Ther Adv Musculoskel Dis
(2011) 3(6) 293–300
DOI: 10.1177/
1759720X11417749

Soy foods: are they useful for optimal bone health?

Amy J. Lanou

Abstract: Numerous studies have investigated the relationship between soy foods, soy protein, or isoflavone extracts and markers of bone health and osteoporosis prevention, and have come to conflicting conclusions. Research on dietary patterns, rather than on specific food ingredients or individual foods, may offer an opportunity for better understanding the role of soy foods in bone health. Evidence is reviewed regarding the question of whether soy foods contribute to a dietary pattern in humans that supports and promotes bone health. Soy foods are associated with improved markers of bone health and improved outcomes, especially among Asian women. Although the optimal amounts and types of soy foods needed to support bone health are not yet clear, dietary pattern evidence suggests that regular consumption of soy foods is likely to be useful for optimal bone health as an integral part of a dietary pattern that is built largely from whole plant foods.

Keywords: plant-based, fracture risk, dietary patterns

Correspondence to:
Amy J. Lanou
University of North Carolina Asheville, Department of Health and Wellness, One University Heights, Asheville, NC 28804, USA
alanou@unca.edu

Introduction

Soy foods contain varying levels of various types of isoflavones known to be weak plant-based estrogenic compounds or phytoestrogens. Because estrogen is protective of bone, postmenopausal estrogen decline is linked with bone loss. Until the last decade, one of the main treatments for postmenopausal bone loss was hormone replacement therapy. Concerns about the negative health impacts of long-term hormone replacement therapy have stimulated interest in alternative treatments and osteoporosis prevention methods. To this end, numerous studies have investigated the relationship between soy foods, soy protein, or isoflavone extracts and markers of bone health and osteoporosis prevention.

Several recent reviews have specifically addressed whether soy isoflavones as part of soy foods or as extracts of soy beans are useful for the prevention or management of bone loss [Zhang, 2009; Atmaca *et al*. 2008; Poulsen and Kruger, 2008], while others have addressed this question as part reviews of the broader potential health effects of soy foods and soy isoflavones [Messina *et al*. 2009; Lampe, 2009; Tempfer *et al*. 2007]. Messina and colleagues sum up the general findings of such reviews with the conclusion that although some studies show strong benefits for bone, 'overall the data are quite mixed' [Messina *et al*. 2009]. The most positive conclusion comes from Atmaca and colleagues who note that most clinical studies with postmenopausal women indicate a positive effect of soy on markers of bone turnover and bone mineral density. However, they conclude that information is not complete enough to warrant recommendations for treatment [Atmaca *et al*. 2008].

All the reviewers indicate that further research is needed to better understand the relationship of soy foods to bone health, and that a number of factors are impeding clear interpretation of the results. The two most comprehensive reviews offer differences in study design, type of isoflavone or soy food preparation utilized, estrogen status of the participants, and other dietary factors as key limitations on our understanding of the meaning of the results of this body of work [Poulsen and Kruger, 2008; Atmaca *et al*. 2008]. An additional important consideration is the bone health endpoints studied. No randomized controlled trials have been undertaken to document the effect of soy foods or soy isoflavones on fracture risk. Instead, all the trials have documented bone mineral density or bone mineral content and/or markers of bone turnover

[Tempfer *et al.* 2007]. In addition, evidence suggests bacterial metabolism of soy isoflavones in the human gut varies among individuals and could impact the efficacy of soy foods across individuals [Lampe, 2009].

Perhaps part of the problem with synthesizing and interpreting these results is a lack of clarity about what the active ingredient might be. Human intervention studies have hypothesized the active ingredients to be individual isoflavones (e.g. genistein, daidzein), soy protein, or both. However, it is possible that the impact of diet on bone health may be more closely related to overall dietary pattern (the sum of a wide number of dietary choices) than to any particular food or active ingredient in a food [Jacobs *et al.* 2009]. The purpose of this paper is to weigh the current evidence regarding the question of whether soy foods contribute to a dietary pattern in humans that supports and promotes bone health.

Cross-sectional studies

Observational studies addressing the relationship between soy foods and bone health generally report a beneficial effect of soy foods on markers of bone health among Asian women [Ho *et al.* 2003; Greendale *et al.* 2002; Mei *et al.* 2001; Horiuchi *et al.* 2000]. Soy food intake has been associated with higher bone mineral density (BMD) in Chinese postmenopausal but not premenopausal women [Mei *et al.* 2001], and positively with BMD in early postmenopausal women [Ho *et al.* 2003]. In a study with postmenopausal Japanese women, soy food intake was positively associated with BMD and negatively associated with bone resorption [Horiuchi *et al.* 2000]. In one study of women living in the USA, soy foods intake was positively associated with BMD in Japanese but not Chinese women [Greendale *et al.* 2002].

Cross-sectional studies showing no significant benefit of soy foods have generally been conducted in populations with much lower mean soy food intakes, as typically found in the USA and Europe [Kritz-Silverstein and Goodman-Gruen, 2002; Greendale *et al.* 2002]. One study with 208 postmenopausal White women in the USA found no significant associations between isoflavone intake and BMD and bone turnover markers. However, after adjustment for covariates, trends toward significant differences in one marker of bone resorption (N-Tx, $p = 0.09$) and BMD at the spine ($p = 0.07$) were observed [Kritz-Silverstein and Goodman-Gruen, 2002]. In a second US study, median intakes of genistein by African–Americans and Whites in the USA were too low to pursue relational analyses [Greendale *et al.* 2002].

In a review article Zhang notes that in the studies in Asian populations, the soy foods listed in the food frequency questionnaires are consumed as a normal part of the diet, and typically include traditional soy foods such as fermented soy bean curd, soybean milk, fresh bean curd, fried bean curd puff, and soybeans [Zhang *et al.* 2008]. By contrast, the US non-Asian populations are more likely to be consuming soy as a vegetarian meat alternative, as soy protein powders and bars, or as soy milk and some other traditional soy foods. In the human intervention studies, even those focused on soy foods rather than isoflavone preparations are likely to be using more processed forms of soy such as soy protein powder, soy protein food, isoflavone rich soy, etc. [Zhang *et al.* 2008].

Prospective studies

Soy foods and fracture risk

Two prospective longitudinal studies have investigated the relationship between soy food intake and fracture risk in Chinese populations. Both found a reduction in fracture risk for Chinese women [Koh *et al.* 2009; Zhang *et al.* 2005], but a similar result was not observed in Chinese men [Koh *et al.* 2009]. In the Shanghai Women's Health Study, the 24,403 postmenopausal women followed for 4.5 years had 1770 incident fractures (of any type other than fingers, toes, skull, or face). Soy food intake was assessed at baseline and during follow up using a validated food frequency questionnaire at personal interviews. The relative risk of fracture across quintiles of soy food intake were 1.00, 0.72, 0.69, 0.64, and 0.63 ($p < 0.001$ for trend) after adjustment of major risk factors of osteoporosis, age, socioeconomic status, and other dietary factors. The strongest reduction in risk between the highest and lowest quintiles of soy food intake for women within 10 years of menopause was 0.52, compared with 0.71 for late postmenopausal women. Similar results were noted for soy isoflavone consumption [Zhang *et al.* 2005].

In the Singapore Chinese Health Study, 63,257 men and women were followed for 7.7 years.

During this time 276 incident hip fractures were observed in men and 692 in women. Soy food intake was measured at baseline using a food frequency questionnaire. Women in the lowest quartile of soy food intake consumed <49.4 g/day of tofu equivalents, <2.7 g/day of soy protein, and <5.8 mg/1000 kcal/day of isoflavones. Compared with these women, those in the second through fourth quartiles of intake exhibited 21–36% reductions in risk (all $p < 0.036$). No association with soy food intake was found in men [Koh *et al.* 2009].

Soy foods and markers of bone health

Soy protein intake was found to be a positive predictor of total body bone mineral content in the Hong Kong Osteoporosis Study. In this 30-month prospective study, 265 premenopausal and perimenopausal Chinese women had bone mass, body composition, and lifestyle factors measured at baseline, 9, 18, and 30 months after entry into the study. The strongest determinant of bone change was menopausal status. Annual bone losses of about 0.5%, 2–2.5%, and 1.5% were observed among premenopausal, perimenopausal, and postmenopausal women, respectively. In multiple regression analysis, soy protein intake (Q1 < 1.07 g/day to Q4 5.72 g/day), maintenance of body weight, and time spent walking were significant positive predictors of total body bone mineral content [Ho *et al.* 2008]. The authors noted that, interestingly, ‘while dietary calcium intake did not seem to play an important role in the prevention of bone loss in perimenopausal women, dietary soy intake may have a protective effect on preserving total BMD’ [Ho *et al.* 2008].

Two prospective studies in younger individuals have demonstrated a positive association between soy foods and measures of bone health [Song *et al.* 2008; Hirota *et al.* 2005]. In a study in 34 young Korean women (aged 20–26 years), BMD was measured three times and dietary intake was assessed up to eight times by 24-hour food recall over 2 years. On average, the participants experienced an increase in BMD and consumed on average 39 g of soybeans and 8 mg of isoflavones daily. Soybean and total isoflavone intake was positively correlated with increases in BMD of the femur in this population [Song *et al.* 2008]. In a study investigating the relationship between changes in diet and bone accrual, bone status (using quantitative ultrasound) was followed over 5 years in 548 Japanese children aged 10–11 years. Annual increase in bone status was associated with increased intake of soy foods in girls. Increased intake of vegetables, fish, and milk products was associated with annual increase in bone status in boys and girls [Hirota *et al.* 2005].

Clinical trials

Soy isoflavones and markers of bone health

Numerous studies have investigated the relationship between one or more isolated soy isoflavones and markers of bone health. Presented here are the conflicting results from the two longest-term studies reported to date [Alekel *et al.* 2010; Atteritano *et al.* 2009; Messina *et al.* 2009; Marini *et al.* 2007] and the results of several meta-analyses addressing this topic [Taku *et al.* 2010; Liu *et al.* 2009; Ma *et al.* 2008a, 2008b]. In the Soy Isoflavones for Reducing Bone Loss Study, a double-blind randomized controlled trial, 224 healthy postmenopausal women were treated with placebo or 80 or 120 mg/day isoflavones for 36 months. All participants received 500 mg calcium and 600 IU vitamin D_3 daily and had BMD declines of the spine, femur, neck, and whole body. In both intent-to-treat and compliant analyses, the results did not show a bone-sparing effect of extracted soy isoflavones [Alekel *et al.* 2010].

These results are in contrast to the findings of a study conducted at three medical centers in Italy. The trial was originally designed to last 2 years. In it, 389 postmenopausal osteopenic women, who were otherwise healthy, were randomly assigned to either placebo plus calcium and vitamin D or 54 mg/day genistein plus calcium and vitamin D. In this study, genistein treatment prevented bone loss and improved quantitative ultrasound parameters [Atteritano *et al.* 2009; Marini *et al.* 2007]. In a 1 year continuation with the 138 women who agreed to continue, spinal and hip BMD increased by approximately 8% and 9%, respectively, in the treated group ($n = 71$) while BMD decreased at those sites by 12% and 8%, respectively, in controls ($n = 67$) [Messina *et al.* 2009]. Because the findings are so dramatically different between these two trials, researchers are trying to understand which factors in experimental design or study populations might account for these discrepancies. One possible explanation is the difference in isoflavone preparations; perhaps genistein is more effective than mixed isoflavone supplements [Messina *et al.* 2009].

Similarly, recent meta-analyses of data on BMD from the randomized controlled trials came to contradictory conclusions. In one that included 10 randomized controlled trials with a total of 896 women, which lasted at least 1 year and had a mean dose of soy isoflavones of 87 mg per day, treatment did not significantly affect BMD changes in the hip or the spine [Liu *et al.* 2009]. In the other, also a meta-analysis of 10 trials, in a total of 608 women consuming between 4.4 and 150 mg soy isoflavones per day for at least 3 months, the authors found that isoflavone intervention significantly attenuated bone loss of the spine in menopausal women, as measured by BMD or bone mineral content. Stronger effects were seen with isoflavone doses of >90 mg/day and for treatment durations of 6 months or longer [Ma *et al.* 2008a].

Two other meta-analyses studied the impact of isoflavone intervention on markers of bone resorption and bone formation. In one analysis, which included nine studies in a total of 432 women, the authors found that even at doses <90 mg/day and with shorter (<12 week) interventions that isoflavone treatment significantly inhibited bone resorption and stimulated bone formation [Ma *et al.* 2008b]. In the other study, the effects of soy isoflavones on urinary deoxypyridinoline (10 studies, 887 participants), serum bone alkaline phosphatase (10 studies, 1210 participants), and serum osteocalcin (8 studies, 380 participants) were analyzed. The authors found a modest decrease in deoxypyridinoline, a bone resorption marker, but no effect on either bone alkaline phosphatase or osteocalcin, bone formation markers [Taku *et al.* 2010].

So what is the bottom line?

Why are the results of the randomized controlled trials so mixed when the observational studies seem quite clear? Differences in study design are likely to explain some of the variations in the results of the randomized controlled trials. The studies varied in length (from 4 to 24 months), they utilized different types of 'active ingredient' (mixed isoflavone extracts, genistein extracts, soy protein powder, or soy milk, sometimes enriched with additional soy isoflavones) at different dosages of isoflavones (e.g. 4.4 mg/day to 118 mg/day) and participants were male, female or both (though most studies had female participants), and among women, menopausal status varied (though most studies were in postmenopausal women).

In addition, the race, ethnicity, culture and dietary norms varied across the observational and randomized controlled trials [Liu *et al.* 2009; Ma *et al.* 2008a, 2008b]. In particular, the results linking soy foods to bone health outcomes in observational studies (cross-sectional and longitudinal) were largely seen with Asian populations in China, Japan, or the USA. In these populations, much of the soy eaten comes from traditional soy foods, whole soybeans, soy milk, fresh bean curd, and fermented bean curd and other fermented soy foods [Zhang *et al.* 2008]. In the observational US studies, the soy was largely consumed as soy milk, soy-based vegetarian meat substitutes, tofu, soy sauce, soy-based protein powders, and miso soup. In the US studies, the Asian–American participants were more likely to have a higher intake of soy isoflavones than participants from other racial or ethnic backgrounds [Greendale *et al.* 2002].

Furthermore, it is not known whether physical activity levels differed among these populations in such a way as to be able to explain the differences in soy food or soy isoflavone associations with markers of bone health. The study that directly compared race and ethnicity subgroups did control for physical activity levels within population groups, but soy food intake was not high enough to do a relational analysis in the African–American and White population groups, so between-group comparisons were not possible [Greendale *et al.* 2002].

In the observational studies, dietary patterns rich in isoflavone-containing foods did tend to have positive associations with markers of bone health [Koh *et al.* 2009; Song *et al.* 2008; Ho *et al.* 2008, 2003; Hirota *et al.* 2005; Zhang *et al.* 2005; Greendale *et al.* 2002; Mei *et al.* 2001; Horiuchi *et al.* 2000]. In clear contrast, most of the 25 or more human trials have been conducted using soy extracts (isoflavone supplements) rather than soy foods [Messina, 2008]. For purposes of standardization and reducing treatment bias, researchers designed the controlled trials using some form of soy extract, and many of these studies (even with more stringent controls to help reduce noise due to variations in source, dose, etc.) did not find a link between soy isoflavones and markers of bone health. These divergent results raise several questions and possible alternative explanations. Are soy isoflavones the 'active ingredient'? If so, do these compounds need to be combined with other substances in soy foods to exert their beneficial effects? Or is there something about a dietary pattern that is rich in soy foods that supports bone health (rather than a specific component in soy foods)?

Researching dietary patterns

Observational studies have limitations. Cross-sectional studies in which populations or groups are compared at one point in time are especially limited in that a causal relationship, a change over time, and the magnitude of the impact cannot be determined. Often, the best use of cross-sectional studies is for hypothesis development (i.e. determining what questions might be useful to address with other types of studies). The longitudinal prospective studies share some of these same limitations.

However, some of the limitations of observational studies may also be benefits. Many common chronic diseases have multifactorial causes and develop over a long period of time, often a decade or more. Osteoporosis is a case in point. Many factors, such as activity level, a variety of dietary constituents, medication use, other health conditions, other lifestyle choices, as well as environmental factors in an individual's life over time, are likely to impact that person's risk of hip fracture. Participants in longitudinal prospective studies are living their lives with only limited interference from researchers. This, of course, creates noise (variation) in the data that makes it more difficult to draw conclusions, but the conclusions drawn are more likely to be applicable to people in real-life situations.

In longitudinal prospective studies, researchers often try to draw conclusions about specific nutrients, behaviors, or dietary patterns and the risk of some disease or condition by categorizing individuals into strata based on estimating a particular behavior (e.g. consumption of soy foods). Estimations, for example, of dietary isoflavone intake, are often calculated from assessment tools that also have limitations. For example, food frequency questionnaires may only be given once or twice over a 2–10 year study. Isoflavone intake is calculated from a food frequency questionnaire by including some foods known to be rich in isoflavones on a long list of possible foods a person might consume (typically 100+), and asking participants to estimate how often they eat each food over a week, month or year. Then the isoflavone intake is estimated from the usual amounts of isoflavones in the servings of those foods consumed in a month or year. Of course, it would be easy to miss foods (protein bars, protein powders in smoothies in the USA for example) or dietary supplements containing isoflavones on a food frequency questionnaire. Of course, the way an individual might fill out a food frequency questionnaire is likely to vary to at least some degree with season, year, current activity level, and other life factors.

These limitations would make it more difficult to see an effect of a particular dietary or lifestyle factor on the outcome of interest, making it all the more interesting when it does happen. In an observational study, researchers can never completely separate the factor of interest from the person's life. This means that even with very good assessment tools and strong statistical techniques to reduce bias, the factor in question (soy food or isoflavone intake) can only be said to be relevant in the context of the dietary and lifestyle patterns of the groups of people studied. But this may be a good thing. Perhaps the most useful information about the use of nutrients for health is that which is embedded in people's lives as they are actually lived.

David R. Jacobs has written eloquently on the need to shift our thinking about nutritional research towards the study of dietary patterns. He states: 'The evidence for health benefit appears stronger when foods are put together in a synergistic dietary pattern than for individual foods or food constituents.' [Jacobs *et al.* 2009]. And in trying to make sense of the contradictory finding from the Nurse's Health Study and the Women's Health Trial, that dietary fat intake is not linked to cancer risk, T. Colin Campbell, explains the problem with what he calls 'reductionistic' science: 'As long as scientists study highly isolated chemicals and food components, and take the information out of context to make sweeping assumptions about complex diet and disease relationships, confusion will result.' [Campbell and Campbell, 2004].

Robust findings from longitudinal prospective studies, well-designed ecological studies and the results of clinical trials addressing dietary patterns offer support for a dietary pattern approach. The few clinical trials that have been done looking at dietary patterns have shown some very strong support for this concept. In the DASH Diet (Dietary Approaches to Stop Hypertension), blood pressure was lowered with a dietary pattern high in fruits and vegetables, containing low-fat dairy products, and limited in meat, total fat and saturated fat compared with a control diet [Appel *et al*. 1997]. Similarly, low-fat, vegetarian, or vegan dietary patterns have been shown to reverse markers of coronary heart disease [Esselstyn, 1999; Ornish *et al*. 1998], diabetes [Barnard *et al*. 2009], and postmenopausal overweight [Turner-McGrievy *et al*. 2007], and to slow prostate cancer progression [Frattaroli *et al*. 2008; Ornish *et al*. 2005]. In a study in which the dietary pattern was optimized for cholesterol reduction, a low-fat vegetarian diet that included soy protein, soluble fiber, plant sterols, and almonds was found to be as effective for lowering cholesterol as a statin drug [Jenkins *et al*. 2006, 2002].

Research on soy isoflavones indicates that overall dietary patterns may be more important to bone health and fracture risk reduction than the individual factors – soy isoflavones – alone. Other reports on diet and bone health support the view that dietary pattern may be more important to supporting bone health than any particular nutrient or active ingredient. For example, a dietary pattern rich in fruits and vegetables has been positively associated with markers of bone health [New, 2003] while dietary pattern research also indicates that calcium consumed via food or supplements neither reduces fracture risk [Warensjö *et al*. 2011; Bischoff-Ferrari *et al*. 2011; 2007; Jackson *et al*. 2006] nor improves bone health in children [Winzenberg *et al*. 2006; Lanou *et al*. 2005]. These studies provide evidence that neither dairy products nor supplemental calcium to the levels of the US recommended daily allowances are necessary for osteoporosis risk reduction or optimal bone health.

Perhaps most importantly for the question of whether soy foods are beneficial to bone is the body of research showing that diets high in animal protein are associated with higher fracture rates than those high in protein from plant sources [Sellmeyer *et al*. 2001; Frassetto *et al*. 2000; Abelow *et al*. 1992]. Soy foods intake may indirectly enhance bone strength by replacing animal protein in the diet. Research has shown that diets high in animal protein increase calcium excretion [Barzel and Massey, 1998] and that soy protein intake decreases calcium excretion in comparison with meat and dairy protein [Zemel, 1988]. These studies indicate that plant-based dietary patterns support bone health. Soy foods are a useful plant-based source of dietary protein and may be consumed at higher levels in plant-based eating styles.

Conclusion

Although more research is needed to understand fully the optimal dietary pattern for supporting bone health across the lifespan, some bone-supporting dietary patterns are clear. A bone-building diet is high in fruits and vegetables, contains a high ratio of plant to animal protein (i.e. a diet low in or devoid of animal products), is built from whole foods, and is nutrient rich so as to provide the myriad nutrients important to bone. Soy foods are associated with improved markers of bone health and improved outcomes (especially among Asian women). Although optimal amounts and types of soy foods needed to support bone health are not yet clear, dietary pattern evidence suggests that regular consumption of soy foods is likely to be useful for optimal bone health as an integral part of a dietary pattern that is built largely from whole plant foods.

With more dietary pattern research scientists may be able to determine whether soy foods benefit bone because of their active ingredients or simply because they may be associated with (or are an integral part of) dietary patterns that are supportive of bone health. Additional dietary pattern research (especially longitudinal prospective trials and clinical trials with appropriate controls) comparing bone health outcomes by focusing on comparing traditional with contemporary soy foods, whole foods with more highly processed foods, the amount of animal *versus* plant foods, and traditional plant-based diets with contemporary plant-based diets is needed. This will help clarify the role of soy foods in bone health and fully characterize the optimal dietary pattern(s) for supporting bone health and osteoporosis prevention.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflicts of interest

The author declares no conflicts of interest in preparing this article.

References

Abelow, B.J., Holford, T.R. and Insogna, K.L. (1992) Cross-cultural association between dietary animal protein and hip fracture: a hypothesis. *Calcif Tissue Int* 50: 14–18.

Alekel, D.L., Van Loan, M.D., Koehler, K.J., Hanson, L.M., Stewart, J.W., Hanson, K.B. *et al.* (2010) The Soy Isoflavones for Reducing Bone Loss (SIRBL) Study: a 3-y randomized controlled trial in postmenopausal women. *Am J Clin Nutr* 91: 218–230.

Appel, L.J., Moore, T.J., Obarzanek, E., Vollmer, W.M., Svetkey, L.P., Sacks, F.M. *et al.* (1997) A clinical trial of the effects of dietary patterns on blood pressure. DASH Collaborative Research Group. *N Engl J Med* 336: 1117–1124.

Atmaca, A., Kleerekoper, M., Bayraktar, M. and Kucuk, O. (2008) Soy isoflavones in the management of postmenopausal osteoporosis. *Menopause* 15: 748–757.

Atteritano, M., Mazzaferro, S., Frisina, A., Cannata, M.L., Bitto, A., D'Anna, R. *et al.* (2009) Genistein effects on quantitative ultrasound parameters and bone mineral density in osteopenic postmenopausal women. *Osteoporos Int* 20: 1947–1954.

Barnard, N.D., Cohen, J., Jenkins, D.J., Turner-McGrievy, G., Gloede, L., Green, A. *et al.* (2009) A low-fat vegan diet and a conventional diabetes diet in the treatment of type 2 diabetes: a randomized, controlled, 74-wk clinical trial. *Am J Clin Nutr* 89: 1588S–1596S.

Barzel, U.S. and Massey, L.K. (1998) Excess dietary protein can adversely affect bone. *J Nutr* 128: 1051–1053.

Bischoff-Ferrari, H.A., Dawson-Hughes, B., Baron, J.A., Burckhardt, P., Li, R., Spiegelman, D. *et al.* (2007) Calcium intake and hip fracture risk in men and women: a meta-analysis of prospective cohort studies and randomized controlled trials. *Am J Clin Nutr* 86: 1780–1790.

Bischoff-Ferrari, H.A., Dawson-Hughes, B., Baron, J.A., Kanis, J.A., Orav, E.J., Staehelin, H.B. *et al.* (2011) Milk intake and risk of hip fracture in men and women: A meta-analysis of prospective cohort studies. *J Bone Miner Res* 26: 833–839.

Campbell, T.C. and Campbell, T.M. (2004) *The China Study: Startling Implications for Diet, Weight Loss, and Long-term Health*, BenBella Books: Dallas, TX, p. 286.

Esselstyn Jr, C.B. (1999) Updating a 12-year experience with arrest and reversal therapy for coronary heart disease (an overdue requiem for palliative cardiology). *Am J Cardiol* 84: 339–341, A8.

Frassetto, L.A., Todd, K.M., Morris Jr, R.C. and Sebastian, A. (2000) Worldwide incidence of hip fracture in elderly women: relation to consumption of animal and vegetable foods. *J Gerontol A Biol Sci Med Sci* 55: M585–M592.

Frattaroli, J., Weidner, G., Dnistrian, A.M., Kemp, C., Daubenmier, J.J., Marlin, R.O. *et al.* (2008) Clinical events in prostate cancer lifestyle trial: results from two years of follow-up. *Urology* 72: 1319–1323.

Greendale, G.A., FitzGerald, G., Huang, M.H., Sternfeld, B., Gold, E., Seeman, T. *et al.* (2002) Dietary soy isoflavones and bone mineral density: results from the study of women's health across the nation. *Am J Epidemiol* 155: 746–754.

Hirota, T., Kusu, T. and Hirota, K. (2005) Improvement of nutrition stimulated bone mineral gain in Japanese school children and adolescents. *Osteoporos Int* 16: 1057–1064.

Ho, S.C., Chan, S.G., Yip, Y.B., Chan, C.S.Y., Woo, J.L.F. and Sham, A. (2008) Change in bone mineral density and its determinants in pre- and perimenopausal Chinese women: the Hong Kong perimenopausal women osteoporosis study. *Osteoporosis Int* 19: 1785–1796.

Ho, S.C., Woo, J., Lam, S., Chen, Y., Sham, A. and Lau, J. (2003) Soy protein consumption and bone mass in early postmenopausal Chinese women. *Osteoporosis Int* 14: 835–842.

Horiuchi, T., Onouchi, T., Takahashi, M., Ito, H. and Orimo, H. (2000) Effect of soy protein on bone metabolism in postmenopausal Japanese women. *Osteoporos Int* 11: 721–724.

Jackson, R.D., LaCroix, A.Z., Gass, M., Wallace, R.B., Robbins, J., Lewis, C.E. *et al.* (2006) Calcium plus vitamin D supplementation and the risk of fractures. *N Engl J Med* 354: 670–683.

Jacobs, D.R., Gross, M.D. and Tapsell, L.C. (2009) Food synergy: an operational concept for understanding nutrition. *Am J Clin Nutr* 89: 1543S–1548S.

Jenkins, D.J., Kendall, C.W., Faulkner, D.A., Nguyen, T., Kemp, T., Marchie, A. *et al.* (2006) Assessment of the longer-term effects of a dietary portfolio of cholesterol-lowering foods in hypercholesterolemia. *Am J Clin Nutr* 83: 582–591.

Jenkins, D.J., Kendall, C.W., Faulkner, D., Vidgen, E., Trautwein, E.A., Parker, T.L. *et al.* (2002) A dietary portfolio approach to cholesterol reduction: combined effects of plant sterols, vegetable proteins, and viscous fibers in hypercholesterolemia. *Metabolism* 51: 1596–1604.

Koh, W.P., Wu, A.H., Wang, R., Ang, L.W., Heng, D., Yuan, J.M. *et al.* (2009) Gender-specific associations between soy and risk of hip fracture in the Singapore Chinese Health Study. *Am J Epidemiol* 170: 901–909.

Kritz-Silverstein, D. and Goodman-Gruen, D.L. (2002) Usual dietary isoflavone intake, bone mineral density, and bone mineral metabolism in postmenopausal women. *J Womens Health Gend Based Med* 11: 69–78.

Lampe, J.W. (2009) Is equol the key to the efficacy of soy foods?. *Am J Clin Nutr* 89: 1664S–1667S.

Lanou, A.J., Berkow, S.E. and Barnard, N.D. (2005) Calcium, dairy products and bone health in children and young adults: A reevaluation of the evidence. *Pediatrics* 115: 736–743.

Liu, J., Ho, S.C., Su, Y., Chen, W., Cai-xia, Z. and Dhen, Y. (2009) Effect of long-term intervention of soy isoflavones on bone mineral density in women: A meta-analysis of randomized controlled trials. *Bone* 44: 948–953.

Ma, D.F., Qin, L.Q., Wang, P.Y. and Katoh, R. (2008a) Soy isoflavone intake increases bone mineral density in the spine of menopausal women: Meta-analysis of randomized controlled trials. *Clin Nutr* 27: 57–64.

Ma, D.F., Qin, L.Q., Wang, P.Y. and Katoh, R. (2008b) Soy isoflavone inhibits bone resorption and stimulates bone formation in menopausal women: meta-analysis of randomized controlled trials. *Eur J Clin Nutr* 62: 155–161.

Marini, H., Minutoli, L., Polito, F., Bitto, A., Altavilla, D., Atteritano, M. *et al.* (2007) Effects of the phytoestrogen genistein on bone metabolism in osteopenic postmenopausal women: a randomized trial. *Ann Intern Med* 146: 839–847.

Mei, J., Yeung, S.S.C. and Kung, A.W.C. (2001) High dietary phytoestrogen intake is associated with higher bone mineral density in postmenopausal but not premenopausal women. *J Clin Endocrinol Metab* 86: 5217–5221.

Messina, M., Watanabe, S. and Setchell, K.D.R. (2009) Report of the 8th International Symposium on the Role of Soy in Health Promotion and Chronic Disease Prevention and Treatment. *J Nutr* 139: 796S–802S.

New, S.A. (2003) Intake of fruit and vegetables: implications for bone health. *Proc Nutr Soc* 62: 889–899.

Ornish, D., Scherwitz, L.W., Billings, J.H., Brown, S.E., Gould, K.L., Merritt, T.A. *et al.* (1998) Intensive lifestyle changes for the reversal of coronary heart disease. *JAMA* 280: 2001–2007.

Ornish, D., Weidner, G., Fair, W.R., Marlin, R., Pettengill, E.B., Raisin, C.J. *et al.* (2005) Intensive lifestyle changes may affect the progression of prostate cancer. *J Urol* 174: 1065–1069, , discussion 1069–1070.

Poulsen, R.C. and Kruger, M. (2008) Soy phytoestrogens: impact on postmenopausal bone loss and mechanism of action. *Nutr Rev* 66: 359–374.

Sellmeyer, D.E., Stone, K.L., Sebastian, A. and Cummings, S.R. (2001) A high ratio of dietary animal to vegetable protein increases the rate of bone loss and the risk of fracture in postmenopausal women. Study of Osteoporotic Fractures Research Group. *Am J Clin Nutr* 73: 118–122.

Song, Y.J., Paik, H.Y. and Joung, H. (2008) Soybean and soy isoflavone intake indicate a positive change in bone mineral density for 2 years in young Korean women. *Nutr Res* 28: 25–30.

Taku, K., Melby, M.K., Kurzer, M.S., Mizuno, S., Watanabe, S. and Ishimi, Y. (2010) Effects of soy isoflavone supplements on bone turnover markers in menopausal women: a systematic review and meta-analysis of randomized controlled trials. *Bone* 47: 413–423.

Tempfer, C.B., Bentz, E.K., Leodolter, S., Tscherne, G., Reuss, F., Cross, H.S. *et al.* (2007) Phytoestrogens in clinical practice: a review of the literature. *Fertil Steril* 87: 1243–1249.

Turner-McGrievy, G.M., Barnard, N.D. and Scialli, A.R. (2007) A two-year randomized weight loss trial comparing a vegan diet to a more moderate low-fat diet. *Obesity (Silver Spring)* 15: 2276–2281.

Warensjö, E., Byberg, L., Melhus, H.K., Gedeborg, R., Mallmin, H., Wolk, A. *et al.* (2011) Dietary calcium intake and risk of fracture and osteoporosis: prospective longitudinal cohort study. *BMJ* 342: d1473.

Winzenberg, T., Shaw, K., Fryer, J. and Jones, G. (2006) Effects of calcium supplementation on bone density in healthy children: meta-analysis of randomised controlled trials. *BMJ* 333: 775.

Zemel, M.B. (1988) Calcium utilization: effect of varying level and source of dietary protein. *Am J Clin Nutr* 48(3 Suppl): 880–883.

Zhang, X., Shu, X.O., Li, H., Yang, G., Li, Q., Gao, Y.T. *et al.* (2005) Prospective cohort study of soy food consumption and risk of bone fracture among postmenopausal women. *Arch Intern Med* 165: 1890–1895.

Zhang, Y., Chen, W.F., Lai, W.P. and Wong, M.S. (2008) Soy isoflavones and their bone protective effects. *Inflammopharmacology* 16: 213–215.