

Alternative treatments for the menopause

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Best Practice & Research Clinical Obstetrics and Gynaecology 23 (2009) 151–161

Concerns about the safety of oestrogen-based hormone replacement therapy after publication of the **Women's Health Initiative study** and **Million Women Study** has led to women turning to alternative therapies, erroneously believing that they are safer and 'more natural'.



Lo Studio “WHI”

Writing Group for the Women’s Health Initiative Investigators.

Risks and benefits of estrogen plus progestin in healthy postmenopausal women:

principal results from the Women’s Health Initiative randomized controlled trial.

JAMA 2002; 288: 321–333.

Studio WHI

alcune caratteristiche del campione

	E + P (n=8506)	Placebo (n=8102)
Età media (SD)	63.2 (7.1)	63.3 (7.1)
Fasce di età:		
50-59	2839 (33.4)	2683 (33.1)
60-69	3853 (45.3)	3657 (45.1) ←
70-79	1814 (21.3)	1762 (21.7) ←
Body Mass Index, kg/m ²		
<25	2579 (30.4)	2479 (30.8)
25-29	2992 (35.3)	2834 (35.2) ←
≥30	2899 (34.2)	2737 (34.0) ←
In trattamento per ipertensione	3039 (35.7)	2949 (36.4) ←

Escluse donne con sintomatologia neurovegetativa severa

Cancer and the Estrogen Plus Progestin Women's Health Initiative

Estrogen Plus Progestin (HT) (N = 8506)				Placebo (N = 8102)			
Cancer	Increased or decreased per 10,000 per year	Number HT	Per 10,000 /yr HT	Number placebo	Per 10,000/yr Placebo	Percent (%) increased or decreased	Hazard ratio/95% nCI
Invasive breast	8 Increased (*)	166	38	124	30	26 % increased	1.26/ (1.00 – 1.59)
Endometrial	No difference	22	ND	25	ND	No increase	0.83/ (0.47 – 1.47)
Colorectal	6 decreased	189	10	245	16	37 % decreased	0.63/ (0.43 – 0.92)
Total	No difference	502	ND	458	ND	No Increase	1.03/ (0.90 – 1.17)

(*) 0,08%/yr

The Women's Health Initiative 2004 - Review and Critique

John A. Goldman - Medscape General Medicine. 2004;6(3):65. ©2004 Medscape

Cancer and the Estrogen-Alone Arm of the Women's Health Initiative^[11]

Estrogen Alone(ET) (N = 5310)				Placebo (N = 5429)				
Cancer	Significance	Decreased or increased per 10,000 per year	Number ET	Per 10,000/yr ET	Number placebo	Per 10,000/yr placebo	Percent (%) reduction or increased	Hazard ratio/ 95% nCI
Invasive breast	None P=0.06	7 Decreased	94	26	124	33	23 % decreased	0.77/ 0.59 – 1.01
Colorectal <i>ND = no data</i>	None	1 Increased	61	17	58	16	8 % increased	1.08/ 0.75 – 1.55
Total	None	7	ND	103	ND	110	6 % decreased	0.93/ 0.81 – 1.07

The Women's Health Initiative 2004 - Review and Critique
John A. Goldman, MD, FACP, FACR, FASLMS
 Medscape General Medicine. 2004;6(3):65. ©2004 Medscape

Ruolo del progestinico?

Indicators of Risk of Breast Cancer

(Adp from: Clemons M & Goss P, *N Engl J Med* 2001;344:276-285)

Indicator	Risk Group		Relative Risk	Reference
	Low	High		
Sex	Male	Female	150.0	Hulka
Age (yr)	30-34	70-74	17.0	Madigan
Breast density	0	> 75	6.0	Boyd
Serum E2 level	Lowest quartile	Highest quartile	1.8-5.0	Toniolo, Thomas
Bone density	Lowest quartile	Highest quartile	2.7-3.5	Cauley, Zhang
Age at birth of first child (yr)	< 20	> 30	1.9-3.5	Hulka, Leon
Age at oophorectomy	< 35	-- †	3.0	Hulka
Family history	No	Yes	2.6	Madigan
Age at natural menopause (yr)	< 45	≥ 55	2.0	Hulka
Postmenopausal BMI	< 22.9	> 30.7	1.6	Hulka
Age at menarche (yr)	> 14	< 12	1.5	Hulka
Parity	≥ 5	0	1.4	Hulka, Madigan
Estrogen-progestin therapy	Never	Current	1.4	Grodstein
Estrogen therapy	Never	Current	1.2-1.4	Hulka, Grodstein
Breast feeding (mo)	≥16	0	1.37	Enger
Oral contraceptives	Never	Previous/current	1.07-1.2	Hulka, Ursin

† There is no association between the risk of breast cancer and oophorectomy performed at 35 years of age or older

Lo studio “MW”

(THE MILLION WOMEN STUDY)

Agosto 2003

Lancet 2003;362:419-427

Current use of HRT is associated with an increased risk of incident and fatal breast cancer;

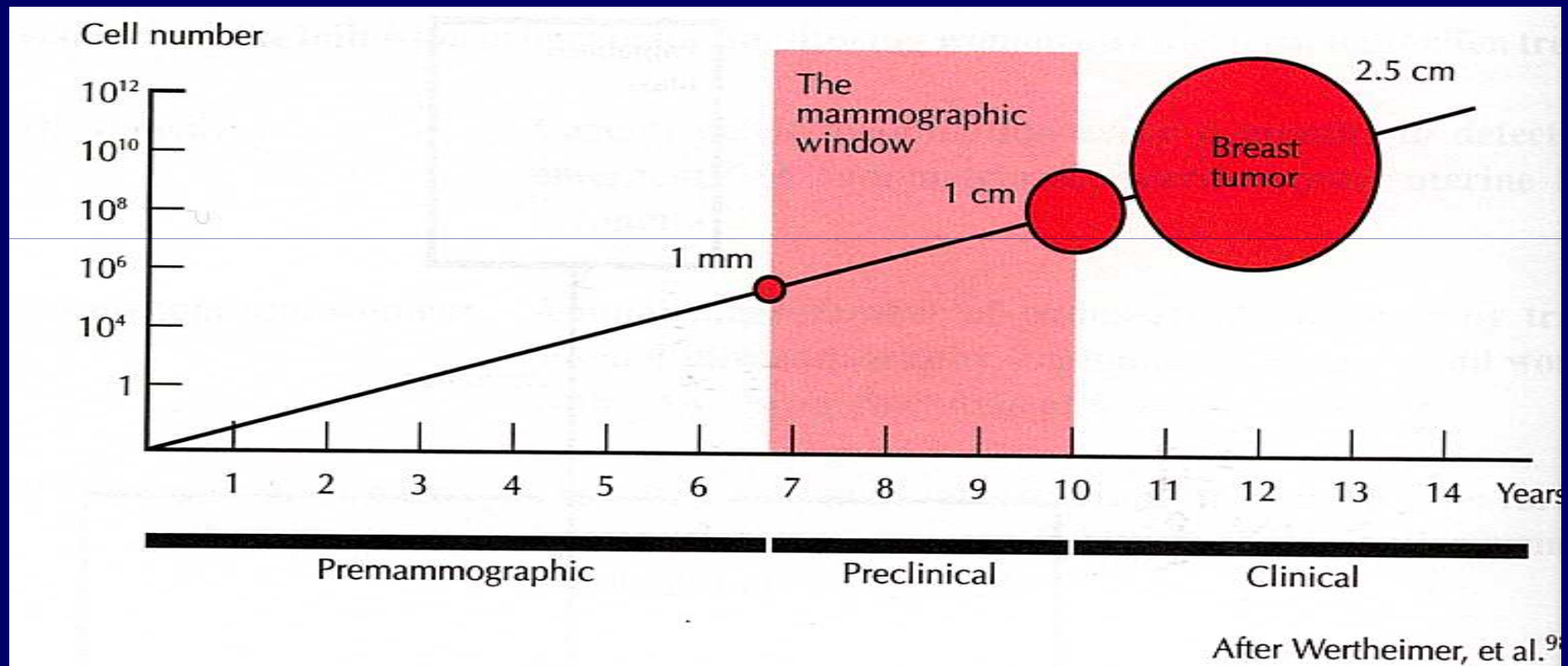
The effect is substantially greater for oestrogen-progestagen combinations than for other types of HRT.

Lo studio MW ("MILLION WOMEN'S STUDY")

PRINCIPALI RISULTATI:

- Metà del 1.084.110 donne esaminate aveva utilizzato HT
- Nel campione globale (senza e con terapia):
 - 9.364 ca mammari invasivi (tempo medio di osservazione: **2.6 anni**)
 - 637 morti da ca mammario (tempo medio di osservazione: **4.1 anni**)
- **RR ca mammario nelle donne-HT:**
 - HT -"current users": 1.66 (1.58-1.75)
 - HT -"past users": 1.01 (0.94-1.09)
- **RR di mortalità per ca mammario nelle donne-HT:**
 - HT -"current users": 1.22 (1.00-1.48)
 - HT -"past users": 1.05 (0.82-1.34)
- I risultati non differiscono in modo significativo tra i vari tipi, dosi e schemi di preparati ormonali

The Natural History of the Breast Cancer



In the USA and Australia, more than half of women use some type of complementary and alternative medicine during midlife.

Menopause 2007; 14: 397–403

Menopause 2007; 14: 612–623

Phyto-oestrogens: soy and red clover

Actaea racemosa (black cohosh)

Angelica sinensis (dong quai)

Oenothera biennis (evening primrose)

Panax ginseng (ginseng)

Piper methysticum (kava kava)

Ginkgo biloba (gingko)

Hypericum perforatum (St John's wort),

Agnus castus (chasteberry)

Liquorice, hops, sage and valerian root

Flavonoids, Phytosterols

Acupuncture, Reflexology, Magnetism Acupressure, Alexander technique, Ayurveda,

Homoeopathy

Clonidine,

Selective serotonin re-uptake inhibitors and serotonin and noradrenaline re-uptake inhibitors

Gabapentin

The Effect of Dietary Soy Supplementation on Hot Flushes

PAOLA ALBERTAZZI, MRCOG, FRANCESCO PANSINI, MD,
GLORIA BONACCORSI, MD, LAURA ZANOTTI, MD, ELENA FORINI, PhD, AND
DOMENICO DE ALOYSIO, MD

Obstet & Gynecol 1998;91:6-11

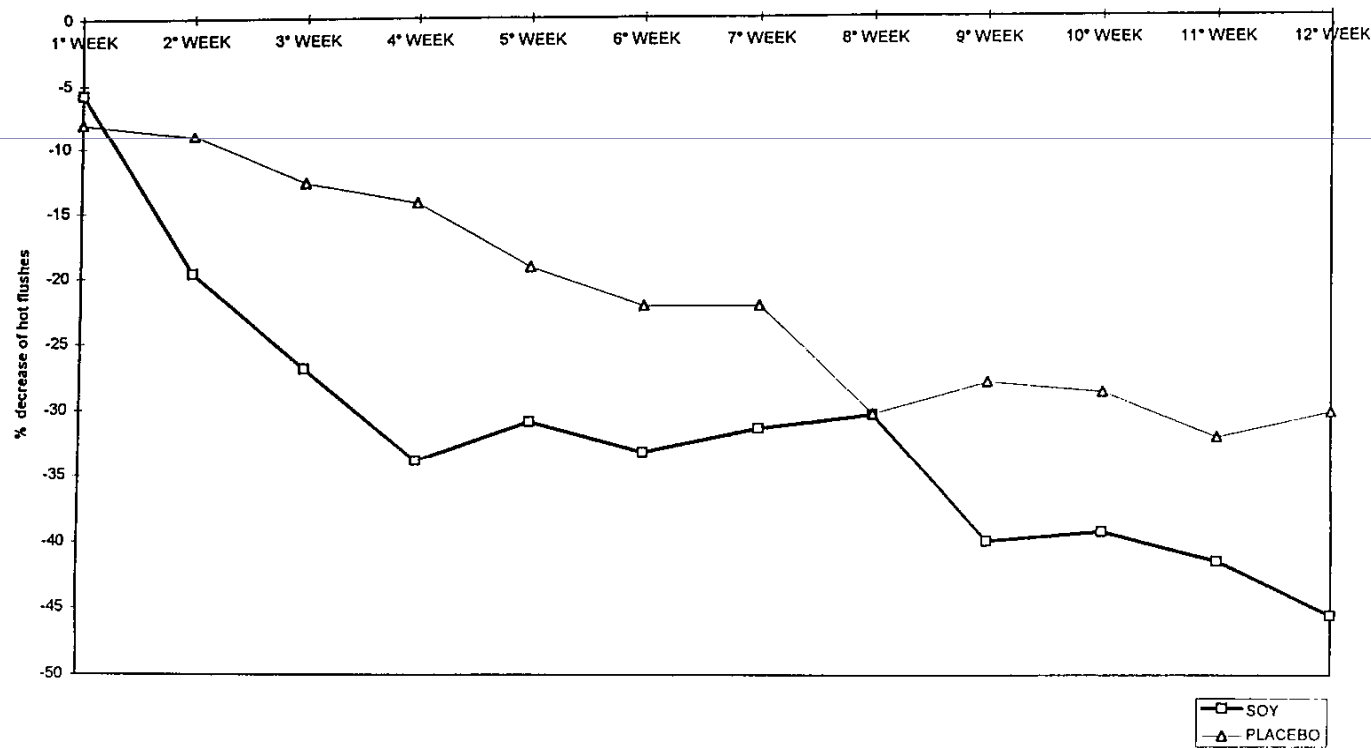


Figure 1. Weekly decrease in number of hot flushes; score expressed as percentage. The difference between soy and placebo was always significant after week 2, with the exception of week 8.

Epidemiological data support clinical utility of phytoestrogens

Phyto-oestrogens are plant substances that have effects similar to those of oestrogens. The main sources are **soy and red clover**.

Epidemiological Evidences comparing Asian and Western populations have been interpreted to indicate that consumption of a diet rich in phytoestrogens **ameliorates oestrogen deficiency symptoms and may protect against breast cancer, bone loss and cardiovascular disease**

Nedrow A, Miller J, Walker M et al. Complementary and alternative therapies for the management of menopause-related symptoms: a systematic evidence review. Arch Intern Med 2006; 166: 1453–1465.

Compounds with estrogen-like activity and common plant sources

Phytoestrogen

Major plant source

lignans

vegetables, fruits, nuts, cereals, spices

isoflavones

soy, peas, beans, spinach, fruits, **clovers**

flavones

beans, green vegetables, fruits, nuts

chalcones

liquorice

diterpenoids

coffee

triterpenoids

liquorice, hops

coumarins

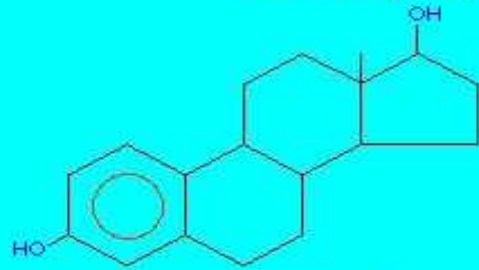
cabbage, peas, spinach, liquorice

acyclics

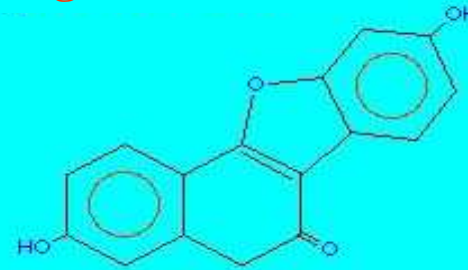
hops

Phytoestrogens (Isoflavones)

Similarity of plant estrogens to estradiol



Estradiol



Coumestrol



Isoflavone nucleus



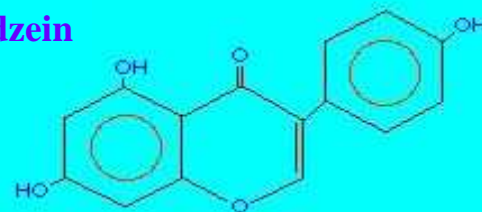
Formonectin



Daidzein



Biochanin A



Genistein

Biochemical observations that:

- Isoflavones link more preferentially to beta ER than alpha ER
- Isoflavones modulate estrogen enzymes

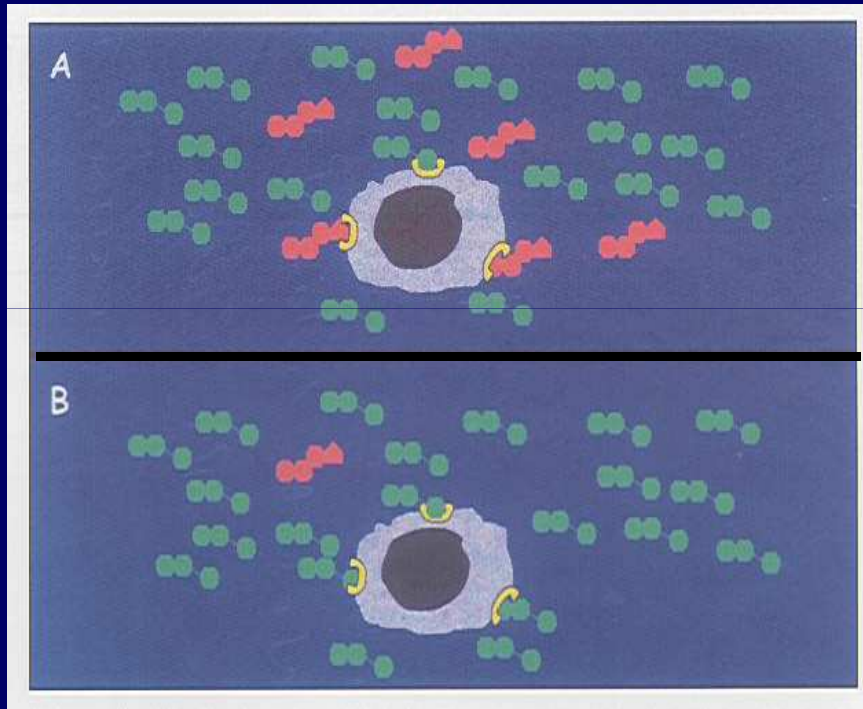
has prompted speculation that Isoflavones are

natural “Selective Estrogen Receptor Modulators” (SERMs),
like tamoxifen and raloxifene,

and natural “Selective Estrogen Enzyme Modulators” (SEEMs),
like tibolone,

And therefore might provide clinical benefits of estrogen without the disadvantages

Isoflavones may exert estrogenic and anti-estrogenic effects



A. Isoflavones (green) can act as antiestrogens when steroidal estrogens (red) are abundant (as in pre-menopause) by competing weakly for cellular estrogen receptors (yellow)

B. In post-menopause, when steroidal estrogens are scarce, isoflavones can provide a weak surrogate estrogen effect

Nutritional Isoflavones (Soy) average intake (mg/die) among World Countries

Japan	China	India	USA	Spain	UK	Sweden	Finland
38.2	10.6	1.2	0.012	0.01	0.0055	0.0002	0.0001

Husband AJ - J Br Menopause Society, Suppl 1, 2001

Prevalence of vasomotor disturbances in different populations

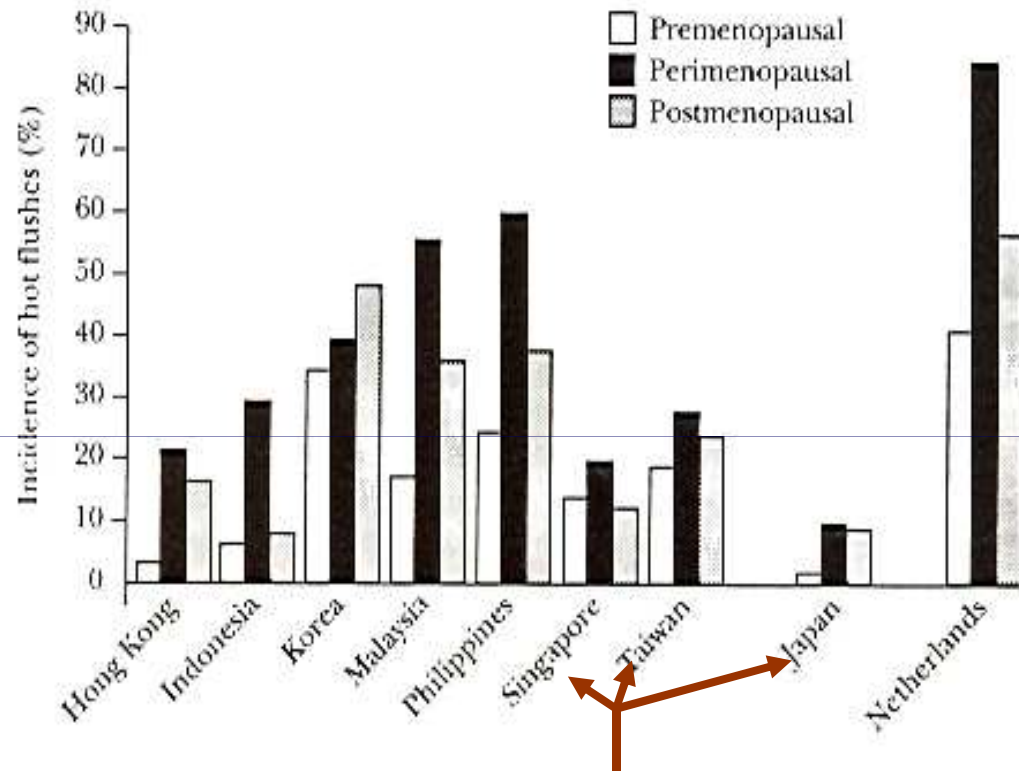
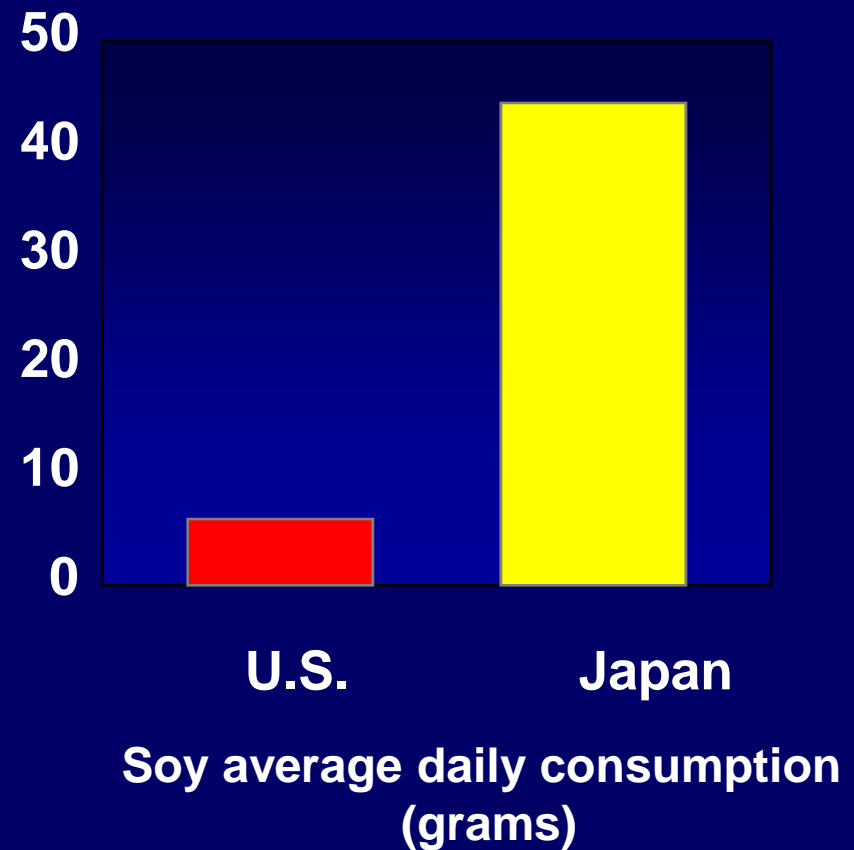
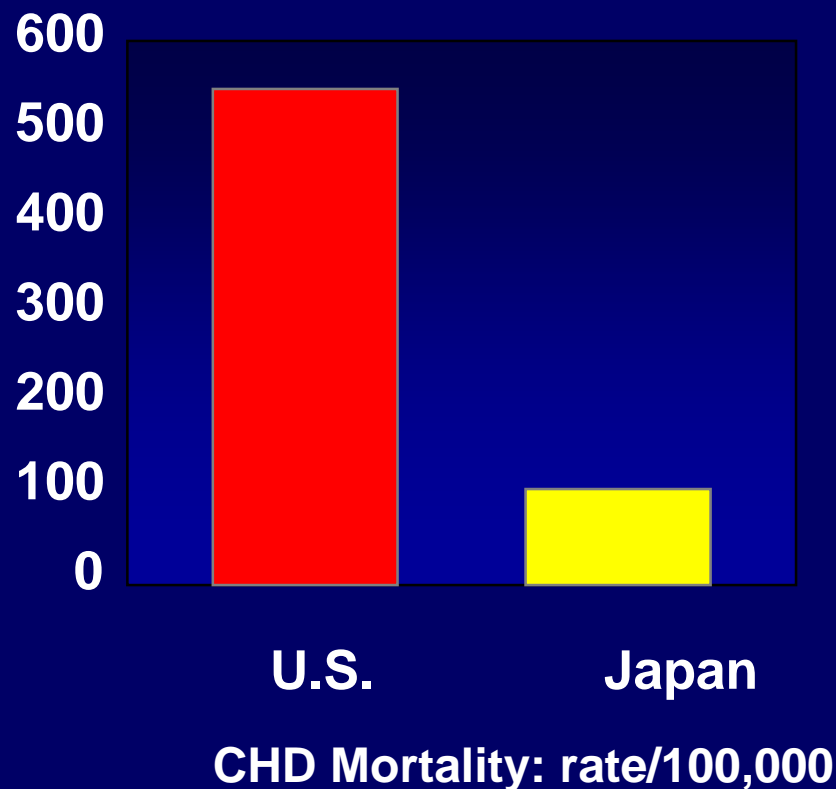


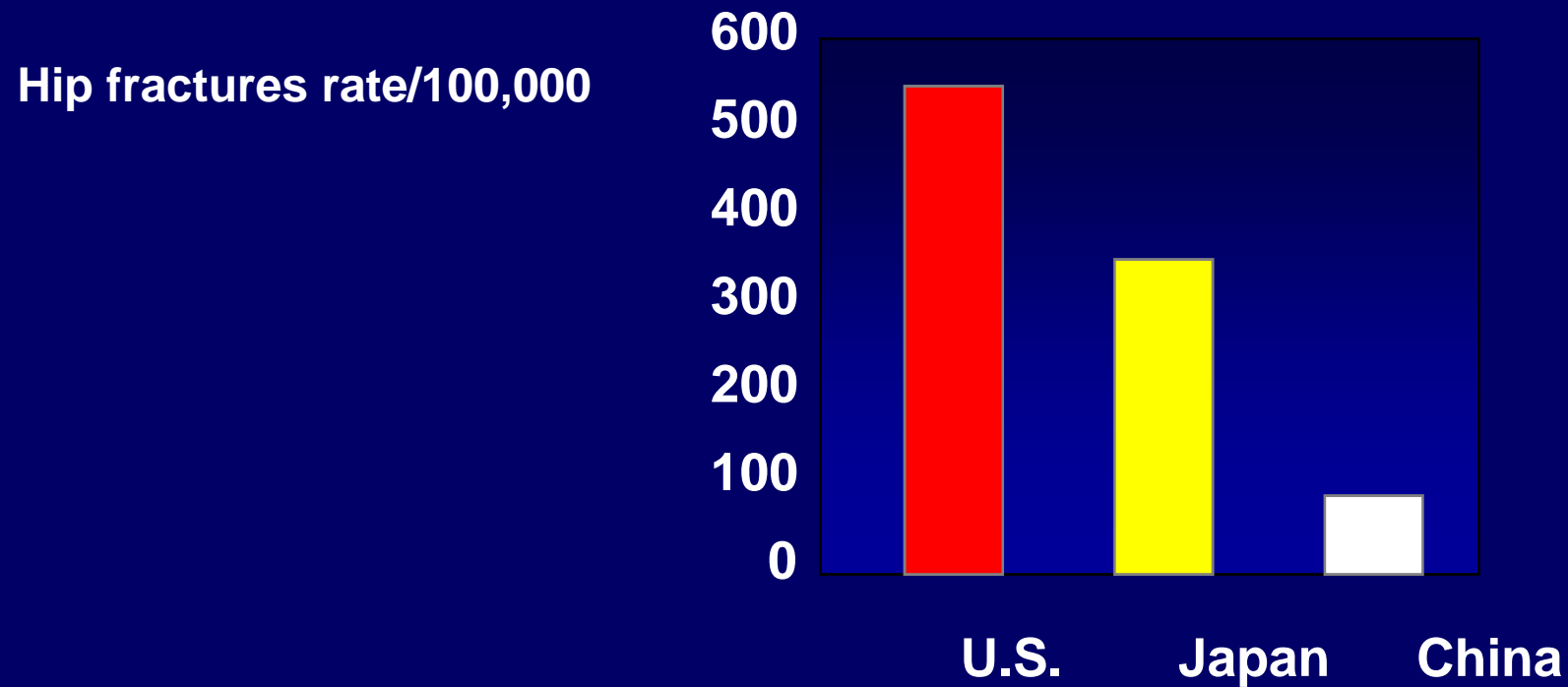
Figure 1 Reported prevalence of vasomotor symptoms across menopausal transition in different populations. Adapted from references 9, 10 and 11

From G Wilcox, in: *Progress in the management of menopause 1997*, Parth Publ Ed

Coronary Heart Disease (CHD) and Soy consumption

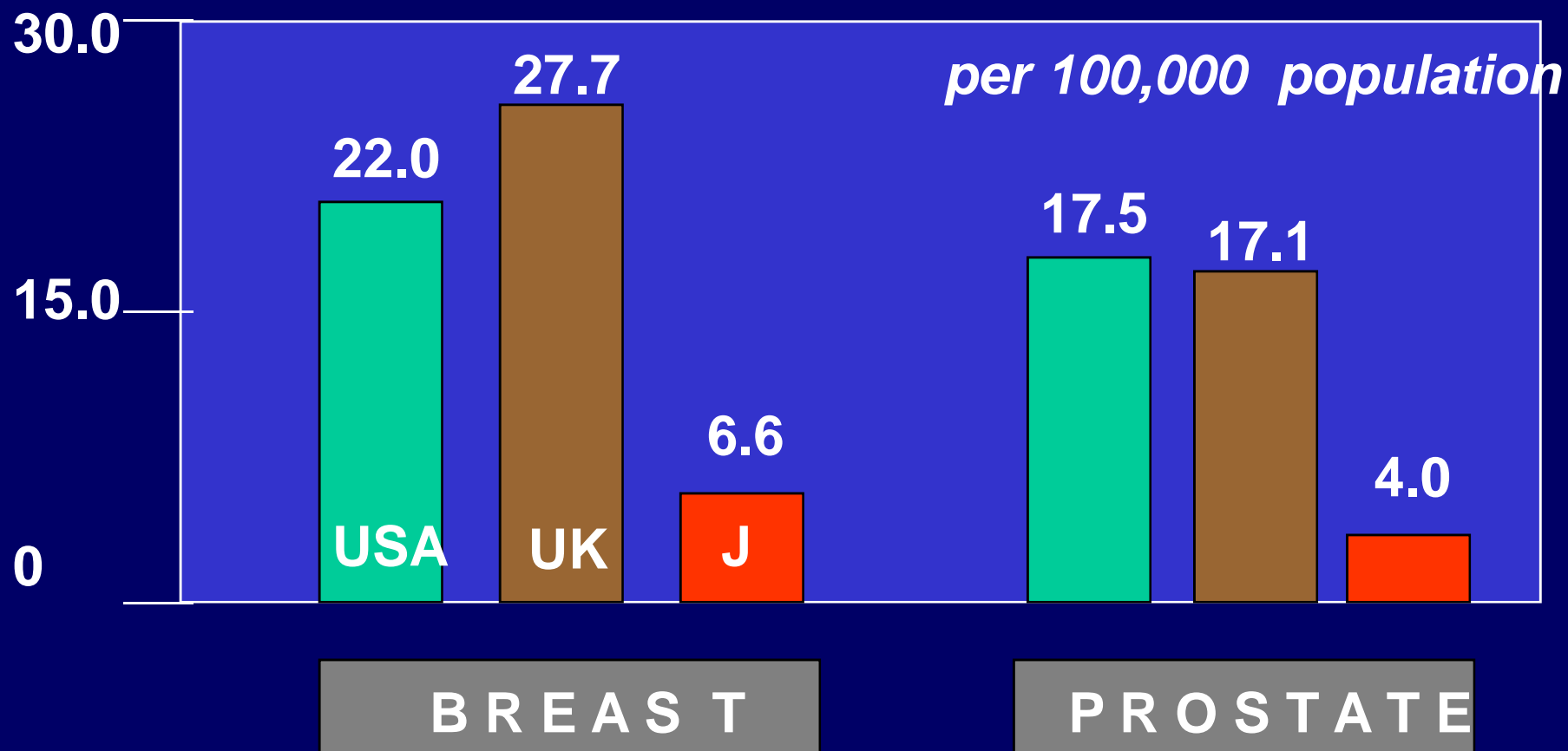


PREVALENCE RATE OF HIP FRACTURES AMONG ASIAN AMERICAN POPULATIONS



Ross PD et al, *Am J Epidemiol* 1991;133:801-809

Death rates from breast and prostate cancers in the United States, the United Kingdom, and Japan



INTEGRAZIONE ALIMENTARE

Isoflavones and Menopausal Hot Flashes

Whole Soy and Hot Flushes

Investigator	Year	Product	Patients size	Hot Flushes
Murkies	1995	45g soy flour vs wheat flour	58	No statist. decrease
Harding	1996	80 mg soy protein drink	20	Decrease
Brzezinski	1997	89 g tofu, miso, 10 g linseed	75	No effect
Albertazzi, Pansini	1998	60 g soy isolate powder	104	Decrease
Woods	1999	candy soy bar		No effect
Washburn	1999	20 g soy protein	51	No effect
Nagata	2001	Various soy foods	1,106	Decrease
Somekawa	2001	Various soy foods	478	No effect

Effects of Red Clover Isoflavones on Hot Flashes

- Hot flashes were **not reduced** in **2 studies** using Clover isoflavones (40 and 160 mg)
Baber et al. Climacteric 1999; 2:85
Knight et al. Climacteric 1999; 2:79
- **One study**, using a Clover derived product, showed **significant reduction** in hot flashes while
- **Another study** using a similar dose showed **no significant effect** (80 and 82 mg/day)


van de Weijer & Barentsen Maturitas 2002; 42:187

Tice et al. JAMA 2003; 290:207

Isoflavones and Breast Cancer

Biphasic Effect of Phytoestrogens on Mammary Cells

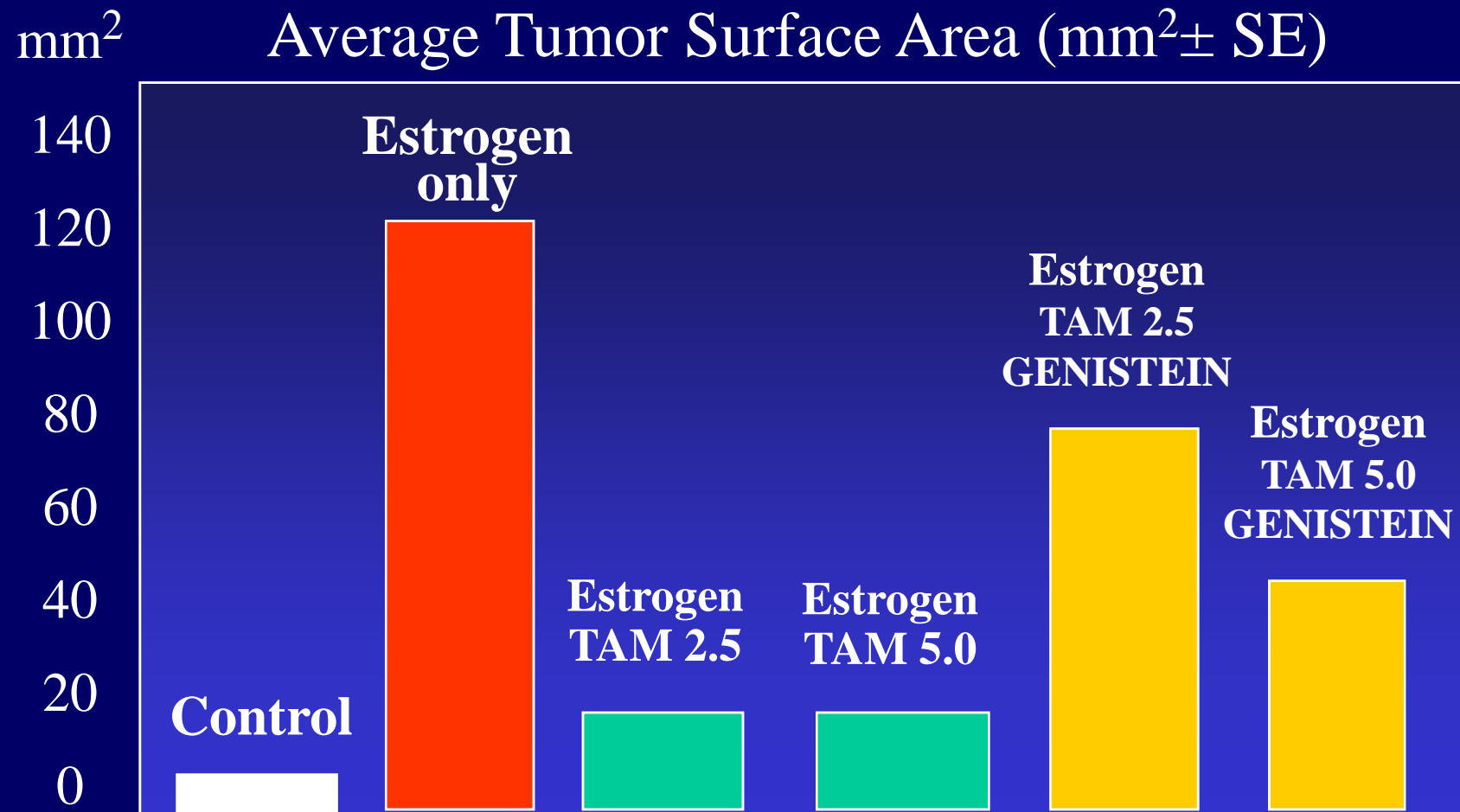
(Davis SR et al. *Recent Prog Horm Res* 1999;54:185-210)

 **In vitro concentrations** of phytoestrogens equivalent in humans with a moderate phytoestrogen intake stimulate cell mammary growth in estrogen positive cells.

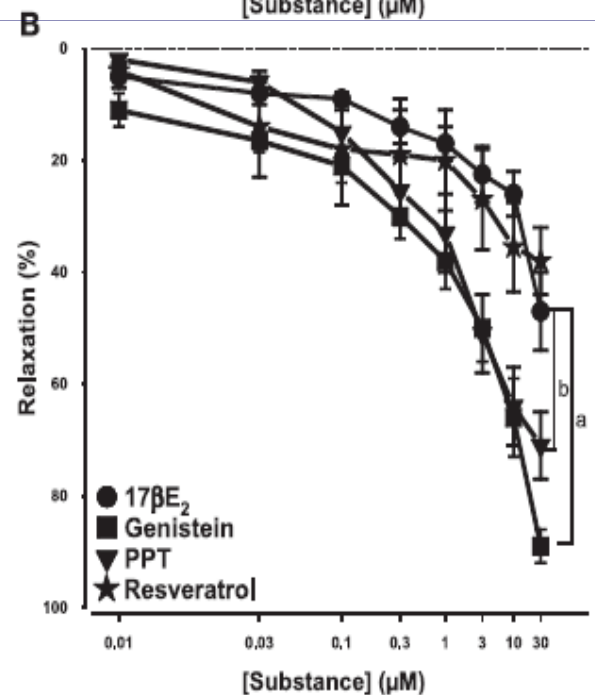
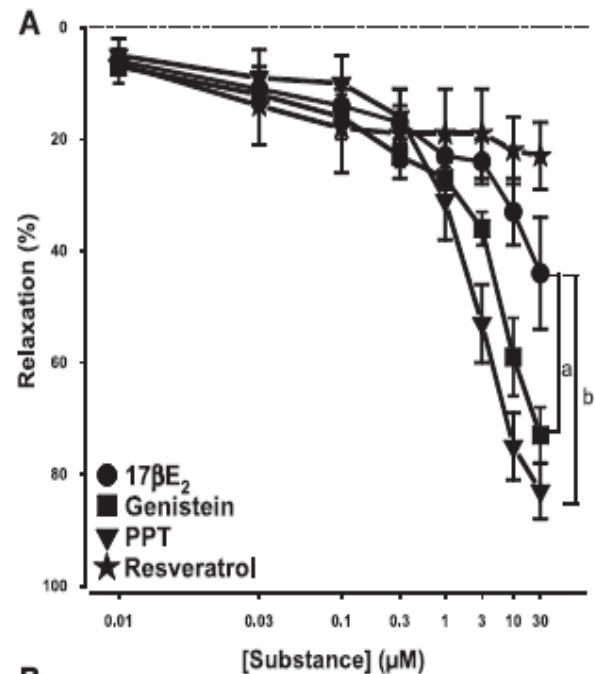
 In contrast, **very high concentrations** (probably greater than circulating levels achievable by diet) inhibit cell growth in both estrogen positive and negative cell lines.

Dietary Genistein Negates the Inhibitory Effect of Tamoxifen on Growth of Estrogen-dependent Human Breast Cancer (MCF-7) Cells Implanted in Athymic mice

(*Young H. Ju. et al. Cancer Research 2002;62:2474-2477*)



Isoflavones and Cardiovascular Disease



Acute responses to phytoestrogens in small arteries from men with coronary heart disease

Maria Natalia Cruz, Leonid Luksha, Henareh Logman, Lucilla Poston, Stefan Agewall and Karolina Kublickiene

Am J Physiol Heart Circ Physiol 290:1969-1975, 2006. First published Dec 16, 2005;

doi:10.1152/ajpheart.01065.2005

Arterial Relaxation Effect of Estradiol, Genistein, PPT and Resveratrol

PPT: Propyl-[1H]-Pyrazole-1,3,5-triyl-tris-Phenol

Fig. 1. Concentration-response curves to propyl-[1H]-pyrazole-1,3,5-triyl-tris-phenol (PPT; $n = 6$ patients), genistein ($n = 6$), resveratrol ($n = 5$), and 17β -estradiol ($17\beta\text{-E}_2$; $n = 7$) in arteries from patients with coronary heart disease (CHD) (A) and concentration-response curves to PPT ($n = 7$), genistein ($n = 6$), resveratrol ($n = 6$) and $17\beta\text{-E}_2$ ($n = 5$) in arteries from healthy male volunteers (B). Data presented as means \pm SE. ^a $P < 0.05$, genistein vs. $17\beta\text{-E}_2$; ^b $P < 0.05$, PPT vs. $17\beta\text{-E}_2$.

Whole Soy and Coronary Heart Disease (CHD)

Whole soybean or foods containing soy protein included in a diet low in saturated fat and cholesterol:

reduce the risk of CHD by lowering blood cholesterol

25 gr of soy protein daily in the diet is needed to show a significant cholesterol lowering effect


The FDA Health Claim is based on scientific evidence from more than 50 independent studies


The FDA Health Claim (October 26, 1999)

Isoflavones and Osteoporosis

Biphasic effect of genistein on bone tissue in the ovariectomized, lactating rat model

(Anderson JJ, *Proc Soc Exp Biol Med* 1998;217:345-350)

 **Genistein at low dose** (0.5 mg/day) appears to act as **agonist** at the estrogen receptor locus of bone cells

 **Genistein at higher doses** (1-6-5.0 mg/day) is less effective in maintaining bone tissue and may even have **adverse effects** on bone cells

(High isoflavone doses are not usually consumed in the human soy protein-based diets)



Clinical Studies on effect of Isoflavones on Bone Density

- Two studies with ISP showed a **significant increase or prevented loss in lumbar spine BMD** compared to control (90 mg isoflavones/day for 6 months)

Potter et al. Am J Clin Nutr 1998; 68:1375S

Alekel et al. Am J Clin Nutr 2000; 72:844

- Isoflavone from Clover isolate **significantly increased BMD** in the proximal radius and ulna (57 or 85 mg isoflavones/day for 24 days)

Clifton-Bligh et al. Menopause 2001;8:259

Herb–drug interactions

A major concern about herbs is herb–drug interactions with potentially fatal consequences as well as **oestrogenic effects**, which is important in women with hormone-dependent tumours such as breast cancer.

The consequences of herb–drug interactions include **bleeding** when combined with warfarin or aspirin; hypertension, coma and mild serotonin syndrome when combined with serotonin re-uptake inhibitors; and **reduced efficacy of anti-epileptics and oral contraceptives**.

Ginkgo biloba can cause **bleeding** when combined with warfarin or aspirin, **high blood pressure** when combined with a thiazide diuretic, and even **coma** when combined with trazodone.

Panax ginseng reduces the blood concentrations of alcohol and warfarin, and can induce mania when used concomitantly with phenelzine.

Hypericum perforatum reduces the blood concentrations of cyclosporin, midazolam, tacrolimus, amitriptyline, digoxin, warfarin and theophylline (organ rejection), breakthrough bleeding and unplanned pregnancies when used concomitantly with oral contraceptives.

It also causes **serotonin syndrome** when used in combination with selective serotonin re-uptake inhibitors (SSRIs) such as sertraline and paroxetine

Hu Z, Yang X, Ho PC et al. Herb-drug interactions: a literature review. *Drugs* 2005; 65: 1239–1282.

Nortier JL & Vanherweghem JL. Renal interstitial fibrosis and urothelial carcinoma associated with the use of a Chinese herb (*Aristolochia fangchi*). *Toxicology* 2002; 181–182: 577–580.

Zhou SF, Zhou ZW, Li CG et al. Identification of drugs that interact with herbs in drug development. *Drug Discov Today* 2007; 12: 664–673.

Medicines and Healthcare Products Regulatory Agency. Traditional herbal medicine registration scheme. Available from: www.mhra.gov.uk/home/.

Black Cohosh: conflicting clinical evidences

- Although some study results suggest that **black cohosh** may help relieve menopausal symptoms, other study results do not.
- Studies of black cohosh have yielded conflicting data, in part because of lack of rigor in study design and short study duration.
- Different amounts of black cohosh from different sources were used in the various studies and their outcome measures were different.
- While black cohosh may act via non-hormonal mechanisms, it may have oestrogenic actions leading to concerns about its use in women with breast cancer.
- There have also been reports of **liver toxicity**.

Medicines and Healthcare Products Regulatory Agency. Traditional herbal medicine registration scheme.
www.mhra.gov.uk/home/.

K.M. Newton, et al. Treatment of Vasomotor Symptoms of Menopause with Black Cohosh, Multibotanicals, Soy, Hormonal Therapy, or Placebo: A Randomized Trial.
Annals of Internal Medicine 2006; 145 (12) 869-879

Il 7 agosto 2006 il Ministero della Salute italiano ha inviato una circolare alle Aziende di settore, invitandole a **sospendere la commercializzazione dei prodotti contenenti *Cimicifuga racemosa***.
La decisione è stata presa in Italia dopo la pubblicazione, a luglio, di un comunicato stampa dell'EMA (Agenzia Europea del Farmaco) circa la presunta tossicità della pianta.

FITOESTROGENI

Popolazioni asiatiche:

DIETA INTEGRALE

Paesi Occidentali:

ASSUNZIONE INTEGRATIVA IN TARDA ETA'

