Hormonal therapy荷爾蒙治療 and menopause停經 for breast cancer survivors 乳癌康復者

Carol Kwok郭子熹

Specialist Clinical Oncologist

15 September 2012

Outline大綱

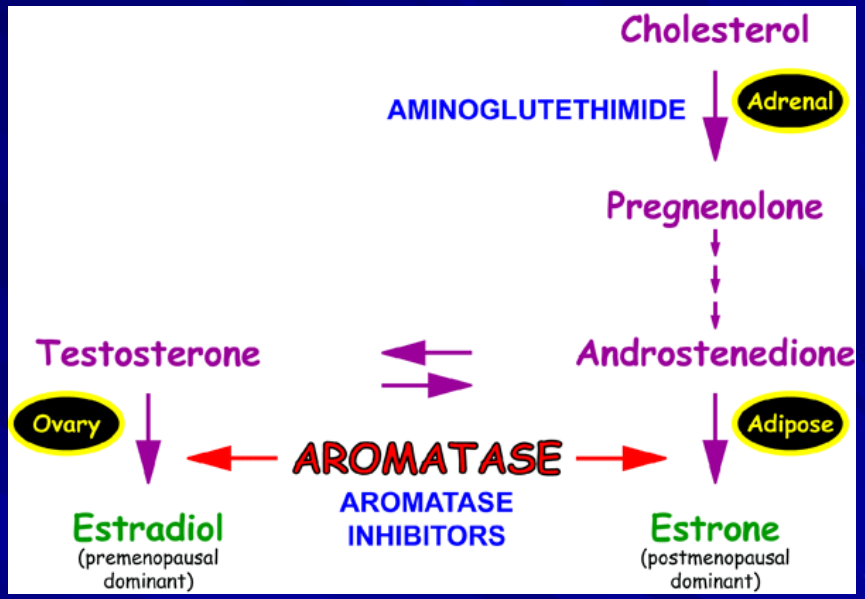
- 最新的乳癌荷爾蒙治療Updated hormonal therapy for breast cancer (BC)
  - 三苯氧胺, 他莫昔芬Tamoxifen
  - 卵巢功能抑制Ovarian function suppression
  - 芳香環轉胺酶抑制劑Aromatase inhibitors
  - 氟維司群Fulvestrant
- Premature提前的menopause for breast cancer survivors
- Implication影响 of premature menopause
- Management of early menopause and its complication

Sex hormones性激素

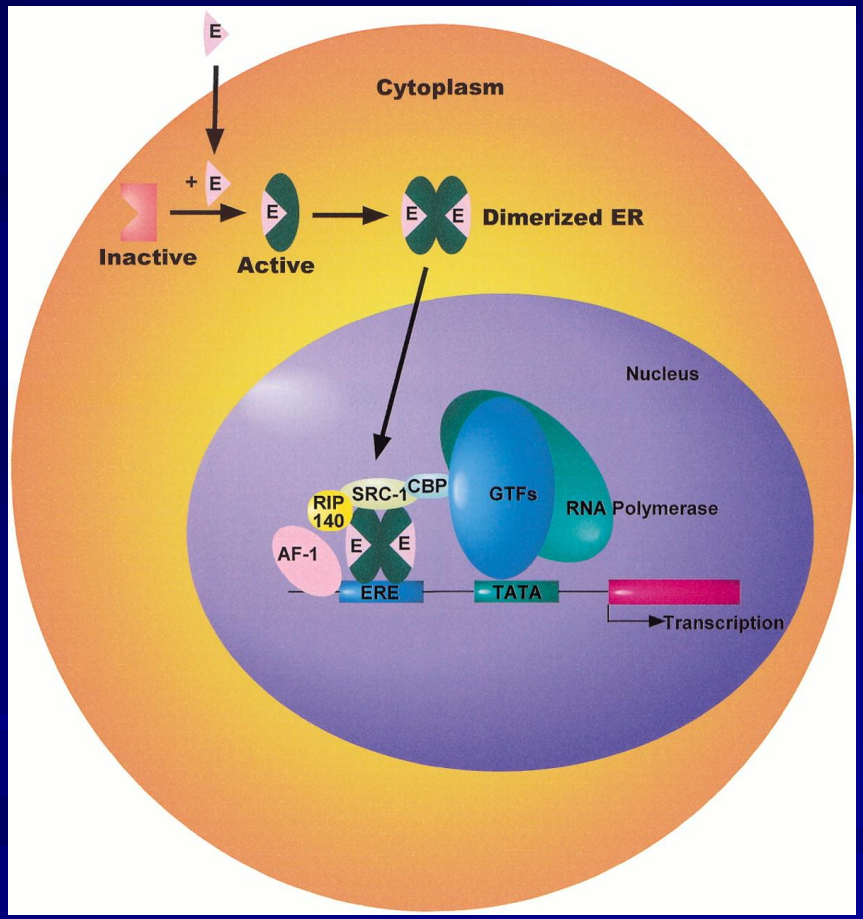
- 雌激素(Estrogen) and 孕激素(黃体酮; Progesterone)
- 雌激素的作用
  - Promotes the development and maintenance of female sex characteristics
  - Growth of long bones
  - Cardioprotective effects
  - Lipid metabolism
- Progesterone plays a role in the menstrual cycle and pregnancy

Production of estrogen

- In premenopausal women, the ovaries are the predominant source of estrogen, only small proportion comes from peripheral organs
- In contrast, the little estrogen produced in postmenopausal women comes predominantly from aromatization of adrenal and ovarian androgens in extragonadal tissues such as liver, muscle and fat tissues

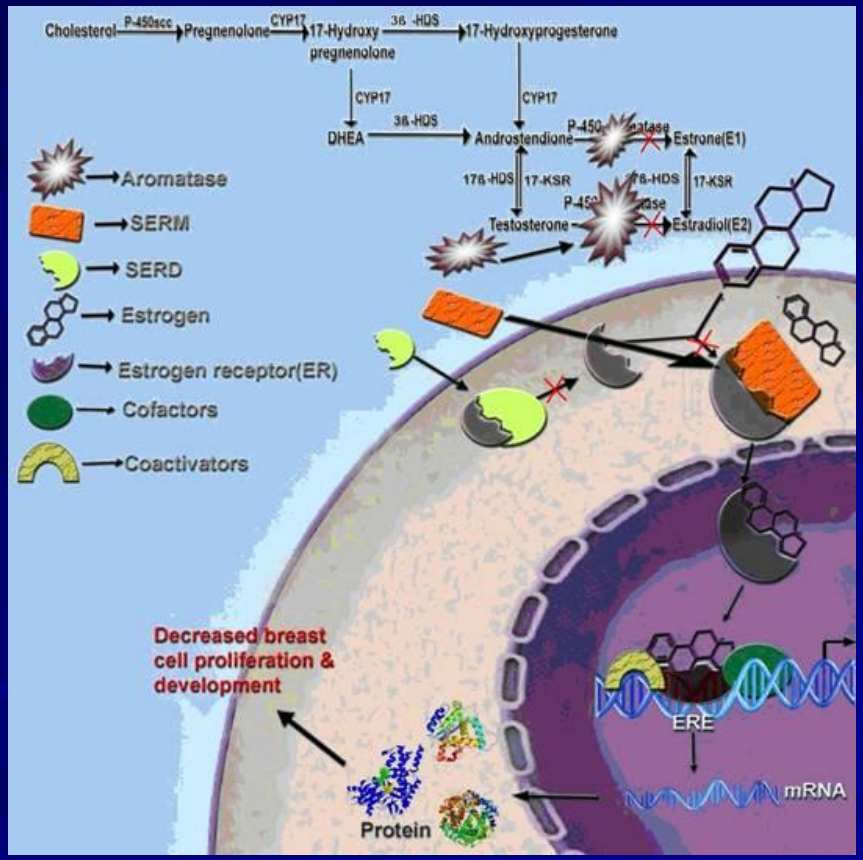


Role of estrogen and estrogen receptor in BC



- Estrogen and progesterone can also promote the growth of some BC, which are called hormone-sensitive (or hormone-dependent) BC
- Hormone-sensitive BC cells contain proteins known as hormone receptors that become activated when hormones bind to them
- The activated receptors cause changes in the expression of specific genes, which can lead to the stimulation of cell growth
- Tumours that are hormone-insensitive do not respond to hormone therapy

Types of hormonal therapy



- Blocking ovarian function – LHRHa
- Blocking estrogen production – AIs
- Blocking estrogen's effects
  - Selective estrogen receptor modulators (SERMs)
    - Tamoxifen
    - Raloxifen
  - Other antiestrogen drugs
    - Fulvestrant (SERD)

Hormone therapy for breast cancer is not the same as female hormone replacement therapy (HRT), in which hormones are given to reduce the symptoms of menopause

FDA approved indication of hormonal therapy in BC

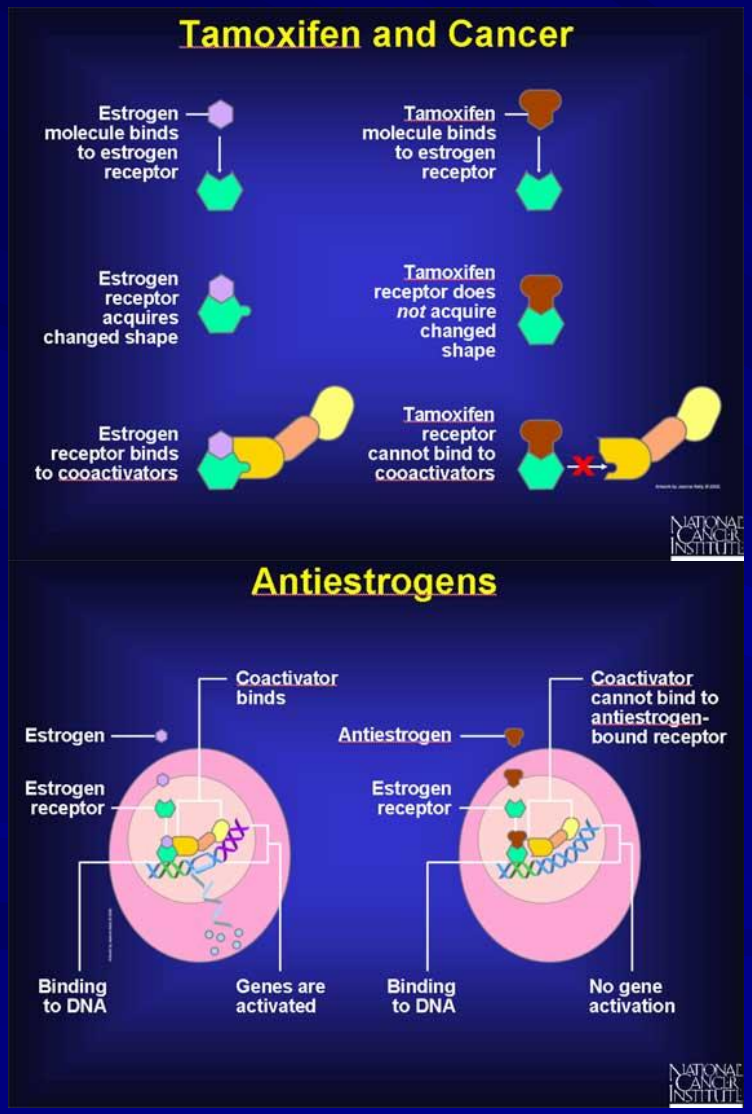
	Prevention	Adjuvant for early BC	Metastatic	Neoadjuvant
Tamoxifen	Yes[1]	Yes[2]	Yes	No
AIs		Yes[3]	Yes	No
Fulvestrant			Yes[4]	No
Raloxifen	Yes[1]			No
Toremifene			Yes	No

1. Tamoxifen is approved for use regardless of menopausal status. Raloxifene is approved for use only in postmenopausal women
2. Premenopausal and postmenopausal women (and men)
3. Postmenopausal women
4. Postmenopausal women with metastatic ER-positive BC after treatment with other antiestrogens

Ovarian ablation or ovarian function suppression

- Ovarian ablation –
  - Surgical oophrectomy
  - Radiation
    - may be incomplete and delayed, biochemical verification is required
- Ovarian function suppression
  - Gonadotropin-releasing hormone (GnRH), also known as luteinizing hormone-releasing hormone (LHRH) agonists
  - Interfere signals from pituitary gland that stimulate the ovaries to produce estrogen
  - Time-limited, reversible
  - Goserelin (Zoladex®) and leuprolide (Lupron®)

Tamoxifen – 三苯氧胺 (他莫昔芬)

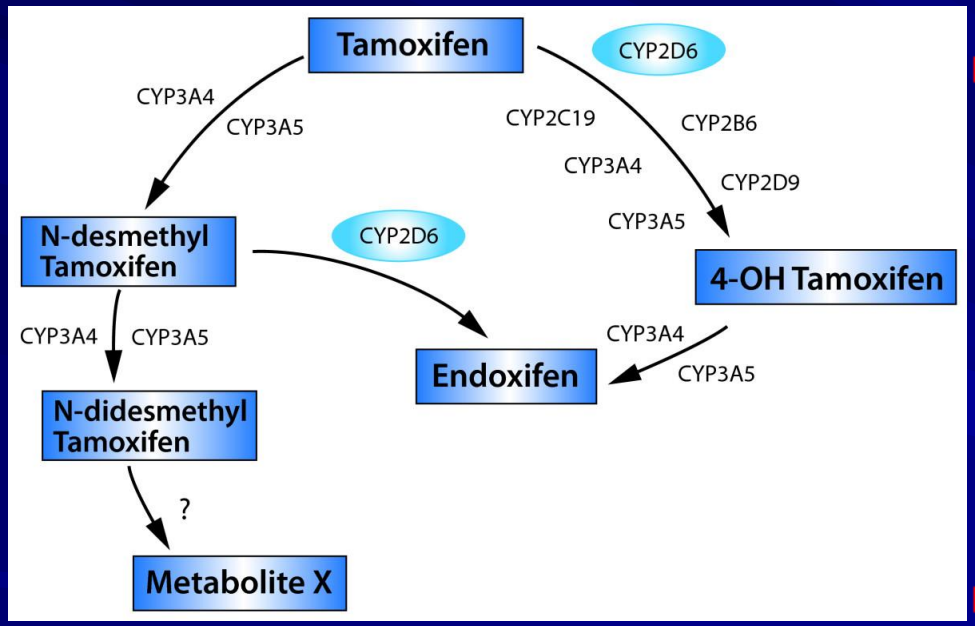


- Acting as anti-estrogen by inhibiting the binding of estrogen to ER
- More properly referred to as selective estrogen-receptor modulators (SERM)
- Because SERMs bind to estrogen receptors, they can potentially also mimic estrogen effects (i.e., serve as estrogen agonists)

SERM (選擇性雌激素受體調節劑)

- A drug that acts like estrogen on some tissues but blocks the effect of estrogen on other tissues
- Examples of SERMS approved by the FDA are tamoxifen (Nolvadex®), raloxifene (Evista®), and toremifene (Fareston®)
- Most SERMs behave as estrogen antagonists in some tissues and as estrogen agonists in other tissues. For example, tamoxifen blocks the effects of estrogen in breast tissue but acts like estrogen in the uterus and bone

Metabolism of tamoxifen

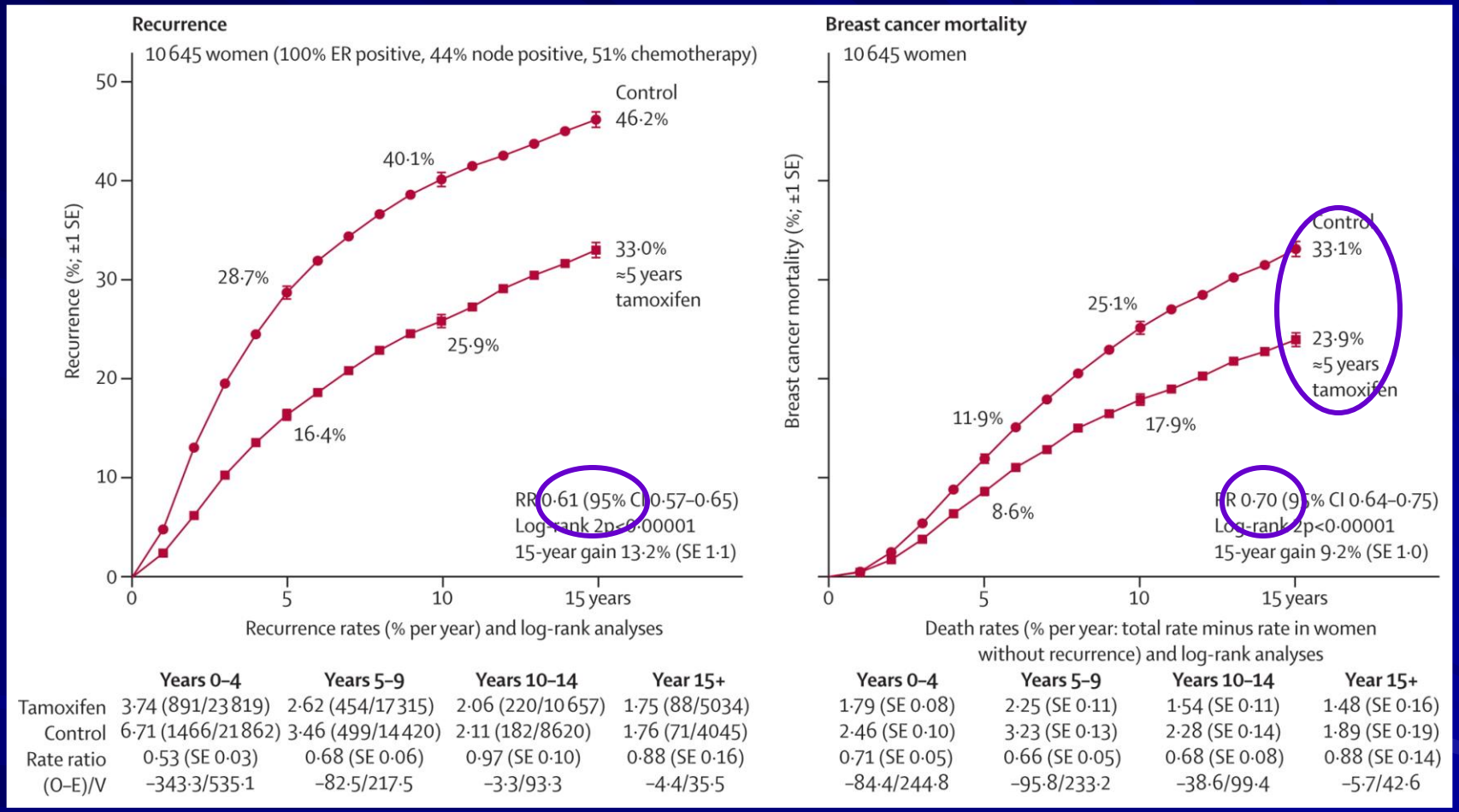


- Tamoxifen itself is a prodrug, having relatively little affinity for its target protein, the estrogen receptor
- It is metabolized in the liver by the cytochrome P450 isoform CYP2D6 and CYP3A4 into active metabolites such as 4-hydroxytamoxifen (afimoxifen) and N-desmethyl-4-hydroxytamoxifen (endoxifen) which have 30-100 times more affinity with the estrogen receptor than tamoxifen itself
- Endoxifen is considered the most important metabolite because its plasma concentrations are several times higher than those of 4-hydroxytamoxifen

Tamoxifen

- Tamoxifen has been used for more than 30 years to treat hormone receptor-positive BC
- In adjuvant setting, tamoxifen decrease disease recurrence and mortality rates by as much as 50% and 30% respectively
- 7-10% of women with BC may not receive the full medical benefit from taking tamoxifen due to their unique genetic make-up
- At this time, based on current data, NCCN does not endorse routine CYP2D6 testing for women being considered for tamoxifen therapy

Effects of ~ 5 yr Tam on 15-yr probabilities of recurrence and of BC mortality, ER+ disease



	Years 0–4	Years 5–9	Years 10–14	Year 15+
Tamoxifen	3·74 (891/23 819)	2·62 (454/17 315)	2·06 (220/10 657)	1·75 (88/5034)
Control	6·71 (1466/21 862)	3·46 (499/14 420)	2·11 (182/8620)	1·76 (71/4045)
Rate ratio	0·53 (SE 0·03)	0·68 (SE 0·06)	0·97 (SE 0·10)	0·88 (SE 0·16)
(O–E)/V	−343·3/535·1	−82·5/217·5	−3·3/93·3	−4·4/35·5

Years 0–4	Years 5–9	Years 10–14	Year 15+
1·79 (SE 0·08)	2·25 (SE 0·11)	1·54 (SE 0·11)	1·48 (SE 0·16)
2·46 (SE 0·10)	3·23 (SE 0·13)	2·28 (SE 0·14)	1·89 (SE 0·19)
0·71 (SE 0·05)	0·66 (SE 0·05)	0·68 (SE 0·08)	0·88 (SE 0·14)
−84·4/244·8	−95·8/233·2	−38·6/99·4	−5·7/42·6

Yearly rate of BC mortality reduced by about 1/3 (RR 0.7, [0·05], p<0·00001) throughout first 15 yrs with highly significant benefit during each of years 0-4, 5-9 and 10-14. Absolute mortality difference only 3% at yr 5, but three times as great 24% vs. 33% by yr 15

EBCTCG. Lancet 2011; 378: 771–84

AIs – Aromatase inhibitors (芳香化酶抑制劑)

- Aromatase is an enzyme of cytochrome P-450, which the body uses to make estrogen in the ovaries and in other tissues. It is present at lower levels in several non glandular tissues including subcutaneous fat, liver, muscle, brain, normal breast, and breast-cancer tissue
- AI markedly suppresses the plasma estrogen levels in postmenopausal women by inhibiting or inactivating aromatase
- Indicated for post-menopausal women hormone receptor positive BC
- Not appropriate in pre-menopausal – presence of ovarian derived estrogens because the ovaries in premenopausal women produce too much aromatase for the inhibitors to block effectively

Aromatase inhibitors - AIs

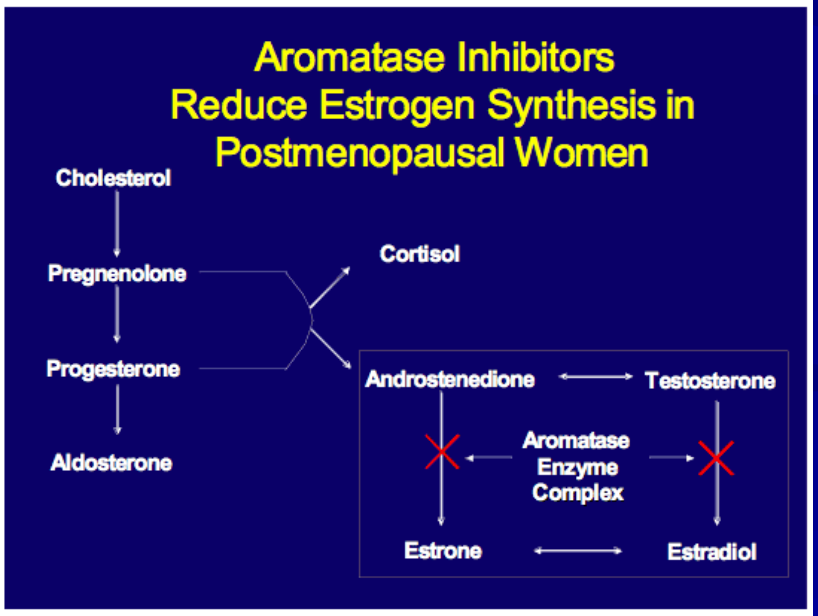
AIs → Inhibits → **Aromatase**

Androgens → Biosynthesis → **Estradiol**

Growth stimulation

Estrogen dependent breast cancer

Figure 1. Mechanism of Action of Aromatase Inhibitors.



Indication of AIs

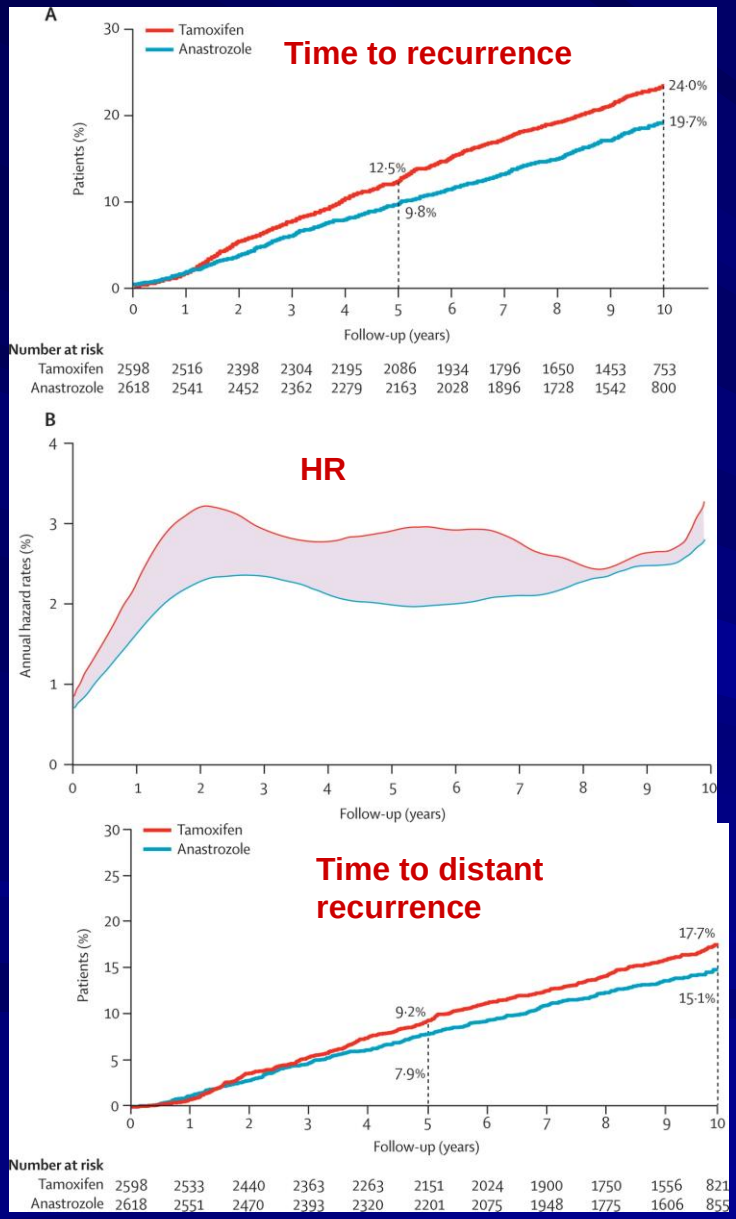
- For ER+ (雌激素受體呈陽性) postmenopausal patients
  - Primary or upfront treatment instead of tamoxifen
  - Sequential therapy after 2-3 yr of tamoxifen
  - Extended therapy after 5 yr of tamoxifen

10-year analysis of the ATAC trial

	Full study population, A=3125 T= 3116			Hormone receptor +ve pts, A=2618, T=2598		
	HR	95% CI	P	HR	95% CI	P
DFS	0.91	0.83-0.99	0.04	0.86	0.78-0.95	0.003
Time to recurrence	0.84	0.75-0.93	0.001	0.79	0.70-0.89	0.0002
Time to distant recurrence	0.87	0.77-0.99	0.03	0.85	0.73-0.98	0.02

Lancet Oncol. 2010 Dec;11(12):1135-41

ATAC – benefit of AI over tamoxifen



- In HR+ patients, those receive anastrozole had a 4.3% lower absolute rate of BC recurrence after 10 yrs, and a 2.6% lower absolute rate of distant metastasis
- Absolute differences increased over time (2·7% at 5 years and 4·3% at 10 years), although the carryover effect – in which benefits extend beyond the treatment period – began to wane after about 8 years

Lancet Oncol. 2010 Dec;11(12):1135-41

ATAC – Deaths in the full study population

	Anastrozole n=3,125 (%)	Tamoxifen n=3,116 (%)
Total deaths	734 (23.5)	747 (24)
Deaths after recurrence	395 (12.6)	441 (14.2)
Deaths without recurrence	339 (10.8)	306 (9.8)
Cardiovascular	91 (2.9)	95 (3)
Cerebrovascular	33 (1.1)	36 (1.2)
Other cancer	108 (3.5)	82 (2.6)
Other	107 (3.4)	93 (3)

The number of patient deaths, with or without breast cancer recurrence, was similar in the two groups after 10 years of follow-up. Thus, treatment with anastrozole did not improve overall survival compared with tamoxifen

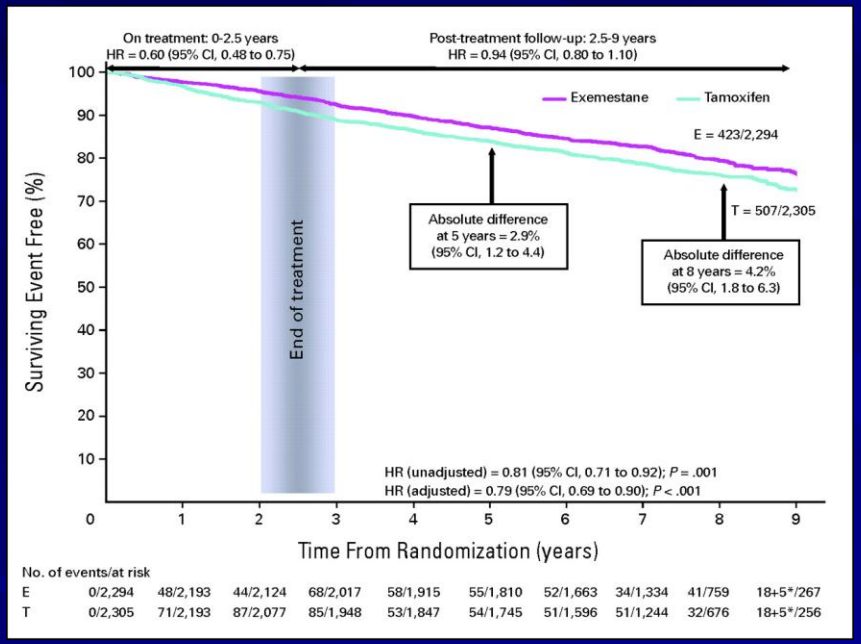
Lancet Oncol. 2010 Dec;11(12):1135-41

Comment on results of ATAC

- Limited magnitude of the average benefit reported in the 10-year analysis of ATAC strongly suggests that only a few patients derive actual benefit from anastrozole – the majority might not
- Evidence base for individualized treatment decisions remains unclear
  - ?Limited benefit of AI for PR+ tumour, pts with very low risk of recurrence
  - ?For pts with HER2+ or enzymatic variations in CYP2D6 metabolism, tamoxifen might not be the optimum treatment

10 years of ATAC: one question answered, many others unresolved: Gnant M. Lancet Oncol. 2010 Dec;11(12):1109-10

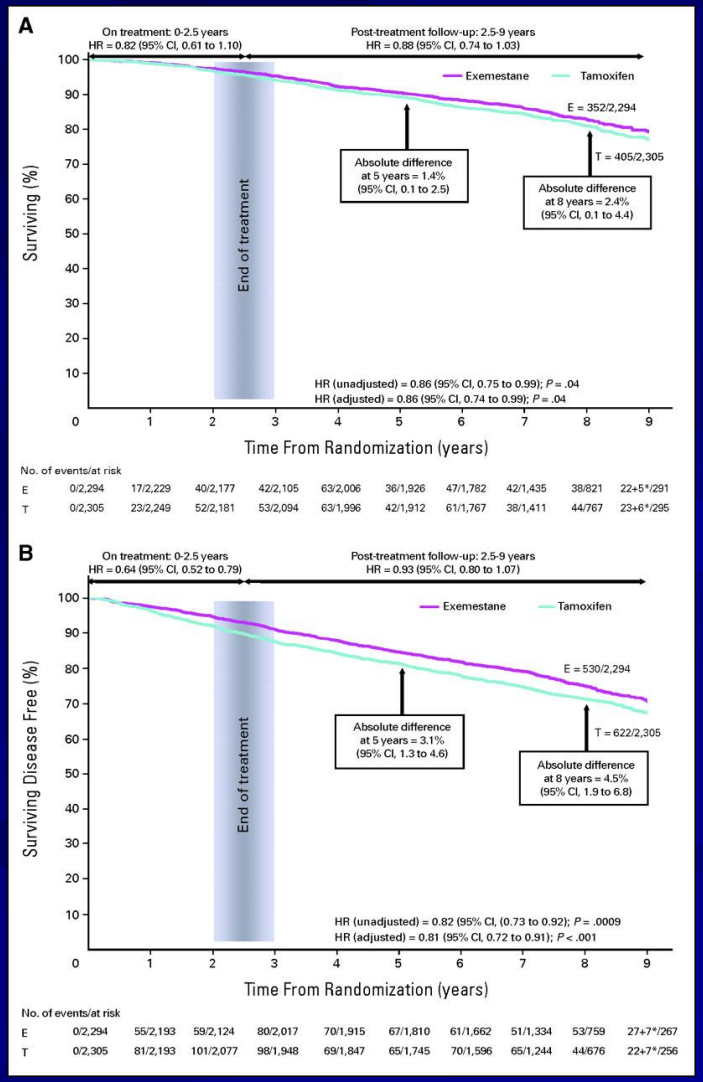
IES – results of 91 month median follow up



- Breast cancer free survival in ER+/unknown population, HR 0.6
- On-treatment benefit was not lost post-treatment, but there was no additional gain once treatment had ceased (HR 0.94, p=0.6)

JM Bliss, et al. J Clin Oncol 2011;30:709-717

IES – OS and DFS



- Patient who switched to exemestane had
  - An absolute difference in survival outcome at 8 yrs of 2.4%, 14% reduction in risk of death (HR 0.86)
  - Absolute difference in DFS of 4.5% (HR 0.81)

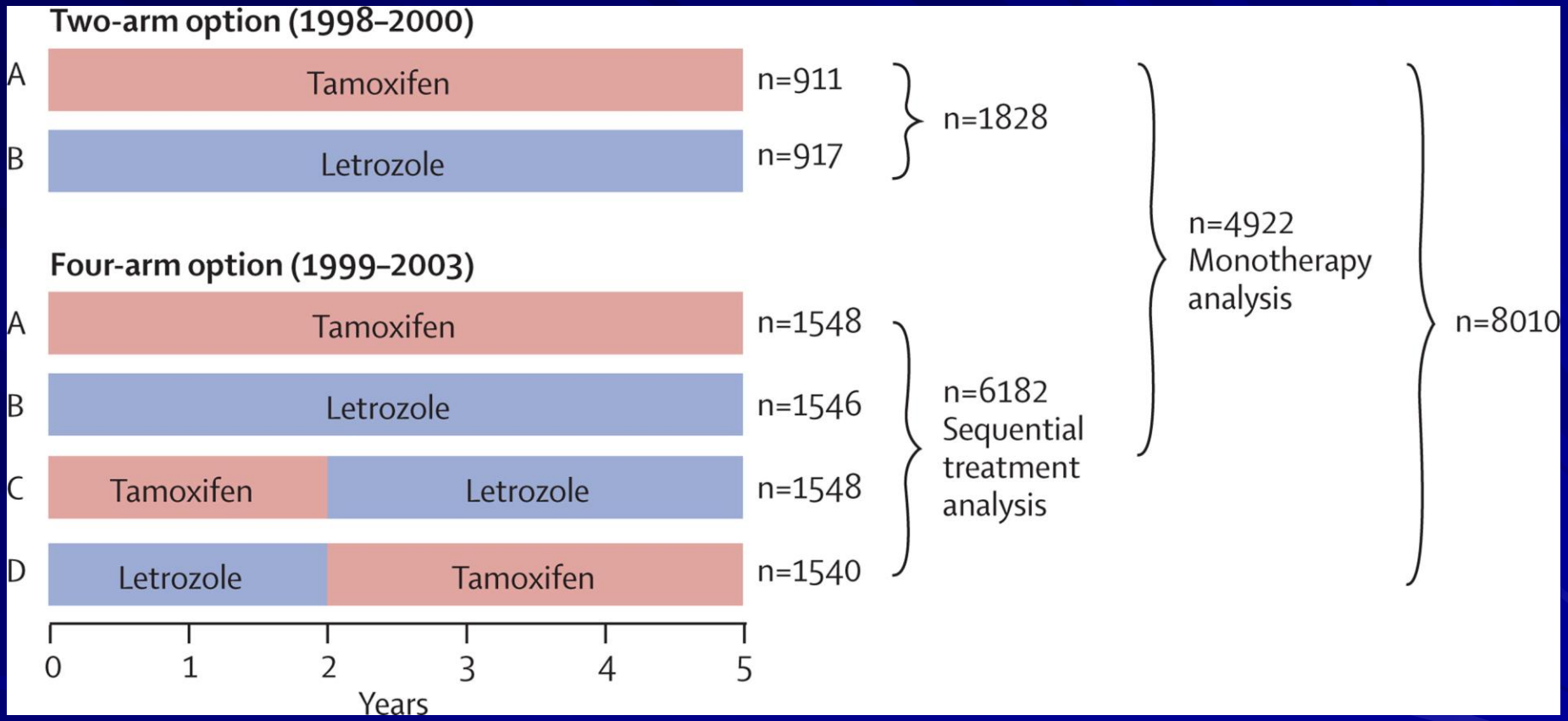
JM Bliss, et al. J Clin Oncol 2011;30:709-717

Update results of IES

- Protective effect of switching to exemestane compared with continuing on tamoxifen on risk of relapse or death was maintained for at least 5 years post-treatment and was associated with a continuing beneficial impact on overall survival

JM Bliss, et al. J Clin Oncol 2011;30:709-717

BIG 1-98 8.1 yr median follow up



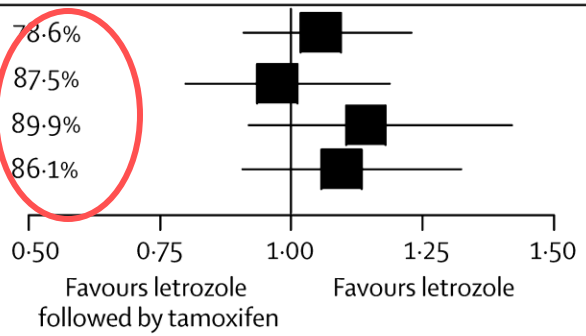
Two analytic populations: the monotherapy population (pts randomly assigned in the two-arm or four-arm option to receive either Tam (n=911+1548=2459) or letrozole (n=917+1546=2463) for 5 yrs) and the sequential treatment population (pts randomized in the four-arm option

Meredith MR et al. Lancet Oncol 2011;12:1101-08

Sequential treatment analysis

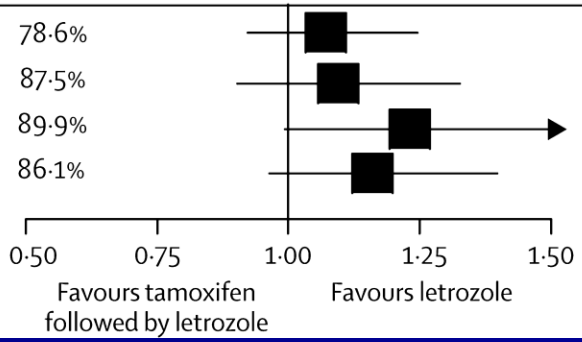
A

	Letrozole followed by tamoxifen (n=1540)			Letrozole (n=1546)			HR (95% CI)	p value
	Events	5-year percentage	8-year percentage	Events	5-year percentage	8-year percentage		
DFS	348	87·4%	77·8%	329	87·6%	78·6%	1·06 (0·91–1·23)	0·48
OS	194	93·6%	87·7%	197	93·3%	87·5%	0·97 (0·80–1·19)	0·79
DRFI	173	93·4%	88·7%	151	94·1%	89·9%	1·14 (0·92–1·42)	0·24
BCFI	226	92·4%	85·3%	206	92·5%	86·1%	1·10 (0·91–1·32)	0·34



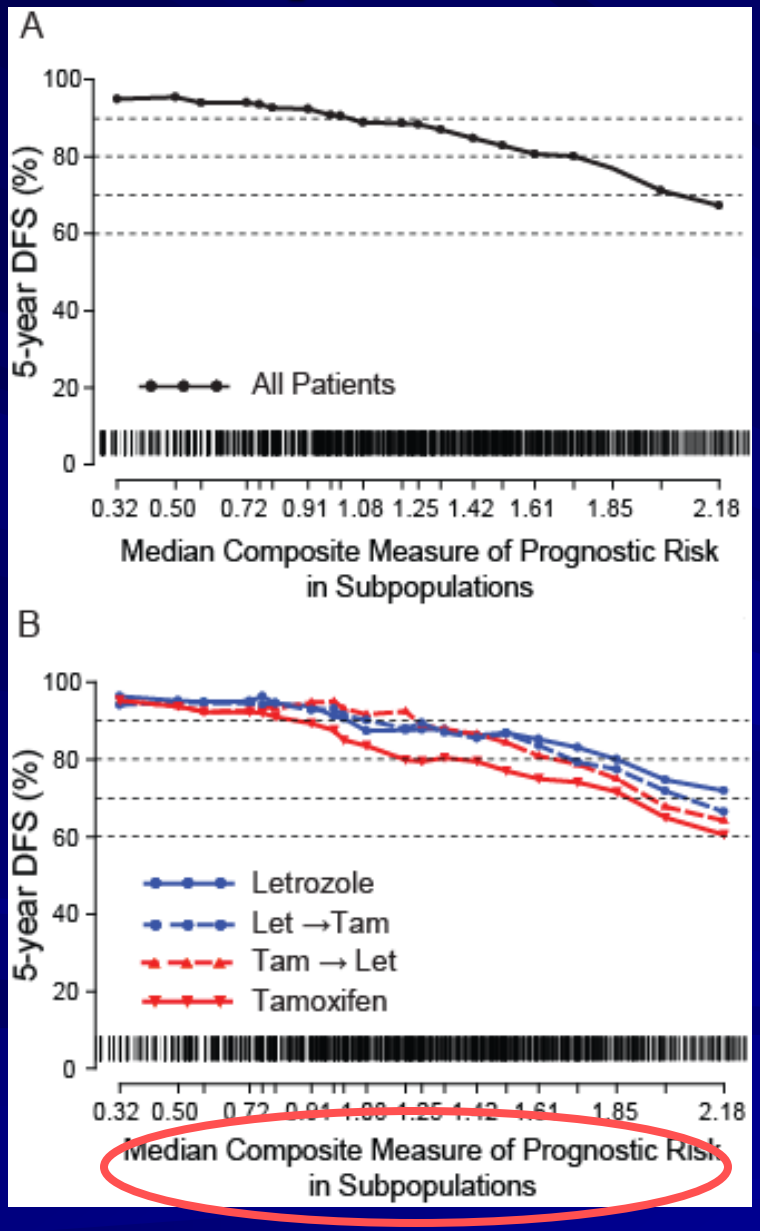
B

	Tamoxifen followed by letrozole (n=1548)			Letrozole (n=1546)			HR (95% CI)	p value
	Events	5-year percentage	8-year percentage	Events	5-year percentage	8-year percentage		
DFS	353	86·2%	77·3%	329	87·6%	78·6%	1·07 (0·92–1·25)	0·36
OS	217	92·5%	85·9%	197	93·3%	87·5%	1·10 (0·90–1·33)	0·36
DRFI	186	92·3%	88·1%	151	94·1%	89·9%	1·23 (0·99–1·53)	0·06
BCFI	239	90·4%	84·3%	206	92·5%	86·1%	1·16 (0·96–1·40)	0·12



At a median fu of 8 yr for the comparison of the sequential groups with letrozole monotherapy, there were no statistically significant differences in any of the four endpoints for either sequence

Which patients benefit most from AI



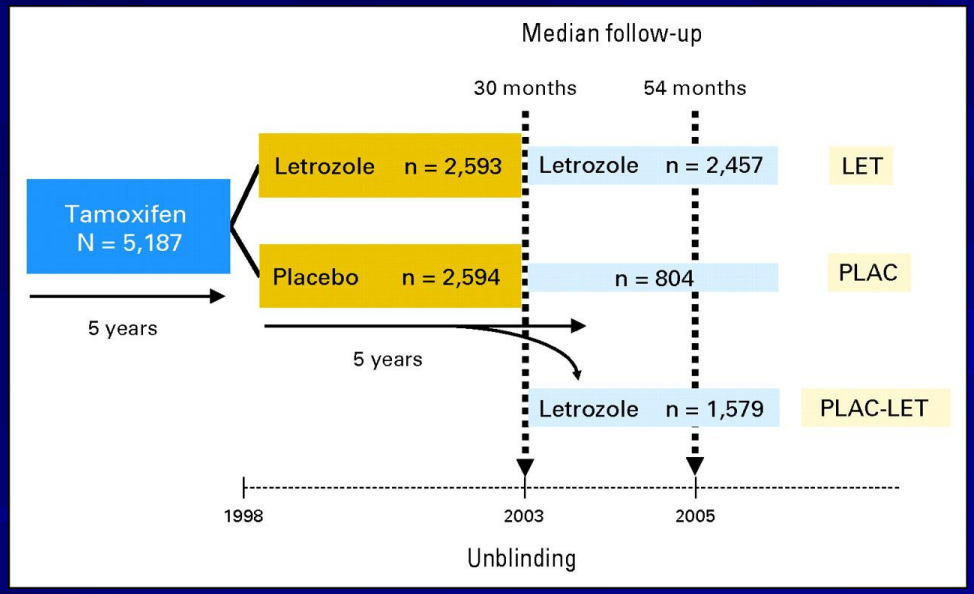
- Non-parametric Subpopulation Treatment Effect Pattern Plot (STEPP)
- All 4 treatments has similar 5 yr DFS for pt at lowest risk (left end of x-axis), the 3 letrozole-containing treatments had similar 5 yr DFS for intermediate risk (middle), where pts given letrozole for 5 yr had better outcome for those at highest risk
- Upfront letrozole might be reasonable for pts at high risk for early relapse, but sequential…useful for others considering tolerability

BIG 1-98 8.1 yr median follow up

- For postmenopausal women with endocrine-responsive early breast cancer, a reduction in breast cancer recurrence and mortality is obtained by letrozole monotherapy when compared with Tam mono
- Sequential treatments involving Tam and Letrozole do not improve outcome c/w letrozole mono, but might be useful strategies when considering an individual patient's risk of recurrence and treatment tolerability

Meredith MR et al. Lancet Oncol 2011;12:1101-08

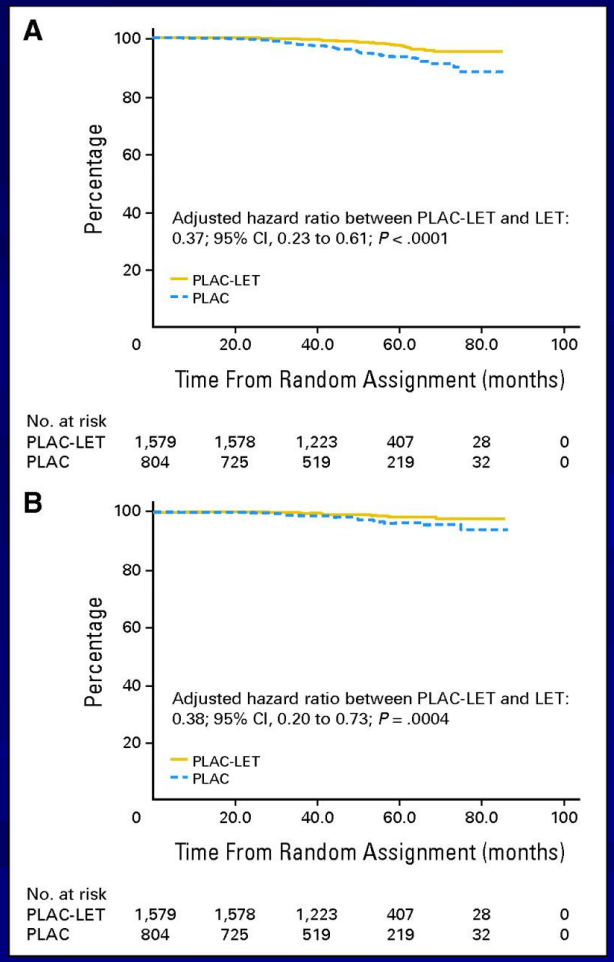
Extended AI – MA.17 trial



- At initial median fu of 2.5 yrs, fewer recurrences or new contralateral BC with extended letrozole (HR 0.58, p<0.001)
- No difference in OS, although a survival advantage in the subset of pts with positive axillary LN

PE Goss et al. J Clin Oncol 2008;26:1948-1955

Extended AI – MA.17 trial

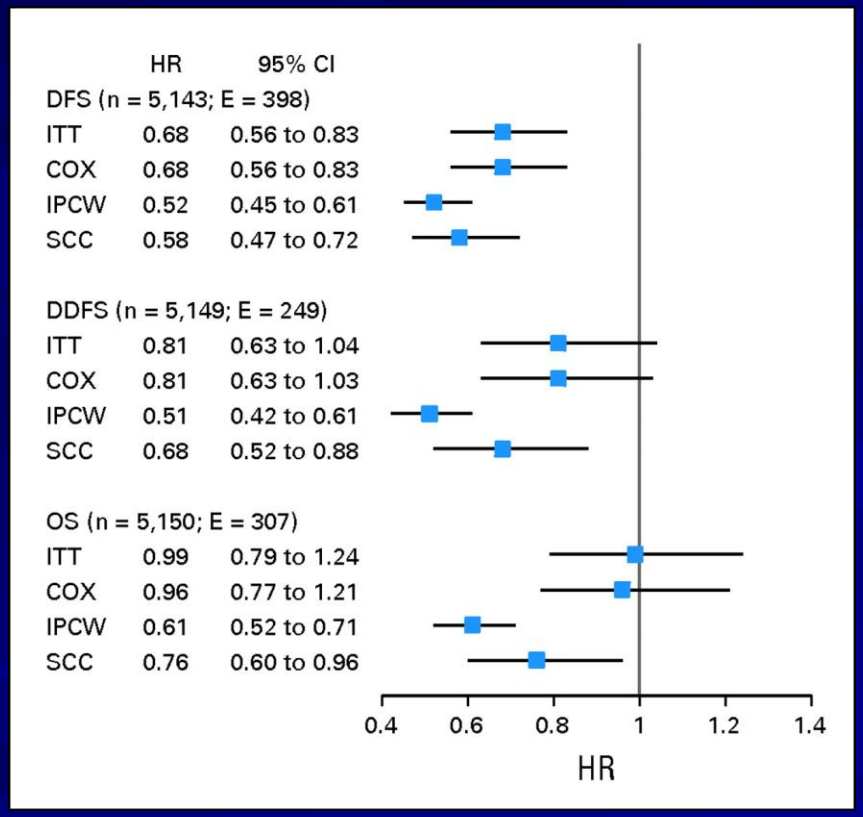


- At a median fu of 5.3 yrs, DFS (HR 0.37, p<0.0001) and distant DFS (HR 0.39, p=0.004) were superior in the plac-let group
- More new osteoporosis and fracture in letrozole group (5.2% vs. 3.1%, p 0.02)
- Providing some evidence for the efficacy of letrozole after no endocrine therapy for an extended period (median time since completion of tamoxifen was 2,8 yrs)

(A) disease-free survival and (B) distant disease free survival; both are calculated from the time of original random assignment

PE Goss et al. J Clin Oncol 2008;26:1948-1955

MA.17 – adjusting for crossover



- HR 0.52, p=0.001 for DFS
- HR 0.51, p=0.001 for distant DFS
- HR 0.61, p=0.001 for OS
- Exploratory analyses based on longer follow-up and adjusting for treatment crossover suggest that extended adjuvant letrozole was superior to placebo in DFS, DDFS, and OS

H Jin et al. J Clin Oncol 2011;30:718-721

Fulvestrant (Faslodex®)

- Work in a somewhat different way to block estrogen's effects
- Like SERMs, fulvestrant attaches to the estrogen receptor and functions as an estrogen antagonist
- However, unlike SERMs, fulvestrant has no estrogen agonist effects. It is a pure antiestrogen. In addition, when fulvestrant binds to the estrogen receptor, the receptor is targeted for destruction
- Called selective estrogen receptor down regulator (SERD)
- Has efficacy in tamoxifen-refractory disease and it has demonstrated an equivalent or superior activity than anastrozole in the metastatic cancers

Can hormonal therapy be used to prevent BC – Tamoxifen

- 由於在臨床上發現接受Tamoxifen治療的侵襲性或原位性乳癌患者，其對側乳房發生乳癌的機會較對照組有顯著降低，因此一般認為Tamoxifen可能可以降低高危險群病人的乳癌發生率
- 因此從1992年開始，美國國家外科輔助乳房及胃腸計劃(National Surgical Adjuvant Breast and Bowel Project，簡稱NSABP)組織進行一項乳癌預防臨床試驗(Breast Cancer Prevention Trial, 簡稱BCPT; P-1 study)

Results of BCPT, P-1 study

Category of patient	Result: ↓ Risk by
Invasive BC	49% (p<0.00001)
Cumulative incidence	43.4 vs. 22 per 1000 women
Age ≤ 49	44%
50 – 59 yr	51%
≥ 60 yr	55%
Hx of LCIS	56%
Hx of atypical hyperplasia	86%
Predicted 5 yr risk	Any category
Noninvasive BC	50% (p <0.002)
ER positive tumour	69%

Study population N=13,388 (White 96.5%); 1. ≥ 60 yr, 2. 35-59 yr with a 5-yr predicted risk for BC of at least 1.66%, 3. Had Hx of LCIS. Tam x 5 yr vs. placebo

J Natl Cancer Inst. 1998 Sep 16;90(18):1371-88

Raloxifen (Evista 鈣穩錠)

- A 2nd generation SERM
- Initially developed for BC, later as alternative to hormonal replacement therapy for treatment of osteoporosis
- Similar activity to Tam in breast and bone, it is devoid of agonist activity in endometrium
- On September 13, 2007, the US FDA approved raloxifene (Evista®) for reduction in the risk of invasive BC in postmenopausal women with osteoporosis and in postmenopausal women at high risk for invasive BC

Benefit of raloxifen

		Incidence of invasive BC		
Study	Patients	Raloxifen	Placebo	HR
MORE	5133	11 in 2557	38 in 2576	0.29
CORE	Subset of 4011 in MORE*	19 in 2716	20 in 1274	0.44
RUTH	10,101	40 in 5044	70 in 5057	0.56

*After a median of three additional years on treatment

STAR trial

Patients = 19,747	Tamoxifen	Raloxifen
Intervention	20mg daily x 5 yr	60mg daily x 5 yr
Invasive BC (cases)	163	168
Non-invasive BC	57	80
Uterine cancer	36	23
Thromboembolic event		Occurred less often in the raloxifene group (RR, 0.70; 95% CI, 0.54-0.91)
Osteoporotc fracture	Similar	Similar
Cataracts	(RR, 0.79; 95% CI, 0.68-0.92)	

Raloxifene is as effective as tamoxifen in reducing the risk of invasive breast cancer and has a lower risk of thromboembolic events and cataracts but a nonstatistically significant higher risk of noninvasive breast cancer. The risk of other cancers, fractures, ischemic heart disease, and stroke is similar for both drugs

JAMA. 2006;295(23):2727-2741

Updated results of STAR trial

	Risk ratio (raloxifen:tamoxifen)	95% confidence interval
Invasive BC	**1.24**	**1.05-1.47**
Noninvasive disease	**1.22**	**0.95-1.59**
Endometrial cancer	**0.55**	**0.36-0.83; P = 0.003**
Uterine hyperplasia	**0.19**	**0.12-0.29**
Thromboembolic events	**0.75**	**0.60-0.93**

Long-term raloxifene retained 76% of the effectiveness of tamoxifen in preventing invasive disease and grew closer over time to tamoxifen in preventing noninvasive disease, with far less toxicity (e.g., highly significantly less endometrial cancer). These results have important public health implications and clarify that both raloxifene and tamoxifen are good preventive choices for postmenopausal women with elevated risk for breast cancer

Cancer Prevention Research 2010; 3(6):696–706

BC prevention – Tamoxifen vs. Raloxifen

- Raloxifen potentially lost up to 35% of Tamoxifen effect on reduction of invasive BC
- Fewer noninvasive BC occurred in Tamoxifen group compared to raloxifen
- Raloxifen had lower incidence of deep vein thrombosis, pulmonary embolism, cataract and hysterectomy than Tamoxifen
- There is a trend of lower incidence of endometrial cancer
- An increased risk of death due to stroke was observed in a trial (on raloxifen) in postmenopausal women with documented coronary heart disease or at increased risk of major coronary events
- Other adverse reactions (>2% or more than placebo) include hot flashes, leg cramps, peripheral oedema, flu syndrome, arthralgia and sweating

Side effects of tamoxifen

Rate per 1000 women

Type of events	Placebo	Tamoxifen	Risk ratio
Endometrial cancer	0.91	2.30	2.53
≤ 49	1.09	1.32	1.21
≥ 50	0.76	3.05	4.01
Ischaemic heart disease	2.37	2.73	1.15
Stroke	0.92	1.45	1.59
Transient ischaemic attack	0.96	0.73	0.76
Pulmonary embolism	0.23	0.69	3.01
DVT	0.84	1.34	1.6
Cataract	21.72	24.82	1.14

Hot flashes, vaginal discharge, depression

All endometrial cancers in the tamoxifen group were stage I (localized disease); no endometrial cancer deaths have occurred in this group. No liver cancers or increase in colon, rectal, ovarian, or other tumors was observed in the tamoxifen group

Incidence of uterus (not cervix) Ca ER+ disease, ~ 5-yr Tam

		incidence (%)	Loss (%)
Entry age < 45	Tam	(10 yr) 0.4	0.1 (se 0.3) 2p=0.97
	Control	0.3	
45 - 54	Tam	(10 yr) 0.9	0.1 (se 0.4) 2p=0.17
	Control	0.8	
55 - 69	Tam	(15-yr) 3.8	2.6 (se 0.6) 2p<0.00001
	Control	1.1	
70+	Tam	(5- yr) 0	0 (se 0.0) 2p =0.11
	Control	0	

Tam ↑ uterine Ca incidence (excl cervix) RR 2.4 (se 0.32), p=0.00002). Risk is strongly correlated with age, with little absolute risk for entry age < 45 or 45-54, but for 55-69 yr, 15-yr incidence was 3.8% in Tam group vs. 1.1% in control group, absolute increase 2.6% ([se 0.6], 95% CI 1.4-3.8)

EBCTCG. Lancet 2011; 378: 771–84

Side effects of AIs

↑ cardiovascular disease*	OR = 1.26, 95% CI = 1.10 to 1.43, P < .001
↑ bone fractures	OR = 1.47, 95% CI = 1.34 to 1.61, P < .001
↓ venous thrombosis	OR = 0.55, 95% CI = 0.46 to 0.64, P < .001
↓ endometrial carcinoma	OR = 0.34, 95% CI = 0.22 to 0.53, P < .001

Five years of aromatase inhibitors was associated with a non-statistically significant increased odds of death without recurrence compared with 5 years of tamoxifen alone or tamoxifen for 2-3 years followed by an aromatase inhibitor for 2-3 years (OR = 1.11, 95% CI = 0.98 to 1.26, P = .09) *Risk of heart attack, angina, heart failure, and hypercholesterolemia

The cumulative toxicity of aromatase inhibitors when used as up-front treatment may explain the lack of overall survival benefit despite improvements in disease-free survival. Switching from tamoxifen to aromatase inhibitors reduces this toxicity and is likely the best balance between efficacy and toxicity

J Natl Cancer Inst 2011; 103(17):1299–1309

AI vs. Tamoxifen – Averse events on treatment or within 14 days of discontinuation

	Anastrozole n=3,092 (%)	Tamoxifen n=3,094 (%)	p-value
潮熱 (hot flushes)	1104 (35.7)	1264 (40.9)	<0.0001
關節疼痛	1100 (35.6)	911 (29.4)	<0.0001
陰道出血	167 (5.4)	317 (10.2)	<0.0001
陰道分泌增加	109 (3.5)	408 (13.2)	<0.0001
子宮癌	5 (0.2)	17 (0.8)	0.02
骨折	340 (11)	237 (7.7)	<0.0001
缺血性心臟病ischaemic cardiovascular disease	127 (4.1)	104 (3.4)	0.1
缺血性中風ischaemic cerebrovascular disease	62 (2)	88 (2.8)	0.03
栓塞事件Venous thrombo-embolic events	87 (2.8)	140 (4.5)	0.0004
靜脈栓塞Deep venous thrombo-embolic events	48 (1.6)	74 (2.4)	0.02

ATAC Trialists' Group Lancet 2005;365:60-62

ATAC – Safety of long term AI

	Anastrozole n=3,092 (%)	Tamoxifen n=3,094 (%)
All cancers	425 (13.7)	431 (13.9)
Endometrial cancer	6 (0.2)	24 (0.8)
Lung	51 (1·6)	34 (1·1)
All gastrointestinal	104 (3·4)	72 (2.3)
Colorectal	66 (2·1)	44 (1.4)
Gastric	12 (0.4)	8 (0.3)
Melanoma	8 (0·3)	19 (0·6)

Lancet Oncol. 2010 Dec;11(12):1135-41

ATAC update

- During treatment, women in the anastrozole group had fewer serious adverse events related to treatment than women in the tamoxifen group. After treatment was completed, however, rates of serious adverse events evened out between the two groups. Patients taking anastrozole reported more fractures during treatment than those taking tamoxifen, but after the completion of treatment fracture rates again became similar in both groups
- Patients taking tamoxifen had higher rates of endometrial cancer and melanoma than those taking anastrozole. There was a slight trend toward more colorectal and lung cancers in patients taking anastrozole compared with those taking tamoxifen. Overall, however, cancers other than breast cancer occurred at similar rates in both groups

Lancet Oncol. 2010 Dec;11(12):1135-41

Adverse events reported post-treatment – IES updates

	Exemestane, n=2,105		Tamoxifen, n=2,036			
Adverse event	**No.**	**%**	**No.**	**%**	**Odds ratio**	**P**
All cardiovascular events (excluding HT and VTE)	**259**	**12.3**	**211**	**10.4**	**1.21**	**0.049**
Ischaemic cardiovascular disease	**127**	**6**	**94**	**4.6**	**1.33**	**0.043**
Angina	**110**	**5.2**	**79**	**3.9**	**1.37**	**0.038**
Hypertension (HT)	**563**	**26.7**	**475**	**23.3**	**1.20**	**0.011**
VTE (Venous thromboembolic event)	**20**	**1**	**19**	**0.9**	**1.02**	**0.955**
DTV (deep vein thrombosis)	**17**	**0.8**	**18**	**0.9**	**0.91**	**0.788**

Denominators include patients who are disease free and have at least 6 months post-treatment follow up

JM Bliss, et al. J Clin Oncol 2011;30:709-717

Adverse events reported post-treatment – IES updates

	Exemestane, n=2,105		Tamoxifen, n=2,036			
Adverse event	**No.**	**%**	**No.**	**%**	**Odds ratio**	**P**
Fractures	**144**	**6.8**	**117**	**5.7**	**1.2**	**0.147**
Osteoporosis	**106**	**5**	**96**	**4.7**	**1.07**	**0.632**
Pain, musculoskeletal	**315**	**15**	**260**	**12.8**	**1.2**	**0.041**
Arthralgia	**135**	**6.4**	**130**	**6.4**	**1.0**	**0.970**
Endometrial hyperplasia	**2**	**0.1**	**4**	**0.2**	**0.49**	**0.408**
Hypercholesterolaemia	**107**	**5.1**	**100**	**4.9**	**1.04**	**0.800**

Denominators include patients who are disease free and have at least 6 months post-treatment follow up

JM Bliss, et al. J Clin Oncol 2011;30:709-717

Adverse events of AI

- Focusing on AEs after treatment cessation, musculoskeletal pain, arthritis, and osteoporosis became less frequent
- No significant differences between treatments were observed for any individual type of AE
- Improvement as time since discontinuation of therapy increases
- Differences in fracture risk between treatment groups is no longer evident, and other AEs are regressing
- Larger no. of patients who switched reported cardiovascular events, but not translate into increased vascular death rate

JM Bliss, et al. J Clin Oncol 2011;30:709-717

Early vs. premature vs. induced menopause

- Menopause is the point at which a woman stops menstruating
- While the average age of menopause in the United States is 51, the usual range is from 45 to 55. If you completely stop having periods before the age of 45, it is called an early menopause. If you stop menstruating even earlier -- before the age of 40 -- it is called premature menopause
- Induced: Menopause induced by an unusual event, such as occurs when the ovaries are damaged by radiation, chemotherapy or other medications; or as occurs when the ovaries are surgically removed (by bilateral oophorectomy)

Menopause

- Any of the followings:
  - Prior bilateral oophorectomy
  - Age ≥ 60 yr
  - Age < 60 y and amenorrhoeic for 12 or more months in the absence of chemo, Tam, toremifene, or ovarian suppression and FSH and estradiol in the postmenopausal range
  - If taking Tam or toremifene, and age < 60 y, then FSH and plasma estradiol level in postmenopausal ranges

NCCN

Diagnosis of menopause

- When estradiol levels are below 30, it may signal that you are in menopause
- FSH causes your ovaries to produce estrogen. When your ovaries slow down their production of estrogen, your levels of FSH increase. When your FSH levels rise above 40 mIU/mL, it usually indicates that you are in menopause

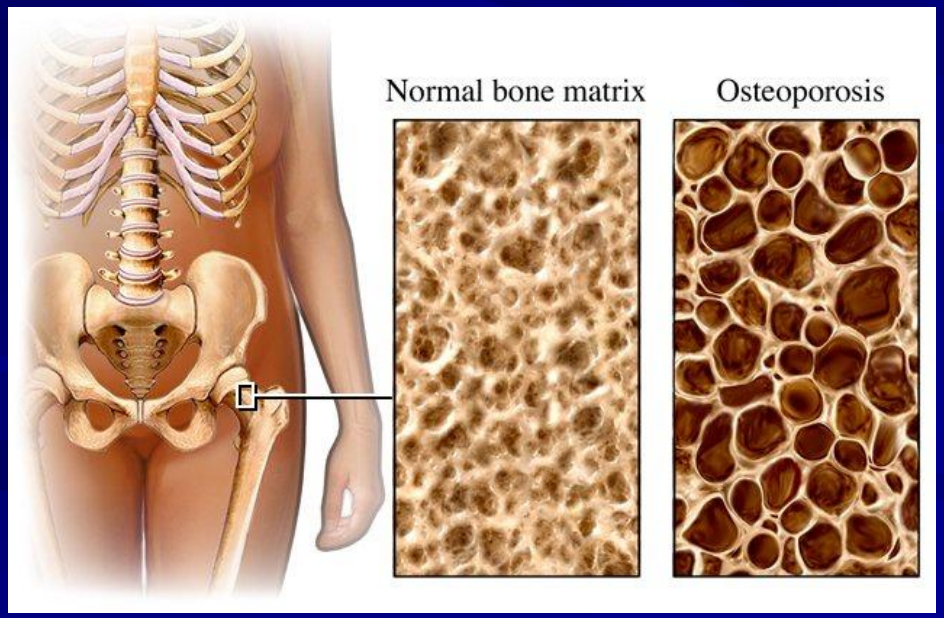
Symptoms of menopause

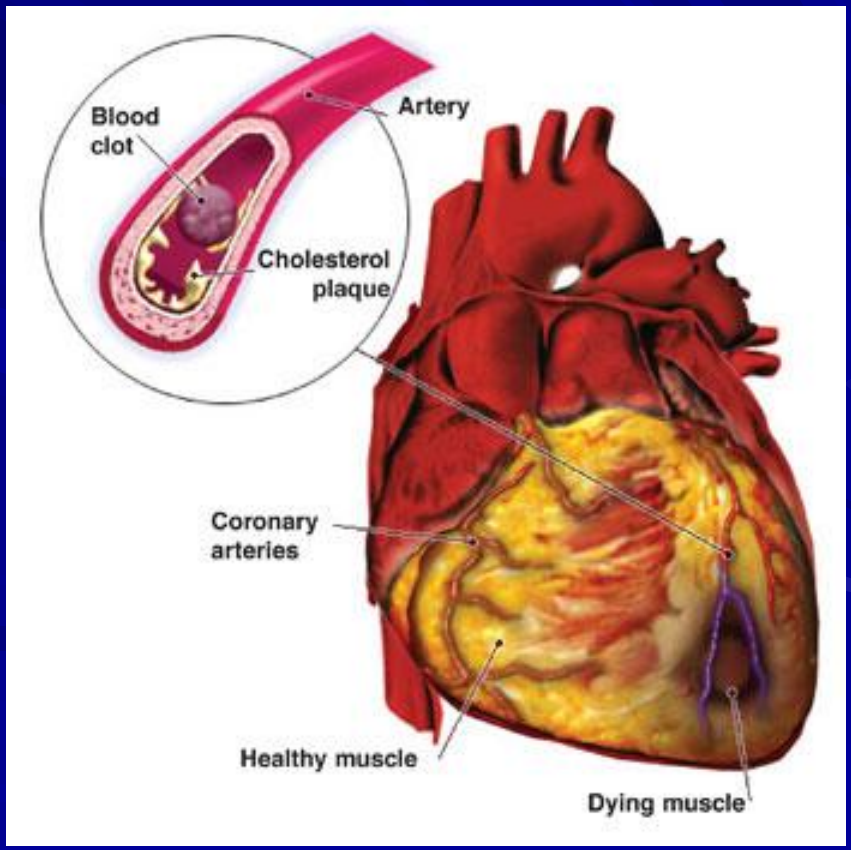
- Hot flashes and night sweats
- Mood swings
- Headaches
- Insomnia
- Vaginal dryness, urinary problem (incontinence, prone to infection)
- Weight gain
- Memory and cognitive changes
- Fatique
- Decreased libido
- Dizziness
- Aching joints and muscles
- Hair loss

...35 Symptoms of Menopause

Complication of premature menopause

- Osteoporosis
  - A skeletal disorder characterized by bone fragility. The reduction in bone mass and bone porosity
- Cardiovascular disease





Relationship hormonal therapy with lipid metabolism and heart disease

- Tamoxifen and toremifene inhibit the conversion of delta 8-cholestenol to lathosterol so that serum total and LDL cholesterol levels are lowered by downregulation of cholesterol synthesis
- Reduced risk of coronary artery disease will probably occur also during long term toremifene treatment because of the drug reduces cholesterol and its synthesis, similar to tamoxifen

Nonestrogen treatment modalities for vasomotor symptoms associated with menopause

- Shown to be safe and effective in short term use include
  - Black cohosh黑升麻
  - Exercise
  - Gabapentin
  - Medroxyprogesterone acetate
  - SSRIs (e.g. paroxetine)
  - Soy protein
  - Megestrol acetate
  - Venlafaxine

SE Fugate, et al. Ann Pharmacother. 2004 Sep;38(9):1482-99

Treatment of menopause-associated vasomotor symptoms

- Lifestyle changes, e.g. keep core body temp cool, paced respiration
- Dietary isoflavones大豆異黃酮, black cohosh, vit E
  - Clinical trial results insufficient
  - No serious side effects with short-term use
- Nonhormonal agents
  - Venlafaxine速悅
  - Paroxetine, fluoxetine
  - Gabapentin加巴噴丁

Position statement of The North American Menopause Society. Menopause. 2004 Jan-Feb;11(1):11-33

Treatment for menopausal symptoms in BC patients

- The use of estrogen, progesterone, or SERMs to treat osteoporosis or osteopenia in women with BC is discouraged (NCCN)
- The use of a bisphosphonate is generally the preferred intervention to improve bone mineral density
- Optimal duration of bisphosphonate therapy has not been established

SSRI / SNRI

- SSRI: Selective serotonin reuptake inhibitor
  - SSRIs are widely used in the treatment of depression, anxiety disorders and some personality disorders. They act by inhibiting the reuptake of serotonin into the presynaptic cell, increasing the levels of serotonin available for binding to postsynaptic receptors and/or prolonging the effects of serotonin
  - The SSRIs are
    - Fluoxetine (brand names Prozac; Oxactin)
    - Paroxetine (Seroxat)
    - Citalopram (Cipramil)
    - Sertraline (Lustral)
- SNRI: Selective serotonin and noradrenaline reuptake inhibitor
  - Dual action serotonin and noradrenaline reuptake inhibitors are a class of antidepressant drug used to treat major depression and other disorders
  - They are a newer class of drug than SSRIs, but act in a similar way, altering neurotransmitter levels in the brain, or prolonging their effects
  - SNRIs act particularly on serotonin and noradrenaline
- SSRIs and SNRIs effectively decrease vasomotor symptoms in healthy menopausal women and women with breast cancer, on or off endocrine therapy

Drugs to avoid in women taking Tam

Avoid		Safe or acceptable	
Generic name	Trade name	Generic name	Trade name
Fluoxetine	Prozac	Venlafaxine	Efexor, Velaxin
Paroxetine	Paxil, Seroxat, Parotin	Citalopram	Cipram, Arpolax
Duloxetine	Cymbalta, Yentreve		
Sertraline	Zoloft, Serlift	Gabapentine	Neurontin
Cimetidine	Tagamet	Ranitidine	Zantac

Other medications that inhibit CYP2D6 include the following:

- Quinidine, which is used to treat abnormal heart rhythms
- Diphenhydramine, which is an antihistamine

Assessment of bone loss

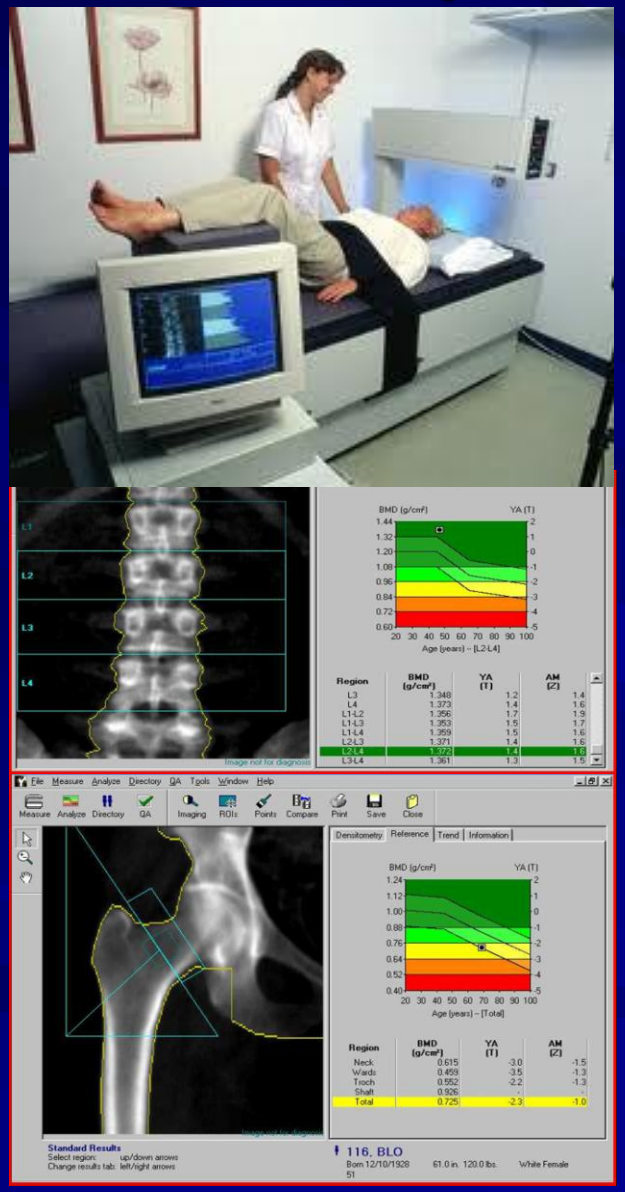
- In terms of BMD, osteoporosis is defined by WHO as a BMD that is 2.5 SD or more below the average value for young healthy women (a T-score of < -2.5SD)
- Breast cancer treatment associated with premature ovarian suppression and hence increased risk of osteoporosis:
  - LHRHa
  - Chemotherapy
  - Surgical ablation
- Adjuvant breast cancer treatment associated with bone loss:
  - Tamoxifen
  - AIs

Tamoxifen: effect on bone health

- Tamoxifen is an estrogen antagonist
- With respect to bone, Tam has a different effect in pre and postmenopausal women
- In premenopausal with high levels of circulating estrogen from ovaries, Tam predominantly has an anti-estrogenic effect causing increased loss of BMD for 1-2 yrs, about 1-2% and is not persistent through 5 yrs of Tam
- In postmenopausal in low estrogen states, Tam has an estrogen agonist effect causing a small but significant increase in BMD, lead to a significant reduction in risk of fractures

(UK expert group consensus position statement 2008)

骨質密度(BMD)檢查 – DEXA scan



- Dual Energy Xray Absorptionmetry
- Means of measuring bone mineral density (BMD)
- Can detect changes after about a 1% change
- A DEXA scan lasts about 10 minutes, and exposes the patient to less radiation than a standard chest x-ray
- Typically used to diagnose and follow osteoporosis

Understand DEXA scan results

- T score
  - Compares your bone density to the optimal peak bone density for your gender
  - It is reported as number of standard deviations below the average
  - T-score of > -1 is considered normal
  - T-score of -1 to -2.5 is considered osteopenia, and a risk for developing osteoporosis
  - A T-score of < -2.5 is diagnostic of osteoporosis
- Z score
  - Compare your results to others of your same age, weight, ethnicity, and gender (age-matched comparison)
  - This is useful to determine if there is something unusual contributing to your bone loss
  - A Z-score of < -1.5 raises concern of factors other than aging as contributing to osteoporosis. These factors may include thyroid abnormalities, malnutrition, medication interactions, tobacco use, and others

Assessment and treatment of bone loss – NICE guideline

- Pts with early invasive breast cancer should have a baseline DEXA scan to assess BMD if they
  - Are starting adjuvant AI
  - Have treatment-induced menopause
  - Are starting ovarian ablation/suppression therapy
- Do not offer a DEXA scan who are receiving Tam alone, regardless of pretreatment menopausal status
- Offer bisphosphonates identified by algorithms 1 and 2

Algorithm 1: Women experience premature menopause

- Development of a treatment-induced menopause or planned ovarian suppression treatment before age of 45 yrs are indications for evaluation of BMD by DAX
- No requirement to obtain a DAX before starting treatment but a baseline within 3 months of commencing OS and within 12 months of developing postchemo amenorrhoea

Algorithm 2: Postmenopausal women

- Use of an AI is an indication of DXA
- Baseline within 3 months of commencing
- Monitoring and treatment depends on baseline BMD, age, and presence of any major risk factors for osteoporotic fracture:
  - Previous fragility fracture > age of 50 yrs
  - Parental Hx of fracture
  - BMI < 22
  - Alcohol consumption of ≥ 4 units/day
  - Diseases known to increase fracture risk such as premature menopause, RA
  - Ankylosing spondylitis, immobility, Crohn's disease
  - Prior oral steroid use for > 6months

Recommendations according to risk group

- High risk
  - Baseline T-score < -2
  - Assess for other causes of osteoporosis
  - Bisphosphonate in addition of lifestyle advice, Ca and vit D supplementation
- Medium risk
  - T-score between –1 and –2
  - Lifestyle advice plus Ca 1g/day and vit D 400-800IU*
  - FU DEXA scan in 24 months
- Low risk
  - Normal BMD (T-score > -1)
  - Lifestyle advice (diet, weight-bearing exercise, reduce alcohol consumption and cessation of smoking)
  - No FU BMD required unless clinically indicated

* Unless dietary intake of Ca >1g/day and serum 25-hydroxyvitamin D > 20 μg/L

UK expert group 2008 recommendation for bisphosphonate

- Elderly (> 75 yrs of age) women with one or more risk factors for osteoporotic fracture irrespective of BMD
- Postmenopausal: T score < -2.0
- Women with premature menopause: T score < -2.0, with exception of those receiving ovarian suppression plus an AI in whom the recommended T-score for intervention is (<) –1, due to very rapid losses of bone occurs in this group

Bisphosphonate therapy 雙磷酸鹽類藥物

- Weekly oral alendronate 70mg or risedronate 35mg
- Monthly oral ibandronate 150mg
- 3-monthly iv ibandronate 3mg
- 6-monthly iv zoledronic acid 4mg
- Contraindicated if CrCl < 30ml/min/1.73m^2 or hypocalcaemia
- Oral bisphosphonates must be used with caution in pts with esophageal disease, although iv will be appropriate in such pts
- FU with a repeat DEXA after 24 months and/or measurement of a bone resorption marker

Assessment and treatment of osteoporosis and osteopenia in post-menopausal women who are about to begin AI

- Baseline BMD – dual energy x-ray absorptiometry (DEXA) of hip and spine
  - T score < -2.5: begin Ca and vit D, and begin therapy with bisphosphonate; repeat BMD annually
  - T score between -1.0 and -2.5: begin Ca and vit D; repeat BMD annually
  - T score> -1: reassure; begin Ca and vit D; repeat BMD annually (ASCO 2003 Recommendations)
- Vit D and Ca levels should be obtained prior to initiating bisphosphonate therapy
- RFT should be monitored prior to initiation of bisphosphonate therapy

Cost-effectiveness of fracture prevention in postmenopausal women who receive aromatase inhibitors for early breast cancer

- The following strategies were compared
  - No intervention
  - One-time bone mineral density (BMD) screening and selective bisphosphonate therapy in women with osteoporosis or osteopenia
  - Annual BMD screening and selective bisphosphonate therapy in women with osteoporosis or osteopenia
  - Universal bisphosphonate therapy
- Outcomes were quality-adjusted life-years (QALYs), lifetime cost, and incremental cost-effectiveness ratio (ICER)

K Ito, et al. J Clin Oncol 2012;30:1468-1475

Results

- ICERs for annual BMD screening followed by oral bisphosphonates for those with osteoporosis, annual BMD screening followed by oral bisphosphonates for those with osteopenia, and universal treatment with oral bisphosphonates were $87,300, $129,300, and $283,600 per QALY gained, respectively
- One-time BMD screening followed by oral bisphosphonates for those with osteoporosis or osteopenia was dominated
- In postmenopausal women receiving adjuvant AIs for HR-positive EBC, a policy of baseline and annual BMD screening followed by selective treatment with oral bisphosphonates for those diagnosed with osteoporosis is a cost-effective use of societal resources

K Ito, et al. J Clin Oncol 2012;30:1468-1475

Screening for osteoporosis – less is more ?

- Whether to screen postmenopausal women who are receiving AI
- How often to screen
- When to treat
- What type of treatment to initiate
  - Preferred route of bisphosphonate therapy (iv or oral) is unknown

Take home message

- Tam
  - Benefit vs. risk
- AI – upfront vs. switching
- Side effects of AI
- Tam and SSRIs
- Bone health in postmenopausal women

Thank you

Q&A