Research Updates

By Mark Messina, Ph.D.

There is much interest in the skeletal benefits of isoflavones and 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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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.

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

Breast Cancer

Breast cancer risk was increased by 26 percent in the WHI. 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. 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, increased breast and mammary 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. 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. Finally, the most telling observation may be that thus far, no increase in
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, 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. 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, 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. Breast tissue density appears to be a reasonably good indicator of breast cancer risk as agents that increase risk increase density and visa versa. 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.

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. Venous Thromboembolic Disease (VTED) and Stroke

Risks of deep vein thrombosis and pulmonary embolism in the WHI were increased approximately two-fold 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, possibly as a result of estrogen altering hepatic production or metabolism of coagulation factors. 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.

Likely Effects of Soy

As noted previously, there are no indications that soy increases clot formation or adversely affects coagulation and fibrinolytic factors 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. 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. There is also some clinical research indicating soy protein reduces blood pressure, a risk factor for stroke.

Colorectal Cancer

CECEPT decreased colorectal cancer risk in the WHI by 37 percent. 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.

Likely Effects of Soy

The evidence that soy reduces colon cancer risk is somewhat mixed with the epidemiologic data being the least supportive. 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. 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

Results From WHI

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

Source: Jama 2002; 288:321-33
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.
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

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

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

Research Updates (Continued from Page 1)

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.

Women’s Health Initiative Puts Spotlight On Soy (Continued from Page 4)

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.55-67 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.58-69

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 FOR THIS ISSUE

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

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47. Wagner JD, Zhang L, Greaves KA, Shaloo AN, Schwenke DC. Soy protein reduces the arterial low-density lipoprotein (LDL) concentration and delivery of LDL cholesterol to the arteries of diabetic and non-diabetic male cynomolgus monkeys. Metabolism 2000; 49:1188-96.


