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The Soy Connection

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HEALTH AND NUTRITION NEWS ABOUT SOY

Research Updates

By Mark Messina, Ph.D.

There is much interest in the skeletal benefits of isoflavones and isoflavone-rich soy protein. Animal research is encouraging as are the clinical trials which involved primarily postmenopausal women but many of these trials have been conducted for less than one year and involved small numbers of subjects.

Two recently published trials provide further insight into the possible effects of soy on bone health. In one, conducted by Anderson and colleagues from the University of North Carolina (well recognized for their work in the bone area), premenopausal women consumed 40 g soy protein that was either high (N=15) or low (N=13) in isoflavones. The women were 21-25 y of age. Bone mineral density (BMD) and bone mineral content (BMC) were measured at several sites. Over the course of one year, consumption of the high-isoflavone (90 mg) soy protein was not associated with greater BMC or BMD. The investigators concluded that in healthy women with normal ovarian function, and therefore with normal serum estrogen levels, isoflavones exert no independent skeletal benefits. Of course, this study design precludes identifying any independent effect of soy protein since both groups received

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Women's Health Initiative Puts Spotlight On HRT, Soy

By Mark Messina, Ph.D.

Introduction

The soybean is a unique natural dietary source of isoflavones, which have estrogen-like, and possibly, anti-estrogenic properties. Primarily for this reason, during the past several years there has been much discussion about soy as an alternative to conventional hormone replacement therapy (HRT). Such discussion is likely to intensify as a result of recently published findings from the Women's Health Initiative (WHI). The WHI found that the potential harm of HRT greatly outweighed the potential benefit and as a result, the trial was terminated after 5.2 years instead of the planned 8.5 years. Consequently, there is need to discuss the possible implications of the WHI for soyfoods and soybean isoflavones. Therefore, in this article the literature relevant to the effects of soy for those diseases whose risk was affected by HRT is briefly reviewed.

Trial Description and Results

The WHI is a National Institutes of Health-sponsored, multicenter trial that began in 1993. One arm of the trial consisted of a randomized, blinded, placebo-controlled hormone study involving 16,608 women (average age, 63.2; range 50-79) who received either a placebo or continuous-combined estrogen (0.625 mg/day of conjugated equine estrogens)-progesterone (2.5 mg/day of medroxyprogesterone acetate) therapy (CCEPT). Among the 8,506 women receiving CCEPT, 33.4 percent were 50 to 59 y, 45.3 percent were 60 to 69 y, and 21.3 percent were 70 to 79 y. The majority of participants were randomized at least 10 years after menopause. Compliance by the end of the trial was approximately 60 percent. Pertinent results are shown in the table on page 2. As can be seen, risk of coronary heart disease, stroke, venous

thromboembolism, and breast cancer was increased, whereas risk of colon cancer and skeletal fracture was decreased.

Coronary Heart Disease (CHD)

CHD risk was increased 29 percent in the WHI. The failure of HRT to reduce CHD events was surprising given the effects of estrogen on coronary vessels noted in previous short-term intervention studies^{1,2} and the generally improved serum lipid profiles in response to estrogen. In fact, in the WHI, CCEPT decreased LDL-C levels by 12.7 percent in a subset of women for whom analysis was done.

Likely Effects of Soy

In 1999, the U.S. Food and Drug Administration approved a health claim for the cholesterol-lowering effects of soy protein and set 25 g/day as the target intake goal for cholesterol reduction.³ In 2000, the American Heart Association endorsed the use of soyfoods for people with elevated cholesterol.⁴ Still, it should be acknowledged that the cholesterol-lowering effects of soy protein are most evident in very hypercholesterolemic subjects⁵ and overall are much less pronounced than those observed for the commonly prescribed cholesterol-lowering drugs, statins.⁶

The hypocholesterolemic effects of soy protein suggest it will decrease CHD risk. But there are of course many CHD risk factors that need to be considered. Obviously, since CCEPT lowers cholesterol, CCEPT adversely affects one or more of these other risk factors. For example, it is known that CCEPT increases serum triglyceride levels,⁷ a

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NAMS Recommendations Post WHI Study

By Mark Messina, Ph.D.

As a result of the findings from the Women's Health Initiative (WHI) and a previously published trial involving continuous-combined estrogen-progestogen therapy (CCEPT), the Heart and Estrogen/progestin Replacement Study (HERS), the North American Menopause Society (NAMS) has issued the following recommendations regarding the use of estrogen therapy (ET) or estrogen-progestogen therapy (EPT):

- Treatment of menopause symptoms (eg, vasomotor and urogenital) remains the primary indication for EPT and ET.
- The only menopause-related indication for chronic progestogen use appears to be endometrial protection from unopposed

estrogen therapy. For all women with an intact uterus who are using estrogen therapy, clinicians are advised to prescribe adequate progestogen, whereas women without a uterus should not be prescribed a progestogen.

- No EPT regimen should be used for primary or secondary prevention of coronary heart disease (CHD). Proven alternate cardioprotective regimens should be considered. The effect of ET on CHD is not yet clear. Until confirming data are available, ET should not be used for primary or secondary prevention of CHD.
- Many EPT and ET products are

FDA-approved for the prevention of postmenopausal osteoporosis; however, because of the risks associated with these forms of therapy, alternatives should also be considered, weighing the risks and benefits of each.

- Use of EPT or ET should be limited to the shortest duration consistent with treatment goals, benefits, and risks for the individual woman.
- An individual risk profile is essential for every woman contemplating any regimen of EPT or ET. Women should be informed of known risks.

www.menopause.org/news.html#advisory

Women's Health Initiative Puts Spotlight On Soy *(Continued from Page 1)*

possible independent CHD risk factor.⁸ In contrast, evidence indicates soy protein either has no effect or decreases serum triglyceride levels.⁵ Also, CCEPT may increase platelet aggregation^{9,10} and C-reactive protein,^{11,12} effects that would increase risk of CHD whereas the evidence suggests soy has either no effect on¹³ or inhibits platelet aggregation.¹⁴

Although still speculative, several studies suggest isoflavones and isoflavone-rich soy protein may favorably affect a number of putative CHD risk factors beyond serum lipid and cholesterol levels such as arterial compliance,¹⁵ endothelial function,¹⁶ and low-density-lipoprotein oxidation.¹⁷ But again, it should be acknowledged that CCEPT is also known to favorably affect these parameters. Only limited epidemiologic investigation of the relationship between CHD risk and soy intake has been conducted, but data from two Japanese epidemiologic studies support the cardioprotective effects of soy in women.^{18,19}

Thus far no intervention trials have actually examined the impact of soy consumption on coronary events. There is no evidence to suggest that soy and isoflavones like CCEPT would increase CHD, whereas short-term intervention trials suggest they may decrease risk.

Breast Cancer

Breast cancer risk was increased by 26 percent in the WHI.²⁰ However, nearly all of the increased breast cancer risk occurred in the final years of the trial which suggests the annual percentage increased risk for those years was as high as 8-9 percent. If CCEPT were to increase risk to this extent annually in a woman using CCEPT for 30 years, risk would be increased 2-3 fold. In fact, subgroup analysis in the WHI noted increases of two-fold and higher in long-time users of CCEPT and several epidemiologic studies have noted increases of this magnitude, especially among women of normal weight.^{21,22} The increased risk in response to CCEPT was not unexpected as breast cancer was the major adverse outcome to be examined in this trial.

Much evidence indicates it is the combination of hormones (estrogen

and progestin), not estrogen alone, that increases breast cancer risk. Including the observations that compared to estrogen alone, the combination of hormones is associated with greater breast tissue density,^{23,24} increased breast²⁵ and mammary²⁶ cell proliferation. Breast cell replication is four times greater during the second two weeks (luteal phase) of the menstrual cycle when endogenous serum progesterone levels are high in comparison to the first two weeks (follicular phase) when progesterone levels are low.²⁷ In support of these observations are several epidemiologic studies which have found that estrogen alone only slightly increases breast cancer risk, whereas the combination hormones markedly increases risk.^{21,22} Finally, the most telling observation may be that thus far, no increase in

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breast cancer risk has been observed in the estrogen only arm of the WHI and as a result, the safety monitoring board recommended that this arm of the trial continue.

Likely Effects of Soy

Despite the considerable interest in the anticancer effects of soy, especially in regard to breast cancer, some concern has been expressed that the estrogen-like properties of isoflavones might increase breast cancer risk in high risk women or stimulate secondary tumor growth in breast cancer survivors. While this concern is not without some merit,²⁸ it should be recognized that isoflavones are different from estrogen. Isoflavones tend to be categorized as selective estrogen receptor modulators (SERMs), such as the breast cancer drug tamoxifen and the osteoporosis drug raloxifene, which appears to have antiestrogenic effects on breast tissue.²⁹ SERMs have estrogen-like effects in some tissues but either no effects or antiestrogenic effects in other tissues, whereas estrogen has estrogenic effects in all tissues which have estrogen receptors.

Most importantly, soy has no progestogen activity,³⁰ and as discussed above, the combination hormones (estrogen plus progestogen), rather than estrogen alone, appears to increase breast cancer risk. Furthermore, year-long trials have found that isoflavones have no effect on breast tissue density in premenopausal women (Gertraud Maskarinec, Cancer Research Center of Hawaii, 2001, personal communication) and actually decrease density in women 56-65 years of age.³¹ Breast tissue density appears to be a reasonably good indicator of breast cancer risk as agents that increase risk increase density and visa versa.³² Thus, the weight of the evidence indicates, unlike estrogen, soy is not likely to increase breast cancer risk in any women. For a review of the effects of soy and isoflavones on breast cancer risk, see Messina and Loprinzi.³³

Finally, whether soy decreases breast cancer risk is highly speculative, although an intriguing body of research suggests early exposure to soy, that is, consumption during the

teenage years, is protective against the development of breast cancer later in life.³⁴⁻³⁷

Venous Thromboembolic Disease (VTED) and Stroke

Risks of deep vein thrombosis and pulmonary embolism in the WHI were increased approximately two-fold²⁰ and stroke risk was increased by approximately 40 percent. Venous thrombosis occurs when red blood cells, fibrin (fibrin forms by cleavage of fibrinogen and is an important component of a blood clot) and, to a lesser extent, platelets and leukocytes, form a mass within an intact cardiovascular system. The biological basis for the relationship between CCEPT and VTED is not understood although this connection may be due to the estrogen component,³⁸ possibly as a result of estrogen altering hepatic production or metabolism of coagulation factors.³⁹ The mechanism by which CCEPT increases risk is also unknown, although one observational study reported that estrogen plus progestin was associated with a slightly higher risk of stroke than estrogen alone.⁴⁰

Likely Effects of Soy

As noted previously, there are no indications that soy increases clot formation¹³ or adversely affects coagulation and fibrinolytic factors^{41, 42} but research is limited. In regard to stroke, one large prospective epidemiologic study involving over 18,000 Chinese men found that fatal stroke risk was unrelated to soy

intake.⁴³ Animal research suggests soy and the main soybean isoflavone genistein may be of value in the prevention of stroke via hormonal and nonhormonal mechanisms but this is highly speculative.⁴⁴⁻⁴⁷ There is also some clinical research indicating soy protein reduces blood pressure,⁴⁸⁻⁵⁰ a risk factor for stroke.⁵¹⁻⁵³

Colorectal Cancer

CCEPT decreased colorectal cancer risk in the WHI by 37 percent.²⁰ Several epidemiologic studies have also found that CCEPT users are less likely to develop colon cancer and there are a variety of mechanisms by which estrogen may decrease colorectal cancer risk.^{54, 55}

Likely Effects of Soy

The evidence that soy reduces colon cancer risk is somewhat mixed with the epidemiologic data being the least supportive.^{56, 57} The most impressive study is one which found that in subjects with a history of colon polyps or colon cancer who were fed 39 g soy protein/day for one year, there was a statistically significant decrease in colon cell proliferation and in the proliferation zone when compared to baseline values, whereas no changes occurred in the group fed a similar amount of casein.⁵⁶ These changes are indicative of a marked reduction in colon cancer risk. But this finding should be considered preliminary.

If soy does reduce risk it is not

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Results From WHI

Disease	Relative risk (95% C.I.)	Events/10,000
Coronary heart disease	1.29 (CI 1.02-1.63)	37 vs 30
Stroke	1.41 (CI 1.07-1.85)	29 vs 21
Breast cancer	1.26 (CI 1.00-1.59)	38 vs 30
Colon cancer	0.63 (CI 0.43-0.92)	10 vs 16
Osteoporotic fracture		
Hip	0.66 (CI 0.45-0.98)	10 vs 15
Spine	0.66 (CI 0.44-0.98)	9 vs 15
Total	0.76 (CI 0.69-0.85)	147 vs 191

Source: *Jama* 2002; 288:321-33

Women's Health Initiative: A Background

In 1991 a huge step was taken regarding the promotion of women's health in America. The National Institutes of Health (NIH) established the Women's Health Initiative (WHI), one of the largest prevention studies in the United States. Launched by Dr. Bernadine Healy, then director of the NIH, the WHI was designed to study strategies for preventing the major causes of death, disability and frailty in postmenopausal women. These strategies predominantly deal with heart disease, breast and colon cancer, and osteoporosis. In addition to the NIH, this 15 year multi-million dollar project is sponsored by the National Heart, Lung, and Blood Institute (NHLBI) and involves over 168,000 women aged 50-79.

The efforts of the WHI can be broken down into three major components: a randomized controlled clinical trial of promising but unproven approaches to prevention; an observational study to identify predictors of disease; and a community prevention study to develop approaches to healthful behavior in the community. This long-term national health study has been recognized as one of the largest and most important prevention studies ever conducted in the U.S.

The randomized clinical trial (CT) attempts to provide women


and their physicians with information regarding the discriminatory elements involved in women's health research. The CT has enrolled over 68,000 postmenopausal women, and was itself comprised of three major components. One was Hormone Replacement Therapy (HRT), which examined the effects of HRT on prominent disease prevention in women (the therapy was halted this past summer); the others are Dietary Modification, evaluating the effects of a well balanced diet on the prevention of cancer and heart disease; and Calcium/Vitamin D, evaluating the effects of these supplements on prevention of osteoporosis and colon cancer. Women can choose to enroll in any or all of the components, if eligible.

The observational study (OS), used to identify disease predictors, examines the relationship between lifestyle, health and risk factors and specific disease outcomes. It will track the health habits and medical history of nearly 100,000 women for 8 to 12 years. Coupled with the clinical trial, the observational study claims over 168,000 participants from 40 different Clinical Centers nationwide.

The Community Prevention Study (CPS) is a 5 year collaborative endeavor with the Centers for Disease Control and

Prevention (CDC) that encourages women of all races and socioeconomic backgrounds to adopt a healthy lifestyle. Health programs dealing with improved diet, nutritional supplementation, smoking cessation, exercise and early detection of health problems are conducted and evaluated. The goal of the CPS is to develop model programs that can be copied and instituted in communities throughout the United States.

These three components have targeted osteoporosis, heart disease, breast cancer and colon cancer as the leading risks to women's health in the United States. Results have shown that heart disease is the leading cause of death in postmenopausal women. Over 240,000 American women die of heart attacks every year. That is 22 percent of all deaths among women in the U.S. Over 46,000 die annually of breast cancer, and more than 183,000 new cases are found each year. More than 28,000 women die of colon and rectal cancer each year, and one-sixth of all women over 50 in the United States will suffer prevalent fractures as a result of osteoporosis.

For more information about the Women's Health Initiative, logon to www.nhlbi.nih.gov/whi/index.html 

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at all clear isoflavones are responsible for the protective effects as isolated genistein has actually been found to increase colon tumorigenesis in animals.⁵⁸ However, in contrast, newly published animal research suggests that genistein may be able to increase colon and prostate tissue vitamin D levels, which provides a potential mechanism by which soy and isoflavones could decrease colon cancer risk.⁵⁹ Overall, at this point, the evidence is too limited to draw conclusions about the impact of soy or isoflavones on colon cancer risk.

Fracture Risk

Fracture risk at all sites combined was decreased by 24 percent, and by 34 percent at the hip and spine.²⁰ These findings are generally consistent with the literature on this subject.⁶⁰

Likely Effects of Soy

Not surprisingly, because of their estrogen-like properties there is much interest in the possible skeletal benefits of isoflavones. Generally, isolated isoflavones as well as isoflavone-rich soy protein inhibit bone loss in ovariectomized rats,⁶¹ a model accepted by the FDA for studying

osteoporosis.⁶² Trials involving postmenopausal women are generally favorable, although a bit inconsistent, and thus far effects have been noted primarily at the spine.^{61, 63} However, very recently, a year long trial actually found that the isoflavone genistein (54 mg), when consumed daily, increased bone mineral density (BMD) at the hip and spine, whereas women in the placebo group lost BMD at both sites.⁶⁴ Furthermore, overall, genistein was more effective than

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Food and Nutrition Board Issues New DRIs For Protein Intake

By Guy H. Johnson, Ph.D.

The Food and Nutrition Board of the National Academy of Science's Institute of Medicine recently issued Daily Reference Intakes for protein and other macronutrients. The DRIs include updated Recommended Dietary Allowances (RDAs) that were last issued by the Food and Nutrition Board in 1989. The most recent RDAs for protein are slightly lower for most life stage groups compared to the previous values, but the allowances for pregnancy and lactation have increased. A Tolerable Upper Intake Level (UL) for protein was not established.

2002 Daily Reference Intakes		1989 Recommended Dietary Allowances	
Life Stage Group	RDA/AI Grams/day	Life Stage Group	RDA Grams/day
<u>Infants</u>		<u>Infants</u>	
• 0-6 months	9.1*	• 0-6 months	13
• 7-12 months	13.5	• 7-12 months	14
<u>Children (girls and boys)</u>		<u>Children (girls and boys)</u>	
• 1-3 years	13	• 1-3 years	16
• 4-8 years	19	• 4-6 years	24
• 9-13 years	34	• 7-10 years	48
<u>Females</u>		<u>Females</u>	
• 14-18	46	• 11-14	46
• 19-30	46	• 15-18	44
• 31-50	46	• 19-24	46
• 51-70	46	• 25-50	50
• >70	46	• >50	50
• Pregnancy	25 g additional	• Pregnancy	60
• Lactating (all stages)	25 g additional	• Lactation (1st 6 mo.)	65
		• Lactation (2nd 6 mo.)	62
<u>Males</u>		<u>Males</u>	
• 14-18	52	• 11-14	45
• 19-30	56	• 15-18	59
• 31-50	56	• 19-24	58
• 51-70	56	• 25-50	63
• >70	56	• >50	63

*The 2002 DRI for infants 0-6 months is an Adequate Intake (AI) rather than an RDA

Source: Food and Nutrition Board, Institute of Medicine, 2002. Dietary Reference Intakes for Energy, Carbohydrates, Fiber, Fat, Protein and Amino Acids (Macronutrients). National Academy Press, Washington, DC www.nap.edu/books/0309085373/html/

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soy. Previous studies have found that soy protein when substituted for animal protein decreases urinary calcium excretion.

In contrast to the findings by Anderson and colleagues, Morabito and colleagues from the University of Messina in Italy, found that the isoflavone genistein (54 mg) had dramatic beneficial effects on several bone sites. Thirty postmenopausal women were given a placebo, genistein, or hormone replacement therapy. At the end of one year, women in the placebo group lost 0.65 percent, 0.36 percent, and 1.6 percent BMD at the hip, Ward's triangle, and spine respectively, whereas

women in the genistein group gained 3.6 percent, 4.0 percent, and 3.0 percent, at each of these sites, respectively. All differences were statistically significant. Effects of genistein exceeded those of HRT at the hip (3.6 percent vs 2.4 percent) and Ward's triangle (4.0 percent vs 3.0 percent) but were less than HRT at the spine (3.0 percent vs 3.8 percent). This study is particularly noteworthy because of the inclusion of the positive control, HRT. As noted in the review article in this issue, in the Women's Health Initiative, women in the treatment group who received HRT experienced a 34 percent reduction in the

incidence of hip and spinal fractures compared to the placebo group. Thus, should the effects of genistein be replicated in longer term trials, there is good reason to think this isoflavone may substantially reduce fracture risk. ☺

REFERENCES FOR THIS ISSUE

Complete references for articles in this issue can be found at *The Soy Connection* link at www.talksoy.com

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CCEPT (see Research Updates). Also, in addition to the possible direct benefits of isoflavones, soy protein, when substituted for animal protein, may improve bone health by decreasing urinary calcium excretion.⁶⁵⁻⁶⁷ All other factors being equal, because net calcium absorption is probably no more than 10 percent, substituting soy protein for animal protein over the course of many years will likely be associated with clinically relevant skeletal benefits.^{68, 69}

Conclusions

Much less is known about the health effects of soy and isoflavones

than of CCEPT. No intervention studies have actually examined the impact of soy consumption on disease outcomes per se, such as fractures and coronary events. Only markers of disease risk such as serum cholesterol levels and BMD have been studied. As evidenced from the WHI, long-term intervention trials that have disease outcomes as endpoints are necessary before drawing definitive conclusions about the health effects of any biologically active agent or diet.

It is clear however that neither soy nor isoflavones are the same chemically or physiologically as

CCEPT. The "estrogen" used in the WHI is actually a complex mixture of estrogens derived from the urine of pregnant mares. Women were also given a synthetic progestogen. Obviously, this chemical mix is very different from soy and isoflavones. On the basis of the available data, there is little reason to think that soy consumption will increase risk of any of the diseases whose risk was increased in the WHI, whereas there is at least preliminary data suggesting soy may provide some of the benefits. ☺

REFERENCES

Fallout From Women's Health Initiative Puts Spotlight On HRT And Soy

1. Blum A, Cannon RO, 3rd. Selective estrogen receptor modulator effects on serum lipoproteins and vascular function in postmenopausal women and in hypercholesterolemic men. *Ann N Y Acad Sci* 2001; 949:168-74.
2. Mikkola TS, Clarkson TB. Estrogen replacement therapy, atherosclerosis, and vascular function. *Cardiovasc Res* 2002; 53:605-19.
3. Food and Drug Administration. Food labeling, health claims, soy protein, and coronary heart disease. *Fed Reg* 1999; 57:699-733.
4. Erdman JW, Jr. Soy protein and cardiovascular disease: A statement for healthcare professionals from the nutrition committee of the AHA. *Circulation* 2000; 102:2555-9.
5. Anderson JW, Johnstone BM, Cook-Newell ME. Meta-analysis of the effects of soy protein intake on serum lipids. *N Engl J Med* 1995; 333:276-82.
6. LaRosa JC, He J, Vupputuri S. Effect of statins on risk of coronary disease: a meta-analysis of randomized controlled trials. *Jama* 1999; 282:2340-6.
7. Hulley S, Grady D, Bush T, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. *Heart and Estrogen/progestin Replacement Study (HERS) Research Group. Jama* 1998; 280:605-13.
8. Jeppesen J, Hein HO, Suadicani P, Gynzelberg F. Triglyceride concentration and ischemic heart disease: an eight-year follow-up in the Copenhagen Male Study. *Circulation* 1998; 97:1029-36.
9. Yoshimura T, Ohshige A, Maeda T, Ito M, Okamura H. Estrogen replacement therapy decreases platelet-activating factor-acetylhydrolase activity in post-menopausal women. *Maturitas* 1999; 31:249-53.
10. Thijs A, Van Baal WM, Van Der Mooren MJ, et al. Effects of hormone replacement therapy on blood platelets. *Eur J Clin Invest* 2002; 32:613-8.
11. Decensi A, Omodei U, Robertson C, et al. Effect of transdermal estradiol and oral conjugated estrogen on C-reactive protein in retinoid-placebo trial in healthy women. *Circulation* 2002; 106:1224-8.
12. Pradhan AD, Manson JE, Rossouw JE, et al. Inflammatory biomarkers, hormone replacement therapy, and incident coronary heart disease: prospective analysis from the Women's Health Initiative observational study. *Jama* 2002; 288:980-7.
13. Gooderham MH, Adlercreutz H, Ojala ST, Wahala K, Holub BJ. A soy protein isolate rich in genistein and daidzein and its effects on plasma isoflavone concentrations, platelet aggregation, blood lipids and fatty acid composition of plasma phospholipid in normal men. *J Nutr* 1996; 126:2000-6.
14. Schoene NW, Guidry CA. Dietary soy inhibits activation of rat platelets. *J Nutr Biochem* 1999; 10:421-426.
15. Nestel PJ, Yamashita T, Sasahara T, et al. Soy isoflavones improve systemic arterial compliance but not plasma lipids in menopausal and perimenopausal women. *Arterioscler Thromb Vasc Biol* 1997; 17:3392-8.
16. Squadrito F, Altavilla D, Morabito N, et al. The effect of the phytoestrogen genistein on plasma nitric oxide concentrations, endothelin-1 levels and endothelium dependent vasodilation in postmenopausal women. *Atherosclerosis* 2002; 163:339-47.
17. Wiseman H, O'Reilly JD, Adlercreutz H, et al. Isoflavone phytoestrogens consumed in soy decrease F(2)-isoprostane concentrations and increase resistance of low-density lipoprotein to oxidation in humans. *Am J Clin Nutr* 2000; 72:395-400.
18. Sasazuki S. Case-control study of nonfatal myocardial infarction in relation to selected foods in Japanese men and women. *Jpn Circ J* 2001; 65:200-6.
19. Nagata C. Ecological study of the association between soy product intake and mortality from cancer and heart disease in Japan. *Int J Epidemiol* 2000; 29:832-6.
20. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. *Jama* 2002; 288:321-33.
21. Schairer C, Lubin J, Troisi R, Sturgeon S, Brinton L, Hoover R. Menopausal estrogen and estrogen-progestin replacement therapy and breast cancer risk. *Jama* 2000; 283:485-91.
22. Ross RK, Paganini-Hill A, Wan PC, Pike MC. Effect of hormone replacement therapy on breast cancer risk: estrogen versus estrogen plus progestin. *J Natl Cancer Inst* 2000; 92:328-32.
23. Lundstrom E, Wilczek B, von Palffy Z, Soderqvist G, von Schoultz B. Mammographic breast density during hormone replacement therapy: effects of continuous combination, unopposed transdermal and low-potency estrogen regimens. *Climacteric* 2001; 4:42-8.
24. Greendale GA, Reboussin BA, Sie A, et al. Effects of estrogen and estrogen-progestin on mammographic parenchymal density. *Postmenopausal Estrogen/Progestin Interventions (PEPI) Investigators. Ann Intern Med* 1999; 130:262-9.
25. Conner P, Skoog L, Soderqvist G. Breast epithelial proliferation in postmenopausal women evaluated through fine-needle-aspiration cytology. *Climacteric* 2001; 4:7-12.
26. Cline JM, Paschold JC, Anthony MS, Obasanjo IO, Adams MR. Effects of hormonal therapies and dietary soy phytoestrogens on vaginal cytology in surgically postmenopausal macaques. *Fertil Steril* 1996; 65:1031-5.
27. Soderqvist G, Isaksson E, von Schoultz B, Carlstrom K, Tani E, Skoog L. Proliferation of breast epithelial cells in healthy women during the menstrual cycle. *Am J Obstet Gynecol* 1997; 176:123-8.
28. Bouker KB, Hilakivi-Clarke L. Genistein: Does it Prevent or Promote Breast Cancer? *Environ Health Perspect* 2000; 108:701-708.
29. Brzezinski A, Debi A. Phytoestrogens: the "natural" selective estrogen receptor modulators? *Eur J Obstet Gynecol Reprod Biol* 1999; 85:47-51.
30. Zava DT, Dollbaum CM, Blen M. Estrogen and progestin bioactivity of foods, herbs, and spices. *Proc Soc Exp Biol Med* 1998; 217:369-78.
31. Atkinson C, Warren RML, Dowsett M, Day NE, Bingham S. Effects of isoflavones on breast density, oestradiol, and gonadotrophins: a double blind randomized placebo controlled trial. *J Nutr* 2002; 132:577S-578S.
32. Boyd NF, Lockwood GA, Martin LJ, Byng JW, Yaffe MJ, Tritchler DL. Mammographic density as a marker of susceptibility to breast cancer: a hypothesis. *IARC Sci Publ* 2001; 154:163-9.
33. Messina MJ, Loprinz CL. Soy for breast cancer survivors: a critical review of the literature. *J Nutr* 2001; 131:3095S-108S.
34. Shimizu H, Ross RK, Bernstein L, Yatani R, Henderson BE, Mack TM. Cancers of the prostate and breast among Japanese and white immigrants in Los Angeles County. *Br J Cancer* 1991; 63:963-6.
35. Lamartiniere CA, Zhao YX, Fritz WA. Genistein: mammary cancer chemoprevention, in vivo mechanisms of action, potential for toxicity and bioavailability in rats. *J Women's Cancer* 2000; 2:11-19.
36. Shu XO, Jin F, Dai Q, et al. Soyfood

- Intake during Adolescence and Subsequent Risk of Breast Cancer among Chinese Women. Cancer Epidemiol Biomarkers Prev* 2001; 10:483-8.
37. Wu AH, Wan P, Hankin J, Tseng CC, Yu MC, Pike MC. Adolescent and adult soy intake and risk of breast cancer in Asian-Americans. *Carcinogenesis* 2002; 23:1491-6.
 38. Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. *J Natl Cancer Inst* 1998; 90:1371-88.
 39. Lip GY, Felmeden DC. Hormone replacement therapy and cardiovascular risk: do abnormalities of coagulation and fibrinolysis matter? *J Intern Med* 2001; 249:201-4.
 40. Grodstein F, Manson JE, Colditz GA, Willett WC, Speizer FE, Stampfer MJ. A prospective, observational study of postmenopausal hormone therapy and primary prevention of cardiovascular disease. *Ann Intern Med* 2000; 133:933-41.
 41. Dent SB, Peterson CT, Brace LD, et al. Soy protein intake by perimenopausal women does not affect circulating lipids and lipoproteins or coagulation and fibrinolytic factors. *J Nutr* 2001; 131:2280-7.
 42. Sanders TAB, Dean TS, Grainger D, Miller GJ, Wiseman H. Moderate intakes of intact soy protein rich in isoflavones compared with ethanol-extracted soy protein increase HDL but do not influence transforming growth factor- β concentrations and hemostatic risk factors for coronary heart disease in healthy subjects. *Am J Clin Res* 2002; 76:373-377.
 43. Ross RK, Yuan JM, Henderson BE, Park J, Gao YT, Yu MC. Prospective evaluation of dietary and other predictors of fatal stroke in Shanghai, China. *Circulation* 1997; 96:50-5.
 44. Trieu VN, Uckun FM. Genistein is neuroprotective in murine models of familial amyotrophic lateral sclerosis and stroke. *Biochem Biophys Res Commun* 1999; 258:685-8.
 45. Trieu VN, Dong Y, Zheng Y, Uckun FM. In vivo antioxidant activity of genistein in a murine model of singlet oxygen-induced cerebral stroke. *Radiat Res* 1999; 152:508-16.
 46. Makela S, Savolainen H, Aavik E, et al. Differentiation between vasculoprotective and uterotrophic effects of ligands with different binding affinities to estrogen receptors alpha and beta. *Proc Natl Acad Sci U S A* 1999; 96:7077-82.
 47. Wagner JD, Zhang L, Greaves KA, Shadoan MK, Schwenke DC. Soy protein reduces the arterial low-density lipoprotein (LDL) concentration and delivery of LDL cholesterol to the arteries of diabetic and nondiabetic male cynomolgus monkeys. *Metabolism* 2000; 49:1188-96.
 48. Rivas M, Garay RP, Escanero JF, Cia PJ, Cia P, Alda JO. Soy milk lowers blood pressure in men and women with mild to moderate essential hypertension. *J Nutr* 2002; 132:1900-1902.
 49. Burke V, Hodgson JM, Beilin LJ, Giangiulio N, Rogers P, Puddey IB. Dietary protein and soluble fiber reduce ambulatory blood pressure in treated hypertensives. *Hypertension* 2001; 38:821-6.
 50. Teede HJ, Dalais FS, Kotsopoulos D, Liang YL, Davis S, McGrath BP. Dietary soy has both beneficial and potentially adverse cardiovascular effects: a placebo-controlled study in men and postmenopausal women. *J Clin Endocrinol Metab* 2001; 86:3053-60.
 51. Weinberger J. Prevention of ischemic stroke. *Curr Cardiol Rep* 2002; 4:164-71.
 52. Cholesterol, diastolic blood pressure, and stroke: 13,000 strokes in 450,000 people in 45 prospective cohorts. Prospective studies collaboration. *Lancet* 1995; 346:1647-53.
 53. Washburn S, Burke GL, Morgan T, Anthony M. Effect of soy protein supplementation on serum lipoproteins, blood pressure, and menopausal symptoms in perimenopausal women. *Menopause* 1999; 6:7-13.
 54. al-Azzawi F, Wahab M. Estrogen and colon cancer: current issues. *Climacteric* 2002; 5:3-14.
 55. Grodstein F, Newcomb PA, Stampfer MJ. Postmenopausal hormone therapy and the risk of colorectal cancer: a review and meta-analysis. *Am J Med* 1999; 106:574-82.
 56. Bennink MR. Dietary soy reduces colon carcinogenesis in human and rats. *Adv Exp Med Biol* 2001; 492:11-7.
 57. Messina M, Bennink M. Soyfoods, isoflavones and risk of colonic cancer: a review of the in vitro and in vivo data. *Baillieres Clin Endocrinol Metab* 1998; 12:707-28.
 58. Rao CV, Wang CX, Simi B, et al. Enhancement of experimental colon cancer by genistein. *Cancer Res* 1997; 57:3717-22.
 59. Farhan H, Cross HS. Genistein action in prostate cancer cells. In: Pfannhauser W, Fenwick GR, Khokhar S, eds. *Biologically-active Phytochemicals in Food. Analysis, Metabolism, Bioavailability and Function*. Cambridge: The Royal Society of Chemistry, 2001:28-31.
 60. Grady D, Cummings SR. Postmenopausal hormone therapy for prevention of fractures: how good is the evidence? *Jama* 2001; 285:2909-10.
 61. Arjmandi BH, Smith BJ. Soy isoflavones' osteoprotective role in postmenopausal women: mechanism of action. *J Nutr Biochem* 2002; 13:130-137.
 62. Thompson DD, Simmons HA, Pirie CM, Ke HZ. FDA guidelines and animal models for osteoporosis. *Bone* 1998; 17:125S-133S.
 63. Messina M, Gugger ET, Alekel DL. Soy protein, soybean isoflavones, and bone health: a review of the animal and human data. In: Wildman R, ed. *Handbook of Nutraceuticals and Functional Foods: CRC Press LLC*, 2001:77-98.
 64. Morabito N, Crisafulli A, Vergara C, et al. Effects of genistein and hormone-replacement therapy on bone loss in early postmenopausal women: a randomized double-blind placebo-controlled study. *J Bone Miner Res* 2002; 17:1904-12.
 65. Spence LA, Lipscomb ER, Cadogan J, Martin BR, Peacock M, Weaver CM. Effects of soy isoflavones on calcium metabolism in postmenopausal women. *Journal of Nutrition* 2002; 132:581S.
 66. Breslau NA, Brinkley L, Hill KD, Pak CY. Relationship of animal protein-rich diet to kidney stone formation and calcium metabolism. *J Clin Endocrinol Metab* 1988; 66:140-6.
 67. Anderson JJB, Thomsen K, Christiansen C. High protein meals, insular hormones and urinary calcium excretion in human subjects. In: Christiansen C, Johansen JS, Riis BJ, eds. *Osteoporosis*. Viborg, Denmark: Nørhaven A/S, 1987:240-245.
 68. Heaney RP. Nutrient interactions and the calcium economy. *J Lab Clin Med* 1994; 124:15-16.
 69. Nordin BC. Calcium requirement is a sliding scale. *Am J Clin Nutr* 2000; 71:1381-3.

Research Updates

1. Anderson JJ, Chen X, Boass A, et al. Soy isoflavones: no effects on bone mineral content and bone mineral density in healthy, menstruating young adult women after one year. *J Am Coll Nutr* 2002; 21:388-93.
2. Morabito N, Crisafulli A, Vergara C, et al. Effects of genistein and hormone-replacement therapy on bone loss in early postmenopausal women: a randomized double-blind placebo-controlled study. *J Bone Miner Res* 2002; 17:1904-12.