Introduction

Soy foods have been a staple in several Asian diets for centuries. However, in recent years, soy has increasingly been incorporated into the Western diet as well. In the year 2000, as many as 27% of Americans reported consuming soy products at least once a week (1). A major contributor to soy's rise in popularity has been the perception that soy offers certain health benefits. Soy's cholesterol-lowering effects have led the American Heart Association to recommend that patients with hypercholesterolemia incorporate soy foods into their diets (2). Soy may also provide protective effects against the development of breast cancer, prostate cancer, and coronary artery disease; it may provide relief from menopausal symptoms as well (3). Besides this, as an excellent source of protein, soy is increasingly turned to as a viable alternative to animal protein for vegetarians (3).

Despite these seemingly excellent nutritional attributes of soy, scientists are cautious and warn that soy may not be as safe and healthy as consumers perceive it to be. While still debatable, soy may have contributed to reproductive health problems in several patients fed soy-based infant formula (4). Recently, concern over soy consumption has elevated again, this time in response to reports of adverse effects on the thyroid gland. Some studies have linked soy consumption and thyroid cancer (5). Still others implicate soy as a precipitating factor in goiter development and disruption of normal thyroid hormone levels (5). The objective of this paper is to examine recent studies to clarify the relationship between soy consumption and the thyroid gland.

Soy Isoflavones

While soy is rich in several vitamins and nutrients, its isoflavones are the most likely source of soy's presumed anti-thyroid actions. Isoflavones are a subtype of flavonoids, a group of nutraceuticals. The isoflavones predominant in soy are genistein (4,5,7-trihydroxyisoflavone) and daidzein (4,7-dihydroxyisoflavone). Isoflavones have a structure similar to estrogen and thus can bind to estrogen receptors, producing estrogen-like effects biologically (3). Recent research has found that soy isoflavones can also inhibit the activity of the enzyme thyroid peroxidase (TPO). TPO activity is essential for proper thyroid hormone synthesis - TPO catalyzes the iodination of tyrosyl residues on thyroglobulin and facilitates the subsequent coupling of iodotyrosyl residues (6). Experiments performed by Divi et al. demonstrated that genistein and daidzein negatively affect TPO activity in vitro, but the mechanism by which these compounds inhibit TPO depends on whether iodide ion is present in the environment (7). In the presence of iodide, genistein and daidzein act as alternate substrates for TPO, competitively inhibiting thyroglobulin from being iodinated and giving mono-, di-, and triiodoisoflavones instead. In contrast, when iodide is absent, the soy isoflavones cause irreversible inactivation of TPO by alteration of the heme group, through a pathway that is not yet understood (7). The prevailing notion in the scientific community is that the inhibition of TPO by soy isoflavones found in vitro likely occurs in vivo, explaining soy's disruption of normal thyroid activity in patients.

Goitrogenesis and Disruption of Normal Thyroid Hormone Levels

Beginning in the 1960s, reports began to emerge that soy consumption might elevate risk of goiter formation. For instance, infants fed soy formula were found to have increased incidence of goiters compared to those who were breastfed (8). More recently, a study on post-menopausal women determined that increased consumption of soy protein had the effect of increasing the

women's T4 and TSH levels (9). Attempts to explain these phenomena centered upon the inhibition of TPO caused by soy isoflavones: soy consumption could decrease T3 and T4 thyroid hormone synthesis. These decreased levels of thyroid hormones could then stimulate TSH secretion through the hypothalamo-pituitary-thyroid axis. The follicular cell hypertrophy induced by TSH could then lead to goiter formation (6). Therefore, soy exposure can cause an increase or decrease in thyroid hormone levels - since follicular cells are not all equally active, systemic hormone levels would depend on whether the specific follicular cells induced to proliferate by TSH happened to have high or low levels of activity (5,6). However, the biological actions of soy upon the thyroid appear to be much more complex than originally thought.

In a study done by Son et al., rats were fed diets enriched with either soy isoflavones or soy protein, both with and without iodine supplementation. Surprisingly, the soy isoflavones had no effect upon thyroid gland size or thyroid hormone levels. In contrast, whole soy protein increased both TSH and T4 levels in the rats. In addition, when soy protein was combined with an iodine-deficient diet, the rats developed goiters that were 75% larger than those achieved from iodine-deficiency alone (10). Consequently, soy isoflavone-induced inhibition of TPO may not be enough to explain the goitrogenic effects of soybeans. It appears that some additional substance in soy protein is required as well for the disruption of normal thyroid function. This additional, unknown substance is not contained in water-extracted soy protein concentrate, as the concentrate produced very similar results as did the soy isoflavones in the rats (10). This result has several practical, clinical applications. While most soy foods such as tofu and soy sauce do use whole soy protein, some protein powders contain soy protein concentrate instead and thus may not exert anti-thyroid actions. Therefore, susceptibility to soy-induced goitrogenesis and thyroid dysfunction may arise from certain soy foods but not others.

Another intriguing finding from this study is the fact that soy cannot single-handedly induce goitrogenesis; it needs to be combined with another goitrogenic risk factor, namely iodine deficiency. The researchers of this study concluded that the irreversible inactivation of TPO by soy isoflavones in an iodine-free environment may cause a greater biological effect than the competitive inhibition of TPO activity that occurs when iodide is present (10). However, it is important to note that the authors fed the rats a maximum of 20% soy protein (10). If more soy protein were consumed, it is possible that goitrogenesis might have been observed, independent of iodine deficiency. However, clinically speaking, these results indicate that at normal soy consumption levels, patients will not likely develop goiters unless some other pre-existing goitrogenic risk factor is also present, namely iodine deficiency. This notion may explain why goitrogenesis in infants dropped after soy formulas were supplemented with iodine (5).

However valuable animal studies like the Son study have been in elucidating soy effects on the thyroid, extrapolation from rats to humans is limited, especially since certain aspects of thyroid metabolism differ between the species. Rats lack thyroid-binding protein, so the biological half-life of thyroid hormones is very short in rats compared to humans (11). Consequently, rats' TSH levels increase much more markedly in response to goitrogens than human TSH levels do. Thus, rat thyroid glands may be more susceptible to the goitrogenic effects of soy than human thyroid glands. More research in human subjects is needed before true conclusions can be reached concerning soy and its effect on goitrogenesis.

Thyroid Cancer and Soy

Interest in the relation between soy consumption and thyroid cancer initiated when it was discovered that Southeast Asian men and women are nearly twice as likely to be diagnosed with thyroid cancer as other populations (12). Since it is widely recognized that Asians typically consume more soy than other populations, soy's possible carcinogenic effects were investigated. Animal studies seem to support the notion that soy is carcinogenic. A pivotal study performed by Kimura and his colleagues found that thyroid carcinoma can be induced in rats by feeding them an iodine-deficient diet fortified with 30% soy protein (13). The mechanism by which soy induces cancer was proposed to be very similar to that by which soy induces goiters. That is, the elevated levels of TSH that result from isoflavone-induced inhibition of TPO lead to increased follicular cell proliferation, which can ultimately lead to cancer. However, as with all these animal experiments, human thyroid metabolism does differ from that of rats, so extrapolation from animal studies may not be very accurate.

In contrast to the rat studies, the Bay Area Thyroid Cancer Study found soy to decrease thyroid cancer risk. This case-controlled study was conducted in the San Francisco Bay Area and compared women who had been diagnosed with thyroid cancer between the years 1992 to 1998 to controls matched for age and ethnicity. In all, 608 women with thyroid cancer and 558 controls were interviewed on a variety of topics. Included in the interviews were questions on dietary intake and estimations of portion size (14). Increased soy consumption was correlated with a 35-55% reduction in thyroid cancer risk (14,15). Many soy farmers and companies have heavily publicized this research conclusion in an effort to promote soy consumption as a preventive measure against thyroid cancer development. However, this research is certainly not conclusive. One of the major disadvantages of this study was the fact that it was retrospective: it relied upon the memory capabilities of the women in recalling how much and how frequently they had consumed soy in the past (14,15). Needless to say, this method was likely inaccurate, throwing doubt on the research conclusions made. Additional research is needed, especially a prospective clinical trial where the amount of soy consumed by subjects is controlled so accurate measures can be taken.

Conclusions

Soy does appear to have an effect upon the thyroid gland, but it remains to be seen how much of that effect can be observed clinically. Animal studies and retrospective human studies have shown that soy does increase risk of goitrogenesis and disruption of normal thyroid function. However, can the amount of soy in the normal diet cause these effects? Here, research is sparse. The typical Asian diet includes approximately 25-100 mg soy protein daily. Small-scale experiments have shown that small changes (about 6%) in thyroid hormone levels can occur in patients at doses of 128 mg soy/day (16). However, these changes were still within the normal range. As a result, it is highly unlikely that the average dietary intake of soy can significantly affect thyroid function and goitrogenesis.

However, there is a subgroup of the population for which soy intake may pose a more real risk of thyroid dysfunction: older women. Older women are very prone to thyroid conditions: up to 10% are hypothyroid (5). Soy products are increasingly marketed to this population group as a way to

curb menopausal symptoms, especially now that estrogen supplementation is discouraged. As a result, older women are more likely to consume large doses of soy in the form of soy nutritional supplements, "which are essentially unregulated products" (5). Hence, this population is more susceptible to soy-induced disruption of thyroid function. What may exacerbate this situation is when the women are hypertensive as well, as many older women are. In efforts to restrict their salt intake, these women may inadvertently limit their iodine intake because a large portion of dietary iodine arises from iodine-supplemented table salt. Their resultant iodine deficiency, though mild perhaps, along with their increased soy consumption put older women at risk for developing soy-induced goiters and thyroid dysfunction.

As for thyroid cancer, animal studies and retrospective human studies contradict one another: the latter claim soy increases thyroid cancer and the former claim soy decreases thyroid cancer. The animal studies are important in that they provide a way to study soy in a controlled, prospective manner that cannot be achieved in human studies. However, extrapolation from rats to humans is limited. Yet, the available human studies are retrospective and rely upon the inaccurate method of dietary recall to measure soy intake. More research is definitely needed, especially prospective clinical trials in which incidence of thyroid cancer and goiters can be measured as human subjects consume controlled amounts of soy. At present, it is likely safe to consume moderate levels of soy in the diet, but high doses of soy in the form of supplements should probably be avoided until more is known about soy's adverse effects on the thyroid gland.

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