Medifast. CHOOSE HEALTH

The Bottom Line...
Soy and Health

For The Healthcare Provider

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INTRODUCTION

Medifast is committed to maximizing health and wellness through it's provision of soy-based meal replacement weight control programs. In light of recent controversy, including books, slanting soy, Medifast feels it is their duty to provide the latest evidence-based recommendations regarding the use of dietary soy for healthcare providers. The following document provides a comprehensive summary of the latest scientific information regarding soy and its relationship with all-cause mortality, cardiovascular disease, metabolic syndrome, cancer, menopause, bone health, and kidney function, as well as addresses any safety concerns regarding soy.

IMPORTANCE OF (SOY) PROTEIN DURING DIETING

Medifast's soy-based meal replacements provide a healthy way of achieving the optimal amount of dietary protein crucial for weight loss while still preserving lean muscle mass. In addition to preserving calorie-burning lean muscle tissue, dietary protein stimulates thermogenesis more than carbohydrates or fats and is the most satiating macronutrient. Soy protein is a healthy alternative to animal-based proteins that tend to be high in fat and saturated fat. Both human and animal studies have demonstrated a favorable effect of soy protein on body weight and fat distribution. In a 12-week study comparing soy protein meal replacements to milk-based protein meal replacements as part of a low energy diet, soy MRs were associated with greater weight loss (Anderson & Hoie, 2005).

Importantly, soy protein has been shown to yield numerous health-related benefits for conditions that overweight individuals are more likely to suffer from. Soy may protect against a range of conditions including cardiovascular disease to cancer and to reductions in overall mortality.

NOT ALL SOY PROTEIN IS CREATED EQUAL

Medifast's soy-based meal replacements are made from isolated soy protein (Solae Brand™), with its naturally-occuring isoflavones (genistein, daidzein, and glycitein) working together to yield health benefits. An innovative water-based technique is used to separate carbohydrate and fat from the soy protein while maintaining healthy isoflavones. Other processing methods, like alcohol-extraction methods, remove a substantial amount of isoflavones and its anti-atherogenic properties (Clair & Anthony, 2005).

Soy is a complete protein whose quality is similar to that of meat, milk, and eggs. Using the FDA-recommended method of qualifying a protein, **Protein Efficiency Digestibility-Corrected Amino Acid Score (PDCAAS)**, Medifast's soy protein (Solae Brand™), has the highest obtainable score (1.0). In addition to high digestibility, it contains all essential amino acids, including methionine and arginine.

BOTTOM LINE: Medifast meal replacements are made from the highest quality soy protein with the highest levels of naturally-occuring isoflavones.

HEALTH BENEFITS

All-Cause Mortality

Japan has the highest life expectancy in the world (Health and Welfare Statistics Association, 1999). Soy is a staple in the Japanese diet. The Takayama Study prospectively examined the relationship between soy intake and mortality among over 13,000 Japanese men and 15, 000 Japanese women residents over a 7 year period. They determined that the average total intake of soy per day for men was 102.3g (44.6mg isoflavones) and for women 93.3g (41.4mg isoflavones). (Negata, Takatsuka, Shimizu, 2002).

FINDINGS:

- A significant inverse association between soy intake (and isoflavone intake) with all-cause mortality for men and women after controlling for age and total energy intake.
- After adjusting for nondietary factors, a decreased risk of death was observed among men (0.83, 95%CI 0.68 to 1.01) and women (0.83, 95%CI 0.68 to 1.02) with the highest compared with the lowest quintile of total soy product intake.

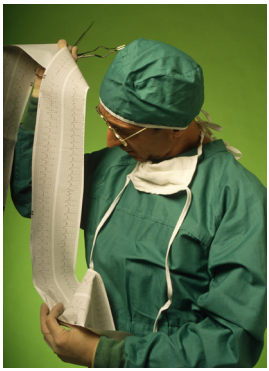
BOTTOM LINE: Soy is inversely associated with all-cause mortality.

Cardiovascular Disease

Soy's isoflavones, genistein and diadzein, protect the heart by boosting the activity of LDL receptors that remove 'bad' cholesterol from the bloodstream. Additional ways soy may protect the heart are through its antioxidant, anti-inflammatory, and potentially anti-thrombogenic properties (Clair & Anthony, 2005). Randomized controlled trials have also shown that soy decreases homocysteine levels in both men and women (generally postmenopausal) (Gehm et al., 1997; Kostelac, Rechkemmer, & Briviba, 2003).

The **Soy Health Claim** issued by the FDA in 1999 arose from 27 studies demonstrating soy protein's utlity in lowering levels of total cholesterol and low-density lipoprotein (LDL, or "bad" cholesterol). To qualify for the claim foods must contain per serving:

- 6.25 grams of soy protein
- low fat (less than 3 grams)
- low saturated fat (less than 1 gram)
- low cholesterol (less than 20 milligrams)
- sodium value of less than 480 milligrams for individual foods, less than 720 milligrams if considered a main dish, and less than 960 milligrams if considered a meal.



Thirty-three of Medifast's meal replacements meet the criteria to carry this health claim.

Seven years after soy's health claim was first issued by the FDA, extensive research has been done to substantiate the original claim. In 2006, Reynolds et al. performed a meta-analysis of 41 randomized controlled trials that evaluated the effect of soy protein supplementation, as the only intervention, on serum lipids. They found that soy protein supplementation was associated with:

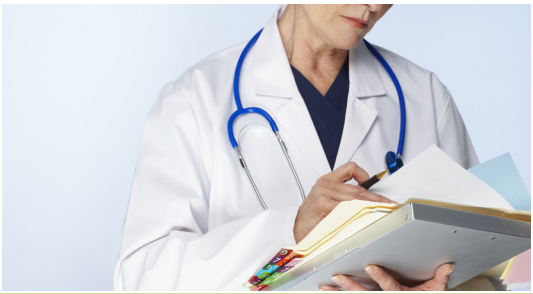
- A significant decrease in mean total cholesterol of more than 5 mg/dl (95% CI -7.14 to -3.38).
- A significant decrease in low density lipoprotein (LDL) cholesterol of more than 4 mg/dl (95% CI -6.00 to -2.50).
- A significant decrease in triglycerides of more than 6 mg/dl (95% CI -9.14 to -3.38).
- A significant increase in high density lipoprotein (HDL) cholesterol of 0.77 mg/dl (95% CI 0.2 to 1.34).

BOTTOM LINE: Soy protein protects against coronary risk factors and 33 of Medifast's meal replacements carry the Heart Healthy Claim.

Metabolic Syndrome

The metabolic syndrome is characterized by a clustering of cardiovascular risk factors, including abdominal obesity, dyslipidemia, increased blood pressure, insulin resistance, and a proinflammatory state (Borgman & McErlean, 2006). Metabolic syndrome is widespread among adults from developed nations and its prevalence continues to rise as rates of obesity do. While causes are not yet fully understood, genetic, metabolic, and environmental factors, like diet, are thought to play a role.

Both animal and human studies have demonstrated that the inclusion of soy protein in the diet is protective against metabolic syndrome (Lukaczer et al., 2006; Davis et al., 2005; Azadbakht et al. 2007). Significant reductions in insulin, fasting plasma glucose, and C-peptide have all been observed among postmenopausal women with metabolic syndrome on a diet incorporating 102 mg/d of soy isoflavones. Thus, it appears that soy foods improve insulin sensitivity and modulate the metabolic abnormalities linked with insulin resistance (Jayagopal et al., 2002).



BOTTOM LINE: Soy may improve the metabolic abnormalities of metabolic syndrome.

Cancer

After cardiovascular disease, cancer is the second leading cause of morbidity and mortality in the United States. Soy protein is associated with a reduced risk of certain cancers. The evidence of a protective effect for soy is particularly strong in cancers of the prostate, breast, and gastro-intestinal (GI) tract.

Prostate Cancer

Lung cancer is the biggest cancer killer among men. However, overweight men who fall into the heaviest weight category are also more likely to die from stomach or prostate cancer according to the American Obesity Association. When compared to Asian men, American men are far more likely to die from prostate cancer and have a death rate that is 18-fold higher than their Eastern counterparts (Jemal et al., 2002). Soy, a dietary staple, may confer the protective effect among Eastern Asian men as Asian men who have emigrated to the US and have adopted the Western diet have higher rates of prostate-related morbidity and mortality.

The mechanism of action may be an anti-androgen substance found in soy, equol, that is formed during digestion when the soy isoflavone, daidzein, is metabolized. In the body, equol inhibits the male hormone dihydrotestosterone (DHT) which normally stimulates prostatic growth. It has been shown that mice fed high doses of soy isoflavones have less prostate cell growth so may prevent prostate cancer. A 2005 meta-analysis of epidemiological studies by Yan & Spitznagel, evaluating the consumption of soy protein (non-fermented), showed that consuming soy protein was associated with a significantly lower risk of prostate cancer in men [Overall risk estimate 0.70 (95% CI=0.59-0.83, $p<0.001$)].

BOTTOM LINE: Men who consume soy may have lower rates of prostate cancer.

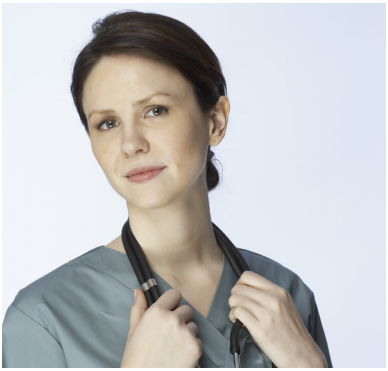
Breast Cancer

Breast cancer rates among women in Asian countries are substantially lower than rates among women in Western nations (Parkin, Muir, & Whelan, 1992). Specifically, the risk of acquiring breast cancer for Asian women is 39 per 100,000 (Fukuda et al., 2002), whereas the risk for Western women is 133 per 100,000 (Weir et al., 2003). Yet, when Asian women emigrate to the US, their rates of breast cancer increase substantially (Ziegler et al., 1993). Based on a meta-analysis, summarizing results from 18 epidemiologic studies, Trock, Hilakivi-Clarke, & Clarke (2006) concluded that a high dietary soy intake was associated with reduced breast cancer risk (odds ratio=0.86, 95%CI 0.75 to 0.99). This association was stronger among premenopausal women than post-menopausal women, and when evaluated in terms of grams per day of soy, a significant reduction was found only among premenopausal women (Trock, Hilakivi-Clarke, Clarke, 2006).

Position of the National Cancer Institute (NCI):

Several studies suggest dietary soy may reduce breast cancer risk and improve survival. The controversy, however, is over the use of soy, by breast cancer patients, especially those with estrogen receptor–positive tumors. The NCI reports the following:

- Research suggests soy's isoflavone's, genistein and daidzein, may act preventatively by binding to estrogen receptors and decreasing plasma estrogen levels.
- A review of the literature found no convincing data to support the claim that soy is either protective against breast cancer or harmful for women with a history of, or at high risk for, breast cancer.
- The Shanghai Breast Cancer Study, a follow-up study using data collected from a large cohort of breast cancer patients, concluded that soyfoods do not have an adverse effect on breast cancer survival.
- While the use of soyfoods, as part of a healthy diet and in moderate amounts, are safe to consume according to researchers, there is not enough evidence to recommend that breast cancer patients begin to consume soy specifically to prevent the reoccurrence of breast cancer.



Also according to the NCI:

•Animal studies have found that genistein inhibited the efficacy of tamoxifen, a drug used to block the body's circulating estrogen.

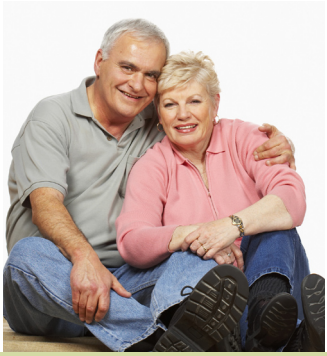
However, a 2007 study of soy's genistein and tamoxifen on prevention of estrogen-dependent breast cancer in mice showed a synergistic effect, especially at lower doses of tamoxifen, in delaying the growth of tumor cells via apoptosis and inhibition of tumor cell proliferation. They recommended that combination tamoxifen and genistein be investigated further for prevention and/or treatment of estrogen-dependent breast cancer (Mai, Blackburn, & Zhou, 2007).

BOTTOM LINE: Soy appears to have a protective effect against premenopausal breast cancer. The verdict is still out among postmenopausal females, or females with a past personal history or family history of breast cancer. The verdict is also still out regarding the use of soy and Tamoxifen. Medifast recommends that patients follow the NCI guidelines and the advice of their physician or breast cancer specialist.

GI Cancers

Five epidemiologic studies evaluating soy and stomach/esophageal/colorectal cancer showed that soy consumption is significantly associated with lower rates of stomach and esophageal cancers (Ji et al., 1998; Lee et al., 1995; Nagata et al., 2002; Ngoan et al., 2002; You et al., 1988). Soy consumption has also been associated with lower rates of Helicobactor pylori (H. Pylori), a risk factor for stomach cancer. A cross-sectional study by Shinchi et al. (1997) showed that cases of seropositive H. Pylori occurred less frequently among those who frequently ate soy products (tofu) than those who consumed soy products less often.

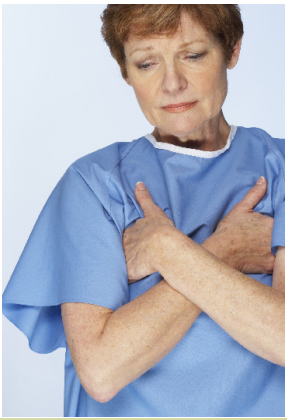
Numerous studies have also found a protective effect of soy against adenomatous polyps (Witte et al., 1996) and colon cancer (Hoshiyama et al., 1993; Nishi et al., 1997). Results of an intervention study showed that an intake of 39 g/d of soy protein for one year significantly reduced colon mucosa cell proliferation vs. 39 g/d of casein protein in "at-risk" patients with colon polyps or colon cancer (Bennink, 2001).



BOTTOM LINE: Soy appears to protect against cancers of the GI tract and may help eradicate H. Pylori infections.

Menopausal Symptoms

Approximately 2/3 of women who reach menopause develop vasomotor menopausal symptoms, primarily in the form of hot flashes and night sweats. Of 21 trials examining the effects of soy and/or its isoflavones effects on hot flashes and night sweats in post-menopausal women, every trial found a decrease in hot flash frequency compared to controls (Balk et al., 2005). Additionally, soy protein helps protect against some other menopause-associated features. A review by Geller & Studee (2006) suggest that soy isoflavones have a small but positive effect on lipids, bone mass, and cognitive function. A randomized, double-blinded, crossover, placebo-controlled trial found that post-menopausal women who received 60mg/day of soy isoflavones had improved cognitive performance and mood (Casini et al., 2006).



BOTTOM LINE: Soy helps with vasomotor symptoms of menopause and positively affects other menopause-related health conditions.

Bone Health

Post-menopausal women may experience rapid declines in bone mineral density (BMD) due to estrogen deficiency. Despite inconsistent results among randomized controlled trials evaluating soy and bone health, the results of numerous studies suggest that the isoflavones in soy may have benefical effects on markers of bone formation, (Arjmandi et al., 2005), bone resorption (Horiuchi et al., 2000), and bone loss (Alekel et al., 2000; Horiuchi et al., 2000). Soy isoflavone extract (54 mg genistein) has been shown to increase lumbar spine and femoral neck BMD after 1-year in postmenopausal women (Morabito et al., 2002). Soy milk with isoflavones has yielded small but significant increases in lumbar spine BMD in comparison to the soy milk without isoflavones (Lydeking-Olsen et al., 2004). Additionally, evidence from in vitro and in vivo, human observational, and dietary intervention studies suggest that diets rich in phytoestrogens have bone-sparing effects in the long term (Setchell & Lydeking-Olsen, 2003).

There are few long-term RCTs and a wide range of interventions used across studies making it difficult to draw conclusions about the effects of soy on bone outcomes. In addition to study design issues, the inconsistent results may be partly due to studies evaluating women in their post-menopausal years who would be less likely to benefit from phytoestrogens because of age-related declines in estrogen receptors on bone (Reinwald & Weaver, 2006). To reap the benefits of soy when it comes to bone health, it may be better to consume soy protein in the peri-menopausal or early post-menopausal years when the more mild estogenic effects of soy might be less opposed by endogenous estrogen, and before the age-related decline in estrogen receptor number occurs (Reinwald & Weaver, 2006).

SAFETY

BOTTOM LINE: There is evidence to suggest that soy confers a protective effect on bone. The benefits of soy on bone health may be garnered most during peri-menopause or early post-menopause.

Thyroid Function

One concern has been that soy protein may adversely affect thyroid function and may interfere with the absorption of synthetic thyroid hormone. A review of 14 clinical trials by Messina & Redmond (2006) that assessed the effects of soy on at least one measure of thyroid function, found that with only one exception, either no effects or only very modest changes were noted. Thus, they concluded that there is little evidence in euthyroid, iodine-replete individuals, that soy foods adversely affect thyroid function.

In contrast, some evidence suggests that soy foods, by inhibiting absorption, may increase the dose of thyroid hormone required by hypothyroid patients. Further, in some individuals who consume marginal amounts of iodine, soy foods may, at least theoretically, increase the risk of developing clinical hypothyroidism.

BOTTOM LINE: Soy has no adverse effects in euthyroid individuals. Individuals with hypothyroidism on synthetic thyroid hormones do not need to avoid soy in their diets. General guidelines are to consume soy meals three hours before or after taking thyroid hormones; closely monitor labs; and ensure adequate iodine is consumed.

Reproductive Function

There is no evidence in animal (Fagi et al., 2004; Cardoso & Bao, 2007) or human studies that the phytoestrogens in soy adversely affect child or adult growth, development, reproduction, or sexual behavior (Merritt & Jenks, 2004). Long-term feeding of high phytoestrogen-containing soy protein formulas in early life does not produce estrogen-like hormonal effects in children (Giampietro et al., 2004). Five studies in adults, before and after soy consumption, found no significant decrease in testosterone or follicle-stimulating hormone (FSH) levels among men and women, respectively (Balk et al., 2005). Twelve studies in pre-menopausal females found no significant effect on estradiol levels during the follicular phase (Balk et al., 2005).

NOTE: The NCI considers high testosterone levels a risk factor for prostate cancer. Soy may provide a slight, yet protective decrease in testosterone levels without affecting male sterility.

BOTTOM LINE: Soy does not alter sexual function, behavior, or affect sterility.

Kidney Stones

Some soy foods have a relatively high concentration of oxalate. This raises a concern for individuals with kidney stones of the calcium oxalate type. The oxalate content of the soy Medifast uses (Solae™) provides relatively small amounts of oxalate per serving. For example, a meal replacement containing 10g of protein would contain 0.9mg of oxalate. The American Dietetic Association (ADA) recommends limiting dietary oxalate intake to 10mg per day for individuals who are stone-formers. Consuming 5 Medifast meal replacements per day would still fall significantly beneath the ADA's cut-off value. Further, soy protein also contains phytates. Studies suggest that phytate is a potential inhibitor of calcium kidney stone formation because of it's antioxidant activity and ability to inhibit crystal formation (Al-Wahsh et al., 2005). The average phytate in Medifast's soy protein is 1.4%.

BOTTOM LINE: The amount of oxalate in 5 Medifast meal replacements, as part of the 5 & 1 diet plan, is well beneath the ADA's daily cut-off value for calcium oxalate stone-formers.

CONCLUDING REMARKS

For most people, the benefits of incorporating soy protein as part of a healthy diet plan far outweigh the potential (or hypothetical) risks. This is particularly true for overweight or obese individuals, who are more likely to suffer from a comorbidity that would be responsive to soy. Medifast is a pioneer in recognizing the dual benefit that can be potentially gained by offering the highest quality soy protein, rich in isoflavones, as part of their clinically-tested weight control program.

References:

Alekel DL, Germain AS, Peterson CT, Hanson KB, Stewart JW, Toda T. Isoflavone-rich soy protein isolate attenuates bone loss in the lumbar spine of perimenopausal women. Am J Clin Nutr 2000;72(3):844-852.

Arjmandi BH, Lucas EA, Khalil DA, et al. One year soy protein supplementation has positive effects on bone formation markers but not bone density in postmenopausal women. J Nutr 2005;4:8.

Azadbakht L, Kimiagar M, Mehrabi Y, Esmaillzadeh A, Padyab M, Hu FB, WW. Soy inclusion in the diet improves features of metabolic syndrome: a randomized crossover study in postmenopausal women. Am J Clin Nutr 2007;85(3):735-741.

Bennink MR. Dietary soy reduces colon carcinogenesis in human and rats. Adv Exp Med Biol 2001;492:11-17.

Borgman M, McErlean E. What is the metabolic syndrome? Prediabetes and cardiovascular risk. J Cardiovasc Nurs 2006;21(4):285-290.

Cardoso JR, Bao SN. Effects of chronic exposure to soy meal containing diet or soy derived isoflavones supplement on semen production and reproductive system of male rabbits. Anim Reprod Sci 2007;97(3-4):237-245.

Casini ML, Marelli G, Papaleo E, Ferrari A, D'Ambrosio F, Unfer V. Psychological assessment of the effects of treatment with phytoestrogens on postmenopausal women: a randomized, double-blind, crossover, placebo-controlled study. Fertil Steril 2006;85(4):972-978.

Clair RS, Anthony M. Soy, isoflavones and atherosclerosis. Handb Exp Pharmacol 2005;170:301-323.

Davis J, Steinle J, Higginbotham DA, Oitker J, Peterson RG, Banz WJ. Soy protein influences insulin sensitivity and cardiovascular risk in male lean SHHF rats. Horm Metab Res 2005;37(5):309-315.

Fagi AS, Johnson WD, Morrissey RL, McCormick DL. Reproductive toxicity assessment of chronic dietary exposure to soy isoflavones in male rats. Reprod Toxicol 2004;18(4):605-611.

Fukuda M, Miyamoto K, Hashizume R, et al. Breast Cancer. Gan To Kagaku Ryoho 2002;29:1900-1906.
Gehm BD, McAndrews JM, Chien PY, Jameson JL. Resveratrol, a polyphenolic compound found in grapes and wine, is an agonist for the estrogen receptor. Proc Natl Acad Sci USA 1997;94:14138-14143.

Geller SE, Studee L. Soy and red clover for mid-life and aging. Climacteric 2006;9(4):245-263.

Giampietro PG, Bruno G, Furcolo G, Casati A, Brunetti E, Spadoni GL, Galli E. Soy protein formulas in children: no hormonal effects in long-term feeding. J Pediatr Endocrinol Metab 2004;17(2):191-196.

Health and Welfare Statistics Association. Life table. (In Japanese). J Health Welfare Stat 1999;46:73.

Horiuchi T, Onouchi T, Takahashi M, Ito H, Orimo H. Effect of soy protein on bone metabolism in postmenopausal Japanese women. Osteoporosis Int 2000;11(8):721-724.

Hoshiyama Y, Sekine T, Sasaba T. A case-control study of colorectal cancer and its relation to diet, cigarettes, and alcohol consumption in Saitama Prefecture, Japan. Tohoku J Exp Med 1993;171:153-165.

Jayagopal V, Albertzaai P, Kilpatrick ES, et al. Beneficial effects of soy phytoestrogen intake in postmenopausal women with type 2 diabetes. Diabetes Care 2002;25:1709.

Jemal A, Thomas A, Murray T, Thun M. Cancer statistics. Cancer J for Clinician 2002;52:23-47.

Ji BT, Chow WH, Yang G, et al. Dietary habits and stomach cancer in Shanghai, China. Int J Cancer 1998;76:659-664.

Kostelac D, Rechkemmer G, Briviba K. Phytoestrogens modulate binding response of estrogen receptors alpha and beta to the estrogen response element. J Mol Biol 2003;326:77-92.

Lee JK, Park BJ, Yoo KY, Ahn YO. Dietary factors and stomach cancer: a case-control study in Korea. Int J Epidemiol 1995;24:33-41.

Lukaczer D, Liska DJ, Lerman RH, Darland G, Schiltz B, Tripp M, Bland JS. Effect of a low glycemic index diet with soy protein and phytosterols on CVD risk factors in postmenopausal women. Nutrition 2006;22(2):104-113.

Lund TD, Munson DJ, Haldy ME, Setchell KDR, Lephart ED, Handa, RJ. Equol Is a Novel Anti-Androgen that Inhibits Prostate Growth and Hormone Feedback. Biol Reprod 2004;70:1188–1195.

Lydeking-Olsen E, Beck-Jensen JE, Setchell KD, Holme-Jensen T. Soymilk or progesterone for prevention of bone loss—a 2 year randomized, placebo-controlled trial. Eur J Nutr 2004;43(4):246-257.

Mai Z, Blackburn GL, Zhou JR. Soy phytochemicals synergistically enhance the preventive effect of tamoxifen on the growth of estrogen-dependent human breast carcinoma in mice. Carcinogenesis 2007;[Epub ahead of print].

Merritt RJ, Jenks BH. Safety of soy-based infant formulas containing isoflavones: the clinical evidence. J Nutr 2004;134(5):1220S-1224S.

Messina M, Redmond G. Effects of soy protein and soybean isoflavones on thyroid function in healthy adults and hypothyroid patients: a review of the relevant literature. Thyroid 2006;16(3):249-258.

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(10):1904-1912.

Nagata C, Takatsuka N, Kawakami N, Shimizu H. A prospective cohort study of soy product intake and stomach cancer death. Br J Cancer 2002;87:31-36.
Nagata C, Takatsuka N, Shimizu H. Soy and fish oil intake and mortality in a Japanese community. Am J Epidemiology 2002;156(9):824-831.

Ngoan LT, Mizoue T, Fujino Y, Tokui N, Yoshimura T. Dietary factors and stomach cancer mortality. Br J Cancer 2002;87:37-42.

Nishi M, Yoshida K, Hirata K, Miyake H. Eating habits and colorectal cancer. Oncol Report 1997;4:995-998.

Peterson G, Barnes S. Genistein inhibits both estrogen and growth factor-stimulated proliferation of human breast cancer cells. Cell Diff Growth 1996;7:1345-1351.

Reinwald S, Weaver CM. Soy isoflavones and bone health: A double-edged sword? J Nat Prod 2006;69:450-459.

Setchell KD, Lydeking-Olsen E. Dietary phytoestrogens and their effect on bone: evidence from in vitro and in vivo, human observational, and dietary intervention studies. Am J Clin Nutr 2003;78(3):593S-609S.

Shinchi K, Ishii H, Imanishi K, Kono S. Relationship of cigarette smoking, alcohol use, and dietary habits with Helicobacter pylori infection in Japanese men. Scand J Gastroenterol 1997;32:651-655.

Trock BJ, Hilakivi-Clarke L, Clarke R. Meta-Analysis of Soy Intake and Breast Cancer Risk. J Natl Cancer Res 2006;98(7):459-471.

Weir HK, Thun MJ, Hankey BF, et al. Annual report to the nation on the status of cancer, 1975-2000, featuring the uses of surveillance data for cancer prevention and control. J Natl Cancer Inst 2003;95:1276-1299.

Witte JS, Longnecker MP, Bird CL, Lee ER, Frankl HD, Haile RW. Relation of vegetable, fruit, and grain consumption to colorectal adenomatous polyps. Am J Epidemiol 1996;144:1015-1025.

Yan L, Spitznagel EL. Meta-analysis of soy food and risk of prostate cancer in men. Int J Cancer 2005;117(4):667-669.

You WC, Blot WJ, Chang YS, et al. Diet and high risk of stomach cancer in Shandong, China. Cancer Res 1988;48:3518-3523.

Ziegler RG, Hoover RN, Pike MC et al. Migration patterns and breast cancer risk in Asian-American women. J Natl Cancer Inst 1993;85:1819-1827.