## Menopause

Menopause, the permanent cessation of menstruation due to loss of function of the ovarian follicles, occurs at an average age of 51 (1). After menopause, changes are seen in the levels of various hormones, including increases in levels of follicle-stimulating hormone and decreases in circulating estrogen. Menopause, and in particular the loss of estrogen activity, has been associated with a number of symptoms and syndromes, among them hot flashes, atrophy of the vaginal epithelium, osteoporosis, coronary artery disease, and possibly Alzheimer's disease. As the 'baby boom' generation continues to age, it has been estimated that the number of postmenopausal women in the U.S. will reach 60 million within the next decade, making the health and economic costs of diseases associated with menopause significant (2).

## Approaches to treatment

In the attempt to prevent or delay the onset of these diseases, some women elect to begin estrogen replacement therapy (ERT) or to take a combination of estrogen and progestin (hormone replacement therapy, or HRT). Estrogen taken this way has been shown to be effective in preventing or reducing the severity of many of the health risks associated with menopause. Cardiovascular disease is the leading cause of death among women, and its incidence increases significantly after menopause (3). Estrogen replacement therapy (ERT) has been shown to decrease the risk of developing the disease significantly, presumably due in part to its ability to decrease total cholesterol, to increase HDL and decrease LDL cholesterol, and to a direct beneficial effect on coronary vasculature (2). These protective effects have been shown to be even greater in women with established heart disease, and will presumably also be of benefit to women with significant risk factors for heart disease. Osteoporosis is also a major health risk after menopause, affecting an estimated 25 million Americans. Although the exact mechanism of action is unclear, estrogen receptors have been localized to osteoblasts, and estrogen activity has been shown to down-regulate osteoclast activity (4). The loss of the antiresorptive effects of estrogen on bone which accompanies menopause means that bone is removed more rapidly than it can be replaced, for a loss of 1-2% of total bone mass/year, or even more after hysterectomy (2). Studies suggest that ERT prevents this loss of bone density, although it has been shown that the benefit is maximal when therapy is begun soon after menopause, and that therapy must be continued essentially for life to confer continued benefits. Hormone replacement has also been shown to decrease the incidence of hot flashes by up to 60% within 3 months of beginning therapy (3), and ERT has also been correlated with reduced risk of Alzheimer's disease and with a significant delay in the age of onset of the disease, with use for more than one year conferring greater benefits (5).

## Why not HRT?

With the significant health benefits that are associated with hormone replacement, it is surprising to note that 75-85% of eligible North American women do not take ERT (2, 6), and that many users discontinue therapy within the first year. This lack of use stems in part from the fear of health risks shown to be associated with hormone replacement. Estrogen alone has been shown to increase the risk of endometrial cancer with increasing duration of use (7), although this risk appears to be removed with the addition of progestin (hormone replacement therapy or HRT;(2) ). However, added progestin may not eliminate the increased risk of breast cancer, (8,9),

thromboembolism (10), gallstones and gallbladder disease, or liver disease (11) also associated with HRT. For many, the risks and benefits of hormone replacement after menopause must be carefully weighed. In particular, many women may not be candidates for traditional replacement therapy at all due to preexisting disease, such as history of breast cancer, colon cancer or thromboembolism.

## Dietary Soy: Its Estrogenic Effects

Clearly, what is needed is a regimen of hormone replacement which will decrease the risk of heart disease, osteoporosis and menopausal symptoms without increasing the risk of breast cancer and other diseases associated with traditional HRT. Soy protein has been known to slow the progression of atherosclerosis for many years (9). In many Asian countries, where soy protein may comprise from 20-60% of daily protein intake (12), a lower incidence of cardiovascular disease is found (13). Rates of other menopause-related diseases, such as breast cancer and osteoporosis, and symptoms, such as hot flashes, are also are also found in populations where soy or other phytoestrogen-containing foods provide a significant proportion of protein (many Asian countries, vegetarians). These effects may be due to compounds called *phytoestrogens*, non-steroidal plant-derived compounds that have been shown to have weak affinity for estrogen receptors. The primary classes of phytoestrogens found as components of the diet are isoflavones, found in legumes including soybeans, lentils and beans, and lignans, found in many cereals, fruits and vegetables. The primary estrogenically active isoflavones are daidzein and genistein, and the active lignans are enterodiol and enterolactone. The dietary precursors of these compounds are converted by bacteria in the intestine, and have structures similar to that of estrogen, including a phenolic ring which is necesary for binding to the estrogen receptor (4).

Phytoestrogens have been shown to have both estrogenic and anti-estrogenic activity (14), including increases in growth hormone and prolactin, and reductions in LH (15) though their activity is much less than that of estradiol (16) and is not measurable in some studies (17). The possibility that the estrogenic effects of soy and other isoflavone-containing foods might alleviate some of the diseases associated with menopause while avoiding certain harmful effects of estrogen replacement has led to a number of controlled studies.

## Hot Flashes

Murkies et. al. (1995;3) found that supplementation with 45g. soy flour daily in 28 postmenopausal women led to a 40% decrease in the number of hot flashes within 12 weeks. Albertazzi et. al. (1998;18) studied 104 postmenopausal women who received either 60g. of soy protein or placebo daily, and found a 33% reduction in the number of hot flashes in the soy treated group by week 4 of treatment, significant at $p<.001$, and this effect was greater for the soy group than for the placebo group ($p<.01$). Although the majority of studies do find at least some ability of phytoestrogens to reduce the frequency of hot flashes, it should be noted that a few do not. These conflicting results and others can be explained in many ways, including differences in the dose and duration of administration of supplements, in the ways that hot flashes were measured, and in individual differences in the extent of conversion of dietary precursors to the active phytoestrogens in the gut.

## Heart Disease

Dietary phytoestrogens also seem to exert beneficial effects on plasma lipoproteins and heart disease, as might be expected from the decreased rate of CAD after menopause in many Asian countries (6,13). Studies in monkeys have demonstrated increases in HDL and decreases in LDL cholesterol after supplementation with isoflavone-intact soy protein, whereas soy protein from which the isoflavones had been extracted did not have the same beneficial effects on plasma lipid profile (4). Similar effects have been demonstrated in surgically postmenopausal monkeys by Clarkson et. al. (19). In humans, Potter et. al. (19) assigned 66 postmenopausal women to one of three dietary supplementation groups: 40 g/day of protein from casein and dry milk, 40 g/day from soy with 1.39 mg of isoflavone per gram of protein, or 40 g/day from soy with 2.25 mg of isoflavone per gram of protein. Decreases in non-HDL cholesterol and increases in HDL-cholesterol ($p<.05$) were found only in the soy-protein groups.

## Osteoporosis

A number of studies in animals and in humans suggest that phytoestrogen consumption may alter factors related to osteoporosis. In the study described earlier by Potter et. al., for the same women assigned to the non-soy, soy + lower isoflavone content or soy + higher isoflavone content groups, only the high-isoflavone group showed significant increases in bone mineral content and bone density in the lumbar spine after 6 months of therapy. Total bone density and content were not altered. Interestingly, the spine is thought to be the area most sensitive to the effects of estrogen due to its higher content of trabecular bone, and faster remodeling than other areas (19). Soy has also been shown to prevent bone loss in ovariectomized rats, used as a model for the effects of the postmenopausal state in women (20,21). This effect is lost when isoflavones are removed, suggesting that these compounds are responsible for the bone-sparing effects of soy. It is hypothesized that the effects of soy on bone may be due in part to enhancement of the intestinal absorption of calcium, since duodenal calcium transport was enhanced by soy protein with or without isoflavones (22). This may in part account for the finding by Mühlbauer et. al. (23) that phytoestrogen-enhanced diets were moderately effective in preventing bone loss in both ovariectomized and intact rats, with no enhancement of the effect in the surgically menopausal animals. This suggested that the effects of phytoestrogens were not due to their estrogenic activity. There appears to be some role for phytoestrogens in preventing bone loss, which would be expected based on epidemiologic data suggesting a lower rate of osteoporosis in populations with high dietary intake (4). It is generally accepted that the beneficial effects are not as great as those found with conventional HRT, and that, as with HRT, long-term intake appears to be most beneficial.

## Phytoestrogens and Cancer

Given the concerns about the relationship between HRT and increased risk of breast cancer and other disorders, it is interesting to note that phytoestrogens possess many nonhormonal actions, including inhibition of protein tyrosine kinases, epidermal growth factor, malignant cell proliferation, differentiation and angiogenesis, as well as antioxidant properties (13). These properties have led to studies of soy proteins and cancer rates, and some have demonstrated significant decreases in tumor formation in animal models of chemically-induced breast cancer, an effect that was lost with the removal of the isoflavones (4). Although an understanding of the role of these compounds in cancer prevention is in its infancy, it is known that dietary

modification on a regular basis alters characteristics of the menstrual cycle. The cycle is significantly longer in Japanese and in Chinese women eating traditional diets, and cycle length is inversely related to breast cancer risk (4). This may account for the finding that breast cancer risk is up to 6 times less in native Asian populations, whereas the risk is increased in women a few generations after migration away from their homelands (24,25), presumably due to lifestyle and dietary changes.

## Conclusion

The decision to use or not to use hormone replacement appears to be a difficult one for many women, despite its significant health benefits. Although the risk of endometrial cancer with the use of unopposed estrogen can be prevented by the addition of progestins, the effects of HRT on breast cancer, venous thromboembolism and other diseases are less well understood. The effects of soy protein and isoflavones on the syndromes and symptoms of menopause are still being studied, but the consensus to this point appears to be that they are generally beneficial although in some cases less so than conventional HRT. For a significant number of women, however, fears of cancer and other diseases which may or may not be associated with HRT appear to be enough to deter them from considering estrogen replacement. Additionally, there are women for whom traditional therapy may not be an option. It is interesting to note that adherence to regimens of hormone therapy is associated with higher levels of education (5); this suggests that by taking the time to talk with and to educate their patients, physicians may be able to increase patients' willingness to consider hormone replacement. As an adjunct to or a replacement for traditional therapies, the use of soy products and other phytoestrogen-rich foods may well be of health benefit to postmenopausal women due both to possible estrogenic effects and to other non-hormonal actions.

## REFERENCES


1. Greendale GA, Lee NP, Arriola ER. The menopause. *Lancet.* 1999;353:571-80.
2. Witt DM, Lousberg TR. Controversies surrounding estrogen use in postmenopausal women. *Annals of Pharmacotherapy.* 1997;31:745-55.
3. Murkies AL, Lombard C, Strauss BJG, Wilcox G, Burger HG, Morton MS. Dietary flour supplementation decreases post-menopausal hot flushes: Effect of soy and wheat. *Maturitas*.1995;21:189-95.
4. Setchell KDR. Phytoestrogens: the biochemistry, physiology and implications for human health of soy isoflavones. *American Journal of Clinical Nutrition.* 1998;68(suppl.):1333S-46S.
5. Tang MX, Jacobs D, Stern Y, Marder K, Schofield P, Gurland B, Andrews H. Effect of oestrogen during menopause on risk and age at onset of Alzheimer's disease. *Lancet.*. 1996;348:429-32.
6. Lindsay SM, Claywell LC. Considering soy: its estrogenic effects may protect women. *AWOHNN Lifelines.* 1998;41-4.
7. Cushing BL, Weiss NS, Voigt LF, Mcknight B, Beresford SAA. Risk of endometrial cancer in relation to use of low-dose, unopposed estrogens. *Obstetrics and Gynecology.* 1998;91(1):35-9.
8. Colditz GA, Hankinson SE, Hunter DJ, Willett WC, Manson JE, Stampfer MJ, Hennekens C, Rosner B, Speizer FE. The use of estrogens and progestins and the risk of breast cancer in postmenopausal women. *New England Journal of Medicine.*

1995;332(24):1589-93.
9. Clarkson TB, Anthony MS, Williams JK, HonorÈ EK, Cline JM. The potential of soybean phytoestrogens for postmenopausal hormone replacement therapy. *Proceedings of the Society for Experimental Biology and Medicine.* 1998;217:365-8.
10. Daly E, Vessey MP, Hawkins MM, Carson JL, Gough P, Marsh S. Risk of venous thromboembolism in users of hormone replacement therapy. *Lancet.* 1996;348:977-80.
11. Andrews WC. The transitional years and beyond. *Obstetrics & Gynecology.* 1995;85(1):1-5.
12. Barnes S. Evolution of the health benefits of soy isoflavones. *Proceedings of the Society for Experimental Biology and Medicine.* 1998;217:386-92.
13. Murkies A. Phytoestrogens - what is the current knowledge? *Australian Family Physician.* 1998;27(suppl 1):S47-51.
14. Zava DT, Dollbaum CM, Blen M. Estrogen and progestin bioactivity of foods, herbs and spices. *Proceedings of the Society for Experimental Biology and Medicine.* 1998;217:369-78.
15. Harding C, Morton M, Gould V, McMichael Phillips D, Howell A, Bundred NJ. Dietary soy supplementation is estrogenic in postmenopausal women (Abstract). *American Journal of Clinical Nutrition.* 1998;68(suppl.):1532S.
16. Reinli K, Block G. Phytoestrogen content of foods - a compendium of literature values. *Nutrition and Cancer.* 1996;26:123-48.
17. Baird DD, Umbach DM, Lansdell L, Hughes CL, Setchell KDR, Weinberg CR, Haney AF, Wilcox AJ, Mclachlan JA. Dietary intervention study to assess estrogenicity of dietary soy among postmenopausal women. *Journal of Clinical Endocrinology and Metabolism.* 1995;80(5):1685-90.
18. Albertazzi P, Pansini F, Bonaccorsi G, Zanotti L, Forini E, De Aloysio D. The effect of dietary soy supplementation on hot flushes. *Obstetrics & Gynecology*. 1998;91(1):6-11.
19. Potter SN, Baum JA, Teng H, Stillman RJ, Shay NF, Erdman JW. Soy protein and isoflavones: their effects on blood lipids and bone density in postmenopausal women. *American Journal of Clinical Nutrition.* 1998;68(suppl.):1375S-9S.
20. Arjmandi BH, Getlinger MJ, Goyal NV, Alekel L, Hasler CM, Juma S, Drum ML, Hollis BW, Kukreja SC. Role of soy protein with normal or reduced isoflavone content in reversing bone loss induced by ovarian hormone deficiency in rats. *American Journal of Clinical Nutrition.* 1998;68(suppl.):1358S-63S.
21. Draper CR, Edel MJ, Dick IM, Randall AG, Martin GB, Prince RL. Phytoestrogens reduce bone loss and bone resorption in oophorectomized rats. *Journal of Nutrition.* 1997;127:1795-9.
22. Arjmandi BH, Birnbaum R, Goyal NV, Getlinger MJ, Juma S, Alekel L, Hasler CM, Drum ML, Hollis BW, Kukreja SC. Bone-sparing effect of soy protein in ovarian hormone-deficient rats is related to its isoflavone content. *American Journal of Clinical Nutrition.* 1998;68(suppl.):1364S-8S.
23. Mühlbauer RC, Li F. Frequency of food intake and natural dietary components are potent modulators of bone resorption and bone mass in rats. *Biomedicine & Pharmacotherapy.* 1997; 51:360-3.
24. Murkies AL, Wilcox G, Davis SR. Clinical review 92:Phytoestrogens. *Journal of Clinical Endocrinology and Metabolism.* 1998;83:297-303.
25. Wu AH, Ziegler RG, Nomura AMY, West DW, Kolonel LN, Horn-Ross PL, Hoover

RN, Pike MC. Soy intake and risk of breat cancer in Asians and Asian Americans. *American Journal of Clinical Nutrition.* 1998;68(suppl.):1437S-43S.