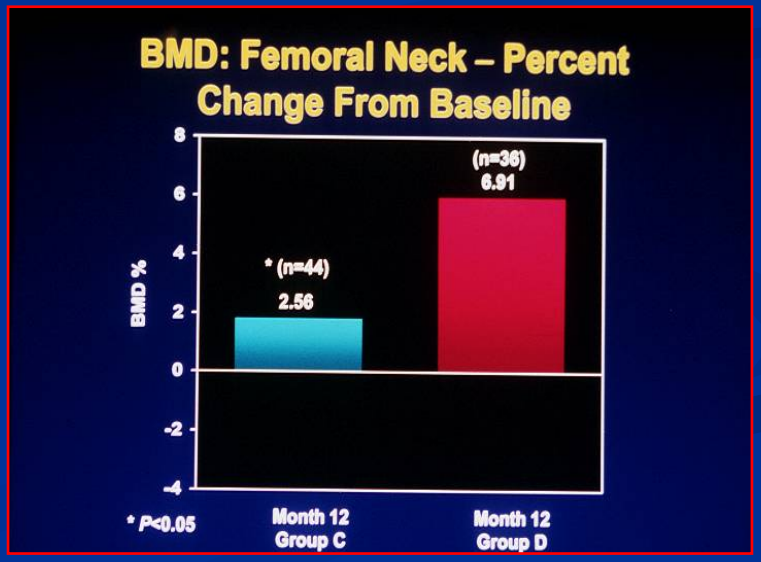
With Uterus, Menopause > 1-5 years
FSH > 40 mIU / mL E2 < 30 pg / mL

A Group	CEE MPA	0.3 mg 5 mg	D 1-30 D 1-30
B Group	CEE MPA	0.625 mg 5 mg	D 1-30 D 1-30
C Group	CEE MPA	0.3 mg 5 mg	D 1-24 D 13-24
D Group	CEE MPA	0.625 mg 5 mg	D 1-24 D 13-24


BMD: L2-4 – Percent Change From Baseline
BMD %
8
6
4
2
0
-2
-4
* (n=49)
1.4
* (n=37)
5.04
* P<0.05
Month 12 Group A
Month 12 Group B


BMD: L2-4 – Percent Change From Baseline
BMD %
8
6
4
2
0
-2
-4
* (n=46)
2.23
(n=47)
4.06
* P<0.05
Month 12 Group C
Month 12 Group D


BMD: Femoral Neck – Percent Change From Baseline
BMD %
8
6
4
2
0
-2
-4
* (n=46)
1.8
*(n=33)
5.92
* P<0.05
Month 12 Group A
Month 12 Group B


BMD: Femoral Neck – Percent Change From Baseline
BMD %
8
6
4
2
0
-2
-4
* (n=44)
2.56
(n=36)
6.91
* P<0.05
Month 12 Group C
Month 12 Group D

- Although estrogen prevents the bone loss associated with the menopause and actually increases the bone mineral density, there is no large scale, prospective, placebo-controlled study to demonstrate that estrogen reduces the fracture risk.
- Observational and retrospective studies are open to a number of biases.

血管舒縮症狀

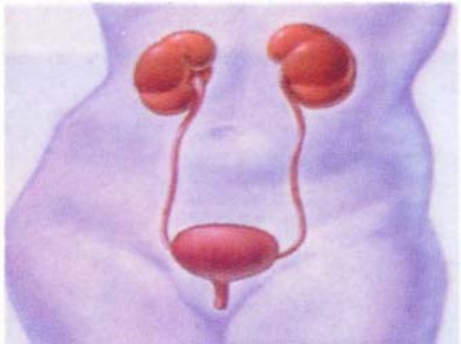
熱潮紅、盜汗、冷顫、暈眩
頭部緊迫感、虛弱、心悸

皮膚變化

皮膚油脂分泌減少，變得乾燥易產生皺紋

生殖泌尿道症狀

萎縮性陰道炎、性交疼痛、尿急、尿失禁、頻尿、夜尿症

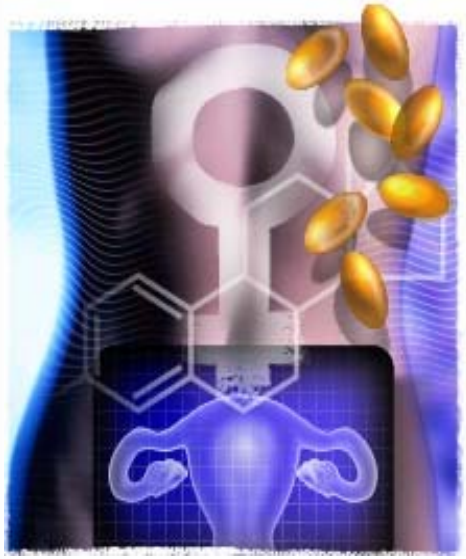


CONCLUSIONS

Limitations of WHI Study

- This trial tested only 1 drug regimen, CEE, 0.625 mg/d, plus MPA, 2.5 mg/d, in postmenopausal women with an intact uterus.
- This trial could not distinguish the effects of estrogen from those of progestin.
- The relatively high rates of discontinuation.
- The trial was stopped early decreases the precision.
- The trial did not address the short-term risks and benefits of hormones given for the treatment of menopausal symptoms.

Regional Impact

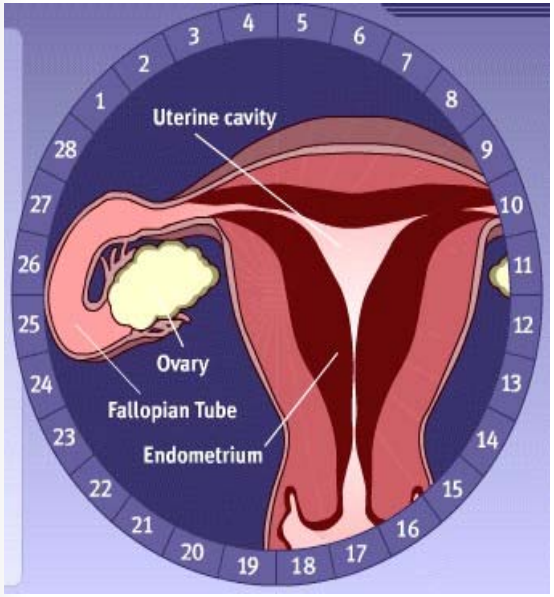


- Women in the United States have a higher incidence of breast cancer than in Asia. The incidence of breast cancer in the Asian countries is approximately 1/3 to 1/6 of that in the US.
- According to statistics, Asian women develop breast cancer at the average age of 48 or younger which is different from the average age of 63.

Regional Impact

- The incidence of cardiovascular events (CHD and deep vein thrombosis) in Asian women is lower than in American women.
- According to the WHO data, the incidence of CHD is 0.1 % in Asia, compared to 0.3 to 0.4% in the US. Lifestyle and diet also play an important role as well as physical activities.

Regional Impact



- Obesity is a risk factor for heart disease and breast cancer.
- The effect of body mass index is important in determining risk. The BMI is much lower in the Asian population.

治療性荷爾蒙無可取代

預防性荷爾蒙才是爭議的焦點

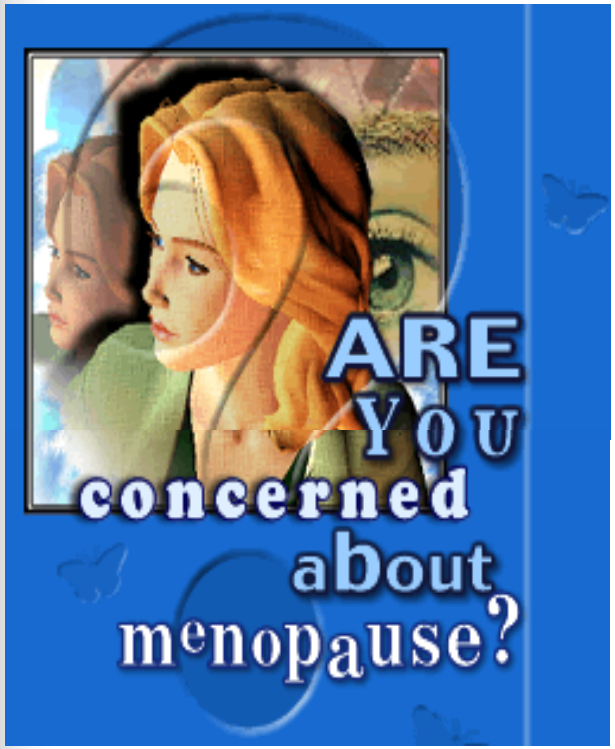
How HRT Will Be Approached in the Future

- The combined post-menopausal hormones should not be initiated or continued for the primary or secondary prevention of CHD.
- The risk of breast cancer is not significantly increased through the first 4 years.

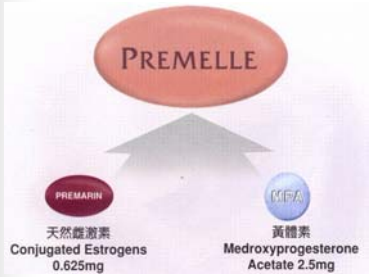
How HRT Will Be Approached in the Future

- HRT increases the risk of venous thromboembolism.
- HRT can increase the bone mineral density and prevent fracture, but there are alternatives.

How HRT Will Be Approached in the Future



- Short-term use of HRT for post-menopausal symptoms should be advised.
- For women with hysterectomy, estrogen-alone therapy can be continued.



NEW HRT FINDINGS TELL OLD STORY