

核心課程編號：F2

更年期症狀

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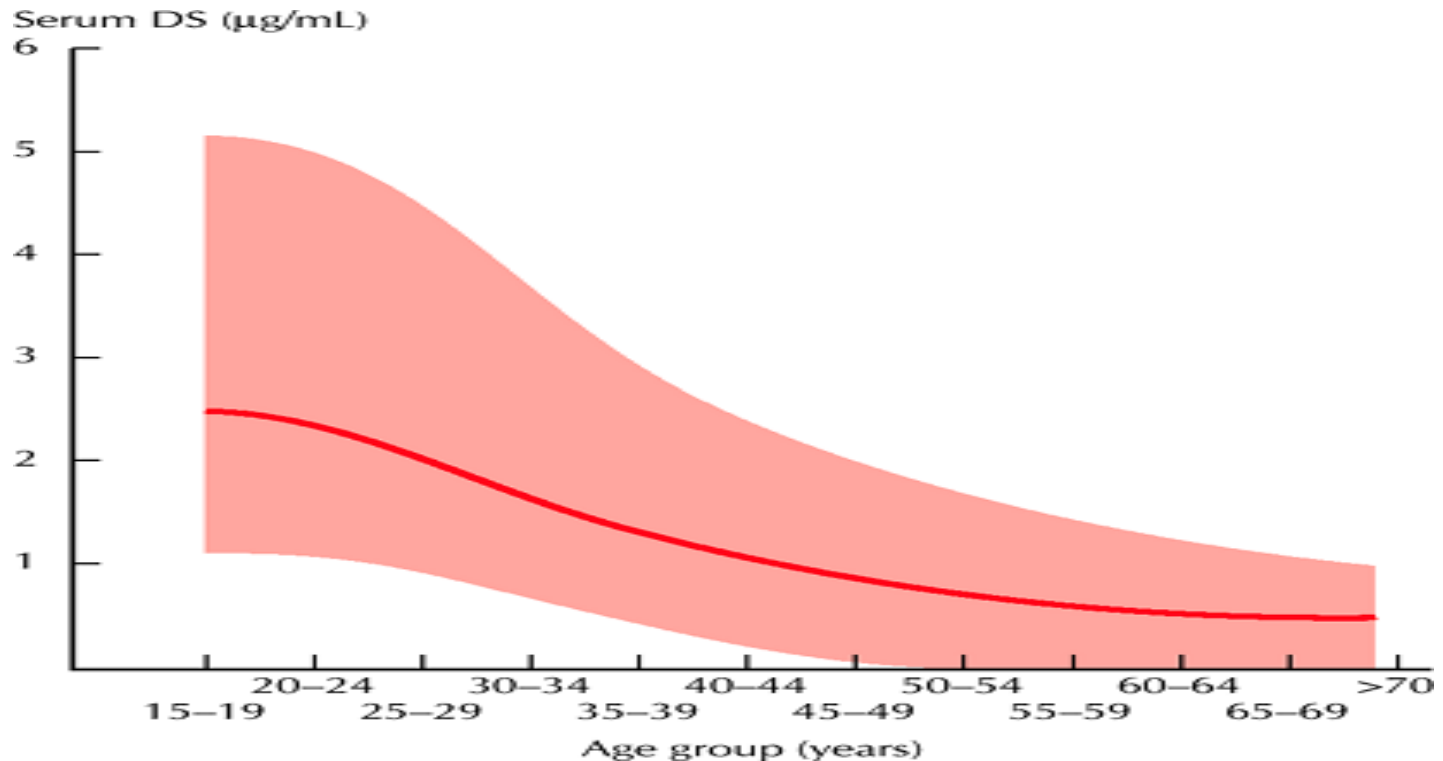
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學習目標

一年期 PGY 核心課程	學習目標	UGY 相關核心課程	學習目標
更年期症狀	<p>知識</p> <ol style="list-style-type: none"> 1. 更年期與心血管疾病、代謝症候群的相關性。(MK) 2. 更年期婦女使用荷爾蒙療法之趨勢。(MK) <p>技能</p> <ol style="list-style-type: none"> 1. WHI 更年期荷爾蒙補充療法內容及目前建議趨勢。(PC、CS) 2. 協助接受安全更年期荷爾蒙治療及評估骨質疏鬆症。(PC、PLI) <p>態度與專業素養</p> <ol style="list-style-type: none"> 1. 應用實證醫學知識與患者討論荷爾蒙治療之優劣。(CS、PLI) 2. 協助婦女面對更年期生活之調適。(MK) 	停經症候群	<p>知識</p> <ol style="list-style-type: none"> 1. 更年期的定義及更年期症候群的症狀。(MK) 2. WHI 更年期荷爾蒙補充療法研究報告之認識。(MK) 3. 瞭解更年期前後各項荷爾蒙之變化。(MK) 4. 骨質疏鬆症對年長患者之衝擊。(MK) <p>技能</p> <ol style="list-style-type: none"> 1. 具備病史詢問和身體檢查技能。(PC、CS) 2. 適時轉介更年期或停經患者至婦產科。(PC、CS、SBP) 3. 學習對患者的生理與心理之不適作出支持與基本治療。(PC) <p>態度與專業素養</p> <ol style="list-style-type: none"> 1. 搜尋與更年期醫學相關的實證醫學知識。(PLI) 2. 對病人因更年期症狀引起之不適，展現同理心。(P) 3. 學習向會診醫師表達患者狀況。(P)

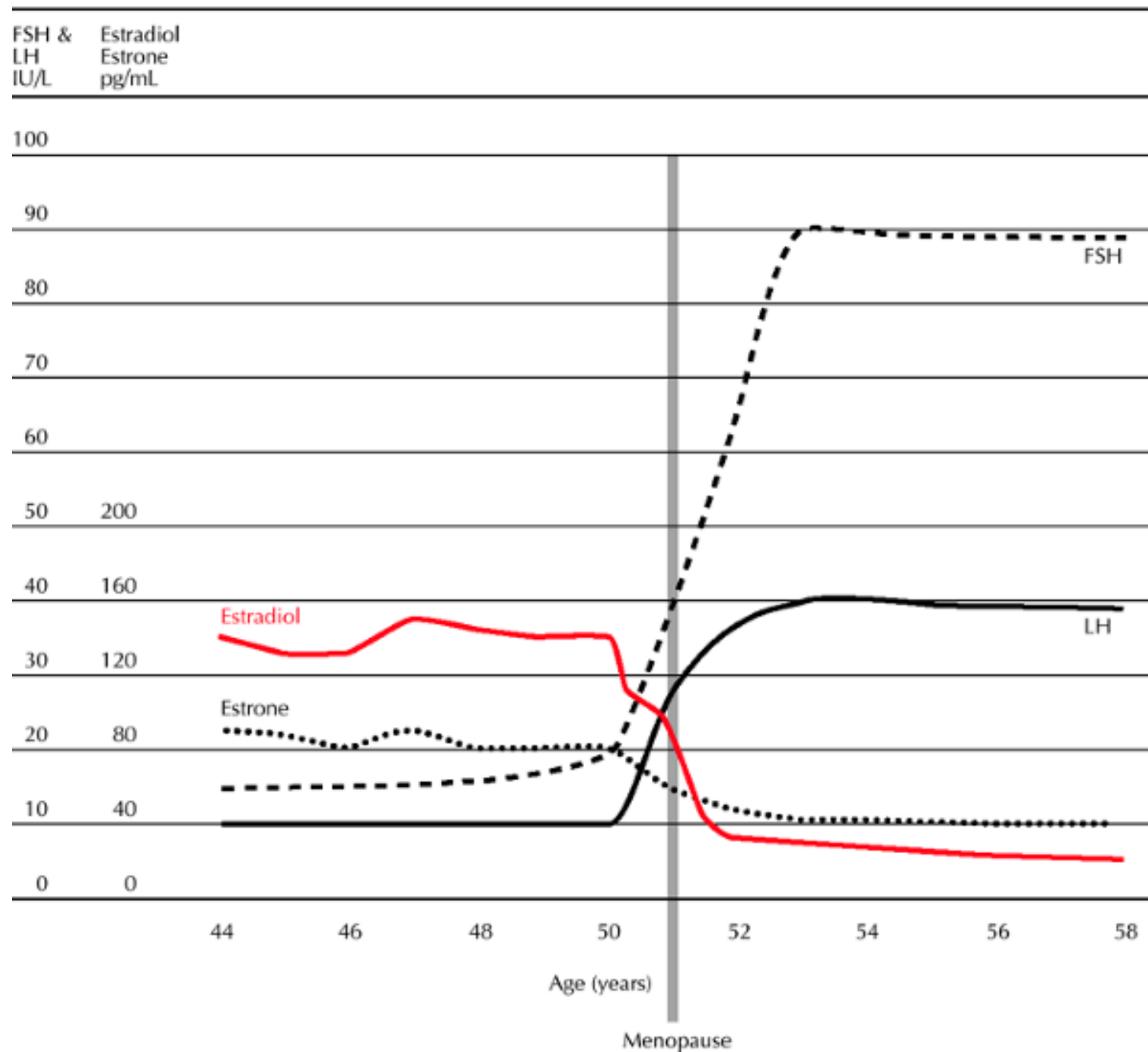
雌激素

「雌激素」是由卵巢分泌的女性荷爾蒙，婦女的健康、美麗以及具有生殖能力都和「雌激素」有關。



The Perimenopausal Transition

(mean circulating hormone levels)



更年期荷爾蒙變化

- Hypergonadotropic Hypogonadism
 - Elevated levels of both FSH and LH
 - FSH > 20 IU/L --- Perimenopausal years
 - FSH > 40 IU/L --- Menopause
 - Decreased levels of inhibin
 - Decreased levels of estradiol (10-20 pg/ml)

更年期之定義

- 婦女在48 ~ 52歲之間，因為卵巢功能萎縮，女性荷爾蒙(雌激素和黃體素)分泌逐漸減少，月經週期變得不規則，終至完全停止，並且一年內不再有月經，稱做停經。
 - 婦女停經的前後的過渡時期稱為「更年期」。
- 這段時期，有些婦女常常會有月經不規則及更年期症狀。

更年期引起的心血管疾病與代謝症候群

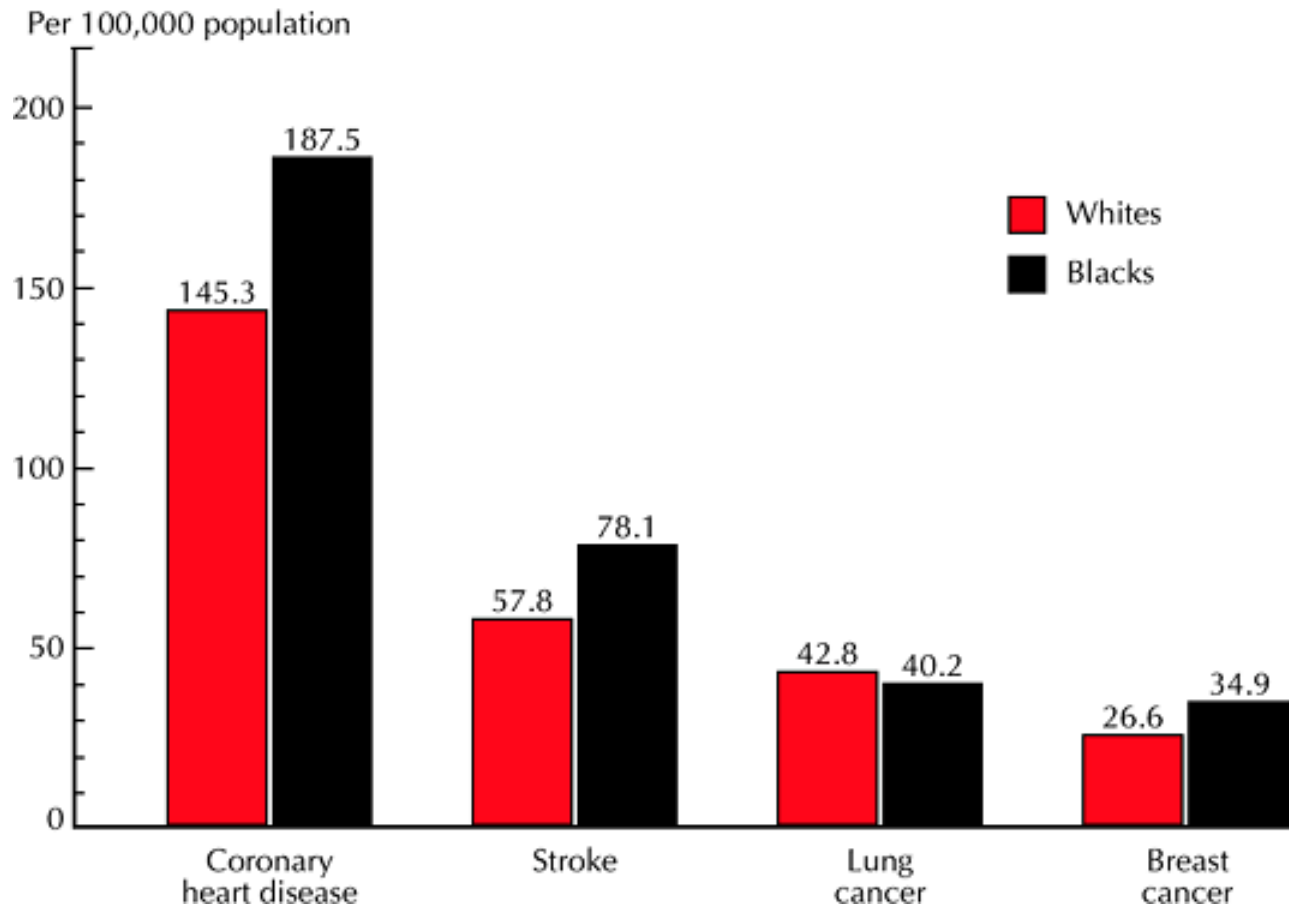
- **腦部**
記憶力減退
失憶症
(阿滋海默症)
- **皮膚**
皮膚乾燥老化
皺紋增加
- **生殖道**
陰道萎縮
陰道感染增加
性交疼痛
- **結腸**
研究指出荷爾蒙
補充療法對結腸癌
有預防意義
- **泌尿道**
尿道萎縮
頻尿
尿失禁
尿道感染增加



- **眼睛**
視網膜黃斑退化
- **血管舒縮症狀**
熱潮紅
盜汗
失眠
心悸
- **牙齒**
牙齒脫落
- **心臟**
心肌梗塞
心絞痛
缺血性心臟病
- **骨骼**
骨質流失
骨質疏鬆症
骨折危險性增加

雌激素缺乏造成心血管疾病的上升

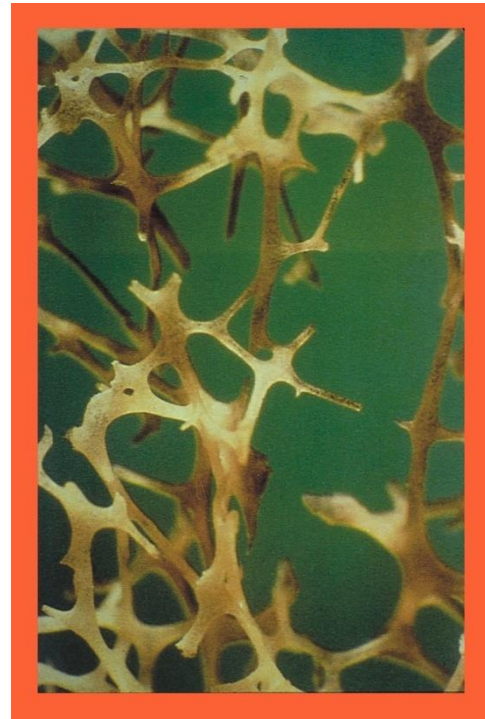
Age-Adjusted Mortality Rates for Women, U.S. 2000¹⁴



更年期晚期問題—骨質疏鬆症



正常骨質



骨質疏鬆

骨質疏鬆症狀

- Back pain
- Decreased height and mobility
- Tooth loss
- Fracture of the vertebral body, humerus, upper femur, distal forearm, and ribs

骨質疏鬆危險因子-體質

- 遺傳
- 家族友骨質疏鬆症或駝背者
- 低骨質（體重小於47公斤）
- 小骨架
- 早停經
- 不正常之月經週期（月經失調）
- 未生育過者
- 先天性軟骨症者
- 老化

骨質疏鬆危險因子-生活

- 抽煙
- 飲酒過量
- 咖啡, 茶, 碳酸飲料過量
- 飲食缺鈣
- 腸胃吸收不良
- 減肥過度
- 缺乏運動
- 嗜好嗜中藥(類固醇)
- 長期不活動, 臥床者

骨質疏鬆危險因子-疾病

- 更年期及性腺功能低下者
- 類固醇長期使用者
- 抗痙攣藥物使用者
- 甲狀腺功能亢進
- 副甲狀腺功能亢進
- 糖尿病(胰島素依賴型)
- 腎臟功能不良
- 風濕性關節炎
- 高血壓, 中風
- 神經性厭食或貪食症

骨折風險因子

- Previous history of a fragility fracture
- Family history of fragility fracture in close relatives
- Smoking
- Being thin and small-frames
- Family history of osteoporosis
- Amenorrhea (hypoestrogenism) before menopause
- Lifelong deficient calcium intake
- Use of bone losing medications
- Sedentary lifestyle
- Excessive use of alcohol

骨密度測量

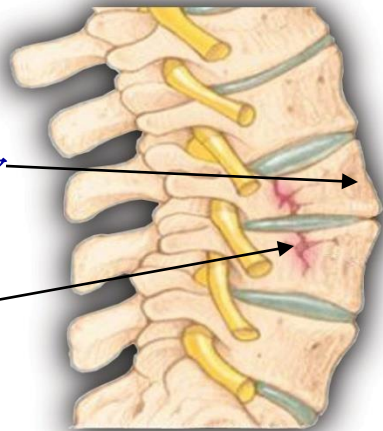
- Standard x-ray
- Single-photon absorptiometry (^{125}I or miniature x-ray tubes)
 - Radius, calcaneus
- Dual-energy absorptiometry (DEXA or DXA)
 - All sites, best information
 - Whole body scans by DEXA can measure total body calcium, lean body mass and fat mass
 - Clinical screening: spine + hip
- Quantitative CT
 - Higher radiation exposure, unavailable for femur
 - Very accurate measurement of spine
- Ultrasound of calcaneus

骨密度診斷標準

正常	骨質密度標準差 > -1
骨質缺乏	骨質密度標準差 $-1 \sim -2.5$
骨質疏鬆	骨質密度標準差 < -2.5
嚴重骨質疏鬆	骨質密度標準差 < -2.5 ，且已有骨質疏鬆造成骨折

骨鬆症對年長患者之衝擊-好發部位

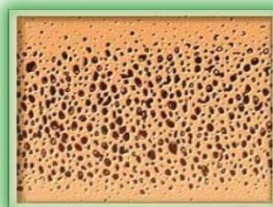
脊椎骨骨折圖



被壓垮的脊椎骨

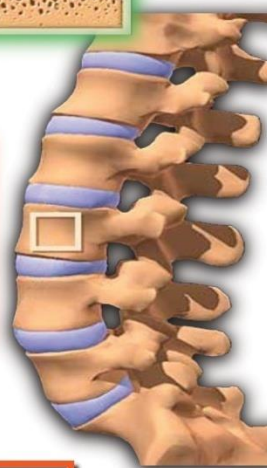
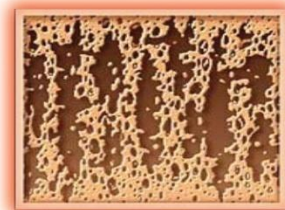
骨折

骨質密度比較

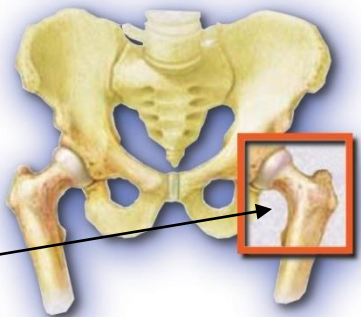


正常骨質

骨質疏鬆



髖部骨折圖



正常髖關節

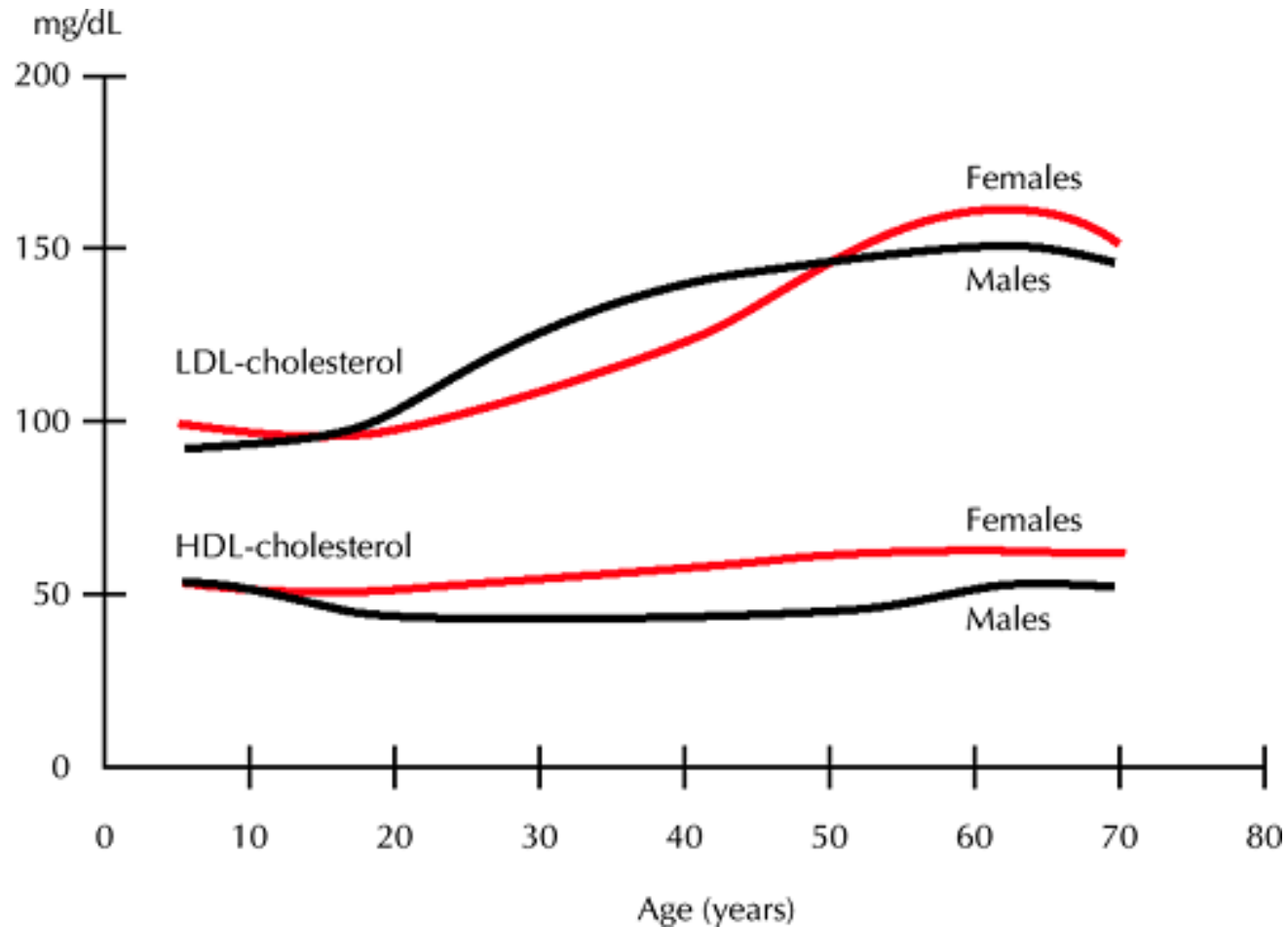


大小轉子間骨折



股骨頸骨折

雌激素缺乏可能影響血中膽固醇濃度的改變 待謝症候群之相關性



更年期晚期問題

- 記憶力減退
- 失憶症
(俗稱老年癡呆症)



WHI對荷爾蒙療法研究之認識-1

更年期婦女，因為卵巢功能萎縮，荷爾蒙分泌逐漸減少，導致身體出現一些症狀，須由外界供給才能維持身體需要的血中荷爾蒙濃度，這種療法稱之為「荷爾蒙療法」

WHI對荷爾蒙療法研究之認識-2

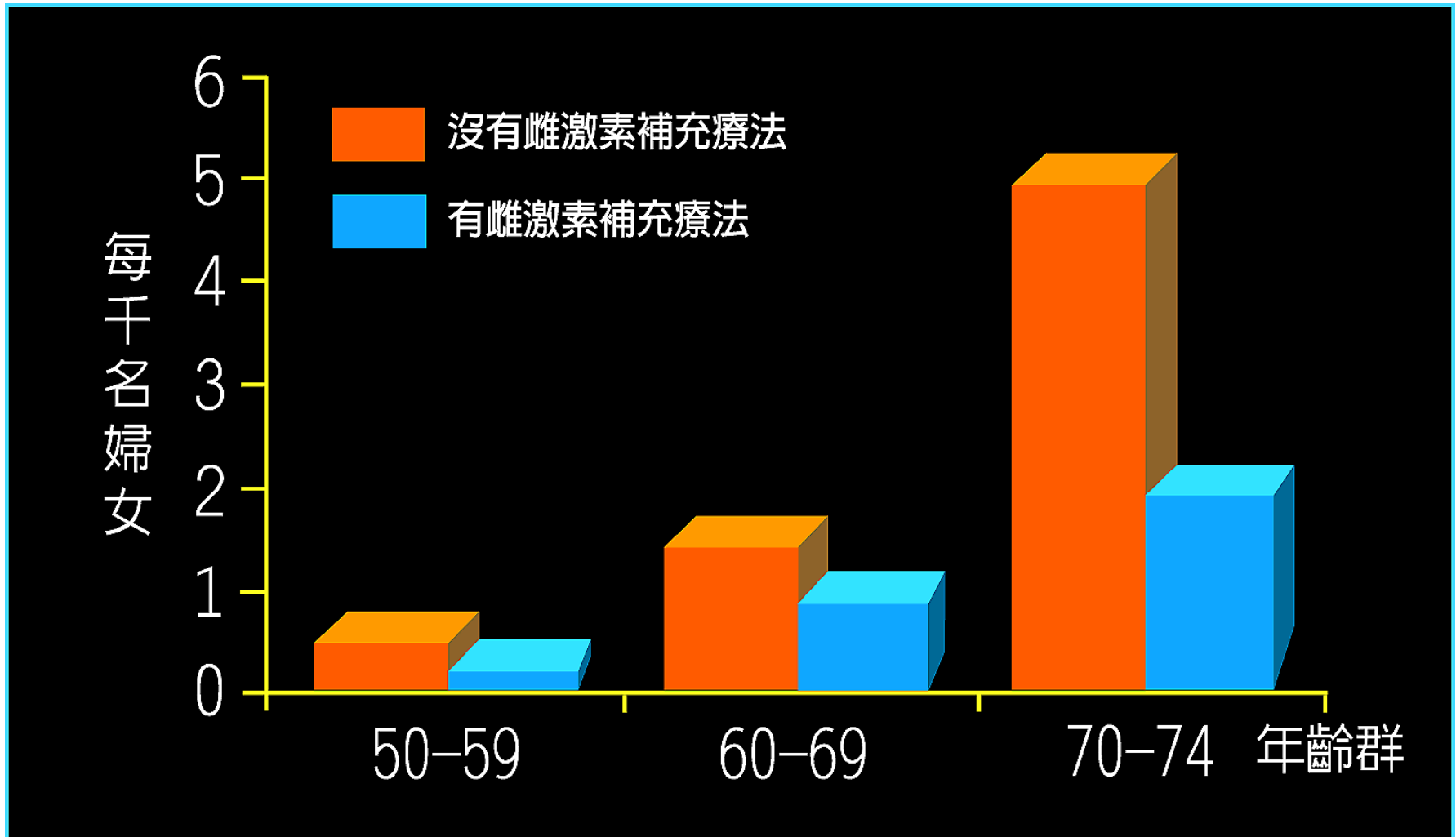
- 治療性—迅速減輕甚至完全

緩解更年期症狀如：

熱潮紅、盜汗、失眠、心悸。

- 預防性—預防骨質疏鬆症。

停經後婦女髖部骨折的發生率



預防骨質疏鬆症的藥物選擇

Table 32.3 Options for Osteoporosis Prevention and Treatment

Bisphosphonates

Fosamax (Alendronate) (35–70 mg/week)

Actonel (Risedronate) (35 mg/week)

Boniva (Ibandronate) (150 mg/month)

- Additional potential benefits: none
- Potential risks: esophageal ulcers
- Side effects: gastrointestinal distress, arthralgias/myalgias

Hormone Therapy

Estrogen or Estrogen/Progestin Therapy

- Additional potential benefits: treatment of vasomotor symptoms and urogenital atrophy
- Potential risks: breast cancer, gallbladder disease, venous thromboembolic events, cardiovascular disease, stroke
- Side effects: vaginal bleeding, breast tenderness

Selective Estrogen Receptor Modulators (SERMS)

Evista (Raloxifene) (60 mg/day)

- Additional potential benefits: reduced risk of breast cancer
- Potential risks: venous thromboembolic events
- Side effects: vasomotor symptoms, leg cramps

Other

Calcitonin (Miacalcin) (200 IU /day intranasally or 100 IU/day subcutaneously or intramuscularly)

- Additional potential benefits: none
- Potential risks: none
- Side effects: rhinitis, back pain

Forteo (Teriparatide) (20 µg/day subcutaneously)

- Additional potential benefits: none
- Potential risks: osteosarcoma after long-term use in rodents, hypercalcemia
- Side effects: leg cramps

婦女面對更年期生活之調適

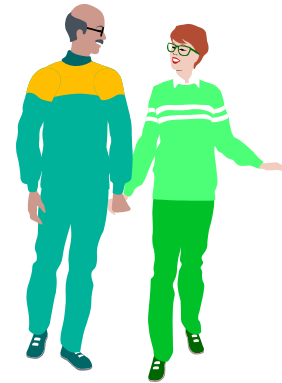
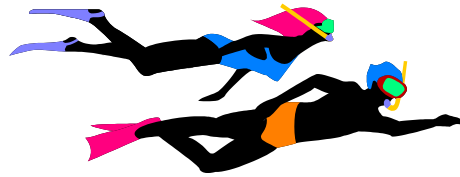
- 每天鈣的需要量
- 運動
- 荷爾蒙療法

每天鈣的需要量

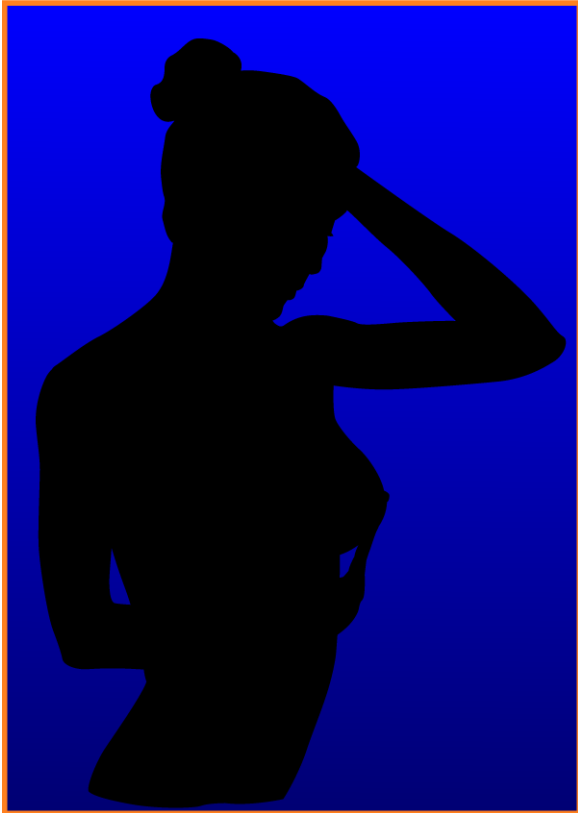
- 一般正常成年人～ 800-1000 毫克
- 更年期婦女(有接受荷爾蒙療法)
～ 1000 毫克
- 更年期婦女(沒有接受荷爾蒙療法)
～ 1500 毫克

運動

適度並持之以恆的運動，可以刺激維持骨骼中的鈣，緩和骨質疏鬆的發生，同時可以增加肌肉彈性。



荷爾蒙療法的副作用



- 子宮點狀或不規則出血
- 乳房脹痛
- 暫時性噁心
- 少許水腫

WHI 更年期荷爾蒙補充療法內容及目前建議

美國國家衛生研究院另一項針對子宮切除後的女性接受荷爾蒙療法的追蹤分析，該報告於2006年發表，指出切除子宮的婦女單獨使用雌激素（conjugated equine estrogens）持續長達7.1年，不但並未增加乳癌發生率，甚至有減少的趨勢。

WHI更年期荷爾蒙補充療法內容 及目前建議趨勢

2002年美國婦女健康促進會WHI (Women's Health Initiative) 卻將更年期荷爾蒙療法判了死刑；由40個美國醫療中心，8千多位使用荷爾蒙女性，相對於8千位不使用荷爾蒙女性的對照組，進行了5.2年的研究，發現更年期後使用荷爾蒙無法預防心臟病，反而增加心臟病；雖然可以減少大腸癌和骨折，卻也增加了中風和乳癌。心臟血管疾病包含腦血管疾病、心臟病及高血壓性疾病，在歐美國家是頭號死亡原因，在國內的死亡人數僅次於癌症。WHI的這份研究，導致國內外荷爾蒙的使用量兩年內減了一半。

荷爾蒙療法與乳癌

Relative Risks of Breast Cancer Associated with Postmenopausal Estrogen-Progestin Treatment — Statistically Significant

Reference	Relative Risk (Confidence Interval)
Colditz, et al, 1995. ⁶⁹⁹	1.41 (1.15–1.74)
Persson, et al, 1999. ⁷⁰⁴	1.70 (1.1–2.6) >6 yrs
Magnusson, et al, 1999. ⁷⁰⁵	1.68 (1.39–2.03)
Schairer, et al, 2000. ⁷⁰⁶	1.40 (1.1–1.9)
Ross, et al, 2000. ⁷⁰⁷	1.24 (1.07–1.45)
Newcomb, et al, 2002. ⁷⁰⁸	1.57 (1.15–2.14)
Porch, et al, 2002. ⁷⁰⁹	1.37 (1.05–1.78)
Weiss, et al, 2002. ⁷¹⁰	1.54 (1.10–2.17)
Li, et al, 2003. ⁷¹¹	1.70 (1.3–2.2)
Olsson, et al, 2003. ⁷¹²	4.60 (2.39–8.84)
Kerlikowske, et al, 2003. ⁷¹³	1.49 (1.36–1.63)

Relative Risks of Breast Cancer Associated with Postmenopausal Estrogen-Progestin Treatment — Not Statistically Significant

Reference	Relative Risk (Confidence Interval)
Kaufman, et al, 1984. ⁶⁸⁸	1.7 (0.9–3.3)
Ewertz, et al, 1988. ⁶⁹⁷	1.36 (0.98–1.87)
Bergvist, et al, 1989. ⁶⁹⁴	4.4 (0.9–22.4)
Yang, et al, 1992. ⁷¹⁴	1.2 (0.6–2.2)
Stanford, et al, 1995. ⁷¹⁵	0.9 (0.6–1.2)
Newcomb, et al, 1995. ⁷¹⁶	0.75 (0.49–1.15) < 5 yrs 1.12 (0.72–1.76) > 5 yrs
LaVecchia, et al, 1995. ⁷¹⁷	1.6 (0.4–6.3)
World reanalysis, 1997. ⁷¹⁸	1.53 (0.80–2.92)
Brinton, et al, 1998. ⁷¹⁹	0.99 (0.7–1.3)
Persson, et al, 1999. ⁷⁰⁴	1.4 (0.9–2.3) 1–6 yrs
Lando, et al, 1999. ⁷²⁰	0.8 (0.6–1.1)
Moorman, et al, 2000. ⁷²¹	0.8 (0.4–1.2)
Kirsh & Kreiger, 2002. ⁷²²	3.48 (1.00–12.11)
De Lignières, et al, 2002. ⁷²³	0.98 (0.65–1.5)

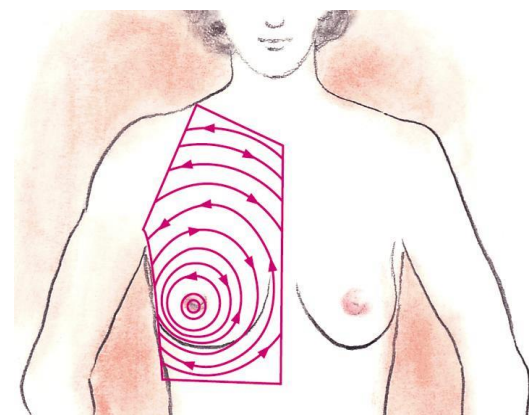
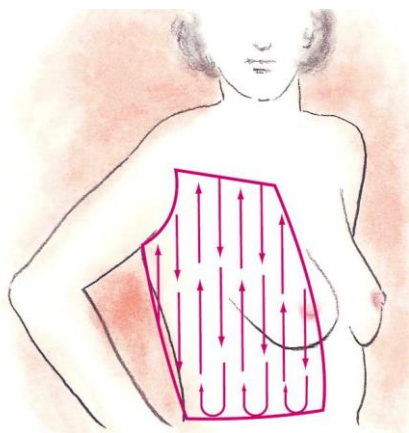
乳癌的危險因子

因子	低危險群	高危險群	相對危險性
性別	男性	女性	150.0
初經年齡(歲)	>14	<12	1.5
第一次生產年齡(歲)	<20	>30	1.9-3.5
餵母乳(月)	>16	0	1.37
自然停經年齡(歲)	<45	>55	2.0
雌激素補充療法	不曾接受	目前使用中	1.2-1.4
停經後體型肥胖指數	<22.9	>30.7	1.6
乳癌家族史	沒有	有	2.6

資料來源:New England Journal of Medicine , 2001 , 344: 276-285

乳房自我檢查

婦女自己定期做乳房自我檢查（每個月一次）及每年接受醫師檢查是很重要的，因為乳癌早期發現，早期治療，治癒率相當高。



雌激素併服黃體素之荷爾蒙療法 與子宮內膜癌之關係

研究者	發生率 / 1000病患		
	未服用	只服用 雌激素	雌激素併 服黃體素
Nachtigall et al, 1979	1.2	--	0
Hammond et al, 1979	0.5	6.5	0
Gambrell, 1987	2.5	3.9	0.5
Persson et al., 1989	1.4	1.8	0.9

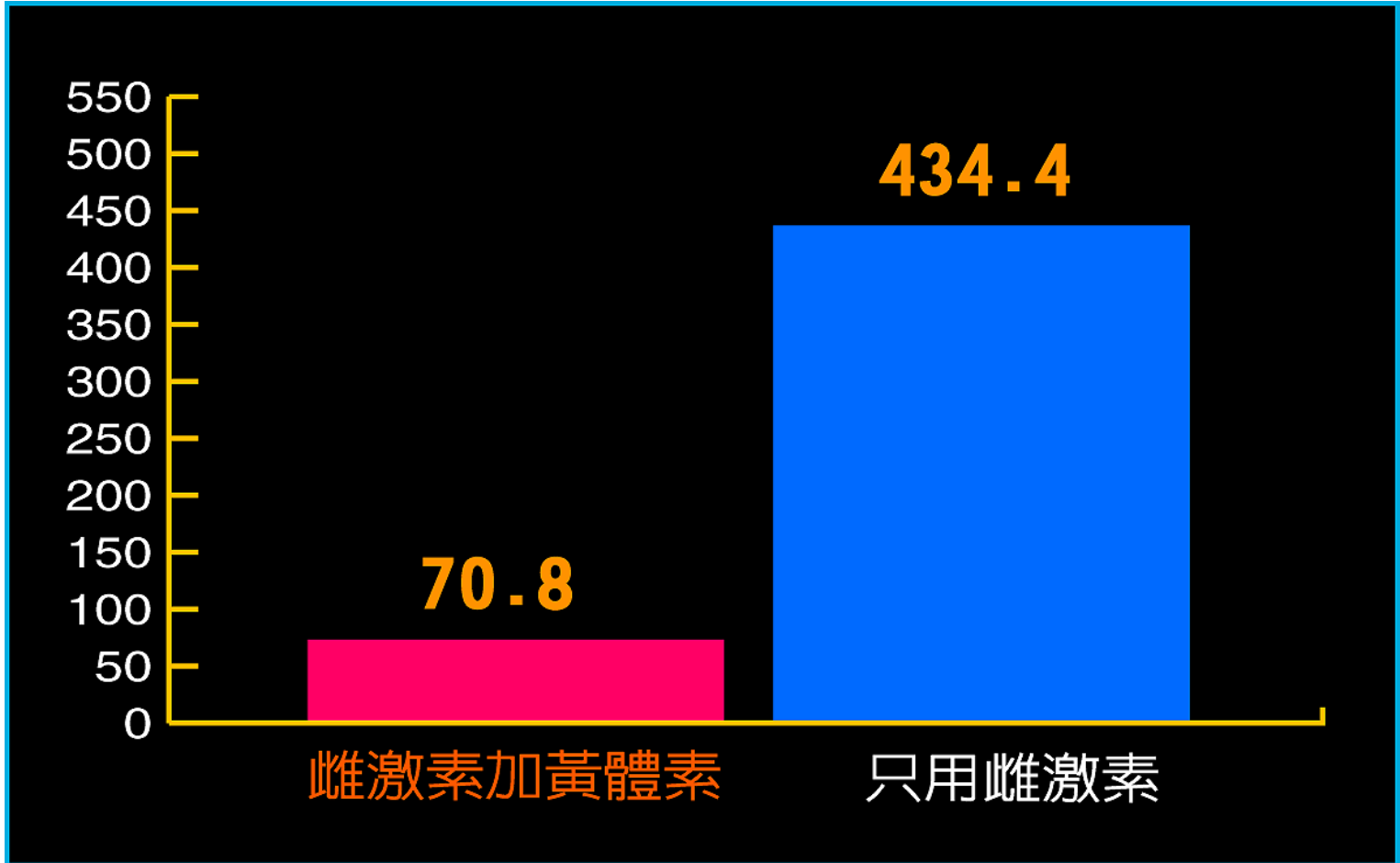
雌激素若與黃體素合併使用，不會增加子宮內膜癌發生率

參考資料：

Nachtigall LE, et al., Obstet Gynecol, 1979;54-79 Hammond CB, et al., Am J Obstet Gynecol. 1979;133:537-547
Gambrell RD., Jr Am J Obstet Gynecol, 1987;156:1304-1313 Perssonl, et al., Br Med J. 989:298:147-151

使用雌激素加黃體素和只用雌激素的 子宮內膜癌個案比較

每十萬名婦女罹患
子宮內膜癌的人數



荷爾蒙療法的禁忌症

- 已知或懷疑罹患乳癌者。
- 已知或懷疑罹患與雌激素有關之惡性腫瘤者。
- 已知或懷疑已懷孕者。
- 未經診斷之生殖道不正常出血者。
- 罹患或曾罹患靜脈血栓性栓塞者。
- 罹患或最近罹患動脈血栓性栓塞疾病者。
- 患有肝臟功能不全或疾病者。

更年期荷爾蒙治療之選擇

Blood production rates of steroids			
	Reproductive age	Postmenopausal	Oophorectomized
Androstenedione	2-3 mg/day	0.5-1.5 mg/day	0.4-1.2 mg/day
DHA	6-8	1.5-4	1.5-4
DHAS	8-16	4-9	4-9
Testosterone	0.2-0.25	0.05-0.18	0.02-0.12
Estrogen	0.35	0.045	0.045

Changes in circulating hormone levels at menopause		
	Premenopause	Postmenopause
Estradiol	40-400 pg/mL	10-20 pg/mL
Estrone	30-200 pg/mL	30-70 pg/mL
Testosterone	20-80 ng/dL	15-70 ng/dL
Androstenedione	60-300 ng/dL	30-150 ng/dL

更年期荷爾蒙治療之選擇

Table 32.5 Hormone Therapy Options^a

Oral Estrogen Products

Composition	Product Name	Dose (mg/day)
Conjugated equine estrogens	Premarin	0.3, 0.45, 0.625, 0.9, 1.25
Synthetic conjugated estrogens	Cenestin	0.3, 0.45, 0.625, 0.9, 1.25
Esterified estrogens	Menest	0.3, 0.625, 1.25, 2.5
17 β -estradiol	Estrace, generics	0.5, 1.0, 2.0
Estrone (estropipate)	Ortho-Est, Ogen, generics	0.625, 1.25

Transdermal/Topical Estrogen Products

Composition	Product Name	Release Rate (mg/day)	Dose
17 β -estradiol matrix patch	Alora	0.025, 0.05, 0.075, 0.1	Twice weekly
	Climara	0.025, 0.0375, 0.05, 0.075, 0.1	Once weekly
	Esclim	0.025, 0.0375, 0.05, 0.075, 0.1	Twice weekly
	Menostar	0.014	Once weekly
	Vivelle (Dot)	0.025, 0.0375, 0.05, 0.075, 0.1	Twice weekly
17 β -estradiol reservoir patch	Estraderm	0.025, 0.05, 0.1	Twice weekly
17 β -estradiol	EstroGel	0.035	Daily application via metered-dose pump
17 β -estradiol	Estrasorb	0.05	Daily application of 2 packets

Vaginal Estrogen Products

Composition	Product Name	Recommended Dose
Vaginal Creams		
17 β -estradiol	Estrace vaginal cream	0.5–1 g, 2–3 times weekly
Conjugated equine estrogens	Premarin vaginal cream	0.5–1 g, 2–3 times weekly
Vaginal Rings		
17 β -estradiol	Estring	Device releases 7.5 μ g/day for 90 days
Estradiol acetate	Femring	Device releases 5 or 10 μ g/day for 90 days (systemic estradiol levels achieved)
Vaginal Tablet		
Estradiol hemihydrate	Vagifem	1 tablet (25 μ g) twice weekly

Progestogens

Composition	Product Name	Dose
Progestin: Oral Tablet		
Medroxyprogesterone acetate	Provera, generics	2.5, 5, 10 mg
Norethindrone	Micronor, Nor-QD, generics	0.35 mg
Norethindrone acetate	Aygestin, generics	5 mg
Megestrol acetate	Megace	20, 40 mg
Progestin: Intrauterine System		
Levonorgestrel IUS	Mirena	20 μ g/day release rate (5-year use)

(Continued)

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Table 32.5 Continued

Progesterone: Oral Capsule

Micronized progesterone USP Prometrium 100, 200 mg

Progesterone: Vaginal Gel

Progesterone Prochieve 4%* 45 mg/applicator

Combination Estrogen-Progestogen Products

Composition	Product Name	Dose (per day)
Oral Continuous-Cyclic Regimen		
Conjugated equine estrogens (E) +medroxyprogesterone acetate (P)	Premphase	0.625 mg E + 5.0 mg P (E alone days 1–14, E + P days 15–28)
Oral Continuous-Combined Regimen		
Conjugated equine estrogens (E) +medroxyprogesterone acetate (P)	Prempro	0.625 mg E + 2.5 or 5.0 mg P 0.3 or 0.45 mg E + 1.5 mg P
Ethinyl estradiol (E) +norethindrone acetate (P)	Femhrt	5 µg E + 1 mg P
17β-estradiol (E) +norethindrone acetate (P)	Activella	1 mg E + 0.5 mg P
Oral Intermittent-Combined Regimen		
17β-estradiol (E) +norgestimate (P)	Ortho-Prefest	1 mg E + 0.09 mg P (E alone for 3 days, followed by E + P for 3 days)
Transdermal Continuous-Combined Regimen		
17β-estradiol (E) +norethindrone acetate (P)	CombiPatch	0.05 mg E + 0.14 or 0.25 mg P Twice weekly
17β-estradiol (E) + levonorgestrel (P)	Climara Pro	0.045 mg E + 0.0015 mg P Once weekly

*Table modified from North American Menopause Society. *Menopause practice: a clinician's guide*. Cleveland, OH: North American Menopause Society, 2004. Used with permission.

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