Phytoestrogens and Thyroid Cancer Risk: The San Francisco Bay Area Thyroid Cancer Study

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Abstract
Epidemiological and pathological data suggest that thyroid cancer may well be an estrogen-dependent disease. The relationship between thyroid cancer risk and dietary phytoestrogens, which can have both estrogenic and antiestrogenic properties, has not been previously studied. We present data from a multiethnic population-based case-control study of thyroid cancer conducted in the San Francisco Bay Area. Of 817 cases diagnosed between 1995 and 1998 (1992 and 1998 for Asian women), 608 (74%) were interviewed. Of 793 controls identified through random-digit dialing, 558 (70%) were interviewed. Phytoestrogen consumption was assessed via a food-frequency questionnaire and a newly developed nutrient database. The consumption of traditional and nontraditional soy-based foods and alfalfa sprouts were associated with reduced risk of thyroid cancer. Consumption of "western" foods with added soy flour or soy protein did not affect risk. Of the seven specific phytoestrogenic compounds examined, the isoflavones, daidzein and genistein [odds ratio (OR), 0.70; 95% confidence interval (CI), 0.44 –1.1; and OR, 0.65, 95% CI, 0.41–1.0, for the highest versus lowest quintile of daidzein and genistein, respectively] and the lignan, secoisolariciresinol (OR, 0.56; 95% CI, 0.35–0.89, for the highest versus lowest quintile) were most strongly associated with risk reduction. Findings were similar for white and Asian women and for pre- and postmenopausal women. Our findings suggest that thyroid cancer prevention via dietary modification of soy and/or phytoestrogen intake in other forms may be possible but warrants further research at this time.

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4 The abbreviations used are: OR, odds ratio; CI, confidence interval; FFQ, food-frequency questionnaire.

Introduction
Thyroid cancer is three times more common in women than men, with age-adjusted incidence rates of 6.5 and 2.5 per 100,000 per year, respectively, in California (1). It is, however, one of the five most common cancers occurring among young women (ages, 15–44) and among recent Asian immigrants to the United States (1–3). These observations suggest that female hormones and changeable life-style factors (e.g., dietary intake) may be important in thyroid carcinogenesis. To the extent that diet is involved in the etiology of thyroid cancer, its effects may be in part mediated through hormonal mechanisms.

Established risk factors for thyroid cancer include radiation to the head or neck, goiter and thyroid nodules, and a family history of proliferative thyroid disease (4–9). The influence of menstrual and reproductive factors on thyroid cancer risk is uncertain but the usual events measured in epidemiological studies (e.g., age at first birth) appear to play only a weak role (10, 11). Recently it has been shown that among parous women of reproductive age a recent pregnancy is associated with approximately a doubling in thyroid cancer risk (12). Because pregnancy is associated with elevations in both estrogen and thyroid hormone levels (13, 14), this finding provides support for the role of estrogens in thyroid carcinogenesis; as does the observation of estrogen receptors in normal and malignant thyroid tissue (15–17).

Phytoestrogens are estrogenic compounds found in plant foods or derived from plant precursors (18–20). In some tissues, however, phytoestrogens have antiestrogenic effects through competitive binding with estrogen receptors (but which, once bound, have a far weaker estrogenic potency than endogenous estrogens) or through their influence on hormone metabolism (resulting in a less estrogenic milieu; Refs. 18, 20–23). To date, the study of dietary intake and thyroid cancer risk has focused predominantly on the effects of fish and shellfish (often interpreted as proxy measures of iodine exposure) and on vegetables containing goitrogens, i.e., chemical substances that can cause hypothyroidism or hyperplasia of the thyroid gland (6–8, 24–27). The relationship between phytoestrogens and thyroid cancer risk has not been examined previously, with the exception of one hospital-based case-control study conducted in Japan, which reported no association between tofu intake (a major source of phytoestrogens) and thyroid cancer risk (OR, 1.4; 95% CI, 0.7–2.8, for the highest versus lowest level of consumption; Ref. 28). Dietary data collected as part of a population-based case-control study conducted in the ethnically and culturally diverse San Francisco

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Bay Area was examined to determine whether phytoestrogen exposure was associated with thyroid cancer risk.

Materials and Methods

The design and methods used in this population-based case-control study have been described previously (7). Briefly, all of the participants were women between the ages of 20 and 74; residents of one of the five counties comprising the area; spoke sufficient English, Spanish, Tagalog, Cantonese, Mandarin, or Vietnamese to complete the interview; and had no prior history of thyroid cancer. Cases were identified through the Greater Bay Area Cancer Registry, a population-based cancer registry that is part of the Surveillance, Epidemiology, and End Results (SEER) program and the California Cancer Registry. All of the women diagnosed with thyroid cancer between June 1, 1995 and May 31, 1998 (June 1, 1992 and May 31, 1998 for Asian women) were eligible as cases. Of the 817 cases identified, 608 (13%) were interviewed, 106 (13%) declined to participate, and 103 (13%) were not interviewed for other reasons.

Controls were identified through random-digit dialing and matched to cases on 5-year age group and broad racial/ethnic group (i.e., white, African American, Latina, Asian, or Native American). Of the 793 eligible controls selected, 558 (70%) were interviewed, 154 (19%) declined to participate, and 81 (10%) were not interviewed for other reasons.

In-person interviews were conducted using a standardized structured questionnaire that included questions on a wide variety of topics (7). Dietary intake during the year before diagnosis or interview for cases and controls, respectively, was assessed using a FFQ designed to capture the diverse diet of the Bay Area population. Portion size was determined using visual aids. Our nutrient database is based on the work of Dr. Gladys Block (29) and updated from other sources, including the United State Department of Agriculture (USDA) databases. To quantify the intake of seven specific phytoestrogenic compounds, we used the nutrient database that we had developed for the assessment of phytoestrogen intake via FFQs (30). The seven compounds examined represent three classes of phytoestrogens found in plant foods: the isoflavones: genistein, daidzein, biochanin A, and formononetin; the coumestan: coumestrol; and the lignans: matairesinol and secoisolariciresinol.

ORs and 95% CIs were estimated using unconditional logistic regression analyses, controlling as appropriate for age (at diagnosis for cases and at selection for controls), race/ethnicity, daily caloric intake, history of goiter or thyroid nodules diagnosed more than 2 years before the cancer diagnosis (for cases) or the date of selection (for controls), history of radiation to the head or neck more than 5 years before diagnosis/selection, and family history of proliferative thyroid disease (i.e., thyroid cancer, goiter, or thyroid nodules), age at menarche, ever use of oral contraceptives, age at first full-term pregnancy/nulliparity (allowing for separate effects for women <45 and ≥45 years of age), and a composite variable including menopausal status and number of pregnancies in the last 5 years among premenopausal women (31, 32). Dietary analyses excluded 18 (3%) cases and 14 (3%) controls who substantially over- or underreported their intake, i.e., reported a usual diet that consisted of more than 5000 or less than 600 calories per day.

Results

As illustrated in Table 1, interviewed cases and controls were similar with respect to age, menopausal status, and race/ethnicity. Seventy-two percent of participants were under age 50 and 70% were premenopausal. Fifty-one percent of participants were white, 35% Asian, and 14% of other race/ethnic background. Despite a slightly lower average caloric intake, controls consumed on average a diet higher in plant-derived nutrients, particularly antioxidant vitamins, than did cases.

Genistein accounted for 51% of total phytoestrogen consumption in this population, daidzein for 42%, other isoflavones for 1%, coumestrol for 4%, and the lignans for 2%. The primary sources of phytoestrogens were tofu (47%), soy milk (22%), and foods that often contain added soy flour or soy protein (e.g., doughnuts, white bread, and canned tuna; 15%). The associations between these and related foods are presented in Table 2. In general, a reduction in thyroid cancer risk of 35 to 55% was associated with increased consumption of nonfermented traditional and nontraditional soy-based foods and sprouts. Consumption of foods with added soy flour or soy protein was not associated with risk.

Table 3 presents the associations between the seven specific phytoestrogenic compounds studied and total isoflavones, total lignans, and total phytoestrogens consumed. Increased consumption of four of the seven specific phytoestrogenic compounds as well as the three summary measures were associated with reduced risk of thyroid cancer in minimally adjusted...
Table 2  Consumption of selected phytoestrogen-rich foods and thyroid cancer risk among women participating in the Bay Area Thyroid Cancer Study  

<table>
<thead>
<tr>
<th>Food (g/day)</th>
<th>Cases</th>
<th>Controls</th>
<th>OR&lt;sup&gt;a&lt;/sup&gt;</th>
<th>95% CI</th>
<th>OR&lt;sup&gt;b&lt;/sup&gt;</th>
<th>95% CI</th>
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<td>0.80</td>
<td>0.53-1.2</td>
<td>0.84</td>
<td>0.55-1.3</td>
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<td>0.1-3.9</td>
<td>149</td>
<td>132</td>
<td>1.3</td>
<td>0.94-1.9</td>
<td>1.3</td>
<td>0.88-1.8</td>
</tr>
<tr>
<td>4.0-9.9</td>
<td>203</td>
<td>165</td>
<td>1.4</td>
<td>1.0-2.0</td>
<td>1.5</td>
<td>1.0-2.1</td>
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<tr>
<td>10.0-29.9</td>
<td>68</td>
<td>59</td>
<td>1.3</td>
<td>0.86-2.1</td>
<td>1.3</td>
<td>0.82-2.1</td>
</tr>
<tr>
<td>≥30.0</td>
<td>56</td>
<td>58</td>
<td>1.1</td>
<td>0.69-1.7</td>
<td>1.1</td>
<td>0.70-1.8</td>
</tr>
</tbody>
</table>

<sup>a</sup> Adjusted for age, race/ethnicity, and daily caloric intake.
<sup>b</sup> Adjusted for age, race/ethnicity, daily caloric intake, goiter or thyroid nodules, radiation to the head or neck, and family history of proliferative thyroid disease.
<sup>c</sup> Among Asian women only.
### Table 3  Phytoestrogen consumption and thyroid cancer risk among women participating in the Bay Area Thyroid Cancer Study

<table>
<thead>
<tr>
<th>Phytoestrogen (µg/day)</th>
<th>Cases</th>
<th>Controls</th>
<th>OR (95% CI)</th>
<th>OR (95% CI)</th>
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<tbody>
<tr>
<td><strong>Isoflavones</strong></td>
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<tr>
<td>Genistein</td>
<td></td>
<td></td>
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<tr>
<td>&lt;525</td>
<td>106</td>
<td>108</td>
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<td>1.0</td>
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<td>525.887</td>
<td>145</td>
<td>109</td>
<td>1.3</td>
<td>0.89-1.9</td>
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<tr>
<td>888.147</td>
<td>135</td>
<td>109</td>
<td>1.1</td>
<td>0.77-1.7</td>
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<td>1472.3680</td>
<td>121</td>
<td>109</td>
<td>0.97</td>
<td>0.65-1.4</td>
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<tr>
<td>83</td>
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<td>0.65</td>
<td>0.42-1.0</td>
<td>0.70</td>
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<td>Trend across quintiles</td>
<td>P = 0.02</td>
<td>0.98</td>
<td>0.97-0.99</td>
<td>0.98</td>
</tr>
<tr>
<td>Per 500 µg/day</td>
<td></td>
<td></td>
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<tr>
<td>Daidzein</td>
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<td></td>
</tr>
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<td>109</td>
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<td>0.77-1.6</td>
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<td>0.78-1.7</td>
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<td>131</td>
<td>109</td>
<td>0.92</td>
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<tr>
<td>3597</td>
<td>79</td>
<td>109</td>
<td>0.60</td>
<td>0.39-0.92</td>
</tr>
<tr>
<td>Trend across quintiles</td>
<td>P = 0.02</td>
<td>0.97</td>
<td>0.96-0.99</td>
<td>0.97</td>
</tr>
<tr>
<td>Per 500 µg/day</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biochanin A</td>
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<td>12-20</td>
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<td>0.69-1.5</td>
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<tr>
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<td>0.82</td>
<td>0.55-1.2</td>
</tr>
<tr>
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<td>144</td>
<td>109</td>
<td>1.2</td>
<td>0.78-1.7</td>
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<tr>
<td>Trend across quintiles</td>
<td>P = 0.78</td>
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<td>0.96-0.99</td>
<td>0.97</td>
</tr>
<tr>
<td>Per 10 µg/day</td>
<td></td>
<td></td>
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<tr>
<td>Formononetin</td>
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<td>1.0</td>
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<tr>
<td>10-18</td>
<td>124</td>
<td>109</td>
<td>0.85</td>
<td>0.59-1.2</td>
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<tr>
<td>19-28</td>
<td>111</td>
<td>109</td>
<td>0.76</td>
<td>0.53-1.1</td>
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<tr>
<td>29-51</td>
<td>115</td>
<td>109</td>
<td>0.77</td>
<td>0.53-1.1</td>
</tr>
<tr>
<td>≥52</td>
<td>102</td>
<td>109</td>
<td>0.65</td>
<td>0.44-0.96</td>
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<tr>
<td>Trend across quintiles</td>
<td>P = 0.03</td>
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<td>0.94-0.99</td>
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<tr>
<td>Per 1000 µg/day</td>
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<td>Coumestans</td>
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<tr>
<td>8.13-123.1</td>
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<td>0.87</td>
<td>0.69-1.3</td>
</tr>
<tr>
<td>123.2-167.7</td>
<td>101</td>
<td>109</td>
<td>0.76</td>
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<tr>
<td>167.8-270.4</td>
<td>154</td>
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<td>0.78-1.7</td>
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<tr>
<td>≥270.5</td>
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<td>109</td>
<td>0.73</td>
<td>0.48-1.1</td>
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<td>Trend across quintiles</td>
<td>P = 0.56</td>
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<tr>
<td>Per 50 µg/day</td>
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<tr>
<td>Lignans</td>
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<tr>
<td>Matairesinol</td>
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<td>&lt;18</td>
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<td>108</td>
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<td>1.0</td>
</tr>
<tr>
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<td>0.87</td>
<td>0.60-1.3</td>
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<td>109</td>
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<td>39-56</td>
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<td>109</td>
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<td>115</td>
<td>109</td>
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<td>0.52-1.2</td>
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<tr>
<td>Trend across quintiles</td>
<td>P = 0.56</td>
<td>0.97</td>
<td>0.94-1.01</td>
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</tr>
<tr>
<td>Per 10 µg/day</td>
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<td>1.0</td>
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<td>109</td>
<td>0.73</td>
<td>0.50-1.1</td>
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<td>59-80</td>
<td>139</td>
<td>109</td>
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<td>0.58-1.2</td>
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<tr>
<td>81-106</td>
<td>101</td>
<td>109</td>
<td>0.57</td>
<td>0.38-0.85</td>
</tr>
<tr>
<td>≥107</td>
<td>93</td>
<td>109</td>
<td>0.47</td>
<td>0.31-0.73</td>
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<tr>
<td>Trend across quintiles</td>
<td>P = 0.0005</td>
<td>0.87</td>
<td>0.80-0.94</td>
<td>0.89</td>
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</tbody>
</table>
models [i.e., those adjusted for matching variables (age and race/ethnicity) and daily caloric intake]. Adjusting simultaneously for a variety of established thyroid cancer risk factors and menstrual and reproductive events important in this population did not affect the observed patterns to any major extent, with the slight attenuation in the estimates and increased width of the CIs most likely reflecting diminished statistical power rather than strong confounding effects. Similar findings were observed for both white and Asian women (Table 4) and for both pre- and postmenopausal women; the associations for the highest versus lowest quintile of total isoflavone consumption were 0.71 (95% CI, 0.42–1.2) and 0.63 (95% CI, 0.25–1.6) for pre- and postmenopausal women, respectively; and for total lignan consumption were 0.61 (95% CI, 0.36–1.0) and 0.78 (95% CI, 0.29–2.1), respectively.

**Discussion**

In this population-based multiethnic study, we observed that thyroid cancer risk was reduced among women who consumed larger amounts of traditional and nontraditional soy-based foods (e.g., tofu and soy burgers) and soybean and alfalfa sprouts. Soy-based foods and soybeans are rich sources of the isoflavone genistein and daidzein, and alfalfa sprouts contain large amounts of the isoflavone formononetin. Indeed, these isoflavones as well as the lignan secoisolariciresinol were associated with reduced risk. Furthermore, these associations were observed among both white and Asian women and among pre- and postmenopausal women, although, as evidenced by the wide CIs, the number of women in some of these subgroups was small. Western foods containing added soy flour or soy protein (e.g., white bread and canned tuna) were not associated with risk. However, accurate measurement of the isoflavone content of these foods via a FFQ is less accurate (compared with soybean-based foods) because not all brands of these western foods contain soy.

To our knowledge, this is the first study to examine the effects of both soy-foods and specific phytoestrogenic compounds on the development of thyroid cancer in humans. The only previous study touching on this issue (28) found a small (40%), nonsignificant elevation in risk associated with tofu
consumption. In addition, soybeans have been associated with an increased risk of goiter. However, in our study, phytoestrogens (and tofu), like cruciferous vegetables, which are also goitrogenic, seem to decrease the risk of thyroid cancer. Cruciferous vegetables, isoflavones, and lignans have all been associated with increased levels of 2-hydroxyestrogens (or the ratio of 2:16α hydroxyestrogens), which is associated with an estrogenic milieu less favorable to the development of estrogen-dependent cancers (33–39). In many (but not all) animal studies, soy protein or isoflavones have been associated with an increase in the thyroid hormone thyroxine (T4); Refs. 40–42.

In a small study, thyroxine used to experimentally induce hyperthyroidism in young men, was associated with a statistically significant increase in 2-hydroxyestrone (43).

Two considerations should be noted in interpreting the findings from this study. First, phytoestrogen consumption was not a primary hypothesis of this study at the time at which the FFQ was designed. Thus, whereas many of the major sources of phytoestrogens were captured, a few were not, potentially resulting in the misclassification of exposure levels for some women. For example, garbanzo beans (the major source of biochanin A) and soybeans were not assessed separately from other beans, corn flakes (which contain added soy) were not assessed separately from other cereal, and dried apricots were not assessed separately from canned peaches; and regular (mung) bean sprouts, breakfast and power bars (containing added soy), raisins, prunes, and coffee were not assessed nor was Chinese black bean sauce (which is made from black soybeans) and may be an important source of isoflavones among Chinese women (44). Second, because of different estrogenic (and antiestrogenic) activity of the various compounds, total phytoestrogen intake as reported here as the sum of the various compounds may not be the most informative measure of biological exposure. A more complex measurement (e.g., one weighted by antiestrogenic activity) may have provided additional information. However, because such measures have not been developed or evaluated and given the consistency of findings for the major isoflavones and lignans, it is unlikely that the interpretation of our findings would materially change based on the weighted measurement.

In conclusion, our findings suggest the possibility that thyroid cancer risk may be modified by soy and phytoestrogen intake. However, given the lack of other data on this issue, additional research is needed in this area. In addition, because soybeans have been associated with the development of goiter and goiter is a major risk factor for thyroid cancer, some attention to the effects of the soy content of childhood and adolescent diet on thyroid cancer risk is warranted.

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References


Phytoestrogens and Thyroid Cancer Risk: The San Francisco Bay Area Thyroid Cancer Study

Pamela L. Horn-Ross, K. J. Hoggatt and Marion M. Lee


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