

HEALTH CLAIM PETITION:

Soy Protein and the Reduced Risk of Certain Cancers

Requested by
Solae, LLC

February 11, 2004

Office of Food Labeling
Center for Food Safety and Applied Nutrition
Food and Drug Administration (HFS-150)
200 C Street SW
Washington, D.C. 20204

**Re: Proposed Health Claim for Soy Protein Containing Products
and a Reduced Risk of Certain Cancers**

The undersigned, Solae, LLC, a Delaware Limited Liability company with offices in St. Louis, Missouri, submits this petition pursuant to Section 403(r)(4) of the Federal Food, Drug and Cosmetic Act (FFDCA) with respect to the relationship between soy protein and a reduced risk of some types of cancer. The data submitted as part of this petition, including epidemiological studies similar to those used to support previously authorized health claims for cancer risk reduction, establish that there is scientific agreement among experts qualified by scientific training and experience to evaluate such claims regarding the relationship between soy protein products and a reduced risk of certain cancers.

Attached hereto, and constituting part of this petition are the following:

A. Preliminary Requirements: Data establishing that soy protein-containing foods and ingredients conform to the requirements of 21 CFR 101.14(b) in that they are commonly consumed foods that are generally recognized as safe (GRAS) based on common use in food prior to 1958. FDA agreed that soy protein products were GRAS in the Final Rule on the health claim for soy protein and coronary heart disease (64 FR 57700).

B. Scientific Evidence: Data establishing that, based on the totality of publicly available scientific evidence (including evidence from well-designed studies conducted in a manner which is consistent with generally recognized scientific procedures and principles), significant scientific agreement exists among experts qualified by scientific training and experience that a strong association exists between the consumption of soy protein products and a reduced risk of certain cancers.

C. Analytical Data: Data establishing the amount of soy protein present in representative foods that qualify for the proposed health claim.

D. Model Health Claim: This petition contains the recommended text for possible model health claims.

E. Environmental Impact: Solae claims a categorical exclusion from the environmental assessment (EA) and environmental impact statements (EIS).

To the best of the knowledge of the undersigned, this petition is a representative and balanced submission that also includes unfavorable information for evaluating of the proposed health claim.

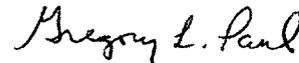
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Yours very truly,

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Table of Contents:

A. PRELIMINARY REQUIREMENTS	4
<i>A.1. The Substance of This Petition is Soy Protein</i>	4
Table 1. Protein content of soyfoods	4
a. The Substance is a Component of Food	5
b. Use of the Substance is Safe and Lawful	5
Table 2. Soybean-derived food products.	6
Table 3. Soy protein-containing ingredients.	6
<i>A.2. The Substance May Help Reduce the Risk of Certain Cancers, a Disease for which the U.S. Population is at Risk.</i>	8
<i>A.3. The Substance and Disease Identified in this Petition (Soy Protein and Cancer) Meet the Preliminary Requirements as Outlined in § 101.70.</i>	9
B. SCIENTIFIC EVIDENCE	11
<i>B.1. Overview</i>	11
Table 4. Results of meta-analysis on breast, prostate, and gastro-intestinal cancer.	11
<i>B.2. Applicability of Epidemiological Studies for Health Claims</i>	12
Figure 1. Types of studies used in FDA authorized health claims.	13
<i>B.3. Details of the Scientific Review</i>	14
B.3.1. Breast Cancer	16
B.3.1(1). Epidemiological Studies	17
Table 5. Summary of epidemiological studies on soy intake and breast cancer in women.	18
Table 6. Summary of epidemiological studies on urinary isoflavones and breast cancer in women.	19
Table 7. Summary of epidemiological studies on soy intake and breast cancer in postmenopausal women.	20
Figure 2. Meta-analysis of studies on consumption of soy protein-containing foods and breast cancer in women.	22
Figure 3. Meta-analysis of studies on urinary isoflavones and breast cancer in women.	23
Figure 4. Meta-analysis of studies on consumption of soy protein-containing foods and breast cancer in postmenopausal women.	24
B.3.1(1)(a). Soy Consumption and Breast Cancer	25
Table 8. Epidemiological studies on soy consumption and breast cancer in women.	33
B.3.1(1)(b). Urinary Isoflavones and Breast Cancer	43
Table 9. Epidemiological studies on urinary isoflavones and breast cancer in women.	47
B.3.1(2). Animal Studies	50

Table 10. Animal studies on dietary soy protein and experimentally induced mammary tumorigenesis. _____	54
B.3.2. Prostate Cancer _____	58
B.3.2(1). Epidemiological Studies _____	59
Figure 5. Meta-analysis of studies on consumption of soy protein-containing foods and prostate cancer in men. _____	60
Table 11. Summary of epidemiological studies of soy intake and prostate cancer in men. _____	61
Table 12. Epidemiological studies on soy consumption and prostate cancer in men. _____	65
B.3.2(2). Animal Studies _____	70
Table 13. Animal studies on dietary soy protein and experimentally induced prostate tumorigenesis. _____	73
B.3.3. Gastro-Intestinal Cancer _____	76
Figure 6. Meta-analysis of studies on consumption of soy protein-containing foods and gastro-intestinal cancer in humans. _____	77
B.3.3(1). Epidemiological Studies – Stomach/Esophageal Cancer _____	78
Table 14. Summary of epidemiological studies on soy intake and stomach and esophageal cancer in humans. _____	80
Figure 7. Meta-analysis of studies on consumption of soy protein-containing foods and stomach/esophageal cancer in humans. _____	81
Table 15. Epidemiological studies on soy consumption and stomach and esophageal cancer in humans. _____	88
B.3.3(2). Epidemiological Studies – Colorectal Cancer _____	96
Table 16. Summary of epidemiological studies on soy intake and colorectal cancer in humans. _____	98
Figure 8. Meta-analysis of studies on consumption of soy protein-containing foods and colorectal cancer in humans. _____	99
Table 17. Epidemiological studies on soy consumption and colorectal cancer in humans. _____	104
B.3.3(3). Animal Studies _____	109
Table 18. Animal studies on dietary soy protein and experimentally induced colon tumorigenesis. _____	113
<i>B.4. There is Significant Scientific Agreement that Soy Protein May Reduce the Risk of Some Types of Cancer</i> _____	116
C. ANALYTICAL DATA _____	116
D. MODEL HEALTH CLAIM _____	116
D.1. Proposed Claims _____	116
D.2. Qualifying Levels of Soy Protein per RACC in Foods _____	117
D.3. Other Qualifying Criteria _____	120

D.4. The Proposed Claim Is Consistent with Other Dietary Recommendations _____ 121
D.5. The Dietary Changes of the Proposed Claim is Feasible and Healthy for Americans 122
E. ENVIRONMENTAL IMPACT _____ 123
References: _____ 125

A. PRELIMINARY REQUIREMENTS

A.1. *The Substance of This Petition is Soy Protein*

The petitioner submits that the substance of this petition be defined specifically as:

Soy protein from the legume seed, *Glycine max.*

The starting materials for soymilk, soybean curd, soy flour, soy protein concentrate, and isolated soy protein are dry soybeans (Table 1). To produce soymilk (50% protein), the dry beans are soaked, ground, and the pulp is extracted. If the protein is coagulated with a calcium salt or some other precipitant, a curd is formed (40-50% protein). Soybean curd is either used in the wet form (tofu) or can be further processed to form soy protein ingredients. These soy protein ingredients made from the curd product of dry soybeans include: soy flour (45-50% protein; SF), soy protein concentrate (70% protein; SPC), texturized soy protein (45-90% protein; TSP), and isolated soy protein (90% protein; ISP). In addition to protein, the previously mentioned soy products contain other nutrients, such as carbohydrate, vitamins, and minerals, as well as naturally occurring constituents such as fibers, isoflavones, and saponins (U.S. Department of Agriculture, 1986).

Table 1. Protein content of soyfoods

Soy Protein Source	Protein (%) (Dry Weight Basis)
Dry Soybeans	40
Soybean Curd	45-50
Soymilk	50
Soy Flour	45-50%
Soy Protein Concentrate	70
Isolated Soy Protein	90
Texturized Soy Protein ¹	45-90

(U.S. Department of Agriculture, 1986)

¹ Texturized soy protein can be made from soy flour, soy protein concentrate, or isolated soy protein.

Historically, soybean curd and soymilk have been viewed as “traditional” Asian foods whereas soy protein ingredients have been and are used to formulate mainstream U.S. foods. However, the soymilk industry has recently made tremendous gains in popularity in the mainstream U.S. food industry. The protein content per Reference Amount Commonly Consumed (RACC) of some soy foods currently available in the market is listed in Appendix I.

a. The Substance is a Component of Food

Soy protein fully conforms to the definition of "substance" as described in 21 CFR 101.14 (a)(2) which states that to be eligible for a health claim, the substance must be a food or a component of a food, and that, in accordance with 101.14 (b)(3)(i), the substance must achieve its effect through its use as a food or component of food, e.g., through its nutritive value, which is retained at the levels consumed to justify the claim.

Soy protein ingredients (ISP, SPC, and SF) and soy protein-based foods are consumed as ingredients in food products or recipes, in soy-based beverages, or as intact food products. The soy protein ingredients can be added to food items as powders, in liquid beverages, or as texturized products. As an ingredient in foods or beverages or as intact foods, soy protein may partially or completely replace animal protein or other grain protein sources in the human diet. Consequently, soy protein provides nutritive value (source of dietary protein) in accordance with §101.14 (a)(3).

b. Use of the Substance is Safe and Lawful

All of the soy protein sources (Table 1), soybean-derived foods (Table 2), and soybean derived food ingredients (Table 3) are generally recognized as safe (GRAS) by self-determination and based on common use in food before January 1, 1958 in conformance with section 201(s) of the Federal Food, Drug and Cosmetic Act (FD & C Act). While soy protein is not listed as GRAS or prior sanctioned in Title 21, CFR, the Agency has stated that these lists "do not include all substances that are generally recognized as safe for their intended use." Further, as noted in §182.1, "It is impractical (for FDA) to list all substances that are GRAS for their intended use."

Table 2. Soybean-derived food products.

Food Product	Derivation
Edamame	Green soybeans
Miso	Fermented soybean paste
Natto	Fermented cooked soybeans
Tempeh	Whole soybeans mixed with other grains, fermented into a cake
Tofu Regular Reduced fat	Dense, solid cake made from hot soy milk, curdled with coagulant same as a regular tofu except derived from reduced fat soy milk
Soy Milk Regular Reduced fat	Finely ground, soaked, strained soybeans with natural oils or with oils removed
Soy Cheese	Coagulated regular or reduced fat soy milk
Soy Yogurt	Fermented regular or reduced fat soy milk
Soy Frozen Desserts	Soy yogurt or soy milk
Soynuts	Whole soybeans soaked in water and baked until brown
Whole Soybeans	Cooked or roasted whole soybeans, green, or dried

Table 3. Soy protein-containing ingredients.

Ingredient	Derivation
Structured vegetable protein	Texturized ISP, SPC, SF or tofu-based mixes
Hydrolyzed vegetable protein	Amino acids from acid hydrolysis of soy protein
Soy grits or meal	Roasted soybeans cracked into coarse pieces
Soy bran	Fibrous material extracted from soybean hulls and refined
Soy isolate fiber	Structured protein fiber or ISP in a fibrous form
Soy sauce	Liquid obtained from fermented soybeans
Okara	Pulp fiber byproduct of soy milk production

In the Proposed Rule, Food Labeling: Health Claims: Soy Protein and Coronary Heart Disease (63 FR 62977), FDA reviewed soy protein in the context of the first soy-related health claim submitted by Solae (then Protein Technologies International) as required in § 101.14(b)(3)(ii). FDA stated:

“Based on the totality of the evidence and, in particular, its common use in food, the agency is not prepared, at this time, to take issue with the

petitioner's view that the use of soy protein is safe and lawful as required in § 101.14(b)(3)(ii). Thus, FDA tentatively concludes that the petitioner has provided evidence that satisfies the requirement in § 101.14(b)(3)(ii) that use of soy protein at the levels necessary to justify the claim is safe and lawful.” (63 FR 62979)

In the Final Rule, Food Labeling: Health Claims: Soy Protein and Coronary Heart Disease (64 FR 57700), FDA addressed numerous comments on safety of soy protein, including safety of soy protein-based infant formulas, potential effects of lysinoalanine, potential effects of nitrates and subsequent nitrosamine formation, potential effects of trypsin inhibitors, potential effects of phytic acid on mineral balance, potential effects of soy isoflavones (estrogenic effects, fertility effects, developmental effects, and goitrogenic effects), and concerns on allergenicity to soy protein. FDA responded to all these concerns and concluded:

“As stated previously, FDA does not take issue with the petitioner's self-determination of GRAS status, and the comments, discussed below, have not convinced the agency to change that conclusion.” (64 FR 57702)

“Under the health claim petition process, FDA evaluates whether the substance is ‘safe and lawful’ under the applicable food safety provisions of the act § 101.14(b)(3)(ii). As discussed in greater detail below, FDA did not receive sufficient evidence from comments to challenge the petitioner's assertion that soy protein ingredients are GRAS by self-determination. The petitioner met the showing required by § 101.14(b)(3)(ii) that the substance be ‘safe and lawful’. (64 FR 57702)

Indeed, a strong administrative record, based on a full and complete review of all relevant science, fully supported FDA's determination as to the appropriateness of soy as the subject of a health claim.

Since authorization of the Soy Protein and Coronary Heart Disease (CHD) Health Claim there has been an increase in the use of soy protein in a variety of foods. In Appendix II we provide per capita soy protein intake before authorization of the soy protein/CHD health claim and the associated increase in use of soy protein in foods after the CHD health claim. We also provide an estimate of a potential additional increase in use of soy protein in foods associated with authorization of the current petition. Per capita consumption of soy protein increased from 0.78 g/day in 1998 (0.54-0.98 g/day for various age/gender groups) to 2.23 g/day in 2002 (1.62-2.85 g/day for various age/gender groups) after the Soy Protein and CHD Health Claim was authorized. Assuming soy protein intake doubled (increased 100%) as a result of the authorization of the proposed health claim, we estimate per capita soy protein intake would be 4.48 g/day (3.24-5.70 g/day for various age/gender groups). These intakes appear reasonable and present no safety concerns.

A.2. The Substance May Help Reduce the Risk of Certain Cancers, a Disease for which the U.S. Population is at Risk.

Cancer is the second leading cause of morbidity and mortality in the United States, exceeded only by cardiovascular diseases. The American Cancer Society reports that cancer death accounted for approximately 23% of all deaths, ranking second only to heart disease (Jemal et al., 2004). It has been estimated that approximately over 1.3 million new cases of cancer will be diagnosed and over a half-million people will die from cancer-related diseases in the United States in the year 2003 (Jemal et al., 2004).

Geographical differences in cancer morbidity and mortality vary dramatically around the world. For example, breast cancer and prostate cancer are the second leading cause of cancer-related death for American women and men, exceeded only by lung cancer for both sexes. The death rate of breast cancer in women is 4-fold and that of prostate cancer in men is 18-fold lower in China than in the United States (Jemal et al., 2002). It is well known that environmental factors, including diet, play an important role in the development of chronic diseases, including cancer. This has been demonstrated in

migration studies. For example, the incidence of breast cancer in Japanese-American women increases with years of residence in the United States compared with women living in Japan (Kolonel et al., 1980). An explanation to this observation is that the acceptance of Western life style, including dietary changes, is responsible for the increase in breast cancer risk in Japanese immigrants.

Consistent with the effects of diet and other lifestyle factors affecting the risk of cancer, the American Cancer Society states in its guidelines on nutrition and physical activity for cancer prevention that:

“There is strong scientific evidence that healthful dietary patterns, in combination with regular physical activity, can reduce cancer risk. Approximately 35% of cancer deaths in the United States may be avoidable through dietary modification.” (Byers et al., 2002)

Additionally, FDA has authorized three health claims on the risk reduction of cancer, largely based on epidemiological evidence (Dietary Fat and Cancer - § 101.73; Fiber-Containing Grain Products, Fruits, and Vegetables and Cancer - § 101.76; and Fruits and Vegetables and Cancer - § 101.78), and has concluded in each of these proceedings that cancer is a disease of concern in the United States. Thus, we conclude that the disease that is the subject of this petition, namely certain cancers, meets the requirements of § 101.14 (b)(1) being a disease for which the general U.S. population is at risk.

A.3. The Substance and Disease Identified in this Petition (Soy Protein and Cancer) Meet the Preliminary Requirements as Outlined in § 101.70.

All of the soy protein sources (Table 1) and soybean-derived food ingredients (Table 3) are generally recognized as safe (GRAS) by self-determination and based on common use in food before January 1, 1958 in conformance with section 201 (s) of the Federal Food, Drug and Cosmetic Act (FD & C Act). Soy protein is not listed as GRAS or prior sanctioned in Title 21, CFR. However, the Agency has stated that these lists "do not

include all substances that are generally recognized as safe for their intended use."

Further, as noted in 21 CFR §182.1, "It is impractical (for FDA) to list all substances that are GRAS for their intended use."

The fractionation procedures employed to convert vegetable flours to vegetable protein isolates and concentrates were commonplace in various sectors of the grain industry (such as corn processing) well before 1958. Therefore, ISP (and SPC) can be defined as soy flour "subject only to conventional processing as practiced prior to January 1, 1958." Furthermore, there are no known safety hazards associated with ISP, SPC, SF, or other soy protein foods.

The FDA has recognized soy protein products as having GRAS status at various times throughout the past three decades. The agency proposed to define ISP, as well as SPC and SF, in standards of identity published in 35 FR at 30,489. These products were identified as "safe and suitable edible products." In addition, the USDA, the Association of American Feed Control Officials, the Codex Alimentarius and others have issued over the years various documents that support the GRAS status of products containing soy protein.

B. SCIENTIFIC EVIDENCE

B.1. Overview

Soy protein is a major source of dietary protein worldwide. Americans have consumed soy protein for more than 40 years, and soy foods have been a dietary staple in Asian populations for centuries (Messina et al., 1994b). There have been many epidemiological studies, particularly in recent years, which examined the relationship between consumption of soyfoods and the risk of various cancers in humans. The totality of the publicly available scientific evidence supports the substance/disease relationship that consumption of soy protein-containing foods is related to a lower risk of certain cancers. The evidence is particularly strong in cancer of breast, prostate, and gastro-intestinal tract. There are 22 publications available to date on breast cancer, 10 on prostate cancer, and 29 on gastro-intestinal cancer. A thorough review and evaluation of these studies reveal that consumption of soy protein-containing foods is associated with a lower risk of breast, prostate, and gastro-intestinal cancer in humans (section B.3. Details of the Scientific Review). This relationship is supported by results of meta-analyses of available studies that provided adequate data for a pooled analysis (Table 4).

Table 4. Results of meta-analysis on breast, prostate, and gastro-intestinal cancer.

Cancer Site	Pooled Estimate of Odds Ratio/Relative Risk	95% Confidence Interval	<i>P</i> -value
Breast	0.78	0.68 – 0.91	0.001
Prostate	0.66	0.54 – 0.81	0.001
Gastro-Intestinal	0.70	0.61 – 0.80	0.001

The relationship is further supported by animal studies that assessed soy protein as a component of a diet and examined the preventive effect of such a diet in experimentally induced tumorigenesis. There are 39 studies available to date. Results of the majority of these studies demonstrate that dietary supplementation with isolated soy protein (the most commonly used form of soy protein in experimental investigations) or a soy protein-containing preparation inhibits experimentally induced tumorigenesis in mammary gland, prostate, and gastro-intestinal tract in animals. Thirty-three of the 39 studies demonstrate

protective effects, three studies show neutral effects, and three show that it is related to experimental tumorigenesis under certain laboratory conditions.

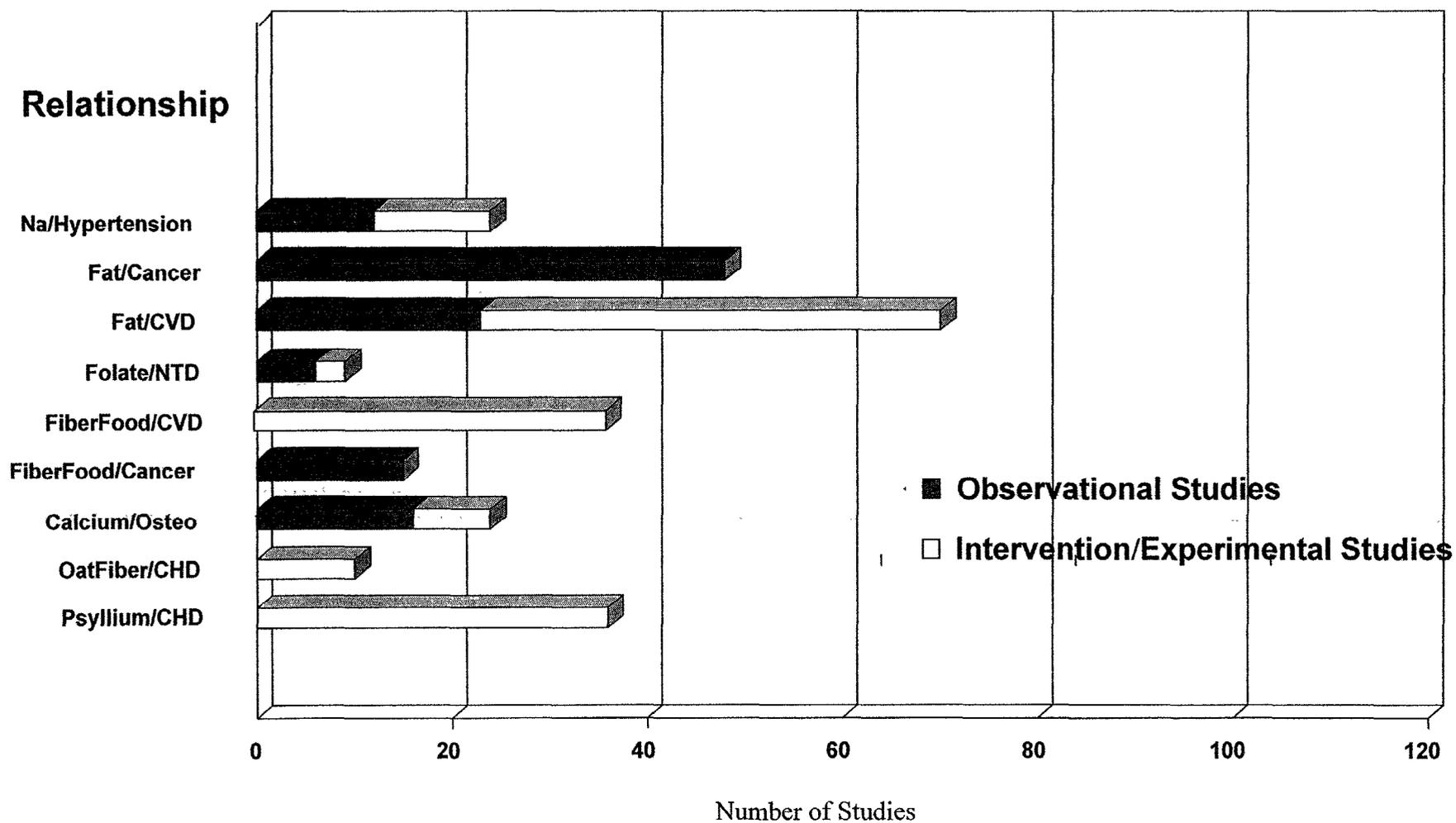
B.2. Applicability of Epidemiological Studies for Health Claims

Given the nature of cancer as a disease, and the fact that there are very few accepted biomarkers of cancer, epidemiological evidence has been extensively used to evaluate diet and lifestyle relationships with cancer risk. The Agency provides direction in their document entitled, “Guidance for Industry – Significant Scientific Agreement in the Review of Health Claims for Conventional Foods and Dietary Supplements” that “in some cases, such as with cancers of different sites, interventional dietary studies are not feasible because diseases with lower frequency of occurrence, such as rare forms of cancer, require very large study samples to detect an effect. Moreover, there frequently are long delays from dietary exposure to onset of disease, often 20 to 30 years. Therefore supporting a substance/disease relationship may have to be derived wholly or in part from observational studies.”

The following diet/cancer prevention health claims have been authorized by FDA based largely on epidemiological evidence (see also Figure 1):

- 1) Dietary Fat and Cancer - § 101.73
 - a. Model claim example: “Development of cancer depends on many factors. A diet low in total fat may reduce the risk of some cancers.”
- 2) Fiber-Containing Grain Products, Fruits, and Vegetables and Cancer - § 101.76
 - a. Model claim example: “Low fat diets rich in fiber-containing grain products, fruits, and vegetables may reduce the risk of some types of cancers, a disease associated with many factors.”
- 3) Fruits and Vegetables and Cancer - § 101.78
 - a. Model claim example: “Low fat diets rich in fruits and vegetables (foods that are low in fat and may contain dietary fiber, vitamin A, and vitamin C) may reduce the risk of some types of cancer, a disease associated with many factors.”

Figure 1. Types of studies used in FDA authorized health claims.



Adapted from FDA

B.3. Details of the Scientific Review

Objective and Scope

The significant amount of relevant scientific literature was carefully reviewed to determine whether there is significant scientific agreement in support of the proposed health claim. This review focuses primarily on epidemiological studies on breast, prostate, and gastro-intestinal cancer. Studies on other types of cancer, because of limited number of publications, are reviewed and presented in Appendix III. These include endometrial/ovarian, thyroid, lung, pancreas, liver, nasopharyngeal, and urinary bladder cancer. Copies of epidemiological studies (breast, prostate, and gastro-intestinal cancer) used in support of this petition are found in Appendix IV. Available studies on each cancer type are presented in descending order of persuasiveness enabling us to reach conclusions about the relationship between diet and disease, e.g., cohort studies, case-control studies, cross-sectional analysis, and ecological studies. Animal studies are reviewed when soy protein or a protein-containing soy preparation is given as a component of a diet and the preventive effect of such a diet on experimentally induced tumorigenesis is examined. This rigorous scientific evaluation follows established principles among experts qualified in this field as well as guidance from FDA in this regard.

The scientific evidence that relates soy to breast, prostate, and gastro-intestinal cancer in humans is also weighed using meta-analyses. Meta-analysis defines an effect size statistic. This enables a representation of quantitative findings from a set of research studies in a standardized form that permits meaningful numerical comparison and analysis across the studies. In brief, studies with reported risk estimate (e.g., odds ratio (OR) or relative risk (RR)) and 95% confidence interval (or 95% confidence interval obtained from the investigators) were included in the analysis. A pooled estimate was calculated using a random-effects model in which the effect measures are log ORs/RRs weighed by the method of DerSimonian and Laird (1986), in which studies with smaller standard error of estimate are given greater weight in the summary measure. Publication bias was tested for each analysis using the trim-and-fill method by Duval and Tweedie (2000). The statistical program STATA (StataCorp, College Station, TX) was used for

the calculation. All reported *P* values are from two-sided statistical tests. Dr. Edward Spitznagel, Professor of Mathematics and Statistics, Washington University conducted all the analyses. (see Appendix V for the detailed meta-analysis methodology and Dr. Spitznagel's Curriculum Vitae.)

Soy products commonly assessed in epidemiological studies include bean curd (tofu), soybeans, soymilk, and their derivative products. Bean curd is assessed in most of these studies. This is because bean curd is a convenient source of dietary protein and the most commonly consumed soyfood. Studies included in this review are those focused on high protein-containing soyfoods. Not included are studies focused on soybean paste, soy sauce, and their derivative products. Soybean paste and soy sauce are salted, fermented products that are low in protein and used primarily as condiments. There are no data available, to our knowledge, on the relationship between the oil portion of soybean and cancer.

B.3.1. Breast Cancer

This review considers the weight of scientific evidence that relates dietary soy protein to the risk of breast cancer in women. It primarily reviews and evaluates the literature of epidemiological studies describing the relationship between soy intake and breast cancer incidence in women. This review also evaluates animal studies that examine the effect of dietary soy protein on experimentally induced mammary tumorigenesis. There are 16 epidemiological studies available to date that relate soy intake to breast cancer in women (three cohort studies, 11 case-control studies, one cross-sectional analysis, and one ecological study). A thorough review of these studies reveals that consumption of soy protein-containing foods is associated with a lower incidence of breast cancer in women. This protective relationship is supported by results of a meta-analysis of studies that provide adequate data for a pooled analysis (pooled estimate of odds ratio/relative risk = 0.78, 95% CI = 0.68-0.91; $P = 0.001$; Figure 2). Furthermore, there are six case-control studies that relate urinary isoflavones (a marker of soy intake) to breast cancer in women. Results of studies show that a higher urinary excretion of isoflavones is related to a lower risk of breast cancer. A meta-analysis of these studies yields a pooled estimate of odds ratio 0.68 (95% CI = 0.49 – 0.94; $P = 0.02$; Figure 3). Results from animal studies support the epidemiological findings. There are 15 publications on dietary soy and mammary tumorigenesis in animals available to date, and isolated soy protein is assessed in most of these studies. Results of these studies show that dietary supplementation with soy protein inhibits experimentally induced mammary tumorigenesis.

In conclusion, the totality of the publicly available scientific evidence supports the substance/disease relationship that consumption of soy protein-containing foods is associated with a lower risk of breast cancer in women.

B.3.1 (1). Epidemiological Studies

Summary

Epidemiological studies demonstrate that consumption of soy protein-containing foods is associated with a lower risk of breast cancer in women. There are 22 publications available to date. Sixteen of these studies relate soy intake to breast cancer in women (three cohort studies, 11 case-control studies, one cross-sectional analysis, and one ecological study; see Table 5 for summary and Table 8 for details). Soy intake was assessed in these studies in three ways, soyfoods (as a group of foods or a specific type of soyfoods, e.g., bean curd), soy protein, and soy isoflavones. The latter two were derived from intake data of soyfoods. Bean curd (tofu), one of the most commonly consumed soyfoods containing a high quantity of protein, was assessed in most of these studies. Six case-control studies relate urinary isoflavones (a marker of soy intake) to the risk of breast cancer (see Table 6 or summary and Table 9 for details). Nine of these 22 studies were conducted with Caucasian women or multi-ethnic populations in the United States or Western countries, and the rest were done in Asian countries where soy was a major source of dietary protein.

Results from the studies that relate soy intake to breast cancer show that consumption of soy protein-containing foods is related to a lower risk of breast cancer in women. Ten of the 14 cohort and case-control studies show that soy consumption is related to a lower incidence of breast cancer (ORs/RRs range, 0.40 – 0.85) (Dai et al., 2001; Hirose et al., 1995; Hirose et al., 2003; Lee et al., 1992; Lee et al., 1991; Shu et al., 2001; Witte et al., 1997; Wu et al., 2002; Wu et al., 1996; Yamamoto et al., 2003). Results are statistically significant in five studies (Lee et al., 1992; Lee et al., 1991; Shu et al., 2001; Wu et al., 2002; Wu et al., 1996; Yamamoto et al., 2003). Four studies show that soy intake is not related to breast cancer (ORs/RRs range, 1.0 – 1.07) (Horn-Ross et al., 2002; Horn-Ross et al., 2001; Key et al., 1999; Yuan et al., 1995). Results of a cross-sectional analysis show that controls consume more tofu than breast cancer cases (Nomura et al., 1978), and results of an ecological study show that soy intake is not related to breast cancer in women (Nagata, 2000). The protective relationship between consumption of soy protein-containing foods and breast cancer risk in women is supported by results of a meta-

analysis of studies that provide adequate data for a pooled analysis (Figure 2). The pooled estimate of odds ratio/relative risk is 0.78 (95% CI = 0.68-0.91; $P = 0.001$).

Table 5. Summary of epidemiological studies on soy intake and breast cancer in women.

Reference	Soy Products Assessed	OR/RR (95% CI) ¹ (highest vs. lowest intake)	P trend
Cohort Studies			
Yamamoto (2003)	Total isoflavones	0.46 (0.25 – 0.84)	0.043
	Soyfoods	0.81 (0.49 – 1.3)	0.44
Horn-Ross (2002)	Genistein	1.0 (0.7-1.3)	0.9
	Daidzein	0.9 (0.7-1.2)	0.6
Key (1999)	Tofu	1.07 (0.78 – 1.47)	0.71
Case-Control Studies			
Hirose (2003)	Soybean curd	0.84 (0.67 – 1.04) (premenopausal)	0.02
		0.83 (0.65 – 1.05) (postmenopausal)	0.15
Wu (2002)	Tofu (adolescence)	0.65 (0.38 – 1.10) (adolescence)	0.04
	Total isoflavones (adult)	0.61 (0.39 – 0.97) (adult)	0.04
		0.65 (0.43 – 0.97) (both)	0.03
Shu (2001)	Soyfoods	0.51 (0.40 – 0.65) (adolescence)	0.01
	Tofu	0.70 (0.55 – 0.90) (adolescence)	0.01
Dai (2001)	Soy protein	0.56 (0.32 – 1.00)	0.02
Horn-Ross (2001)	Total isoflavones	1.0 (0.79 – 1.3)	
	Soymilk	0.57 (0.38 – 0.85)	
	Soy-burger	0.74 (0.55 – 0.99)	
	Tofu	0.89 (0.70 – 1.10)	
Witte (1997)	Tofu	0.5 (0.2 – 1.1)	
Wu (1996)	Tofu	0.85 (0.74 – 0.99)	0.03
Hirose (1995)	Bean curd	0.78 (0.6- 1.0) (premenopausal)	
		0.96 (0.7-1.31) (postmenopausal)	
Yuan (1995)	Soy protein	1.0 (0.7 – 1.4)	0.36
Lee (1992)	Soya protein	0.4 (0.2 – 0.8) (premenopausal)	
		1.8 (0.8 – 3.6) (postmenopausal)	
Lee (1991)	Soya products	0.44 (0.24 – 0.81)	
	Soya protein	0.43 (0.23 – 0.79)	
Cross-Sectional Analysis			
Nomura (1978)	Tofu	117 g/wk (cases) vs. 151 g/wk (ctls)	$P = 0.16$
Ecological Study			
Nagata (2000)	Soy protein	$r^2 = -0.08$	

¹OR/RR (95% CI) = Odds ratio/relative risk (95% confidence interval). ²Correlation coefficient.

The association of soy consumption with a lower risk of breast cancer is strongly supported by studies that relate urinary isoflavones to breast cancer in women. Urine is a major route of isoflavone excretion, and urinary isoflavones have been used as markers of soyfood intake in the research community. Six case-control studies are available to date (Table 6). Results of two studies show that a higher urinary isoflavone content is related to a significantly lower risk of breast cancer in women (OR = 0.46 (Dai et al., 2003), OR

= 0.62 (Dai et al., 2002a)). One study shows that a higher excretion of equol (a metabolite of daidzein) is related to a significantly lower risk of breast cancer (Ingram et al., 1997). Murkies et al (2000) reported that controls excrete more isoflavones than breast cancer cases. Two studies show that a higher urinary content of isoflavones is associated with a lower risk of breast cancer (OR = 0.50 (Zheng et al., 1999), OR = 0.83 (den Tonkelaar et al., 2001)), but these results are not statistically significant. The association of a higher urinary isoflavones with a lower risk of breast cancer is supported by results of a meta-analysis of studies that provide adequate data for a pooled analysis (Figure 3). The pooled estimate of odds ratio is 0.68 (95% CI = 0.49-0.94; $P = 0.02$).

Table 6. Summary of epidemiological studies on urinary isoflavones and breast cancer in women.

Reference	Urinary Excretion	OR (95% CI) ¹ (highest vs. lowest)	P trend
Case-control studies			
Dai (2003)	Total isoflavones	0.46 (0.22 – 0.95)	0.04
Dai (2002a)	Isoflavones	0.62 (0.39 – 0.99)	0.04
Murkies (2000)	Daidzein	31 nmol/d (cases) vs. 427 nmol/d (ctls)	$P = 0.03$
	Genistein	25 nmol/d (cases) vs. 155 nmol/d (ctls)	$P = 0.08$
Zheng (1999)	Isoflavones	0.50 (0.19 – 1.31)	0.04
Den Tonkelaar (2001)	Genistein	0.83 (0.46 – 1.51)	0.60
Ingram (1997)	Equol	0.27 (0.10 – 0.69)	0.009
	Daidzein	0.47 (0.17 – 1.33)	0.24

¹OR (95% CI) = Odds ratio (95% confidence interval).

Seven of the 16 publications on soy consumption and breast cancer provide data in postmenopausal women (Table 7). Three of these studies show that soy intake is associated with a significantly lower risk of breast cancer (ORs/RRs range, 0.32 – 0.49) (Shu et al., 2001; Wu et al., 2002; Yamamoto et al., 2003). Three studies show a lower risk of breast cancer in postmenopausal women (ORs/RRs range, 0.83 – 0.96) (Hirose et al., 1995; Hirose et al., 2003; Wu et al., 1996), but these results are not statistically significant. One study shows that soy intake is not related to breast cancer in postmenopausal women (OR = 1.8, 95% CI = 0.8 – 3.6) (Lee et al., 1992). The association of soy consumption and a lower risk of breast cancer in postmenopausal women is supported by results of a meta-analysis of these studies (Figure 4). The pooled estimate of odds ratio/relative risk is 0.64 (95% CI = 0.47-0.88; $P = 0.005$).

Table 7. Summary of epidemiological studies on soy intake and breast cancer in postmenopausal women.

Reference	Soy Products Assessed	OR/RR (95% CI) ¹ (highest vs. lowest intake)	P trend
Cohort Studies			
(Yamamoto et al., 2003)	Total isoflavones	0.32 (0.14 – 0.71)	0.006
Case-Control Studies			
Hirose (2003)	Soybean curd	0.83 (0.65 – 1.05)	0.15
(Wu et al., 2002)	Tofu	0.41 (0.21 – 0.81) ² (adolescence)	0.007
	Total isoflavones	0.39 (0.21 – 0.70) ² (adult)	0.005
(Shu et al., 2001)	Soyfoods	0.49 (0.33 – 0.74) (adolescence)	0.01
(Wu et al., 1996)	Tofu	0.86 (0.66 – 1.13)	0.28
(Hirose et al., 1995)	Bean curd	0.96 (0.7- 1.31)	
Lee (1992)	Soya protein	1.8 (0.8 – 3.6)	

¹OR/RR (95% CI) = Odds ratio/relative risk (95% confidence interval). ²95% CI, unpublished data and obtained from the first author of the publication.

Available data also demonstrate that soy consumption during adolescence is associated with a lower incidence of breast cancer in later life. There are two case-control studies that relate adolescent soy intake to breast cancer in postmenopausal women (Shu et al., 2001; Wu et al., 2002). Both studies show that adolescent soy intake is related to a significantly lower risk of breast cancer in postmenopausal women (Table 7).

Results of four studies show that soy intake is not related to the risk of breast cancer in women (Horn-Ross et al., 2002; Horn-Ross et al., 2001; Key et al., 1999; Yuan et al., 1995). Two of these studies were conducted in the United States and isoflavone intake (derived from intake of soyfoods) was assessed. One is a cohort study in which 87% of the participants are White (Horn-Ross et al., 2002). The other is a case-control study with a non-Asian multiethnic population (African-American, Latina, and White) (Horn-Ross et al., 2001). The highest intake of isoflavones in these studies is >2.1 mg/d (Horn-Ross et al., 2002) and >2.8 mg/d (Horn-Ross et al., 2001), and the average daily intake is 1.8 mg/d (Horn-Ross et al., 2002). These levels of intake are markedly lower than those reported in Asian countries where an inverse relationship between soy intake and breast cancer risk is observed. For example, Yamamoto et al (2003) reported that isoflavone intake (derived from soy intake) is related to a significantly lower risk of breast cancer in Japanese women. The highest and lowest intakes in this study are 25 mg/d and 7 mg/d with a median intake of 16 mg/day. The median intake of isoflavones among Asian-

Americans in Southern California is 12 mg/d (Wu et al., 2002). Horn-Ross et al (2002) stated that, “despite the reduction in breast cancer risk observed in some Asian populations associated with higher levels of consumption of phytoestrogen-rich, soy-based foods or soy protein (Hirose et al., 1995; Lee et al., 1992; Wu et al., 1996), the present study, as well as a recent case-control study of non-Asian women, found no apparent association between phytoestrogen consumption and breast cancer risk. However, in both these American studies the lack of an association may well have been due to the low level of consumption of phytoestrogens in these populations, with the highest quintile of exposure being equivalent to only one or more servings of tofu per week.”

The other two studies are done in Asian countries. Key et al (1999) reported that soy intake is not related to the risk of breast cancer in Japanese women in a cohort study conducted in Hiroshima and Nagasaki. Approximately 80% of the cohort were in Hiroshima or Nagasaki at the time of atomic bombing, and they were exposed to high doses of ionizing radiation. A high incidence of breast cancer has been reported in this population (Tokunaga et al., 1994). Although radiation exposure has been adjusted for all dietary factors analyzed in this study (Key et al., 1999), this powerful risk factor and its likely impact to dietary factors should be considered in data interpretation. Yuan et al (1995) reported that soy intake is not related to breast cancer in Chinese women living in Shanghai and Tianjin, two major cities in China. The estimated soy protein intake is 3.5 g/d and 2.8 g/d for women living in Shanghai and Tianjin, respectively. This level of intake is one third of the average intake (10.3 g/d) reported in a recently completed Shanghai Breast Cancer Study with a large study population (Dai et al., 2001; Shu et al., 2001). The primary sources of soy protein reported by Yuan et al (1995) are soymilk and tofu. Shu et al (2001) reported that in their study soy protein intake is 1 g/d from soy milk and 2 g/d from tofu. This accounts for only one third of total soy protein intake in their study, but approximates to the intake level reported by Yuan et al (1995). It is likely that the intake is underestimated in Yuan study (1995) as the study is not specifically designed to evaluate the effect of soyfoods and soy intake ascertainment is incomplete.

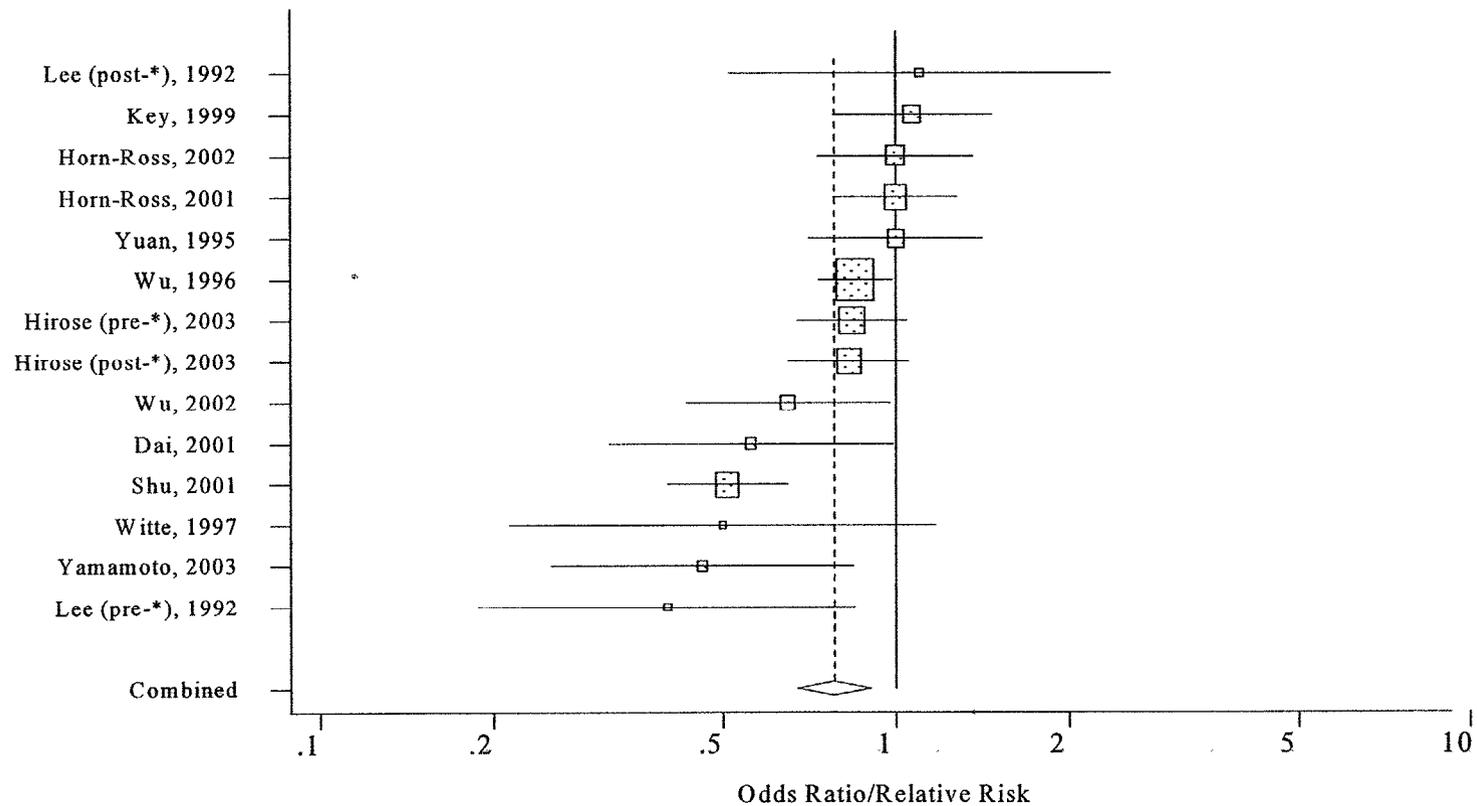


Figure 2. Meta-analysis of studies on consumption of soy protein-containing foods and breast cancer in women. Each study-specific point estimate is plotted as a square box. The size of the box is proportional to the precision of the estimate, and its 95% CI is denoted by a line through the box. The vertical dashed line and the lower vertices of the diamond indicate the pooled estimate of odds ratio/relative risk, and left and right vertices of the diamond represent its 95% CI. The pooled estimate of odds ratio/relative risk is 0.78 (95% CI = 0.68 – 0.91; $P = 0.001$), and no publication bias was detected. Post-* = post-menopausal women. Pre-* = premenopausal women. Results of this analysis show that consumption of soy protein-containing foods is associated with a lower risk of breast cancer in women.

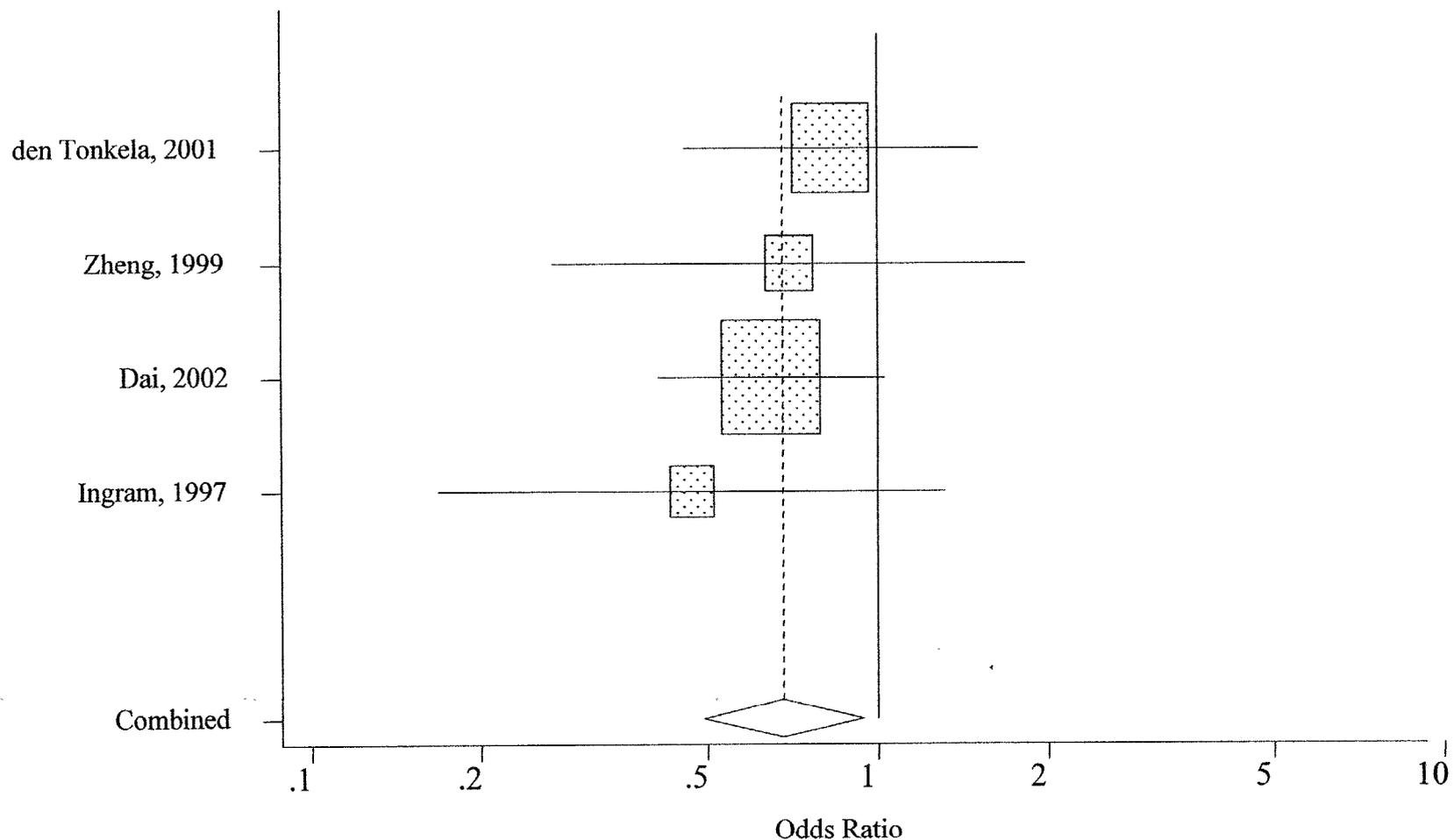


Figure 3. Meta-analysis of studies on urinary isoflavones and breast cancer in women. Each study-specific point estimate is plotted as a square box. The size of the box is proportional to the precision of the estimate, and its 95% CI is denoted by a line through the box. The vertical dashed line and the lower vertices of the diamond indicate the pooled estimate of odds ratio, and left and right vertices of the diamond represent its 95% CI. The pooled estimate odds ratio is 0.68 (95% CI = 0.49 – 0.94; $P = 0.02$), and no publication bias was detected. Results of this analysis show that consumption of soy protein-containing foods, measured as urinary isoflavones, is associated with a lower risk of breast cancer women.

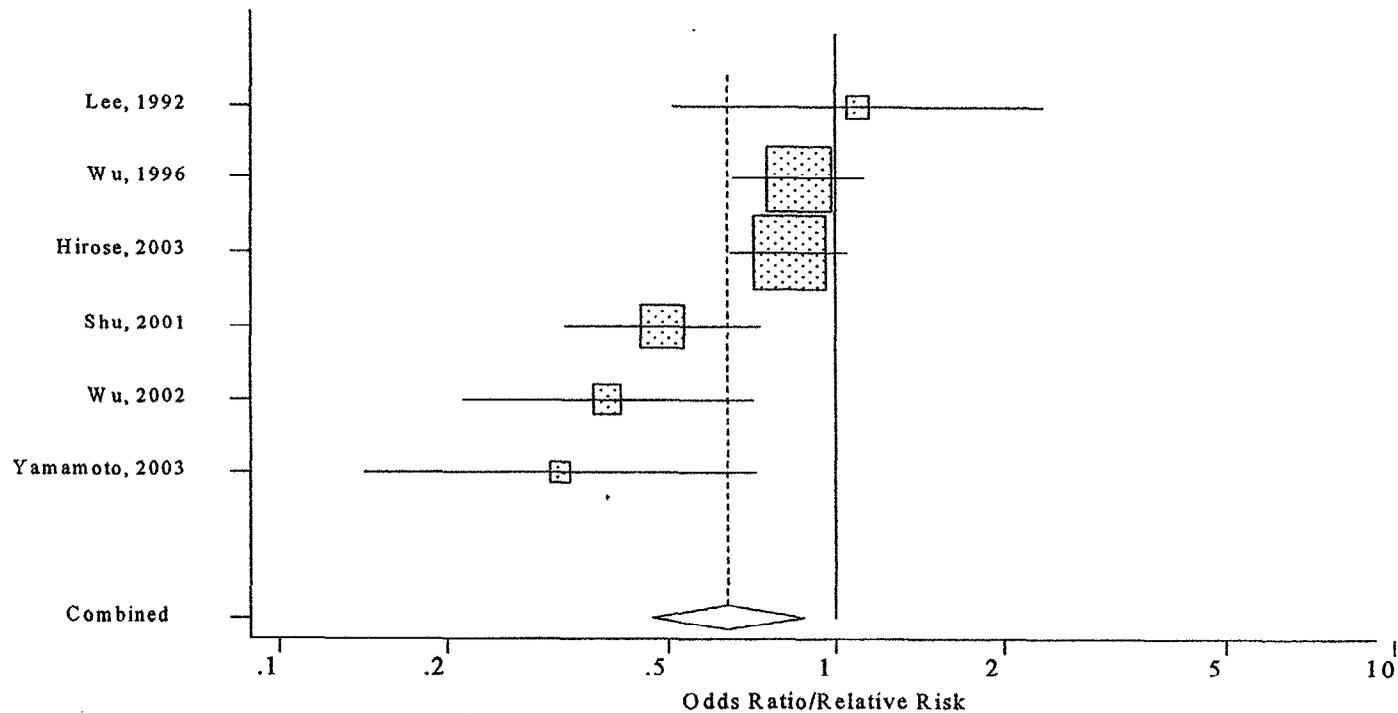


Figure 4. Meta-analysis of studies on consumption of soy protein-containing foods and breast cancer in postmenopausal women. Each study-specific point estimate is plotted as a square box. The size of the box is proportional to the precision of the estimate, and its 95% CI is denoted by a line through the box. The vertical dashed line and the lower vertices of the diamond indicate the pooled estimate of odds ratio/relative risk, and left and right vertices of the diamond represent its 95% CI. The pooled estimate of odds ratio/relative risk is 0.64 (95% CI = 0.47 – 0.88; $P = 0.005$), and no publication bias was detected. Results of this analysis show that consumption of soy protein-containing foods is related to a lower risk of breast cancer in postmenopausal women.

B.3.1 (1)(a). Soy Consumption and Breast Cancer

There are 16 studies available to date that relate soy consumption to breast cancer in women (Table 8).

Cohort Studies

Yamamoto et al (2003) investigated the association of isoflavone intake (derived from soy consumption) with breast cancer in a prospective cohort study in Japan. A total of 179 incident cases of breast cancer were identified from 21,852 cohort members during a 10-year follow-up period. Consumption of isoflavones is related to a significantly lower risk of breast cancer in Japanese women (P trend = 0.043). The adjusted RR is 0.46 (95% CI = 0.25-0.84) when the highest quartile of intake (25.3 mg/d) is compared with the lowest (6.9 mg/d). The median level of intake in this study population is 16 mg/d. When consumption of soyfoods (soybeans, tofu, deep-fried tofu, and natto) and miso are separately analyzed, both are related to a lower risk of breast cancer, but results are not statistically significant. The adjusted RR is 0.81 (95% CI = 0.49-1.3) for soyfoods when daily users are compared with weekly users (<2 times/wk), and the adjusted RR for miso is 0.6 (95% CI = 0.34-1.1) when users (≥ 3 times/d) are compared to less-often users (<1 time/d). The lack of a significant relationship between soyfoods and breast cancer is likely due to a small number of breast cancer cases. The authors stated, "possible associations between breast cancer risk and soyfoods that were not statistically significant in our study may be detected among larger sample sizes." When data are analyzed on the basis of menopausal status, consumption of isoflavones or soyfoods is related to a significantly lower risk of breast cancer in postmenopausal women. The test for trend is $P = 0.006$ for isoflavones with an adjusted RR 0.32 (95% CI = 0.14-0.71) and $P = 0.031$ for soyfoods (RR not presented). The authors concluded, "In a population-based, prospective cohort study in Japan, frequent miso soup and isoflavone consumption was associated with a reduced risk of breast cancer."

Horn-Ross et al (2002) examined the association of diet with breast cancer in a cohort study (California Teachers Study) in the United States. Of the 111,526 at-risk cohort

members (87% of them were Caucasian), 711 incident cases of breast cancer were identified after they joined the cohort and before January 1, 1998. Isoflavone intake was derived from the intake of isoflavone-containing foods using a food frequency questionnaire and a nutrient database. Consumption of isoflavones is not related to breast cancer in this study population (P trend = 0.9 for genistein and P trend = 0.6 for daidzein). The adjusted RR is 1.0 (95% CI = 0.7-1.3) for genistein and 0.9 (0.7-1.2) for daidzein when the highest quintile of isoflavone intake (>2.1 mg/d) is compared with the lowest (0.6 mg/d). The mean level of isoflavone intake in this study population is 1.8 mg/d. The authors indicated, “despite the reduction in breast cancer risk observed in some Asian populations associated with higher levels of consumption of phytoestrogen-rich soy-based foods or soy protein (Hirose et al., 1995; Lee et al., 1992; Wu et al., 1996), the present study, as well as a recent case-control study of non-Asian women, found no apparent association between phytoestrogen consumption and breast cancer risk (Horn-Ross et al., 2001). However, in both these American studies the lack of an association may well have been due to the low level of consumption of phytoestrogens in these populations, with the highest quintile of exposure being equivalent to only one or more servings of tofu per week.”

Key et al (1999) investigated the association of soyfoods with the risk of breast cancer in a prospective study conducted in Hiroshima and Nagasaki in Japan. The subjects were participants in the Life Span Study of the Radiation Effects Research Foundation. A total of 34,759 women completed dietary questionnaires during 1969-1970 and/or 1979-1981 and was followed for the incident breast cancer until 1993. During this period of follow-up (10-20 yrs), 427 incident cases were identified. Results of this study show that consumption of tofu is not related to breast cancer (P trend = 0.712). The adjusted RR is 1.07 (95% CI = 0.78-1.47) when the highest intake (≥ 5 times/wk) is compared with the lowest (≤ 1 time/wk).

Case-Control Studies

Hirose et al (2003) examined dietary factors protective against breast cancer in Japanese women in a hospital-based case-control study (2,385 cases, 19,013 controls) in Japan. Soybean curd was one of the food items assessed in this study. A higher intake of soybean curd is related to a lower risk of breast cancer (P trend = 0.02 for premenopausal and P trend = 0.15 for postmenopausal women). The adjusted OR is 0.84 (95% CI = 0.67-1.04) for premenopausal and 0.83 (95% CI = 0.65-1.05) for postmenopausal women when the highest quartile of intake (≥ 5 times/wk) is compared with the lowest ($\leq 1-3$ times/m).

Wu et al (2002) investigated the association of adolescent and adult soy intake with breast cancer in Asian-American women in the United States (501 cases, 594 controls). Tofu intake was assessed for adolescent soy intake, and total isoflavone intake (derived from intake of a variety of soyfoods) for adult soy intake. Soy intake at least once per week during adolescence is related to a significantly lower risk of breast cancer (P trend = 0.04). There is also a significant reduction in breast cancer risk with a high soy consumption during adult life (P trend = 0.04). The adjusted OR is 0.61 (95% CI = 0.39-0.97) for adult intake and 0.65 (95% CI = 0.38-1.10) for adolescent intake when the highest quartile of intake is compared with the lowest. When soy intake during both adolescence and adult life are considered, women with a high soy intake during both time periods have the lowest risk compared with those who are low in soy intake during both periods (adjusted OR = 0.65, 95% CI = 0.43-0.97). The test for trend is statistically significant ($P = 0.03$). When data are analyzed on the basis of menopausal status, soy consumption is related to a lower risk of breast cancer in both premenopausal and postmenopausal women. The highest and the lowest quartile of tofu intake in adolescence is ≥ 4 times/wk and < 1 time/m, and that of isoflavone intake in adults is > 12.7 mg/1,000 kcal and ≤ 1.8 mg/1,000 kcal. Wu et al (2002) concluded, "These results show that high soy intake in childhood in Asian-Americans is associated with reduced breast cancer risk. Risk may be further reduced by intake as an adult."

Shu et al (2001) studied the relationship between adolescent soy intake and the risk of breast cancer in later life with 1,459 breast cancer cases and 1,556 controls in Shanghai, China. Information of dietary intake at ages 13 to 15 years was collected from participants and from mothers of those who were ≤ 45 years old. Adolescent soy consumption is related to a significantly lower risk of breast cancer in later life. The adjusted OR is 0.51 (95% CI = 0.40-0.65) when the highest quintile of intake is compared with the lowest. Analysis of soy intake data reported by participants' mothers also shows a significantly lower risk of breast cancer in this study population (adjusted OR = 0.35, 95% CI = 0.21-0.60). The risk reduction is observed in both premenopausal (adjusted OR = 0.53, 95% CI = 0.39-0.72) and postmenopausal women (adjusted OR = 0.49, 95% CI = 0.33-0.74). Furthermore, significantly inverse association is observed when tofu and soyfoods (excluding tofu) are separately analyzed. The adjusted OR is 0.70 (95% CI = 0.55-0.90) for tofu and 0.65 (95% CI = 0.50-0.80) for soyfoods when the highest quintile intake is compared with the lowest. The test for trend of all measured variables discussed above is statistically significant ($P < 0.01$). The highest and the lowest quintile of total soyfood intake is > 11.0 g/d and < 2.2 g/d, and that of tofu is > 2.2 g/d and < 0.44 g/d. Shu et al (2001) concluded, "Our study suggests that high soy intake during adolescence may reduce the risk of breast cancer in later life."

Dai et al (2001) investigated soy intake in relation to breast cancer in Chinese women in Shanghai, China (1,495 cases, 1,556 controls). Soy protein intake was derived from soyfood intake before data were analyzed. There is a 44% reduction in breast cancer risk in subjects who claimed no recent change in soy intake (adjusted OR = 0.56, 95% CI = 0.32-1.00) when the highest quintile of intake (> 91.0 g/wk) is compared with the lowest (< 1 time/wk). A higher soy protein consumption is related to a significantly lower risk of breast cancer (P trend = 0.02), and the inverse association is observed in both premenopausal and postmenopausal women (data not provided). Furthermore, there is a significant risk reduction in breast cancer positive for estrogen and progesterone receptors (ER^+/PR^+) when the highest quartile of intake is compared with the lowest (adjusted OR = 0.28, 95% CI = 0.13-0.57), and the test for trend is statistically significant ($P = 0.004$). The risk reduction is greater than those with other receptor status, e.g.,

negative for estrogen and progesterone receptors (ER⁻/PR⁻) or positive for estrogen receptor/negative for progesterone receptor or vice versa (ER⁺/PR⁻ or ER⁻/PR⁺). The estimated average daily intake of soy protein among controls is 10.3 g/d. Dai et al (2001) pointed, "In summary, our study showed that regular soyfood intake, especially at a very high level, may be associated with a reduced risk of breast cancer, particularly to those positive for ER and PR."

Horn-Ross et al (2001) investigated the association of phytoestrogen-containing foods with breast cancer in a non-Asian multiethnic population (African-American, Latina, and White) in San Francisco Bay area in the United States (1,326 cases, 1,657 controls). Tofu, doughnuts, soymilk, and white bread were among the largest contributors to phytoestrogen intake in this study. Consumption of phytoestrogens is not related to breast cancer in this study population. The adjusted OR is 1.0 (95% CI = 0.79-1.3) when the highest quartile of intake (≥ 2.8 mg/d) is compared with the lowest (< 1 mg/d). Consumption of soymilk and soy burgers at ≥ 1 time/m is associated with a significantly lower incidence of breast cancer. The adjusted OR is 0.57 (95% CI = 0.38-0.85) for soymilk and 0.74 (95% CI = 0.55-0.99) for soy burgers when soy consumers are compared with non-consumers. The adjusted OR for tofu is 0.89 (95% CI = 0.70-1.1) when tofu consumers (≥ 1 time/m) are compared with the non-consumers. Horn-Ross et al (2001) concluded, "Phytoestrogens appears to have little effect on breast cancer risk at the levels commonly consumed by non-Asian U.S. women: an average intake equivalent to less than one serving of tofu per week."

Witte et al (1997) examined the relationship between diet and premenopausal bilateral breast cancer in Caucasian women in a familial matched case-control study (140 cases, 222 controls). Tofu was one of the food items assessed in this study. Tofu consumption is associated with a 50% reduction in breast cancer risk. The adjusted OR is 0.5 (95% CI = 0.2-1.1) when women with 1 serving/wk are compared with those who reported no tofu intake.

Wu et al (1996) assessed tofu intake in relation to breast cancer in Asian-American women in the United States (597 cases, 966 controls). The risk of breast cancer decreases significantly with increasing the frequency of tofu intake (P trend <0.03). The adjusted OR associated with each additional serving per week is 0.85 (95% CI = 0.74-0.99). The trend in reduction in breast cancer risk exists in both premenopausal ($P = 0.04$) and postmenopausal women ($P = 0.28$), and the adjusted OR is 0.84 (95% CI = 0.70-0.99) for premenopausal and 0.86 (95% CI = 0.66-1.13) for postmenopausal women. Wu et al (1996) explained the lack of statistical significance in postmenopausal women, "The protective effect of tofu was observed in both premenopausal and postmenopausal women and was of similar magnitude. The result was statistically significant only in premenopausal women. This appears to be solely an effect of the larger number of premenopausal than postmenopausal women since the magnitudes of the effects are very similar." The highest quartile of tofu intake in this study is >55 times/yr and the lowest is ≤ 12 times/yr.

Hirose et al (1995) examined risk factors of breast cancer in Japanese women in a hospital-based case-control study (1,052 cases, 23,163 controls). They found a downward trend in breast cancer risk with increasing frequency of bean curd intake in premenopausal women, but not in postmenopausal women. The age-adjusted OR is 0.78 (95% CI = 0.6-1.0) for premenopausal and 0.96 (95% CI = 0.7-1.31) for postmenopausal women when the highest intake (≥ 3 times/wk) is compared with the lowest (≤ 3 times/m).

Yuan et al (1995) studied the association of diet and breast cancer in Chinese women (834 cases, 834 controls) in Shanghai and Tianjin, two major cities in China. Soy protein intake (derived from the intake of soyfoods) was assessed in this study. Soy protein intake is not related to breast cancer (adjusted RR = 1.0, 95% CI = 0.7-1.4), and the test for trend is not statistically significant ($P = 0.36$). There is no significant difference in soy consumption between cases and controls. The median intake of soy protein is 3.5 g/d and 2.8 g/d in controls and 3.5 g/d and 3.5 g/d in cases from Shanghai and Tianjin, respectively. Yuan et al (1995) concluded, "Our study does not support the hypothesis that high intake of soy protein protects against breast cancer."

Lee et al (1992; 1991) studied dietary effects on breast cancer in Chinese women in a hospital-based case-control study in Singapore (200 cases, 420 controls). Soy consumption was assessed as soya protein intake (derived from intake of soya products) and total soya products intake. Soy protein intake is related to a significantly lower risk of breast cancer in premenopausal women (P trend = 0.01), but not in postmenopausal women. The adjusted OR is 0.4 (95% CI = 0.2-0.8) for premenopausal women and 1.8 (95% CI = 0.8-3.6) for postmenopausal women when the upper tertile of intake is compared with the lower tertile. Similar association exists when data are analyzed as total soy products intake. The upper and the lower tertile of soy protein intake among controls is >3.5 g/d and <1.6 g/d, and that of total soya products is >55 g/d and <20.3 g/d, respectively. Lee et al (1991) concluded, "Our findings indicate that a diet low in fat and high in soy(a) (and possibly other vegetable) proteins, vegetable oils, and vegetables containing carotene will confer a low risk of breast cancer."

Cross-Sectional Analysis

Nomura et al (1978) studied diet in relation to breast cancer in Hawaiian Japanese women using data from a prospective study on risk factors of gastrointestinal cancer in 6,860 Japanese men who previously participated in the Honolulu Heart Study. Eighty-six men reported that their wives had breast cancer. The husbands of the 86 women were compared with the rest of the men ($n = 5,729$) for dietary history under the assumption that husbands and wives consumed similar diet. It was found that spouses of women with breast cancer consume less tofu (117 g/wk) compared with those of women without breast cancer (151 g/wk). The difference is not statistically significant ($P = 0.16$).

Ecological Studies

Nagata et al (2000) assessed the relationship between soy intake and cancer mortality in an ecological study in Japan. Soy intake data from a National Nutritional Survey Report were correlated with mortality data (breast, prostate, stomach, colorectal, and lung cancer) from Vital Statistics and Population Census of Japan. Soy consumption was converted to soy protein intake before data were analyzed. Results of the analysis show

that soy protein intake is not associated with breast cancer in Japanese women ($r = -0.08$). This analysis also shows that soy intake is correlated with a lower mortality of stomach cancer, no correlation with prostate and lung cancer, and positively correlated with the mortality of colorectal cancer (see the respective sections for details).

Table 8. Epidemiological studies on soy consumption and breast cancer in women.

Cohort Studies						
Reference	Design, Dietary Assessment Methods	Description of Subjects, Race, and Study site	Confounding Factors Adjusted	Soy Products Assessed and Intake Levels	OR/RR (95% CI) ¹ (Highest vs. Lowest Intake)	Major Findings
Yamamoto (2003)	Prospective study (1990-1999), self-administered questionnaire.	179 incident cases identified from 21,852 cohort members during a 10-year follow-up period. Ages at baseline: 40-59 yrs, Japanese/Japan	Area, age, age at menarche, number of pregnancies, menopausal status, age at first pregnancy, active and passive smoking, alcohol consumption, leisure-time physical activity, education level, total energy, and meat, fish, vegetable, and fruit consumption.	<p>Isoflavones* Q4: 25 ± 2 mg/d Q1: 7 ± 3 mg/d median: 16 mg/d</p> <p>Soyfoods** Almost daily vs. <2 times/wk</p> <p>Miso ≥3 cups/d vs. <1 time/d</p> <p>*Derived from intake of soyfoods and miso.</p> <p>**Included soybeans, tofu, deep-fried tofu, and natto.</p>	<p>Isoflavones: 0.46 (0.25-0.84)</p> <p>Data assessed by menopausal status: Premenopausal: 0.66 (0.25-1.7)</p> <p>Postmenopausal: 0.32 (0.14-0.71)</p> <p>Soyfoods: 0.81 (0.49-1.3)</p> <p>Miso: 0.60 (0.34-1.1)</p>	<p>Consumption of isoflavones is associated with a significantly lower risk of breast cancer in Japanese women (<i>P</i> trend = 0.043). When data are analyzed on the basis of menopausal status, the results remain statistically significant for postmenopausal women (<i>P</i> = 0.006), but not for premenopausal women.</p> <p>Intake of soyfoods is related to a lower risk of breast cancer (<i>P</i> trend = 0.44), but results are not statistically significant. Consumption of soyfoods is related to a significantly lower risk of breast cancer in postmenopausal women (<i>P</i> trend = 0.031)(RR not presented), when data are analyzed on the basis of menopausal status.</p> <p>Intake of miso is inversely related to the risk of breast cancer in this study population (<i>P</i> trend = 0.042).</p>

Table 8. Epidemiological studies on soy consumption and breast cancer in women (continued).

Cohort Studies						
Reference	Design, Dietary Assessment Methods	Description of Subjects, Race, and Study site	Confounding Factors Adjusted	Soy Products Assessed and Intake Levels	OR/RR (95% CI) ¹ (Highest vs. Lowest Intake)	Major Findings
Horn-Ross (2002)	Cohort study (California Teachers Study)(1995-1997), food frequency questionnaire (mail survey)	711 incident cases of invasive breast cancer identified from 111,526 cohort members, Ages at baseline (mean): 52.5 yrs, 87% participants were white/U.S.A.	Age, race, daily caloric intake, family history of breast cancer, age at menarche, nulliparity/age at first full-term pregnancy, physical activity, and an interaction term for body mass index and menopausal status.	Isoflavones* Q5: >2.1 mg/d Q1: <0.6 mg/d mean: 1.8 mg/d *Derived from the intake of isoflavone-containing foods.	Genistein: 1.0 (0.7-1.3) Daidzein: 0.9 (0.7-1.2)	Consumption of isoflavone-containing foods is not related to breast cancer in this study population (<i>P</i> trend = 0.9 for genistein, and <i>P</i> trend = 0.6 for daidzein).
Key (1999)	Prospective study (1969-1993), mail survey questionnaires.	427 incident cases from 34,759 women who participated in the Life Span Study of Radiation Effects Research Foundation in Hiroshima and Nagasaki, Japan, Attained ages: Majority were 40 – 80 yrs, Japanese/Japan.	The probability of not having migrated out of the area covered by the cancer registries.	Tofu high: ≥5 times/wk low: ≤1 time/wk	1.07 (0.78-1.47)	Consumption of tofu is not related to breast cancer in this study population (<i>P</i> trend = 0.712).

Table 8. Epidemiological studies on soy consumption and breast cancer in women (continued).

Case-Control Studies						
Reference	Design, Dietary Assessment Methods	Description of Subjects, Race, and Study Site	Confounding Factors Adjusted	Soy Products Assessed and Intake Levels	OR/RR (95% CI) ¹ (Highest vs. Lowest Intake)	Major Findings
Hirose (2003)	Hospital-based case-control study (1989-2000), self-administered questionnaire during clinic visit.	Cases: 2,385, Controls: 19,013, Ages: ≥30 yrs, Japanese/Japan	Age, visit year, family history, age at menarche, parity and age at first full-term pregnancy, and in addition body mass index for postmenopausal women.	Soybean curd Q4: ≥5 times/wk Q1: <1-3 times/m	Premenopausal: 0.84 (0.67-1.04) Postmenopausal: 0.83 (0.65-1.05)	A higher intake soybean curd is related to a lower risk of breast cancer in premenopausal (<i>P</i> trend = 0.02) and postmenopausal women (<i>P</i> trend = 0.15).

Table 8. Epidemiological studies on soy consumption and breast cancer in women (continued).

Case-Control Studies						
Reference	Design, Dietary Assessment Methods	Description of Subjects, Race, and Study site	Confounding Factors Adjusted	Soy Products Assessed and Intake Levels	OR/RR (95% CI) ¹ (Highest vs. Lowest Intake)	Major Findings
Wu (2002)	Population-based case-control study (1995-1998), standardized, structured questionnaire (in-person interview).	Cases: 501, Controls: 594, Ages: 25-74 yrs, Asian-Americans (Chinese, Japanese, and Filipino)/U.S.A.	Age, Asian-ethnicity, birth place, education, age at menarche, pregnancy, current body mass index, menopausal status, use of menopausal hormones, intake of dark-leafy greens during adolescence, smoking history, alcohol intake, and family history of breast cancer.	Tofu (assessed for adolescent intake) Q4: >4 times/wk Q1: <1 time/m Isoflavones* (assessed for adult intake) Q4: >12.7mg/1,000 kcal Q1: <1.8 mg/1,000 kcal *Derived from intake of soyfoods (fresh green soy beans, dried soy beans, fresh tofu, fried tofu, dried or pressed tofu, natto, miso, Chinese and Western vegetarian meats, soymilk, and soy bean desserts).	Adolescent intake: 0.65 (0.38-1.10) Adult intake: 0.61 (0.39-0.97) Adolescent and adult intake: 0.65 (0.43-0.97) Data assessed by menopausal status: Premenopausal: 0.64 (adoles intake) 0.60 (adult intake) Postmenopausal: 0.41 (adoles intake) 0.39 (adult intake)	Soy consumption during adolescence and adult life is associated with a significantly lower risk of breast cancer in later life (<i>P</i> trend = 0.04, for both). Women with a high soy intake during adolescence and adult life have the lowest risk of breast cancer compared with those who are low in soy intake during both periods (<i>P</i> trend = 0.03). When data are analyzed on the basis of menopausal status, both adolescent and adult soy intake is related to a lower risk of breast cancer in premenopausal and postmenopausal women. Premenopausal women: <i>P</i> trend = 0.005 (adolescent intake) <i>P</i> trend = 0.14 (adult intake) Postmenopausal women: <i>P</i> trend = 0.007 (adolescent intake) <i>P</i> trend = 0.25 (adult intake)

Table 8. Epidemiological studies on soy consumption and breast cancer in women (continued).

Case-Control Studies						
Reference	Design, Dietary Assessment Methods	Description of Subjects, Race, and Study Site	Confounding Factors Adjusted	Soy Products Assessed and intake levels	OR/RR (95% CI) ¹ (Highest vs. Lowest Intake)	Major Findings
Shu (2001)	Population-based case-control study (1996-1998), food frequency questionnaire (in-person interview).	Cases: 1,459, Controls: 1,556 age-matched, Ages: 25-64 yrs, Chinese/China	Intake level of rice and wheat products, age, education, family history of breast cancer, history of breast fibroadenoma, waist to hip circumference ratio, age at menarche, physical activity, ever had live birth, age at first live birth, menopausal status, and age at menopause.	<p>Adolescent intake:</p> <p>Total soyfoods* Q5: >11.0 g/d Q1: <2.2 g/d</p> <p>Tofu Q5: >2.2 g/d Q1: <0.44 g/d</p> <p>Soyfoods (not include tofu) (not reported)</p> <p>*Included tofu, soy milk, and soy products other than tofu.</p>	<p>Adolescent intake:</p> <p>Total soyfoods: 0.51 (0.40-0.65)</p> <p>Tofu: 0.70 (0.55-0.90)</p> <p>Soyfoods (not included tofu): 0.65 (0.50-0.80)</p> <p>Data assessed by menopausal status: Premenopausal: 0.53 (0.39-0.72) Postmenopausal: 0.49 (0.33-0.74)</p>	<p>Adolescent soy consumption is associated with a significantly lower risk of breast cancer in later life (<i>P</i> trend <0.01).</p> <p>The significantly lower incidence of breast cancer is also observed when tofu and soyfoods (excluding tofu) are analyzed separately (<i>P</i> trend <0.01, for both).</p> <p>When data are analyzed on the basis of menopausal status, adolescent soy intake is related to a significantly lower risk of breast cancer in both premenopausal and postmenopausal women (<i>P</i> trend <0.01, for both).</p>

Table 8. Epidemiological studies on soy consumption and breast cancer in women (continued).

Case-Control Studies						
Reference	Design, Dietary Assessment Methods	Description of Subjects, Race, and Study Site	Confounding Factors Adjusted	Soy Products Assessed and intake levels	OR/RR (95% CI) ^a (Highest vs. Lowest Intake)	Major Findings
Dai (2001)	Population-based case-control study (1996-1998), food frequency questionnaire (in-person interview).	Cases: 1,459, Controls: 1,556 age-matched, Ages: 25-64 yrs, Chinese/China	Age, education, first degree family history of breast cancer, history of breast fibroadenoma, waste to hip ratio, age at menarche, physical activity, birth of ≥ 1 child, age at first birth, menopause status, age at menopause, and intake of meats and total energy.	Soy protein* high: >13.0 g/d low: occasionally mean: 10.3 g/d *Derived from intake of soyfoods (including tofu, soymilk, soy products other than tofu, fresh and dry soybeans, and soybean sprouts).	0.56 (0.32-1.00) When data were analyzed on the basis of receptor expression: ER ⁺ /PR ⁺ : 0.28 (0.13-0.57) ER ⁻ /PR ⁻ : 0.69 (0.21-2.25) ER ⁺ /PR ⁻ or ER ⁻ /PR ⁺ : 0.75 (0.20-2.88)	Consumption of soyfoods is related to a significantly lower risk of breast cancer in women (<i>P</i> trend = 0.02). The risk reduction is observed in both premenopausal and postmenopausal women (data not shown). When data are analyzed on the basis of types of receptors expressed in breast cells, there is a significantly lower risk of breast cancer in subjects positive for estrogen and progesterone receptors (ER ⁺ /PR ⁺) (<i>P</i> trend = 0.004). The risk reduction is greater than those with other receptor status, e.g., ER ⁻ /PR ⁻ , or ER ⁺ /PR ⁻ or ER ⁻ /PR ⁺ .

Table 8. Epidemiological studies on soy consumption and breast cancer in women (continued).

Case-Control Studies						
Reference	Design, Dietary Assessment Methods	Description of Subjects, Race, and Study Site	Confounding Factors Adjusted	Soy Products Assessed and Intake Levels	OR/RR (95% CI) ^f (Highest vs. Lowest Intake)	Major Findings
Horn-Ross (2001)	Population-based case-control study (1995-1998), food frequency questionnaire (in-person interview).	Cases: 1,326, Controls: 1,657, Ages: 35-79 yrs, Non-Asian American women (African-American, Latino, and White)/USA	Age, race/ethnicity, age at menarche, parity, lactation, history of benign breast disease, family history of breast cancer, education, a composite variable including menopausal status, body mass index, hormone replacement therapy use, and daily caloric intake.	Total isoflavones* Q4: ≥ 2.8 mg/d Q1: < 1 mg/d Soy milk Consumers vs. non-consumers Soy burgers ≥ 1 time/m vs. non-consumers Tofu ≥ 1 time/m vs. non-consumers *Derived from isoflavone-containing foods.	Total isoflavones 1.0 (0.79-1.3) Soy milk 0.57 (0.38-0.85) Soy burgers 0.74 (0.55-0.99) Tofu 0.89 (0.70-1.10)	Intake of isoflavones (derived from isoflavone-containing foods) is not related to breast cancer in this study population. Consumption of soymilk and soy burgers is associated with a significantly lower risk of breast cancer in women. Tofu intake is related to a lower risk of breast cancer, but results are not statistically significant.
Witte (1997)	Familial matched case-control study (1989), food frequency questionnaire (mail survey)	Cases: 140, Controls: 222, Caucasian/USA and Canada	Age, age at menarche, parity, oral contraceptive use, alcohol consumption, body mass index, and energy.	Tofu 1 serving/wk vs. none	0.5 (0.2-1.1)	Tofu intake is related to a lower risk of premenopausal bilateral breast cancer in this study population.

Table 8. Epidemiological studies on soy consumption and breast cancer in women (continued).

Case-Control Studies						
Reference	Design, Dietary Assessment Methods	Description of Subjects, Race, and Study Site	Confounding Factors Adjusted	Soy Products Assessed and Intake Levels	OR/RR (95% CI) ¹ (Highest vs. Lowest Intake)	Major Findings
Wu (1996)	Population-based case-control study (1983-1987), food frequency questionnaire (in-person interview).	Cases: 597, Controls: 966, Ages: 20-55 yrs, Asian-American women (Chinese-, Japanese-, and Filipino-American women)/USA	Age, study area, ethnicity, and migration status.	Tofu Q4: >55 times/yr Q1: ≤12 times/yr	0.85 (0.74-0.99) Data assessed by menopausal status: Premenopausal: 0.84 (0.70-0.99) Postmenopausal: 0.86 (0.66-1.13)	A higher intake of tofu is related to a significantly lower risk of breast cancer (<i>P</i> trend = 0.03). When data are analyzed on the basis of menopausal status, tofu intake is related to a significantly lower risk of breast cancer in premenopausal women (<i>P</i> trend = 0.04), but not in postmenopausal women (<i>P</i> trend = 0.28).
Hirose (1995)	Hospital-based case-control study (1988-1992), self-administered questionnaire during clinic visit.	Cases: 1,052, Controls: 23,163, Ages: ≥29 yrs, Japanese/Japan	Age.	Bean curd high: ≥3 times/wk low: ≤3 times/m	Premenopausal: 0.78 (0.6-1.0) Postmenopausal: 0.96 (0.7-1.31)	A high intake of bean curd is associated with a downward trend in breast cancer risk in premenopausal women, but not in postmenopausal women.

Table 8. Epidemiological studies on soy consumption and breast cancer in women (continued).

Case-Control Studies						
Reference	Design, Dietary Assessment Methods	Description of Subjects, race, and Study Site	Confounding Factors Adjusted	Soy Products Assessed and Intake Levels	OR/RR (95% CI) [†] (Highest vs. Lowest Intake)	Major Findings
Yuan (1995)	Community-based case-control study (1984-1985), questionnaire (in-person interview).	Cases: 834, Controls: 834, Ages: 20-69 yrs, Chinese/China (conducted in Shanghai and Tianjin)	Energy intake and non-dietary risk factors including age at menarche, usual cycle length under 25 days, number of full term pregnancies, duration of nursing (years), first used oral contraceptives at age 35+, 61+ kg average body weight, benign breast disease, female first degree relatives had breast cancer, and level of education.	Soy protein* Shanghai (ctls): high: >12.6 g/d low: <2.4 g/d median: 3.5 g/d Tianjin (ctls): high: >7.1 g/d low: <1.2 g/d median: 2.8 g/d *Derived from the intake of soyfoods.	1.0 (0.7-1.4)	Soy consumption is not related to breast cancer in this study population.
Lee (1992) (1991)	Hospital-based case-control study (1986-1990), food frequency questionnaire (in-person interview).	Cases: 200, Controls: 420, Ages: 24-58 yrs, Chinese /Singapore	Age and age at birth of the first child including nulliparous as a category for premenopausal women. Age, nulliparity, height, education, and family history of breast cancer for postmenopausal women.	Soy protein* T3: >3.5 g/d T1: <1.6 g/d Median: 2.5 g/d (ctls), 2.2 g/d (cases) Soy products T3: >55 g/d T1: <20.3 g/d Median: 35.6 g/d (ctls), 28.5 g/d (cases)	Premenopausal: 0.4 (0.2-0.8) Postmenopausal: 1.8 (0.8-3.6) *Derived from total soya product intake.	Consumption of soy protein is associated with a significantly lower risk of breast cancer in premenopausal women (<i>P</i> trend = 0.01), but not in postmenopausal women. Similar association exists when data are analyzed as total soy product intake.

Table 8. Epidemiological studies on soy consumption and breast cancer in women (continued).

Cross-Sectional Analysis						
Reference	Design, Dietary Assessment Methods	Description of Subjects, Race, and Study Site	Confounding Factors Adjusted	Soy Products Assessed and Intake Levels	OR/RR (95% CI) ¹ (Highest vs. Lowest Intake)	Major Findings
Nomura (1978)	Case-control comparison (1971-1975) on husbands of women with or without breast cancer using data from a prospective study (Honolulu Heart Study), food frequency questionnaire during clinic visit.	Cases: 86, Controls: 5,729, Ages: Japanese/USA	Age.	Tofu (intake levels, not presented)	N/A	The study was done using data from a prospective study that assessed risk factors of gastrointestinal cancer in Japanese men and under the assumption that husbands and wives had the similar dietary practice. It was found that husbands of breast cancer cases consume less tofu compared with those of controls (117 g/wk vs. 151 g/wk, $P = 0.16$).
Ecological Study						
Reference	Design, Dietary Assessment Methods	Description of Subjects, Race, and Study Site	Confounding Factors Adjusted	Soy Products Assessed and Intake Levels	OR/RR (95% CI) ¹ (Highest vs. Lowest Intake)	Major Findings
Nagata (2000)	Ecological study	Correlation analysis using data from National Nutritional Survey Report 1980-1985 and National Vital Statistics 1995, Japanese/Japan.	Mean age, proportion of current smokers, and intake of alcoholic and animal fat.	Soy protein* 6.5 ± 0.8 g/d (mean ± SD) *Derived from soyfoods (miso, tofu, fried tofu, soybeans, soy milk, and yuba).	$R^{**} = -0.08$ **correlation coefficient.	Intake of soy protein is not correlated with the mortality of breast cancer in Japanese women.

¹OR/RR (95% CI) = odds ratio/relative risk (95% confidence interval).

B.3.1 (1)(b). Urinary Isoflavones and Breast Cancer

There are six case-control studies that relate urinary isoflavones to breast cancer in women (Table 9).

Case-Control Studies

Dai et al (2003) examined potential effects of endogenous estrogens and anthropometrics on the association of urinary phytoestrogens with breast cancer in Chinese women (300 case-control pairs). Blood and urine specimen were collected in the morning before breakfast, and urinary phytoestrogens were analyzed using liquid chromatography mass spectrometry. In nearly 50% of the cases, specimen collection and in-person interview were completed before any cancer therapy. A higher urinary excretion of isoflavonoids is related to a significantly lower risk of breast cancer (P trend = 0.04). The adjusted OR is 0.46 (95% CI = 0.22-0.95) when the highest tertile of excretion is compared with the lowest. The median excretion of total isoflavones is 18.4 nmol/mg creatinine for the cases and 26.4 nmol/mg creatinine for the controls (P = 0.04). When data are analyzed on the basis of body mass index, waist:hip ratio, or blood levels of sex hormones, an inverse association between isoflavonoid excretion and breast cancer risk exists in subjects with a high body mass index (≥ 25) (P trend = 0.06), a high waist:hip ratio (≥ 0.84) (P trend = 0.02), and a high blood level of estradiol (> 5.73 pg/ml) (P trend = 0.01). The adjusted OR is 0.38 (95% CI = 0.13-1.17) for subjects with a high body mass index, 0.18 (95% CI = 0.05-0.68) for those with a high waist:hip ratio, and 0.22 (95% CI = 0.07-0.68) for women with a high level of blood estradiol when the highest tertile of isoflavone excretion is compared with the lowest. Dai et al (2003) concluded, "In summary, we found that the association of phytoestrogens with breast cancer may be modified by body mass index, waist:hip ratio, and blood level of sex hormones and sex hormone binding globulin. These results are consistent with findings from in vitro and in vivo studies. Our findings, if confirmed in future larger studies, could have significant public health implications, as women with a high risk of breast cancer could be specifically targeted for increasing phytoestrogen intake."

Dai et al (2002a) assessed urinary phytoestrogens (isoflavonoids, mammalian lignans, and citrus flavonoids) in relation to breast cancer in Chinese women (250 case-control pairs). Overnight urine was used for analysis, and samples from cases were collected after their initial diagnosis but before they received any treatment for cancer. Urinary phytoestrogens were analyzed using liquid chromatography mass spectrometry. A higher urinary excretion of isoflavonoids is related to a significantly lower risk of breast cancer (P trend = 0.04). The adjusted OR is 0.62 (95% CI = 0.39-0.99) when the highest tertile of excretion is compared with the lowest. The mean (mean \pm SD) excretion of total isoflavones is 32.3 ± 43.7 nmol/mg creatinine for the cases and 40.5 ± 62.6 nmol/mg creatinine for the controls ($P = 0.01$). When data are analyzed on the basis of menopausal status, a significant inverse association between isoflavonoid excretion and breast cancer risk exists in postmenopausal women (P trend = 0.07). The greatest reduction in breast cancer risk is observed in women with a high excretion rate of both isoflavonoids and mammalian lignans (adjusted OR = 0.28, 95% CI = 0.15-0.50). Dai et al (2002a) concluded, "The results from this study suggest that high intake of certain phytoestrogens may reduce the risk of breast cancer."

Murkies et al (2000) investigated the association of urinary daidzein and genistein with breast cancer in postmenopausal women in Australia. Eighteen cases with recently diagnosed breast cancer and 20 controls were recruited. A 24-h urine was collected from cases before admission for surgery and from controls at their early convenience. Urinary isoflavones were analyzed using high-performance liquid chromatography. The controls excrete a greater amount of daidzein and genistein compared with the cases (427 nmol/24 h vs. 31 nmol/24 h for daidzein, $P = 0.03$; 155 nmol/24 h vs. 25 nmol/24 h for genistein, $P = 0.08$). Murkies et al (2000) concluded, "This preliminary study is the first report of low urinary daidzein and genistein in postmenopausal women with breast cancer. These findings are in keeping with the increasing observational data demonstrating a protective effect from phytoestrogens on breast cancer risk."

Zheng et al (1999) examined the association of urinary isoflavones with breast cancer in a case-control study (60 case-control pairs) in Shanghai, China. Urine samples were

collected from breast cancer cases before they received any cancer therapy, and analyzed using high-performance liquid chromatography. Controls were individually matched to cases by age, menopausal status, and date of sample collection. The controls excrete a greater amount of isoflavonoids compared with the cases (19.5 nmol/mg creatinine vs. 14.0 nmol/mg creatinine, $P = 0.04$). A higher excretion of isoflavonoids is related to a lower risk of breast cancer (P trend = 0.11). The adjusted OR is 0.50 (95% CI = 0.19-1.31) when the highest tertile of excretion (≥ 18.7 nmol/mg creatinine) is compared with the lowest (< 5.6 nmol/mg creatinine). Furthermore, a higher excretion of both total isoflavonoids and phenols is related to a significantly lower risk of breast cancer (adjusted OR = 0.14, 95% CI = 0.02-0.88). Zheng et al (1999) concluded, "The results from this study support the hypothesis that a high intake of soy foods may reduce the risk of breast cancer."

Ingram et al (1997) assessed urinary phytoestrogens in relation to breast cancer in a case-control study in Western Australia. A total of 144 women with newly diagnosed breast cancer before receiving any treatment for cancer was compared with an equal number of controls. Urinary isoflavones were analyzed using isotope-dilution gas chromatography mass spectrometry. A higher excretion of daidzein and its metabolite equol is associated with a substantially lower risk of breast cancer (P trend = 0.09 for equol, P trend = 0.241 for daidzein). The adjusted OR is 0.27 (95% CI = 0.10-0.69) for equol and 0.47 (95% CI = 0.17-1.33) for daidzein when the highest quartile of excretion is compared with the lowest. The highest and the lowest quartiles are ≥ 185 nmol/24 h and ≤ 70 nmol/24 h for equol, and $\geq 1,300$ nmol/24 h and ≤ 600 nmol/24 h for daidzein, respectively. Ingram et al (1997) concluded, "There is a substantial reduction in breast cancer risk among women with a high intake (as measured by excretion) of phytoestrogens – particularly the isoflavonic phytoestrogen equol and the lignan enterolactone. These findings could be important in the prevention of breast cancer."

den Tonkelaar et al (2001) examined the association of urinary phytoestrogens with breast cancer in 88 cases and 268 controls selected from a population-based breast cancer screening program in Netherlands. Urinary specimens were collected 1-9 years prior to

the diagnosis of the disease, and urinary isoflavones were analyzed using time-resolved fluoroimmunoassay. A higher urinary genistein excretion is associated with a lower risk of breast cancer, although results are not statistically significant. The OR is 0.83 (95% CI = 0.46-1.51) when the highest tertile of excretion (196.6 $\mu\text{mol/mol}$ creatinine) is compared with the lowest (48.4 $\mu\text{mol/mol}$ creatinine). den Tonkelaar et al (2001) pointed, "We were not able to detect the previously reported protective effects of genistein and enterolactone on breast cancer risk in our postmenopausal population of Dutch women. Such an effect may be smaller than expected and/or limited to specific subgroups of the population."

Table 9. Epidemiological studies on urinary isoflavones and breast cancer in women.

Case-Control Studies						
Reference	Design, and Assessment methods	Description of Subjects, Race, and Study Site	Confounding Factors Adjusted	Urinary Isoflavones and Levels of Excretion	OR (95% CI) ¹ (Highest vs. Lowest Level)	Major Findings
Dai (2003)	Population-based case-control study (1996-1998), structured questionnaires (in-person interview), and urinary isoflavone analysis (LC/MS) ² .	Cases: 300, Controls: 300, Ages: 25-64 yrs Chinese/China	Age at first live birth, ever diagnosed with fibroadenoma, total meat intake, and ever physically active.	Total isoflavonoids Ctls: 26.4 (8.3,62.3)* Cases: 18.4 (5.4,44.9) *Median (25 th , 75 th percentile), expressed as nmol/ mg creatinine.	Isoflavonoids: 0.46 (0.22-0.95) Data assessed by body mass index: 0.38 (0.16 – 1.17) Data assessed by waist:hip ratio 0.18 (0.05 – 0.68) Data assessed by blood estradiol: 0.22 (0.07 – 0.68)	A higher urinary excretion of isoflavonoids is related to a significantly lower risk of breast cancer (<i>P</i> trend = 0.04). Controls excrete a greater amount of isoflavonoids than the cases (<i>P</i> <0.04). When data are analyzed on the basis of body mass index, waist:hip ratio, or blood sex hormone levels, an inverse association between urinary isoflavonoids and breast cancer risk exists in subjects with high body mass index (<i>P</i> trend = 0.06), high waist:hip ratio (<i>P</i> trend = 0.02), and high blood estradiol level (<i>P</i> trend = 0.01).
Dai (2002a)	Population-based case-control study (1996-1998), food frequency questionnaires (in-person interview), and urinary isoflavone analysis (LC/MS) ² .	Cases: 250, Controls: 250, Ages: 25-64 yrs Chinese/China	Age at first live birth, ever diagnosed with fibroadenoma, total meat intake, and physical activity level.	Isoflavonoids Ctls: 40.5 ± 62.6* Cases: 32.3 ± 43.7 *Mean ± SD, expressed as nmol/ mg creatinine.	Isoflavonoids: 0.62 (0.39-0.99) Data assessed by menopausal status Postmenopausal: 0.54 (0.28-1.06) Premenopausal: 0.72 (0.36-1.44)	Urinary excretion of isoflavonoids is significantly greater in controls than in cases (<i>P</i> <0.01), which is related to a significantly lower risk of breast cancer in this study population (<i>P</i> trend = 0.04). When data are analyzed on the basis of menopausal status, a higher isoflavonoid excretion is related to a significantly lower risk of breast cancer in postmenopausal women (<i>P</i> trend = 0.07).

Table 9. Epidemiological studies on urinary isoflavones and breast cancer in women (continued).

Case-Control Studies						
Reference	Design, and Assessment Methods	Description of Subjects, Race, and Study Site	Confounding Factors Adjusted	Urinary Isoflavones and Levels of Excretion	OR (95% CI) [†] (Highest vs. Lowest Level)	Major Findings
Murkies (2000)	Case-control study (1997-1998), food frequency questionnaire (in-person interview), and urinary isoflavone analysis (HPLC) [‡] .	Postmenopausal women, Cases: 18, Controls: 20, Ages (mean): 59.3 yrs (cases) 57.3 yrs (ctls), Australian /Australia	Age, body mass index, family history of breast cancer, intake of nutrient and phytoestrogen supplements, alcohol use, smoking status, level of exercise, reproductive variables, and previous use of HRT.	Daidzein Controls: 427 (96, 1,906)* Cases: 31 (4, 234) Genistein Controls: 155 (43, 550) Cases: 25 (5, 132) *Median (95% CI), expressed as nmol/24 h.	N/A	Controls excrete a greater amount of daidzein ($P < 0.03$) and genistein ($P < 0.08$) than cases in this study population of postmenopausal women.
Zheng (1999)	Population-based case-control study (1996-1997), structured questionnaire (in-person interview), and urinary isoflavone analysis (HPLC) [‡] .	Cases: 60, Controls: 60, Ages: 25-64 yrs, Chinese/China	Age at first pregnancy and physical activity levels.	Isoflavonoids Ctls: $19.5 \pm 25.4^*$ Cases: 14.0 ± 20.8 *Mean \pm SD, expressed as nmol/mg creatinine.	0.50 (0.19-1.31)	An inverse relationship exists between urinary isoflavonoid excretion and breast cancer risk in this study population (P trend = 0.11). Controls excrete a greater amount of isoflavonoids compared with the cases ($P = 0.04$).

Table 9. Epidemiological studies on urinary isoflavones and breast cancer risk in women (continued).

Case-Control Studies						
Reference	Design, and Assessment Methods	Description of Subjects, Race, and Study Site	Confounding Factors Adjusted	Urinary Isoflavones and Levels of Excretion	OR (95% CI) ¹ (Highest vs. Lowest Level)	Major Findings
Ingram (1997)	Case-control study (1992-1994), standard questionnaire (in-person interview), and urinary isoflavone Analysis (GC-MS) ⁴ .	Cases: 144, Controls: 144, Ages: 30-84 yrs, Australian /Australia	Age at menarche, alcohol intake, and total fat intake.	Equol Ctls: 109 (70, 181)* Cases: 97 (64, 162) Daidzein Ctls: 913 (612, 1,274) Cases: 783 (463, 1,180) *Median (95% CI), expressed as nmol/ 24 h.	Equol: 0.27 (0.10-0.69) Daidzein: 0.47 (0.17-1.33)	A higher urinary excretion of equol and daidzein is associated with a substantially lower risk of breast cancer (<i>P</i> trend = 0.009 for equol, <i>P</i> trend = 0.241 for daidzein).
den Tonkelaar (2001)	Case-control study nested in a prospective study (1977-1985), self-administered questionnaire and urinary isoflavone analysis (TR-FIA) ⁵ .	Postmenopausal women, Cases: 88, Controls: 268, Ages: 50-64 yrs, Dutch /Netherlands	None.	Genistein Ctls: 111.6 ± 82.0* Cases: 107.7 ± 85.7 *Mean ± SD, expressed as genistein/creatinine (µmol/mol).	0.83 (0.46-1.51)	A high urinary genistein is associated with a lower risk breast cancer in this study population (<i>P</i> trend = 0.6), although results are not statistically significant.

¹OR (95% CI) = odds ratio (95% confidence interval). ²Liquid chromatography mass spectrometry. ³High-performance liquid chromatography. ⁴Isotope-dilution gas chromatography mass spectrometry. ⁵Time-resolved fluorimmunoassay.

B.3.1 (2). Animal Studies

Summary

Animal studies support epidemiological findings that consumption of soy-protein containing foods is related to a lower risk of breast cancer in women. This section reviews studies that related soy protein to experimentally induced mammary tumorigenesis in animals. It includes studies that assessed soy protein as a component of a diet and examined the preventive effect of such a diet (the experimental diet was given to animals prior to carcinogen administration). Fifteen publications are available to date (Table 10). Isolated soy protein (ISP) was assessed in most of these studies. Other soy protein-containing preparations included soy protein concentrate, powdered soybeans, soybean chips, and soymilk. In these studies, ISP or a soy protein-containing preparation was supplemented to the diet at the expense of casein (a protein source of standard research diets), and ISP was compared with casein as the sole source of dietary protein (e.g., 20% soy protein vs. 20% casein) in most studies. The dietary levels of soy protein and casein in each of studies are summarized in Table 10. Tumor-causing agents used in these studies include chemical carcinogens, malignant cells, χ -ray irradiation, and spontaneous mammary tumor development and metastasis. A thorough review of these studies reveals that dietary supplementation with soy protein inhibits experimentally induced mammary tumorigenesis in animals.

Isolated Soy Protein

There are 12 studies that examined the effect of isolated soy protein on experimentally induced mammary tumorigenesis in animals.

Results of six studies demonstrate that dietary supplementation with 10-20% ISP reduces 7,12-dimethylbenz(a)anthracene (DMBA)-induced mammary tumor development in female rats compared with the controls fed a casein diet (Appelt & Reicks, 1999; Badger et al., 2001; Barnes et al., 1990; Barnes et al., 1994; Constantinou et al., 2001; Hakkak et al., 2000). DMBA is a pre-carcinogen. It must be metabolized to its active form in the host before being carcinogenic. Two of these studies are multi-generation feeding studies (Badger et al., 2001; Hakkak et al., 2000). In these studies, offspring from female rats on

a soy protein diet were mated and maintained on the same diet for two generations before receiving a DMBA treatment. Dietary supplementation with ISP significantly decreases tumor incidence and increases tumor latency period in the offspring fed the ISP diet compared with the controls on a casein diet.

Results of three studies show that ISP inhibits *N*-nitrosomethylurea (NMU)-induced mammary tumorigenesis. NMU is a direct carcinogen. Hawrylewicz et al (1991) reported that maintaining rats on a diet containing 19% ISP increases tumor latency period ($P<0.01$) and decreases tumor incidence ($P<0.01$), tumor number, and tumor weight compared with the controls. Zaizen et al (2000) found that feeding rats a diet containing 20% ISP prolongs tumor latency period ($P<0.02$) and reduces tumor incidence. Cohen et al (2000) reported that dietary supplementation with 20% ISP or 20% alcohol-extracted ISP reduces the number and the volume of mammary tumors and prolongs tumor latency compared with the casein-fed controls. The inhibition by the 20% ISP or the 20% alcohol-extracted ISP diet tends to be greater than that by the 10% ISP or the 10% alcohol-extracted ISP diet.

Yan et al (2002) reported that ISP reduces spontaneous metastasis of mammary carcinoma in mice. In this study, metastatic 4526 mammary carcinoma cells were inoculated into mammary fat pad to develop a primary tumor, and the malignant tumors formed in the lungs were examined at the end of the experiment. Dietary supplementation with 10% and 20% ISP reduces the spread of mammary carcinoma cells to the lungs in mice. The differences in the incidence of metastasis, the number, and the size of malignant tumors formed in the lungs are statistically significant between the 20% ISP group and the control group maintained on a casein diet ($P<0.05$, for all the above variables).

Gridley et al (1983) examined the long-term effect of different sources of protein (including soy), fat, and carbohydrate on spontaneous mammary tumor development in mice. Animals were maintained on one of the experimental diets or a commercial control diet for two years. At the end of the experiment, there is no significant difference in

spontaneous mammary tumor development between the soy protein group (33% soy protein in the diet) compared with the controls fed the commercial diet. The type of soy protein tested in this study was not specified.

Soy Protein Concentrate

Barnes et al (1994) compared the anti-tumorigenic effect of ISP with alcohol-extracted soy protein concentrate using the DMBA mammary tumor model. Isolated soy protein inhibits DMBA-induced mammary tumorigenesis, whereas alcohol-extracted soy protein concentrate does not inhibit tumor development, compared with the casein-fed controls.

Soybeans and Soybean Chips

Gotoh et al (1998) reported that feeding rats a diet containing 10% powdered soybeans significantly decreases tumor multiplicity (number of tumors/rat) induced by NMU compared with the controls. Troll et al (1980) found that providing rats a diet containing 50% raw soybeans inhibits χ -irradiation-induced mammary tumor development in rats. Barnes *et al* (1990) found that dietary supplementation with 10-40% powdered soybean chips (equivalent to 5-20% soy protein) reduces the number of histologically confirmed mammary tumors induced by MNU in a dose-dependent manner in rats.

Connolly et al (1997) reported that dietary supplementation with soy chips reduces spontaneous metastasis of mammary carcinoma in mice. The MDA-MB-435 human breast cancer cells were orthotopically inoculated into mice, and the malignant tumors development in the lungs was determined at the end of the experiment. Soy chips were supplemented to a high-fat diet (20% fat) at 5%, 10%, or 20% at the expense of casein and carbohydrates. Dietary supplementation with 10% and 20% soy chips significantly reduces the incidence of metastasis ($P < 0.05$) and the number of macro-metastatic tumors formed in the lungs ($P < 0.05$) compared with the casein-fed controls. There are no significant differences in these measurements between the 5% soy group and the control group.

Soymilk

Ohta et al (2000) investigated the effect soymilk (fermented with *Bifidobacterium breve* strain Yakult) on 2-amino-1-methyl-6-phenylimidazo (4,5-*b*) pyridine (PhIP)-induced mammary tumorigenesis in rats. Fermented soymilk contained a larger amount of isoflavone aglycones compared with the non-fermented soymilk. The basal diet used in this study was a high fat diet (23.5% fat). Dietary supplementation with 10% fermented soymilk significantly reduces tumor multiplicity ($P<0.05$), tumor volume ($P<0.05$), and tumor incidence (not statistically significant) compared with the controls.

Studies on the growth of estrogen-dependent mammary tumor in ovariectomized animals are discussed in Appendix VI, Section 2.

Table 10. Animal studies on dietary soy protein and experimentally induced mammary tumorigenesis.

Reference	Species/Strain, Sex	Carcinogen	Dietary Comparison	Major Findings
Badger (2001)	Rats/Sprague-Dawley, female	DMBA ¹	Casein (20%) ISP ² (20%)	Feeding rats a diet containing 20% ISP for two generations significantly decreases tumor incidence ($P<0.05$) and increases tumor latency period (P value not presented) in F2 offspring compared with the controls maintained on a casein-based diet.
Hakkak (2000)	Rats/Sprague-Dawley, female	DMBA	Casein (20%) ISP (20%)	Feeding rats a diet containing 20% ISP for two generations significantly decreases tumor incidence ($P<0.002$) and increases tumor latency period ($P<0.009$) in F2 offspring compared with the controls fed a casein-based diet.
Constantinou (2001)	Rats/Sprague-Dawley, female	DMBA	Casein (17.4%) ISP* (16%) Alcohol-washed ISP** (16%)	Dietary supplementation with ISP ($P<0.05$) or alcohol-washed ISP ($P<0.01$) significantly reduces tumor multiplicity (number of tumors/rat) and increases tumor latency period (NSS ³) compared with the controls. However, there are no significant differences between these two ISP groups. *Containing total isoflavones at 2.89 mg/g. **Containing total isoflavones at 0.2 mg/g.
Appelt (1999)	Rats/Sprague-Dawley, female	DMBA	Casein (20%) ISP (20%), three types containing isoflavones at 0.03 mg/g, 0.4 mg/g, or 0.81 mg/g diet.	Feeding rats an ISP diet containing low, medium, or high level of isoflavones results in a dose-dependent reduction in tumor incidence ($P<0.09$), a decrease in the number of tumors ($P<0.10$), and an increase in phase II enzyme activities compared with the controls.
Barnes (1994)	Rats/Sprague-Dawley, female	DMBA	Casein (20%) ISP* (11% or 22%) Alcohol-extracted soy protein concentrate** (20%)	Dietary supplementation with 11% and 22% ISP results in a dose-dependent reduction in the number of histologically confirmed mammary tumors compared with the controls (P value not presented). There is no difference in the number of histologically confirmed mammary tumors between the group with alcohol-extracted soy protein concentrate and the casein controls. *Containing total isoflavones at 0.4 mg/g. **Containing total isoflavones at <0.1 mg/g.

Table 10. Animal studies on dietary soy protein and experimentally induced mammary tumorigenesis (continued)

Reference	Species/Strain, Sex	Carcinogen	Dietary Comparison	Major Findings
Barnes (1990)	Rats/Sprague-Dawley, female	DMBA MNU ^d	Casein (20%) ISP (11%, 22%) Casein (20%) Powdered soybean chips (10%, 20%, 40%)	Feeding rats a diet containing 11% or 22% ISP results in a 40% reduction in the number of DMBA-induced palpable mammary tumors compared with the controls (<i>P</i> value not presented). Dietary supplementation with powdered soybean chips results in a dose-dependent reduction in the number of histologically confirmed mammary tumors induced by MNU compared with the controls (<i>P</i> value not presented). There is no difference in the degree of inhibition between the autoclaved and the non-autoclaved soybean chips, suggesting other soy constituents, in addition to protease inhibitors, are responsible for the protective effects.
Hawrylewicz (1991)	Rats/Sprague-Dawley, female	MNU	Casein (20%) ISP (19%)	Feeding rats a diet containing 19% ISP increases the mean tumor latency period (<i>P</i> <0.01) and decreases tumor incidence (<i>P</i> <0.01), tumor number (NSS), and tumor weight (NSS) compared with the controls.
Zaizen (2000)	Rats/F344, female	MNU	Casein (20%) ISP (20%)	Dietary supplementation with 20% ISP significantly increases tumor latency period (<i>P</i> <0.02) and reduces tumor incidence (NSS) compared with the controls.
Cohen (2000)	Rats/F344, female	NMU	Casein (20%) ISP* (10%, 20%) Alcohol-washed ISP** (10%, 20%)	Dietary supplementation with 20% ISP or 20% alcohol-washed ISP decreases the number and volume of tumors, and increases tumor latency period compared with the casein-fed controls (NSS). The diet supplemented with 20% ISP or alcohol-washed ISP tends to have a greater inhibitory effect than that with 10% ISP or alcohol-extracted ISP (NSS). There are no significant differences in tumor numbers, volume, and latency between ISP and alcohol-washed ISP at either level. *Containing total isoflavones at 2.89 mg/g. **Containing total isoflavones at 0.2 mg/g.

Table 10. Animal studies on dietary soy protein and experimentally induced mammary tumorigenesis (continued).

Reference	Species/Strain, Sex	Carcinogen	Dietary Comparison	Major Findings
Yan (2002)	Mice/BALB/c, female	4526 murine mammary carcinoma cell line (orthotopic inoculation)	Casein (20%) ISP (10%, 20%)	This study examined the effect of dietary supplementation with ISP on spontaneous metastasis of mammary carcinoma in mice. Feeding mice a diet containing 10% or 20% ISP reduces the incidence of metastasis, the number, and the size (cross-sectional area and volume) of metastatic tumors formed in the lungs compared with the casein-fed controls. Differences in these measurements between the 20% ISP and the control groups are statistically significant ($P<0.05$).
Gridley (1983)	Mice/C3H/HeJ, female	Spontaneous mammary tumor development	Commercial control diet Soy protein* (33%)	The long-term effect (two years) of different sources of protein (including soy), fat, and carbohydrate on spontaneous mammary tumor development was determined in mice. There is no significant difference in tumor development between the soy group and the controls fed a commercial diet at the end of the study. *The type of soy protein was not reported.
Gotoh (1998)	Rats/Sprague-Dawley, female	MNU	Commercial control diet Powdered soybeans (2%, 10%)	Feeding rats a diet containing 10% powdered soybeans significantly reduces tumor multiplicity ($P<0.05$) compared with those fed a commercial control diet. There is no significant difference in tumor multiplicity between the 2% soybean group and the control group.
Troll (1980)	Rats/Sprague-Dawley, female	X-irradiation	Casein (32%) Raw soybeans (50%)	Dietary supplementation with 50% raw soybeans significantly reduces tumor incidence (adenocarcinoma and fibroadenoma) compared with the controls ($P=0.01$).
Connolly (1997)	Mice/NCr-nu-nu, female	MDA-MB-435 human breast cancer cells (orthotopic injection)	High-fat diet (20% fat with 21% casein) High-fat diet (20% fat with 5%, 10%, or 20% soy chips, adjusted to have a total of 21% protein)	Dietary supplementation with 10% or 20% soy chips significantly reduces the incidence of metastasis ($P<0.05$) and the number of macroscopic metastatic tumors formed in the lungs ($P<0.05$) compared with the controls maintained on the casein diet.

Table 10. Animal studies on dietary soy protein and experimentally induced mammary tumorigenesis (continued).

Reference	Species/Strain, Sex	Carcinogen	Dietary Comparison	Major Findings
Ohta (2000)	Rats/Sprague-Dawley, female	PhIP ⁵	High-fat diet (23.5% corn oil with 23.5% casein) High-fat diet (21.1% corn oil with 19.1% casein and 10% fermented soymilk*)	Feeding rats a high-fat diet containing 10% fermented soymilk significantly reduces tumor multiplicity (number of tumors/rat) ($P<0.05$), tumor volume ($P<0.05$), and tumor incidence (NSS) compared with the controls. *Fermented with <i>Bifidobacterium breve</i> strain Yakult and contained a larger amount of isoflavone aglycones compared with the unfermented soymilk.

¹DMBA: 7,12-dimethylbenz (a) anthracene; ²ISP: isolated soybean protein; ³NSS: not statistically significant; ⁴MNU: *N*-nitroso-*n*-methylurea; ⁵PhIP: 2-amino-1-methyl-6-phenylimidazol (4,5-*b*) pyridine.

B.3.2. Prostate Cancer

This section considers the weight of scientific evidence that relates consumption of soy protein-containing foods to the risk of prostate cancer in men. It reviews and evaluates the literature of epidemiological studies on the relationship between soy and prostate cancer in men. It also reviews animal studies that investigate the effect of dietary soy protein on experimentally induced prostate tumorigenesis. There are 10 epidemiological studies available to date (two cohort studies, six case-control studies, one cross-national analysis, and one ecological study). Results from these studies show that consumption of soy protein-containing foods is associated with a lower incidence of prostate cancer in men. The relationship between soy consumption and a lower risk of prostate cancer is supported by results of a meta-analysis of available studies that provide adequate data for a pooled analysis (pooled estimate of odds ratio/relative risk = 0.66, 95% CI = 0.54 – 0.81, $P < 0.001$) (Figure 5). Animal studies support the epidemiological findings. Of 12 studies that examine the effect of dietary supplementation with soy protein or soy protein-containing preparations, 11 show an inhibitory effect on experimentally induced prostate tumorigenesis. In conclusion, the totality of the publicly available scientific evidence supports the substance/disease relationship that consumption of soy protein-containing foods is related to a lower risk of prostate cancer in men.

B.3.2 (1). Epidemiological Studies

Summary

Results of epidemiological studies demonstrate that consumption of soy protein-containing foods is related to a lower risk of prostate cancer in men. There are 10 studies available to date (two cohort studies, six case-control studies, one cross-national analysis, and one ecological study)(see Table 11 for summary and Table 12 for details). Six of these studies were conducted with Caucasian or multiethnic populations in the United States and Western countries, and the rest were done with Asians in China and Japan. Six of these studies show that soy consumption is related to a lower incidence of prostate cancer (ORs/RRs range 0.3 – 0.8) (Jacobsen et al., 1998; Kolonel et al., 2000; Lee et al., 2003; Severson et al., 1989; Strom et al., 1999; Villeneuve et al., 1999). Results are statistically significant in three studies (Jacobsen et al., 1998; Kolonel et al., 2000; Lee et al., 2003). Lee et al (1998) reported that controls consume more soy than prostate cancer cases. Akaza et al (2002) reported that cases and patients with poorly differentiated prostate cancer have fewer daidzein-metabolizers than the controls and patients with well to moderately differentiated prostate cancer. Hebert et al (1998) conducted a cross-national analysis of available data from 42 countries and reported that soy consumption is correlated to a significantly lower mortality from prostate cancer, and the protection from soy is four-fold greater than any other dietary factors analyzed. Nagata et al (2000) conducted an ecological study in Japan and reported that soy intake is not correlated to prostate cancer. The relationship between soy consumption and a lower risk of prostate cancer in men is supported by results of a meta-analysis of available studies that provide adequate data for a pooled analysis (Figure 5). The pooled estimate of odds ratio/relative risk is 0.66 (95% CI = 0.54 – 0.81; $P < 0.001$).

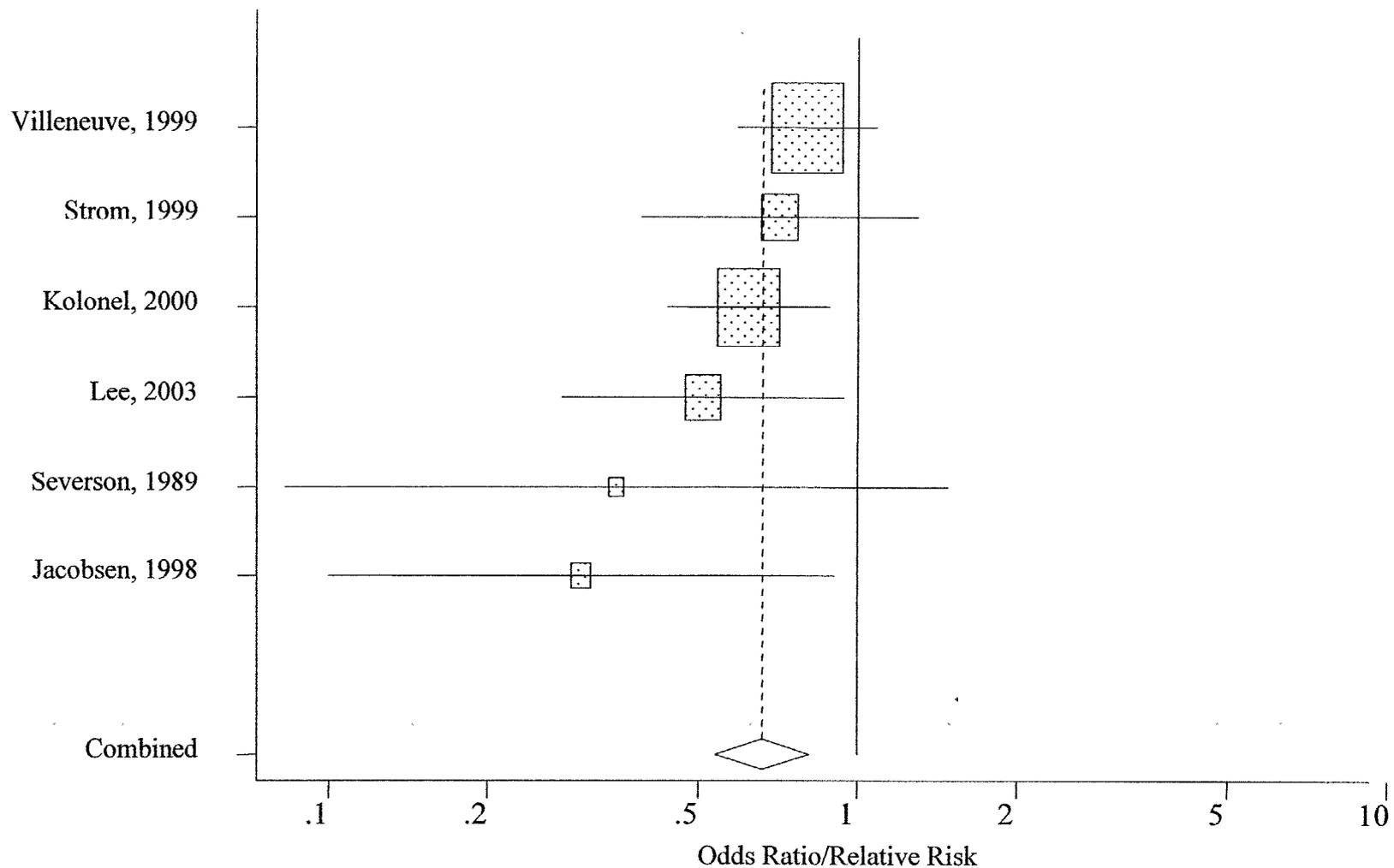


Figure 5. Meta-analysis of studies on consumption of soy protein-containing foods and prostate cancer in men. Each study-specific point estimate is plotted as a square box. The size of the box is proportional to the precision of the estimate, and its 95% CI is denoted by a line through the box. The vertical dashed line and the lower vertices of the diamond indicate the pooled estimate of odds ratio/relative risk, and left and right vertices of the diamond represent its 95% CI. The pooled estimate of odds ratio/relative risk is 0.66 (95% CI = 0.54 – 0.81; $P < 0.001$), and no publication bias was detected. Results of this analysis show that consumption of soy protein-containing foods is associated with a lower risk of prostate cancer in man.

Table 11. Summary of epidemiological studies of soy intake and prostate cancer in men.

Reference	Soy Products Assessed	OR/RR (95% CI) ¹ (highest vs. lowest intake)	P trend
Cohort Studies			
Jacobsen (1998)	Soymilk	0.3 (0.1 – 0.9)	0.03
Severson (1989)	Tofu	0.35 (0.08 – 1.43)	0.054
Case-Control Studies			
Lee (2003)	Soyfoods	0.51 (0.28 – 0.95)	0.061
Akaza (2002)		Fewer daidzein metabolizers in cases than in controls ($P < 0.10$) and in poorly differentiated cases than in well and moderate differentiated cases ($P < 0.04$).	
Kolonel (2000)	Soyfoods	0.62 (0.44 – 0.89)	0.06
Villeneuve (1999)	Tofu	0.8 (0.6 – 1.1)	0.01
Strom (1999)	Daidzein intake	0.57 (0.31 – 1.05)	0.07
	Genistein intake	0.71 (0.39 – 1.30)	0.26
Lee (1998)	Soy	495 g/wk (cases) vs. 585 g/wk (ctls)	$P = 0.16$
Cross-National Analysis			
Hebert (1998)	Soy	$r^2 = -0.62$	$P = 0.0001$
Ecological Study			
Nagata (Nagata, 2000)	Soy protein	$r^3 = 0.19$	

¹OR/RR (95% CI) = Odds ratio/relative risk (95% confidence interval). ²Regression coefficient.

³Correlation coefficient.

Cohort Studies

Jacobsen et al (1998) assessed soymilk consumption in relation to prostate cancer in a prospective study with 12,935 Seventh Day Adventist men in the United States. A total of 225 prostate cancer cases were identified during a 15-year follow-up period. A higher consumption of soymilk is associated with a significantly lower incidence of prostate cancer (P trend = 0.02). The adjusted RR is 0.3 (95% CI = 0.1-0.9) when the highest intake (>1 time/d) is compared with the lowest (never consumed). Jacobsen et al (1998) concluded, “Our study suggests that men with high consumption of soy milk are at reduced risk of prostate cancer.”

Severson et al (1989) examined the relationship between diet, demographics, and prostate cancer in a prospective study with 7,999 men of Japanese ancestry in Hawaii. A total of 174 incident cases of prostate cancer were recorded during an 18-year follow-up period. A higher intake of tofu is associated with a lower risk of prostate cancer (P trend = 0.054). The age-adjusted RR is 0.35 (95% CI = 0.08-1.43) when the highest level of intake (≥ 5 times/wk) is compared with the lowest (≤ 1 time/wk).

Case-Control Studies

Lee et al (2003) investigated soy and isoflavone (genistein and daidzein) consumption in relation to prostate cancer in a case-control study in China (133 cases, 265 controls). Isoflavone intake was derived from soyfood intake. Consumption of soyfoods is associated with a lower risk of prostate cancer (P trend = 0.061). The adjusted OR is 0.51 (95% CI = 0.29-0.95) when the highest quartile of soyfood intake (>111.8 g/d) is compared with the lowest (<27.5 g/d). Tofu intake is related to a lower risk of prostate cancer (P trend = 0.032), when it is separately analyzed from soyfoods. The adjusted OR is 0.58 (95% CI = 0.35-0.96) when the highest quartile of tofu intake (>34.5 g/d) is compared with the lowest (<14.3 g/d). Similar trend in reduction of prostate cancer risk exists when data are analyzed as isoflavone intake (P = 0.058 for genistein, P = 0.116 for daidzein). The adjusted OR is 0.53 (95% CI = 0.29-0.97) for genistein and 0.56 (95% CI = 0.31-1.04) for daidzein when the highest intake is compared with the lowest. The highest and the lowest intake of genistein is >62.0 mg/d and <17.9 mg/d, and that of daidzein is >36.3 mg/d and <10.0 mg/d, respectively. Lee et al (2003) concluded, "Our results indicate a reduced risk of prostate cancer associated with consumption of soy foods and isoflavones."

Akaza et al (2002) compared differences in serum levels of isoflavones between 144 prostate cancer patients and 112 cancer- and urological disease-free patients in a case-control study. Blood was collected from participants before breakfast. Fewer number of daidzein metabolizers were identified in cases than in controls (P <0.10) and in patients with poorly differentiated prostate cancer than in those with well to moderately differentiated prostate cancer (P <0.042). Akaza et al (2002) suggested that equol played an inhibitory role in the progression of prostate cancer. Unexpected to the investigators is that serum levels of genistein, daidzein, and equol in cases (daidzein metabolizers only) are significantly higher than that in the controls (P <0.005 for genistein, P <0.002 for daidzein, P <0.001 for equol). Akaza et al (2002) pointed, "Hence our result is difficult to explain, but it may be related to recent findings regarding dietary habits, which indicate

that prostate cancer patients increase their consumption of soybean-based foods after having been diagnosed with this malignancy.”

Kolonel et al (2000) investigated the relationship between dietary intake of vegetables, fruits, and legumes and prostate cancer risk in men in a multiethnic case-control study in the United States and Canada (1,619 cases, 1,618 controls). The risk of prostate cancer decreases with increasing the intake of soyfoods (P trend = 0.06). The adjusted OR is 0.62 (95% CI = 0.44-0.89) when the highest quintile of intake (>39.4 g/d) is compared with the lowest (none). The reduction in risk is comparable when soyfoods are analyzed with all other legumes as one food group (adjusted OR = 0.62, 95% CI = 0.49-0.80), and the trend for a lower risk with increasing intake is more obvious (P = 0.0002).

In a population-based case-control study conducted in Canada, Villeneuve et al (1999) compared the difference in prostate cancer risk between tofu users and nonusers (1,623 cases, 1,623 controls). Weekly consumption of tofu is associated with a significantly lower risk of prostate cancer (P trend = 0.01). The minimally adjusted OR is 0.5 (95% CI = 0.4-0.7)(adjusted for age and province of residence). The trend persists after further adjustment for confounding factors including smoking history, body mass index, income, family history of cancer, and many other dietary factors, but the significance does not exist (P trend = 0.29). The adjusted OR is 0.8 (95% CI = 0.6-1.1).

Strom et al (1999) assessed isoflavone intake in relation to prostate cancer in the United States (83 cases, 107 controls). The main food sources of isoflavones were tofu, imitation bacon bites, and breakfast/diet shakes. Data were converted to isoflavone (daidzein and genistein) intake before being analyzed. Consumption of daidzein (adjusted OR = 0.57, 95% CI = 0.31-1.05) and genistein (adjusted OR = 0.71, 95% CI = 0.39-1.30) is associated with a lower risk of prostate cancer in this study population, although these results are not statistically significant. The test for trend is P = 0.07 for daidzein and P = 0.26 for genistein. The median level of intake of daidzein is 23 μ g/d for the controls and 14 μ g/d for the cases, and that of genistein is 30 μ g/d for the controls and

20 µg/d for the cases. The investigator concluded, “These results are suggestive of a possible relationship between phytoestrogen intake and prostate cancer risk.”

Lee et al (1998) compared the difference in intake of various food items between 133 prostate cancer cases and 265 controls in China. The controls tend to have a higher consumption of soy (585 g/wk) compared with the cases (495 g/wk). The difference between the groups is not statistically significant ($P = 0.16$).

Cross-National Analysis

Hebert et al (1998) assessed soy consumption in relation to the mortality of prostate cancer in men in a cross-national analysis. In this analysis, the investigators correlated nutritional and socioeconomic factors with prostate cancer mortality using data from 59 countries from United Nations sources. Food intake was analyzed as energy intake on a kilocalorie per person per day basis. In 42 countries where the appropriate data are available, soy consumption is correlated with a significantly lower mortality rate of prostate cancer (regression coefficient = -0.62, $P = 0.0001$). The protective association for soy is at least four times greater than that of any other dietary factors when data are analyzed on an effect size per kilocalorie basis.

Ecological Study

Nagata et al (2000) assessed the association between soy intake and cancer mortality in an ecological study in Japan. Soy intake data from a National Nutritional Survey Report were correlated with mortality data (prostate, breast, stomach, colorectal, and lung cancer) from Vital Statistics and Population Census of Japan. Soy consumption was standardized to soy protein intake before data were analyzed. Results of the analysis show that soy protein intake is not correlated with the mortality of prostate cancer in men (correlation coefficient = 0.19). This analysis also shows that soy intake is correlated with a lower mortality of stomach cancer, no correlation with breast and lung cancer, and positively correlated with the mortality of colorectal cancer (see the respective sections for details).

Table 12. Epidemiological studies on soy consumption and prostate cancer in men.

Cohort Studies						
Reference	Design, Dietary Assessment Methods	Description of Subjects, Race, and Study Site	Confounding Factors Adjusted	Soy Products Assessed and Intake Levels	OR/RR (95% CI) ¹ (Highest vs. Lowest Intake)	Major Findings
Jacobsen (1998)	Prospective study (1976-1992), questionnaire (mail survey)	225 incident cases from a study population of 12,295 men during a 15-year follow-up period, Seventh-Day Adventist men/ USA.	Age, body mass index, frequency of consumption of coffee, whole fat milk, eggs and citrus fruits, and age at first marriage.	Soy milk high: >1 time/d low: never	0.3 (0.1-0.9)	Consumption of soymilk is associated with a significantly lower incidence of prostate cancer in Seventh-day Adventist men (<i>P</i> trend = 0.02).
Severson (1989)	Prospective study (1965-1986), Questionnaire (in-person interview and 24-h diet recall interview).	174 incident cases from a study population of 7,999 men of Japanese ancestry during an 18-year follow-up period, Japanese/USA.	Age.	Tofu high: ≥5 times/wk low: ≤1 time/wk	0.35 (0.08-1.43)	Consumption of tofu is associated with a lower incidence of prostate cancer in men of Japanese ancestry living in Hawaii (<i>P</i> trend = 0.054).

Table 12. Epidemiological studies on soy consumption and prostate cancer in men (continued).

Case-Control Studies						
Reference	Design, Dietary Assessment Methods	Description of Subjects, Race, and Study Site	Confounding Factors Adjusted	Soy Products Assessed and Intake Levels	OR/RR (95% CI) ¹ (Highest vs. Lowest Intake)	Major Findings
Lee (2003)	Case-control study (1989-1992), Questionnaire (in-person interview)	Cases: 133, Controls: 265, Ages: 50-89 yrs, Chinese/China.	Age and total calories.	Soy foods* Q4 >111.8 g/d Q1 <27.5 g/d Tofu T3 >34.5 g/d T1 <14.3 g/d Genistein Q4 >62.0 mg/d Q1 <17.9 mg/d Daidzein Q4 >36.3 mg/d Q1 <10.0 mg/d	Soy foods 0.51 (0.28-0.95) Tofu 0.58 (0.35-0.96) Genistein 0.53 (0.29-0.97) Daidzein 0.56 (0.31-1.04)	Consumption of soy foods is related to a lower risk of prostate cancer (<i>P</i> trend = 0.061). Tofu intake is associated with a significantly lower risk of prostate cancer (<i>P</i> trend = 0.032). Similar trend in risk reduction exists when data are analyzed as isoflavone intake (<i>P</i> trend = 0.058 for genistein, <i>P</i> trend = 0.116) for daidzein). *Soybean milk, tofu, dried/fried tofu, dry bean milk cream, and fermented beans and bean milk.
Akaza (2002)	Case-control study, quantification of serum isoflavone content in cases and controls.	Cases: 144, Controls: 112 cancer-free and urological disease-free patients, Ages (mean): 69.2 ± 7.3 yrs, Japanese/Japan.	N/A	Serum genistein* Cases: 113 ng/ml Ctls: 77.6 ng/ml <i>P</i> <0.005 Serum daidzein* Cases: 35.7 ng/ml Ctls: 21.5 ng/ml <i>P</i> <0.002 Serum equol* Cases: 16.0 ng/ml Ctls: 5.2 ng/ml <i>P</i> <0.001	N/A	Fewer daidzein metabolizers are identified in cases than in controls (<i>P</i> <0.10) and in patients with poorly differentiated prostate cancer than in those with well to moderate differentiated ones (<i>P</i> <0.042). *The authors explained the high serum isoflavones in cases than in controls, "it may be related to recent findings regarding dietary habits, which indicate that prostate cancer patients increase their consumption of soybean-based foods after having been diagnosed with this malignancy."

Table 12. Epidemiological studies on soy consumption and prostate cancer in men (continued).

Case-Control Studies						
Reference	Design, Dietary Assessment Methods	Description of Subjects, Race, and Study Site	Confounding Factors Adjusted	Soy Products Assessed and Intake Levels	OR/RR (95% CI) ¹ (Highest vs. Lowest Intake)	Major Findings
Kolonel (2000)	Multi-center case-control study (1987-1991), Questionnaire (in-person interview),	Cases: 1,619, Controls: 1,618, Ages: ≤ 84 yrs, Multi-ethnic (African-American, White, Chinese, and Japanese)/USA and Canada	Age, education, ethnicity, geographic area, and calories.	Soyfoods (soybeans, tofu, and miso) Q5: >39.4 g/d Q1: none Soyfoods and all other legumes Q5: 81.0 g/d Q1: ≤10.0 g/d	Soyfoods 0.62 (0.44-0.89) Soyfoods and all other legumes 0.62 (0.49-0.80)	Consumption of soyfoods is related to a lower risk of prostate cancer (<i>P</i> trend = 0.06). The reduction in risk is comparable when soyfoods are analyzed with all other legumes, and the trend for a lower risk with increasing intake is more obvious (<i>P</i> trend = 0.0002).
Villeneuve (1999)	Population-based case-control study (1994-1997), questionnaire (mail survey)	Cases: 1,623, Controls: 1,623 Ages: 50-74 yrs, Multi-ethnic (Western European and Asian descents, aboriginal, black, Indian, and others)/Canada	Age, province of residency, race, years since quitting smoking, cigarette pack-years, body mass index, rice and pasta, coffee, grains and cereals, alcohol, fruit and fruit juices, tofu, meat, income, and family history of cancer.	Tofu Some/wk vs. none	Minimally adjusted* 0.5 (0.4-0.7) Fully adjusted 0.8 (0.6-1.1) *Adjusted for age and province of residence.	Weekly intake of tofu is associated with a lower risk of prostate cancer in this study population (<i>P</i> trend <0.01, for minimally adjusted data). The statistical significance does not exist after adjustment for other potential confounding factors (<i>P</i> trend = 0.29).

Table 12. Epidemiological studies on soy consumption and prostate cancer in men (continued).

Case-Control Studies						
Reference	Design, Dietary Assessment Methods	Description of Subjects, Race, and Study Site	Confounding Factors Adjusted	Soy Products Assessed and Intake Levels	OR/RR (95% CI) ¹ (highest vs. lowest intake)	Major Findings
Strom (1999)	Case-control study (1996-1998), questionnaires (self-administered) and a phytoestrogen database.	Cases: 83, Controls: 107, Age (mean): 61 yrs Caucasian/USA.	Age, family history of prostate cancer, alcohol intake, and total calorie intake.	Daidzein* Ctls: 23 (0-20,950)** Cases: 14 (0-4,384) Genistein* Ctls: 30 (0-947) Cases: 20 (0-970) **Median (range), expressed as µg/d.	Daidzein 0.57 (0.31-1.05) Genistein 0.71 (0.39-1.30)	Consumption of daidzein ($P = 0.07$) and genistein ($P = 0.26$) is associated with a lower risk of prostate cancer in this study population. *Sources were tofu, imitation bacon bits, and breakfast/diet shakes.
Lee (1998)	Case-control study (1989-1992), questionnaire (in-person interview)	Cases: 133, Controls: 265 (neighborhood control), Ages: 50-89 yrs, Chinese/China	N/A	Soy Controls: 83.6 g/d Cases: 70.7 g/d	N/A	Controls consume more soy than the cases ($P = 0.16$).

Table 12. Epidemiological studies on soy consumption and prostate cancer in men (continued).

Cross-National Analysis						
Reference	Design, Dietary Assessment Methods	Description of Subjects, Race, and Study Site	Confounding Factors Adjusted	Soy Products Assessed and Intake Levels	OR/RR (95% CI) ¹ (Highest vs. Lowest Intake)	Major Findings
Hebert (1998)	Cross-national analysis on nutritional and socioeconomic factors and prostate cancer mortality, regression analyses.	Data from 52 countries from United Nations sources were analyzed. The analysis was conducted in the USA.		Soy intake was analyzed as soy energy intake.	$r^* = -0.62$ *Regression coefficient.	In 42 countries with appropriate data available, soy consumption is correlated with a significantly lower mortality from prostate cancer ($P = 0.0001$). The protective association is at least four times greater than any other dietary factors when data are analyzed on an effect size per kilocalorie basis.
Ecological Study						
Reference	Design, Dietary Assessment Methods	Description of Subjects, Race, and Study Site	Confounding Factors Adjusted	Soy Products Assessed and Intake Levels	OR/RR (95% CI) ¹ (Highest vs. Lowest Intake)	Major Findings
Nagata (2000)	Ecological study	Correlation analysis using data from National Nutritional Survey Report 1980-1985 and National Vital Statistics 1995, Japanese/Japan	Mean age, proportion of current smokers, and intake of alcoholic and animal fat.	Soy protein* 6.5 ± 0.8 g/d (mean \pm SD) *Standardized from soyfoods (miso, tofu, fried tofu, soybeans, soy milk, and yuba).	$r^{**} = 0.19$ **Correlation coefficient.	Consumption of soyfoods is not correlated to prostate cancer risk in this study population.

¹OR/RR (95% CI) = odds ratio/relative risk (95% confidence interval).

B.3.2 (2). Animal Studies

Summary

Animal studies support the epidemiological findings that consumption of soy protein-containing foods is associated with a lower incidence of prostate cancer in men. This section reviews studies that related dietary soy protein to experimentally induced prostate tumorigenesis in animals. It includes studies that assessed soy protein as a component of a diet and examined the preventive effect of such a diet (the experimental diet was given to animals prior to carcinogen treatment). Twelve publications are available to date (Table 13). Isolated soy protein (ISP) was assessed in nine of these studies. Other soy products evaluated in these investigations included defatted soy flour and soybean meal. In these studies, ISP or a soy protein-containing preparation was supplemented to the diet at the expense of casein (a protein source of standard research diets), and ISP was compared with casein as the sole source of dietary protein (e.g., 20% soy protein vs. 20% casein) in most studies. The dietary levels of soy protein and casein in each of these studies are summarized in Table 13. Results of 11 studies show that dietary supplementation with ISP, defatted soy flour, or soybean meal inhibits prostate tumorigenesis or benign lesions in animals, and one study shows that ISP stimulates the growth of Dunning R-3327-AT-1 androgen-independent prostate tumor in rats (Cohen, 2002).

Isolated Soy Protein

Results of four studies show that ISP inhibits tumor growth in mice inoculated with human LNCaP prostate adenocarcinoma cells. Bylund et al (2000) reported that feeding mice a diet containing 22.5% ISP results in a significant reduction in tumor volume ($P<0.05$), tumor weight ($P<0.05$), and serum prostate specific antigen (PSA) ($P<0.05$) compared with the controls fed a casein-based diet. Zhou et al (1999) reported that dietary supplementation with 20% ISP results in a decrease in proliferation index, tumor volume, and micro-vessel density and an increase in apoptotic index compared with the controls. The effects on these variables are significantly greater in groups fed an ISP diet supplemented with 0.2% or 1% soy phytochemical concentrate (isoflavone content 170 mg/g). In another study, Zhou et al (2002) found that dietary supplementation with 20%

isoflavone-depleted ISP inhibits prostate tumor growth in mice orthotopically inoculated LNCaP cells. Aronson et al (1999) compared casein to ISP plus 0.18% soy isoflavone extract on LNCaP tumor growth in mice when each of them was added to a low-fat and a high-fat diet. The isoflavone extract contained 43.7% genistein, 21.8% daidzein, and 3.4% glycitein. A low-fat diet supplemented with 20% ISP plus the isoflavone extract results in a significant reduction in tumor growth rates ($P<0.05$) and the final tumor weight ($P<0.05$) compared with all other groups combined.

Results of two studies show that ISP reduces spontaneous prostate tumor development in Lobund-Wistar rats. In one study, rats were maintained on a 20% ISP diet or a soybean meal-based control diet for 22 months from the age of two months. At the end of the experiment, there is a 90% reduction in tumor incidence ($P<0.001$) in the ISP group compared with the controls (Pollard & Wolter, 2000). In another study, Pollard et al (2001) found that providing rats a 20% ISP diet for 12 months, starting at the age of one year, results in a 75% reduction in tumor incidence ($P<0.05$) compared with the controls maintained on a soybean meal diet. The age of one year to 24 months is the stage of spontaneous prostate tumor development in this model. No protein from other sources was compared in these two studies.

Results of two studies show that ISP inhibits methyl-nitroso-urea (MNU)-induced prostate tumorigenesis in animals. Pollard and Luckert (1997) compared the anti-tumorigenic effect of ISP (isoflavones 1.69 mg/g protein) with a low-isoflavone ISP (isoflavones 0.11 mg/g protein). Feeding rats a 20% ISP diet three weeks before MNU treatment results in a 21% reduction in tumor incidence and a 27% increase in tumor-free period compared with a 20% low-isoflavone ISP diet. Providing rats the ISP diet seven days after the MNU treatment results in a 15% reduction in tumor incidence compared with rats fed the low-isoflavone ISP diet. In another study, dietary supplementation with 20% ISP results in a significant reduction in tumor incidence ($P<0.001$) compared with a commercial soy meal control diet (Pollard et al., 2000). No protein from other sources was compared in these two studies.

Sharma et al (1992) compared the effects of soy protein, casein, and a commercial control diet on spontaneous prostatitis development in adult rats. They found that soy protein reduces benign prostate lesions in animals. There are increases in severity and the incidence of prostatitis in rats fed the casein diet compared with the controls maintained on the commercial diet. However, there is no evidence of prostatitis in rats maintained on the soy protein diet. The type of the soy protein assessed in this study was not specified.

Cohen (2003) investigated the effect of dietary supplementation with ISP on the growth of Dunning R-3327-AT-1 androgen-independent prostate tumor in male Copenhagen rats. Four diets were compared, a soy-free basal diet, or the basal diet containing 5%, 10%, or 20% ISP. Animals were fed the experimental diet for three days before and six weeks after receiving a subcutaneous injection of AT-1 cells. Tumor size was an endpoint measurement. There is a two-fold increase in tumor volume in the 10% and the 20% ISP groups compared with the soy-free controls, and there is no difference between the 5% ISP group and the controls.

Defatted Soy Flour

Landstrom et al (1998) examined the effect of a variety of plant foods, including soy flour, on tumor growth in rats subcutaneously implanted Dunning R3327 prostate adenocarcinoma. Feeding mice a diet containing 33% defatted, heat-treated soy flour results in fewer palpable tumors ($P<0.05$) and lower tumor volume ($P<0.05$) compared with the controls maintained on a milk protein-based diet.

Soybean Meal

Makela et al (1995) reported that dietary supplementation with 7% soybean meal reduces neo-natal estrogen-induced prostatic growth inhibition ($P<0.05$) and dysplastic development ($P<0.04$) in mice compared with the controls maintained on a non-soy crude protein diet.

Table 13. Animal studies on dietary soy protein and experimentally induced prostate tumorigenesis.

Reference	Species/Strain, Sex	Carcinogen	Dietary Comparison	Major Findings
Bylund (2000)	Mice/athymic, BALB/cABom, male	LNCaP human prostate adenocarcinoma cells (subcutaneous inoculation)	Milk protein (28%) ISP ¹ (22.5%)	Dietary supplementation with ISP significantly reduces tumor volume ($P<0.05$), tumor weight ($P<0.05$), and serum PSA level ($P<0.05$), and significantly increases apoptotic index ($P<0.05$) in mice subcutaneously inoculated with LNCaP cells compared with the controls fed a milk protein diet.
Zhou (1999)	Mice/severe combined immunodeficient, male	LNCaP human prostate adenocarcinoma cells (subcutaneous inoculation)	Casein (20%) ISP (20%)	Feeding mice an ISP-containing diet reduces tumor micro-vessel density ($P<0.01$), tumor volume (NSS ²), and proliferation index (NSS), and increases apoptotic index (NSS) compared with the controls. Supplementing the ISP diet with 0.2% or 1% soy phytochemical concentrate* enhances the ISP effect on the above variables. *A mixture of alcohol soluble soy constituents including isoflavones.
Zhou (2002)	Mice/severe combined immunodeficient, male	LNCaP human prostate adenocarcinoma cells (orthotopic inoculation)	Casein (20%) ISP* (20%)	Dietary supplementation with ISP results in a 42% reduction in tumor weight ($P=0.07$), 58% reduction in micro-vessel density ($P<0.01$), 10% decrease in bFGF expression ($P<0.05$), and a 56% increase in apoptotic index ($P<0.05$) in tumor tissues compared with the controls. *Isoflavone-depleted ISP containing 0.01% isoflavones as aglycone equivalents.
Aronson (1999)	Mice/CB17 beige severe combined immunodeficient, male	LNCaP human prostate adenocarcinoma cells (subcutaneous inoculation)	High-fat diet (17.5% corn oil, 20% casein) High-fat diet (17.5% corn oil, 20% ISP*) Low-fat diet (5% corn oil, 20% casein) Low-fat diet (5% corn oil, 20% ISP*)	Feeding mice a low-fat diet containing 20% ISP and 0.18% isoflavone extract significantly reduces tumor growth rate ($P<0.05$), final tumor weight ($P<0.05$) compared with all other groups combined. *The ISP diet was further supplemented with 0.18% soy isoflavone extract (The isoflavone extract contained 43.7% genistein, 21.8% daidzein, and 3.4% glycitein).

Table 13. Animal studies on dietary soy protein and experimentally induced prostate tumorigenesis (continued).

Reference	Species/Strain, Sex	Carcinogen	Dietary Comparison	Major Findings
Pollard (2000)	Rats/Lobund-Wistar, male	Spontaneous prostate tumor development	Soy meal (30%) ISP (20%)	Long-term (age 2-24 months) intake of an ISP diet significantly reduces the incidence of prostate tumor ($P = 0.001$) compared with the controls on a soy meal diet.
Pollard (2001)	Rats/Lobund-Wistar, male	Spontaneous prostate tumor development	Soy meal (30%) ISP (20%)	Providing rats an ISP diet during age 12-24 months, the stage of spontaneous prostate tumor development, significantly reduces tumor incidence ($P = 0.001$) compared with the controls on a soy meal diet.
Pollard (2000)	Rats/Lobund-Wistar, male	MNU ³	Soy meal (30%) ISP (20%)	Feeding rats a diet containing 20% ISP significantly decreases tumor incidence (numbers of rats developed prostate tumors/group) ($P = 0.001$) compared with the controls.
Pollard (1997)	Rats/Lobund-Wistar, male	MNU	Low isoflavone ISP* (20%) ISP** (20%)	Providing rats a diet containing 20% ISP before or after MNU treatment reduces tumor incidence (NSS) and increases tumor latency period (NSS) compared with the controls fed a low-isoflavone ISP diet. *Containing isoflavones at 0.11 mg/kg protein. **Containing isoflavones at 1.69 mg/kg protein.
Sharma (1992)	Rats/Sprague-Dawley, male	Spontaneous prostatitis development	Commercial diet Casein (17%) Soy protein* (17%)	The spontaneous prostatitis development was compared in adult rats fed different diets. There are increases in severity and incidence of prostatitis in casein-fed rats compared with the controls maintained on a commercial diet, but there is no evidence of prostatitis in rats maintained on a soy protein diet. *The type of soy protein assessed was not presented.

Table 13. Animal studies on dietary soy protein and experimentally induced prostate tumorigenesis (continued).

Reference	Species/Strain, Sex	Carcinogen	Dietary Comparison	Major Findings
Cohen (2003)	Rats/Copenhagen, male	AT-1 androgen independent prostate tumor cells (subcutaneous inoculation)	Casein (20%) ISP (5%, 10%, 20%)	Dietary supplementation with 10% or 20% ISP results in a two-fold increase in tumor volume compared with the controls ($P<0.05$). There is no significant difference between the 5% ISP and the control group.
Landstrom (1998)	Rats/Copenhagen-Fisher, male	Dunning R3327 prostate adenocarcinoma cells (subcutaneous inoculation)	Low-fat milk powder (28.1%) Defatted soy flour (33.3%)	Dietary supplementation with soy flour significantly decreases tumor incidence ($P<0.05$) and tumor volume ($P<0.05$) during 14-16 weeks after tumor transplantation, and reduces tumor growth rate ($P<0.05$) during 12-14 weeks compared with the controls fed a milk powder-based diet.
Makela (1995)	Mice/Han-NMRI, male	Neonataly estrogen-induced prostatic growth inhibition and dysplasia	Crude protein (non-soy)(25%) Soybean meal (7%)	Dietary supplementation with 7% soybean meal significantly reduces neonatal estrogen-induced prostatic growth inhibition ($P<0.05$, 12 month feeding data) and dysplastic development ($P<0.04$, 9 month feeding data) in mice compared with the controls fed a crude protein diet.

¹ISP: isolated soybean protein; ²NSS: non-statistical significant. ³MNU: Methyl-nitroso-urea.

B.3.3. Gastro-Intestinal Cancer

This section considers the weight of scientific evidence that relates consumption of soyfoods to the risk of gastro-intestinal cancer in humans. It reviews and evaluates literature of epidemiological studies that relate soy to stomach/esophageal and colorectal cancer. This review also evaluates animal studies that investigate the effect of dietary soy protein on experimentally induced gastro-intestinal tumorigenesis. There are 19 studies available on stomach/esophageal cancer (four cohort studies, 10 case-control studies, one cross-national analysis, one prognostic analysis, one nutrition survey, and two ecological studies) and 11 studies on colorectal cancer (one intervention study, eight case-control studies, one cross-national analysis, and one ecological study). A thorough review of these studies reveals that consumption of soyfoods is related to a lower incidence of gastro-intestinal cancer in humans. This protective relationship is supported by results of a meta-analysis of available studies that provide adequate data for a pooled analysis. The pooled estimate of odds ratio/relative risk is 0.70 (95% CI = 0.61 – 0.80, $P < 0.001$) (Figure 6). Animal studies support the epidemiological findings. There are 12 animal studies available to date that examine the effect of dietary soy protein on experimentally induced gastro-intestinal tumorigenesis. Results of seven studies show an inhibitory effect. Three studies show no effect (two of them use a high-fat diet as the basal diet), and two show an enhanced effect (one is a comparison between a high-fat, high-soy protein diet and a low-fat, low soy protein diet). In conclusion, the totality of the publicly available scientific evidence supports the substance/disease relationship that consumption of soy protein-containing foods is related to a lower risk of gastro-intestinal cancer in humans.

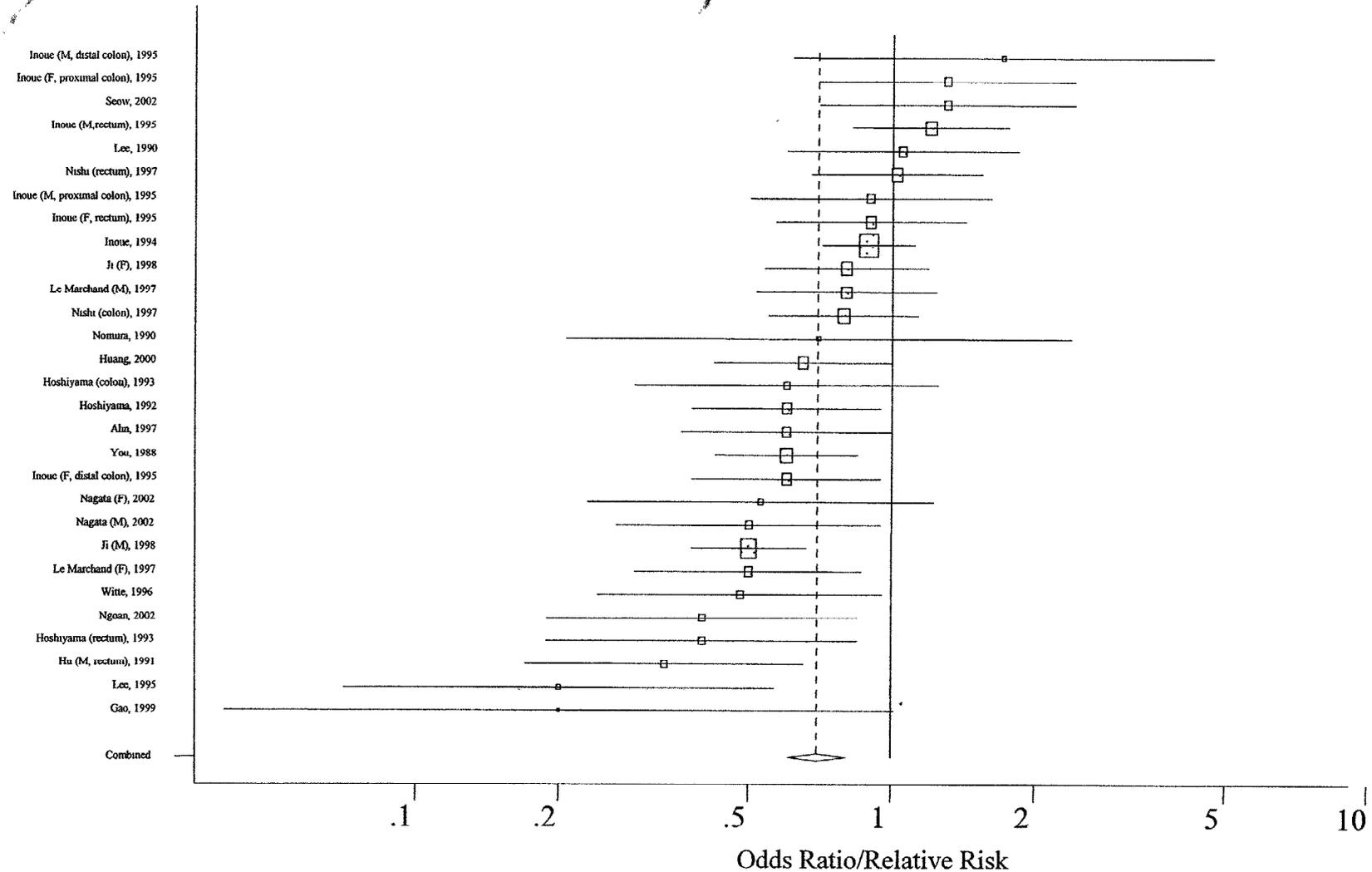


Figure 6. Meta-analysis of studies on consumption of soy protein-containing foods and gastro-intestinal cancer in humans. Each study-specific point estimate is plotted as a square box. The size of the box is proportional to the precision of the estimate, and its 95% CI is denoted by a line through the box. The vertical dashed line and the lower vertices of the diamond indicate the pooled estimate of odds ratio/relative risk, and left and right vertices of the diamond represent its 95% CI. The pooled estimate of odds ratio/relative risk is 0.70 (95% CI = 0.61 – 0.80; $P < 0.001$), and no publication bias was detected. M = male and F = female. Results of this analysis show that consumption of soy protein-containing foods is related to a lower risk of gastro-intestinal cancer in humans.

B.3.3 (1). Epidemiological Studies – Stomach/Esophageal Cancer

Summary

There are 19 publications available to date that relate soy consumption to stomach/esophageal cancer in humans (see Table 14 for summary and Table 15 for details). Four of these studies are cohort studies, 10 are case-control studies, one is cross-national analysis, one is prognostic analysis, one is nutrition survey, and two are ecological studies. A thorough review of these studies shows that consumption of soy protein-containing foods is associated with a lower risk of stomach/esophageal cancer in humans. This relationship is supported by a meta-analysis of these studies that yields a pooled estimate of odds ratio/relative risk 0.62 (95% CI = 0.52 – 0.75; $P < 0.001$) (Figure 7).

Twelve of these 14 cohort and case-control studies show that intake of fresh soyfoods or soy products is associated with a lower risk of stomach and esophageal cancer (ORs/RRs range, 0.20 – 0.89) (Ahn, 1997; Gao et al., 1999; Haenszel et al., 1972; Hoshiyama & Sasaba, 1992; Inoue et al., 1994; Ji et al., 1998; Lee et al., 1995; Nagata et al., 2002; Ngoan et al., 2002; Nomura et al., 1990; Sasaki et al., 1990; You et al., 1988). Results are statistically significant in five studies (Ji et al., 1998; Lee et al., 1995; Nagata et al., 2002; Ngoan et al., 2002; You et al., 1988). Three studies show that soy consumption is not related to stomach and esophageal cancer. Ngoan et al (2002) found that tofu is related to a lower death rate of stomach cancer, but soy milk is not related to death rate of esophageal cancer (RR = 1.2). Gao et al (1999) reported that soy is related to a lower risk of stomach cancer but not esophageal cancer (OR = 1.28). Lee et al (1990) reported that consumption of bean milk is not related to stomach cancer. One study show that intake of bean curd is related to the risk of stomach cancer (OR = 1.52, 95% CI not presented) (Tajima & Tominaga, 1985). Results of a cross-sectional study show that cases of seropositive to *Helicobacter pylori* (a risk factor of stomach cancer in humans) in often tofu eaters are significantly lower than in less often users (Shinchi et al., 1997). Results of a prognostic analysis show that consumption of bean curd is related to a significantly lower death rate from stomach cancer in post-surgery stomach cancer patients (Huang et al., 2000). A nutrition survey conducted in Japan shows that tofu intake is correlated with a significantly lower risk of stomach cancer, but not esophageal cancer (Nagai et al.,

1982). There are two ecological studies on soy intake and stomach/esophageal cancer to date. One shows that consumption of soy products is related to a significantly lower risk of stomach cancer in men, but not in women (Nagata, 2000). The other shows that people residing in a high risk area of stomach cancer eat significantly less soy compared with those living in a low risk area (Takezaki et al., 1999).

Table 14. Summary of epidemiological studies on soy intake and stomach and esophageal cancer in humans.

Reference	Soy Products Assessed	OR/RR/HR (95% CI) ¹ (highest vs. lowest intake)	P trend
Cohort Studies			
Nagata (2002)	Soy products	0.50 (0.26 – 0.93) (men)	0.03
		0.53 (0.23 – 1.22) (women)	0.15
Ngoan (2002)	Nonfermented soy products	0.49 (0.26 – 0.92) (men)	0.03
		0.51 (0.22 – 1.18) (women)	0.13
Ahn (1997)	Tofu	0.4 (0.2 – 0.9)	
Nomura (1990)	Soybean foods	1.2 (0.6 – 2.7)	
	Tofu	0.6 (0.4 – 1.1)	0.09
	Tofu	0.7 (0.2 – 2.3)	
Case-Control Studies			
Gao (1999)	Soybean products	0.2 (0.04 – 1.02) (stomach) 1.28 (0.26 – 6.31) (esophagus)	
Ji (1998)	Soybean products	0.5 (0.4 – 0.7) (men) 0.8 (0.5 – 1.1) (women)	0.0001 0.26
Lee (1995)	Tofu	0.2 (0.1 – 0.8)	0.01
Inoue (1994)	Bean curd	0.89 (0.71 – 1.11)	
Hoshiyama (1992)	Soybean products	0.6 (0.4 – 1.0) (vs. population ctls)	0.01
Sasaki (1990)	Cooked beans	0.5 (lower esophagus) 0.6 (middle esophagus) 0.1 (upper esophagus)	
Lee, (1990)	Bean milk	1.09	
You (1988)	Soybean	0.6 (0.4 – 0.8)	
Tajima (1985)	Bean curd	1.52	
Haenszel (1972)	Bean curd	0.69	
Cross-Sectional Analysis			
Shinchi (1997)	Tofu	Few cases of seropositive to <i>H. Pylori</i> are in often users than in less often users.	0.013
Prognostic Analysis			
Huang (2000)	Bean curd	0.65 (0.42 – 0.98)	0.05
Nutritional Survey			
Nagai (1982)	Tofu	Stomach: $r^2 = -0.094$ (men) $r^2 = -0.091$ (women) Esophagus: $r^2 = -0.03$ (men) $r^2 = 0.02$ (women)	$P < 0.01$ $P < 0.01$
Ecological Studies			
Nagata (2000)	Soy products	$r^3 = -0.31$ (men) $r^3 = -0.10$ (women)	$P < 0.04$
Takezaki (1999)	Soybean products	People in high-risk area of stomach cancer eat less soy than those in low-risk area.	$P < 0.001$

¹OR/RR/HR (95% CI) = odds ratio/relative risk/hazard ratio (95% confidence interval). ²Regression coefficient. ³Correlation coefficient.

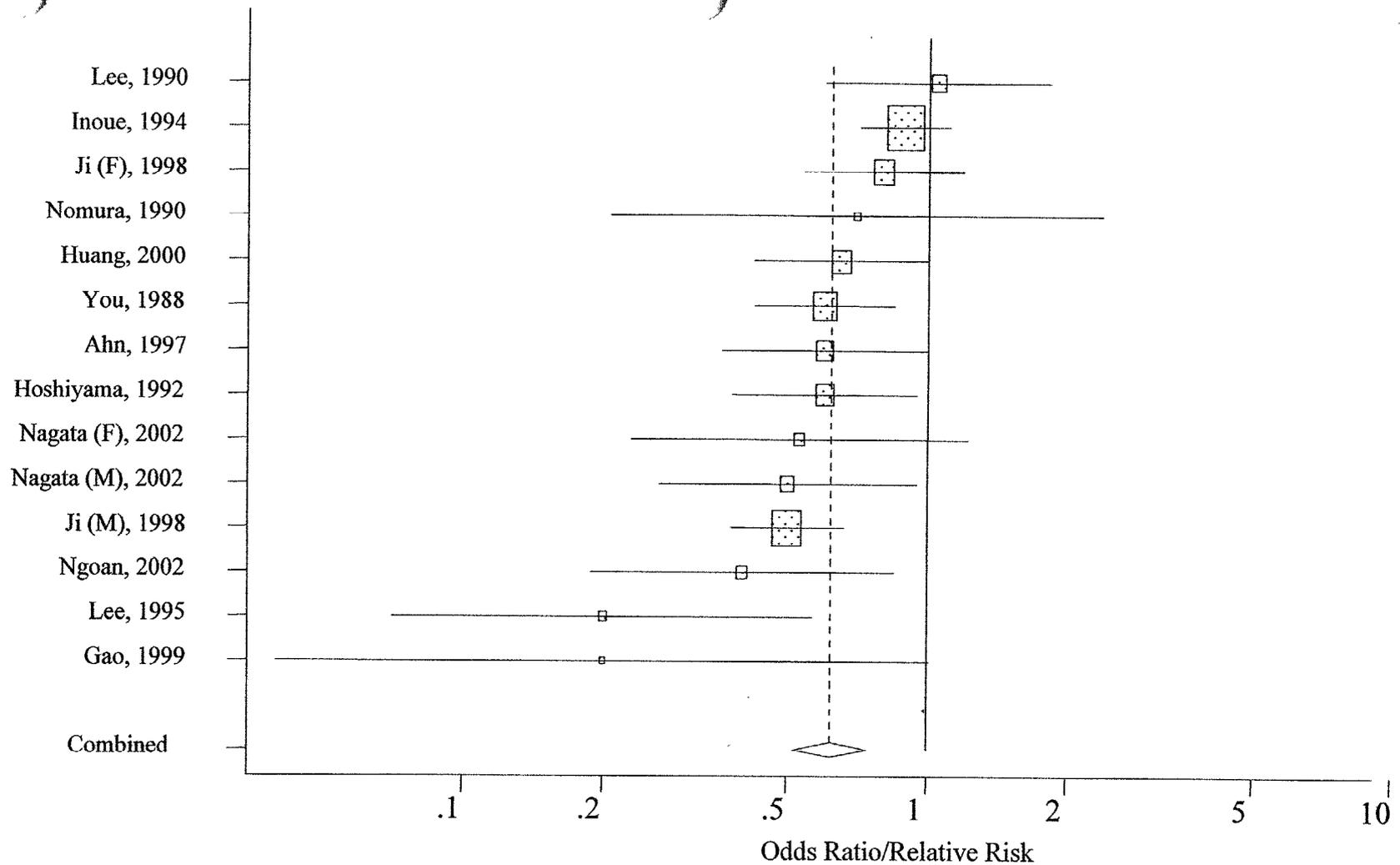


Figure 7. Meta-analysis of studies on consumption of soy protein-containing foods and stomach/esophageal cancer in humans. Each study-specific point estimate is plotted as a square box. The size of the box is proportional to the precision of the estimate, and its 95% CI is denoted by a line through the box. The vertical dashed line and the lower vertices of the diamond indicate the pooled estimate of odds ratio/relative risk, and left and right vertices of the diamond represent its 95% CI. The pooled estimate of odds ratio/relative risk is 0.62 (95% CI = 0.52 – 0.75; $P < 0.001$), and no publication bias was detected. M = male and F = female. Results of this analysis show that consumption of soy protein-containing foods is related to a lower risk of stomach/esophageal cancer in humans.

Cohort Studies

Nagata et al (2002) conducted a prospective cohort study on soy product intake and stomach cancer mortality in Japan. A total of 121 deaths from stomach cancer occurred from 30,304 participants during a 7-year follow-up period. Consumption of soy products is related to a lower death rate from stomach cancer (P trend = 0.03 for men, P trend = 0.15 for women). The adjusted hazard ratio (HR) is 0.50 (95% CI = 0.26-0.93) for men and 0.53 (95% CI = 0.23-1.22) for women when the highest tertile of intake is compared with the lowest. The highest tertile of soy product intake is 140 g/d for men and 127 g/d for women, and the lowest is 50 g/d and 47 g/d, respectively. When non-fermented and fermented soy products (miso and natto) are separately analyzed, the intake of non-fermented soy products is related to a lower death rate of stomach cancer in men (P trend = 0.03) and women (P trend = 0.13). The adjusted HR is 0.49 (95% CI = 0.26-0.92) for men and 0.51 (95% CI = 0.22-1.18) for women. Nagata et al (2002) concluded, "These data suggest that soy intake may reduce the risk of death from stomach cancer."

Ngoan et al (2002) assessed dietary factors in relation to stomach cancer mortality in a prospective cohort study in Japan. Tofu and soymilk were two food items assessed in this study. A total of 116 deaths from stomach cancer occurred from a study population of 13,250 during a 10- to 13-year follow-up period. Consumption of tofu is associated with a significantly lower in death rate of stomach cancer (adjusted RR = 0.4, 95% CI = 0.2-0.9) when the high intake (≥ 2 times/d) is compared with the low intake (seldom or never). Consumption of soymilk is not related to death rate of stomach cancer in this study population (adjusted RR = 1.2, 95% CI = 0.6-2.7).

Ahn (1997) reported preliminary findings from an on-going cohort study assessing the relationship between soybean foods and stomach cancer with a study population of 14,533 men in Korea. Soy consumption is associated with a lower risk of stomach cancer (P trend = 0.09). The OR is 0.6 (95% CI = 0.4-1.1) when the highest quartile of intake is compared with the lowest.

Nomura et al (1990) investigated stomach cancer risk in relation to diet, cigarettes, and alcohol consumption in a prospective cohort study in Hawaii. Tofu was assessed in this study. After a 19-year follow-up period, 150 incident cases of stomach cancer were identified from 7,990 men of Japanese ancestry. Consumption of tofu is associated with a lower risk of stomach cancer (age-adjusted RR = 0.7, 95% CI = 0.2-2.3) when frequent users (≥ 5 times/wk) are compared with the occasional users (≤ 1 time/wk), but results are not statistically significant.

Case-Control Studies

Gao et al (1999) investigated the association of diet with stomach and esophageal cancer in people residing in Yangzhou, a high-risk area of stomach cancer in China (234 cases, 234 controls). Soybean products were analyzed as one category of foods. Consumption of soy is associated with an 80% reduction in stomach cancer risk (adjusted OR = 0.20, 95% CI = 0.04-1.02), but not related to esophageal cancer (adjusted OR = 1.28, 95% CI = 0.26-1.31), when the upper level of intake (≥ 3 times/wk) is compared with the lower level (< 1 time/wk).

Ji et al (1998) assessed dietary habits in relation to stomach cancer risk in Shanghai, China (1,124 cases and 1,451 controls). Soybean and soybean products were analyzed as one category of foods. A higher soy consumption is related to a lower risk of stomach cancer (P trend = 0.0001 for men, P trend = 0.26 for women). The adjusted OR is 0.5 (95% CI = 0.4-0.7) for men and 0.8 (95% CI = 0.5-1.1) for women when the highest quartile of intake (≥ 23.4 servings/m) is compared with the lowest (≤ 7.5 servings/m).

Lee et al (1995) investigated lifestyle and dietary factors in relation to stomach cancer with 213 cases and an equal number of hospital controls in Korea. Tofu was assessed in this study. Consumption of tofu is associated with a significantly lower risk of stomach cancer (P trend < 0.01). The adjusted OR is 0.2 (95% CI = 0.1-0.8) when the high intake ($\geq 2-3$ times/wk) is compared with the low intake (none or 4-5 times/yr).

Inoue et al (1994) studied lifestyle in relation to gastric cancer in a hospital-based case-control study in Japan (668 cases, 668 controls). Bean curd was assessed in this study.

Consumption of bean curd is related to a lower incidence of stomach cancer (adjusted OR = 0.89, 95% CI = 0.71-1.11) when frequent users (≥ 3 -4 times/wk) are compared with the less-often users (< 3 -4 times/wk), although results are not statistically significant.

Hoshiyama and Sasaba (1992) assessed diet, cigarettes, and alcohol consumption in relation to stomach cancer in a case-control study in Japan. Cases ($n = 294$) were compared with population controls ($n = 294$) and hospital controls ($n = 202$). Soybean products (excluding miso soup) were assessed as one category of foods. A higher consumption of soybean products is associated with a significantly lower risk of stomach cancer (P trend < 0.01) when cases are compared with population controls. The adjusted RR is 0.6 (95% CI = 0.4-1.0) when the upper level of intake (≥ 8 times/wk) is compared with the lower level (≤ 4 times/wk). Intake of soybean products is associated with a lower risk of stomach cancer when cases are compared with hospital controls (P trend = 0.36). The adjusted OR is 0.8 (95% CI = 0.4-1.4) when the upper and lower levels of intake are compared. These results are not statistically significant.

Sasaki et al (1990) investigated dietary habits in relation to esophageal cancer in men in Japan (201 cases, 403 non-digestive cancer patients as hospital controls). Cooked beans and fried bean curd were two items of soyfoods assessed. Consumption of cooked beans is associated with a lower risk of esophageal cancer, whereas fried bean curd is related to an increase in risk. The RR for cooked bean is 0.5, 0.6, and 0.1 for the lower, middle, and upper esophageal cancer, and that for fried bean curd is 3.0, 3.9, and 7.4, respectively, when users are compared with the non-users. The 95% confidence interval of these estimates was not reported, but Sasaki et al (1990) indicated that they all excluded 1.0. The finding with fried bean curd is consistent with the existing knowledge in epidemiology that intake of fried foods, particularly deep-fried foods, is associated with an increase in cancer risk in humans (Dai et al., 2002b; Gao & McLaughlin JK, 1994; Huang et al., 1992; Ji et al., 1995).

Lee et al (1990) investigated risk factors of stomach cancer in a hospital-based case-control study in Taiwan (210 cases, 810 controls). Bean milk was assessed in this study.

Consumption of bean milk is not related to stomach cancer in this study population when the high intake (>2 meals/wk) is compared with the low intake (<1 meal/wk). The OR is 1.09 (95% CI not presented). Factors adjusted for analysis of soyfoods were not specified in this publication.

You et al (1988) examined diet in relation to stomach cancer risk in a high-risk area in Shandong province (564 cases, 1,131 controls), where the mortality of stomach cancer was two-fold greater than the national average in China. Soybean intake was assessed in this study. A high intake of soybean is related to a significantly lower risk of stomach cancer (adjusted OR = 0.6, 95% CI = 0.4-0.8) when the highest quartile of intake (>5 kg/yr) is compared with the lowest (\leq 1 kg/yr).

Tajima et al (1985) investigated dietary habits in relation to gastro-intestinal cancer in a hospital-based case-control study in Japan (93 cases of stomach cancer, 93 cases of colorectal cancer, 186 controls). Bean curd was one of the food items assessed in this study. Intake of bean curd is related to the risk of stomach cancer (adjusted RR = 1.52, 95% CI not presented) in this population when the frequent users (\geq 4 times/wk) are compared with the occasional users (<1 time/wk). The 95% confidence interval was not presented in this publication.

Haenszel et al (1972) conducted a hospital-based case-control study on the association of dietary history, along with migration history and other lifestyle factors, with the risk of stomach cancer in Hawaiian Japanese in the United States (220 cases, 440 controls). Bean curd was assessed in this investigation. Intake of bean curd is associated with a 30% reduction in stomach cancer risk (adjusted RR = 0.69, 95% CI not presented).

Cross-Sectional Analysis

Infection with *Helicobacter pylori* (*H. pylori*) is a major risk factor for stomach cancer in humans (International Agency for Research on Cancer, 1994; Miehlke et al., 2000; Yamagata et al., 2000). To determine whether dietary factors that influenced the risk of stomach cancer could also affect the infection of *H. pylori*, Shinchi *et al* (1997) examined

the association of various food items, including tofu, with seropositivity of *H. pylori* in 565 Japanese men. A high tofu intake is related to a significant reduction in the number of subjects who are seropositive to *H. pylori* (P trend = 0.013). A total of 88.6% of participants in the low intake group (<2 times/wk) is seropositive to *H. pylori* compared with 75.8% in the high intake group (≥ 4 times/wk).

Prognostic Analysis

To determine whether dietary factors that influenced the incidence of gastric cancer could also affect survival rate of gastric cancer patients, Huang et al (2000) conducted a prognostic analysis on dietary, drinking, and smoking habits in relation to prognosis of gastric cancer in Japan. A total of 877 post-operative patients who were surgically treated for pathologically confirmed gastric adenocarcinoma were recruited. Data on dietary habits, including bean curd intake, and lifestyles were collected during 1988 to 1994, and the survival status of all patients was followed until 1998. A frequent intake of bean curd (>3-4 times/wk) is related to a significantly lower risk of stomach cancer death compared with the less frequent intake (≤ 3 times/wk)(adjusted hazard ratio (HR) = 0.65, 95% CI = 0.42-0.98; $P < 0.05$). Huang et al (2000) concluded, "Frequent consumption of raw vegetables or tofu is a favorable prognostic factor for gastric cancer."

Nutrition Survey

Using food intake data from a nationwide nutrition survey conducted by Japanese Ministry of Health and Welfare during 1974-1976, Nagai et al (1982) correlated the intake of various foods, including tofu, with the mortality of stomach and esophageal cancer in Japan. Results of a multiple regression analysis show that consumption of tofu is correlated with a significantly lower mortality rate of stomach cancer in men and women. The standard partial correlation coefficient is -0.094 for men ($P \leq 0.01$) and -0.091 for women ($P \leq 0.01$). Tofu intake is not correlated to esophageal cancer mortality in either sex in this study.

Ecological Studies

Nagata et al (2000) assessed the relationship between soy intake and cancer mortality in Japan. Soy intake data from the National Nutritional Survey Report 1980-1985 were correlated with mortality data (stomach, breast, prostate, colorectal, and lung cancer) from the National Vital Statistics 1995. Soy consumption was standardized to soy protein intake before data were analyzed. Results of the analysis show that soy protein intake is correlated with a significantly lower mortality of stomach cancer in men ($r = -0.31, P < 0.04$), but not in women ($r = -0.10$). This analysis also shows that soy intake is not correlated to the mortality of breast, prostate and lung cancer, but positively correlated with the mortality of colorectal cancer (see the respective sections for details).

Takezaki et al (1999) compared dietary differences in residents living in low-risk (Pizhou city, $n = 425$) and high-risk areas of stomach cancer (Yangzhou city, $n = 414$) in a comparative ecological study in China. Soybean products were analyzed as one group of food. Participants living in the low-risk area consume soy at significantly greater frequencies than those living in the high-risk area. For example, 60% of men and 57% of women in the low-risk area consume soybean products at a frequency of ≥ 3 times/wk, whereas only 5% of men and 4% of women in the high-risk area are at the same frequency of intake ($P < 0.001$ for both sexes).

Table 15. Epidemiological studies on soy consumption and stomach and esophageal cancer in humans.

Cohort Studies						
Reference	Design, Dietary Assessment Methods	Description of Subjects, Race, and Study Site	Confounding Factors Adjusted	Soy Products Assessed and Intake Levels	OR/RR/HR (95% CI) ¹ (Highest vs. Lowest)	Major Findings
Nagata (2002)	Prospective study (1992-1999), self-administered questionnaire.	121 deaths from stomach cancer occurred from a study population of 30,304 during a 7-year follow-up period, Ages: ≥35 yrs, Japanese/Japan	Men: age, total energy, smoking status (current, former, and never-smokers), body mass index at age about 21 years, and intake of salt and rice. Women: age, total energy, marital status, age at menarche, body mass index at age about 21 years, and intake of coffee.	Soy products* Men (median): T3: 140.0 g/d T1: 49.7 g/d Mean: 60.3 g/d Women (median): T3: 126.9 g/d T1: 46.7 g/d Mean: 53.5 g/d	Men: 0.50 (0.26-0.93) Women: 0.53 (0.23-1.22) Non-fermented: Men: 0.49 (0.26-0.92) Women: 0.51 (0.22-1.18)	Consumption of soy products is related to a lower death rate from stomach cancer in men and women. The test for trend is statistically significant for men ($P = 0.03$), but not for women ($P = 0.15$). When non-fermented and fermented soy products (miso and natto) are separately analyzed, intake of non-fermented soyfoods is related to a lower death rate from stomach cancer in men (P trend = 0.03) and women (P trend = 0.13). *Tofu, miso, soybeans, natto, soymilk, okara, dried tofu, fried tofu, deep-fried tofu, and fried tofu with minced vegetables or seaweed.
Ngoan (2002)	Prospective study (1986-1999), self-administered questionnaire.	116 deaths from stomach cancer occurred from a study population of 13,250 during a 10-13 year follow-up period, Ages: ≥15 yrs, Japanese/Japan	Age, sex, smoking, processed meat, liver, cooking or salad oil, and pickled food.	Tofu high: ≥2 times/d low: seldom/ never Soymilk high: ≥2 times/d low: seldom/ never	Tofu 0.4 (0.2-0.9) Soymilk 1.2 (0.6-2.7)	Consumption of tofu is related to a significantly lower death rate of stomach cancer. Consumption of soymilk is not related to the death rate of stomach cancer in this study population.

Table 15. Epidemiological studies on soy consumption and stomach and esophageal cancer in humans (continued).

Cohort Studies						
Reference	Design, Dietary Assessment Methods	Description of Subjects, Race, and Study Site	Confounding Factors Adjusted	Soy Products Assessed and Intake Levels	OR/RR/HR (95% CI) ¹ (Highest vs. Lowest)	Major Findings
Ahn (1997)	Cohort study (on-going)	Participants: 14,533 men, Ages: >40 yrs, Korean/Korean	Not reported.	Soybean foods (Intake data not reported)	0.6 (0.4-1.1)	Preliminary findings from this study show that consumption of soybean foods is associated with a lower risk of stomach cancer (<i>P</i> trend = 0.09).
Nomura (1990)	Prospective study (1965-1986), questionnaire (in-person interview).	150 incident cases identified from a study population of 7,990 men of Japanese ancestry during a 19-year follow-up period, Ages (mean): 58 yrs, Hawaiian Japanese/USA	Age.	Tofu high: ≥5 times/wk low: ≤1 time/wk	0.7 (0.2-2.3)	Consumption of tofu is related to a 30% reduction in stomach cancer risk in this study population.

Table 15. Epidemiological studies on soy consumption and stomach and esophageal cancer in humans (continued).

Case-Control Studies						
Reference	Design, Dietary Assessment Methods	Description of Subjects, Race, and Study Site	Confounding Factors Adjusted	Soy Products Assessed and Intake Levels	OR/RR/HR (95% CI) ¹ (Highest vs. Lowest)	Major Findings
Gao (1999)	Population-based case-control study* (1995), questionnaire (in-person interview)	Cases: 234, Controls: 234, Ages: 30-79 yrs, Chinese/China	Age and sex.	Soybean Products high: ≥ 3 times/wk low: < 1 time/wk	Stomach: 0.20 (0.04-1.02) Esophagus: 1.28 (0.26-6.31)	Consumption of soybean products is related to an 80% reduction in stomach cancer risk, but not related to esophageal cancer in this study population. *Conducted in a high-risk area of stomach cancer in China.
Ji (1998)	Population-based case-control study (1988-1989), questionnaire (in-person interview).	Cases: 1,124, Controls: 1,451, Ages: 20-69 yrs, Chinese/China	Age, income, education, smoking (men only), and alcohol drinking (men only).	Soybean and products* Q4: ≥ 23.4 svgs/m Q1: ≤ 7.5 svgs/m	Men: 0.5 (0.4-0.7) Women: 0.8 (0.5-1.1)	Consumption of soybean and soybean products is associated with a lower risk of stomach cancer in men (P trend = 0.0001) and women (P trend = 0.26). *Soybean milk, bean curd, fried bean curd, and other bean products.
Lee (1995)	Hospital-based case-control study (1990-1991), questionnaire (in-person interview).	Cases: 213, Controls: 213, Ages: 25-70 yrs, Korean/Korea	Age, sex, education, economic status, residence, and mutually adjusted for other dietary factors.	Tofu high: $\geq 2-3$ times/wk low: none or 4-5 times/yr	0.2 (0.1-0.8)	Frequent consumption of tofu is associated with a significantly lower risk of stomach cancer (P trend < 0.01).
Inoue (1994)	Hospital-based case-control study (1988-1991), self-administered questionnaire	Cases: 668, Control: 668, Ages (mean): 58 yrs, Japanese/Japan	Sex	Bean curd $\geq 3-4$ times/wk vs. < 3 times/wk	0.89 (0.71-1.11)	Intake of bean curd is associated with a lower risk of stomach cancer, but results are not statistically significant.

Table 15. Epidemiological studies on soy consumption and stomach and esophageal cancer in humans (continued).

Case-Control Studies						
Reference	Design, Dietary Assessment Methods	Description of Subjects, Race, and Study Site	Confounding Factors Adjusted	Soy Products Assessed and Intake Levels	OR/RR/HR (95% CI) ¹ (Highest vs. Lowest)	Major Findings
Hoshiyama (1992)	Case-control study (1984-1990), food frequency questionnaire (in-person interview).	Cases: 294, Population controls: 294, Hospital controls: 202, Ages: most of the participants were in the range of 45-75 yrs, Japanese/Japan	Sex, age, administrative division, and smoking status.	Soybean products (except miso soup) T3: ≥8 times/wk T1: ≤4 times/wk	0.6 (0.4-1.0) (vs. population controls) 0.8 (0.4-1.4) (vs. hospital controls)	An increase in consumption of soybean products is related to a lower risk of stomach cancer when cases are compared with population controls (<i>P</i> trend <0.01). There is a 20% risk reduction when cases are compared with hospital controls, but results are not statistically significant. The test for trend is <i>P</i> = 0.36.
Sasaki (1990)	Hospital-based case-control study (duration of study not reported), questionnaire (in-person interview).	Cases: 201, Controls: 403, Ages: not presented, Japanese/Japan	Not reported.	Cooked beans Users vs. non-users Fried bean curd Users vs. non-users	0.5* (lower) 0.6* (middle) 0.1* (upper) 3.0* (lower) 3.9* (middle) 7.4* (upper)	Consumption of cooked beans is associated with a lower risk of esophageal cancer in lower, middle, and upper esophagus. Intake of fried bean curd is related to an increase in esophageal cancer risk in lower, middle, upper esophagus. *95% CI not reported, but all excludes 1.0.
Lee (1990)	Hospital-based case-control study (1954-1988), structured questionnaire (in-person interview).	Cases: 210, Controls: 810, Age: 0-84 yrs, Chinese/Taiwan	Not specified.	Bean milk low: <1 meal/wk high: >2 meals/wk	1.09	Consumption of bean milk is not related to stomach cancer risk in this study population.

Table 15. Epidemiological studies on soy consumption and stomach and esophageal cancer in humans (continued).

Case-Control Studies						
Reference	Design, Dietary Assessment Methods	Description of Subjects, Race, and Study Site	Confounding Factors Adjusted	Soy Products Assessed and Intake Levels	OR/RR/HR (95% CI) ¹ (Highest vs. Lowest)	Major Findings
You (1988)	Population-based case-control study* (1965-1980), questionnaire (in-person interview).	Cases: 564, Controls: 1,131, Ages: 35-64 yrs Chinese/China	Sex, age, and family income.	Soybean Q4: >5 kg/yr. Q1: ≤1 kg/yr.	0.6 (0.4-0.8)	Consumption of soybean is associated with a significantly lower risk of stomach cancer. *The study was conducted in a high-risk area of stomach cancer in China. The mortality of stomach cancer in this area was two-fold greater than the national average in China.
Tajima (1985)	Hospital-based case-control study (1981-1984), questionnaire (interview)	Cases: 186, Controls: 186, Ages: 40-70 yrs Japanese/Japan	Age and sex.	Bean curd Frequent users (≥4 times/wk) vs. occasional users (<1 time/wk)	Stomach: 1.52	Bean curd intake is related to the risk of stomach cancer.
Haenszel (1972)	Hospital-based case-control study (1963-1969), questionnaire (in-person interview).	Cases: 220, Controls: 440, Ages: most of the participants were in the range of 50-70 yrs, Hawaiian Japanese/USA	Age, sex, and nativity.	Bean curd (no intake data presented)	0.69	Consumption of bean curd is associated with a lower risk of stomach cancer in Hawaiian Japanese.

Table 15. Epidemiological studies on soy consumption and stomach and esophageal cancer in humans (continued).

Cross-Sectional Analysis						
Reference	Design, Dietary Assessment Methods	Description of Subjects, Race, and Study Site	Confounding Factors Adjusted	Soy Products Assessed and Intake Levels	OR/RR/HR (95% CI) ¹ (Highest vs. Lowest)	Major Findings
Shinchi (1997)	Cross-sectional analysis (1993-1994), self-administered questionnaire	Participants: 565 men, Ages: 50-55 yrs, Japanese/Japan	Rank of Self-Defense Force	Tofu high: ≥4 times/wk low: <2 times/wk	Participants who were seropositive to <i>H. pylori</i> (%): high: 88.6% low: 76.1%	Consumption of tofu is associated with a significant reduction in number of subjects who are seropositive to <i>Helicobacter pylori</i> * (<i>P</i> trend = 0.013). * <i>Helicobacter pylori</i> infection is a major risk factor for stomach cancer in humans.
Prognostic Analysis						
Reference	Design, Dietary Assessment Methods	Description of Subjects, Race, and Study Site	Confounding Factors Adjusted	Soy Products Assessed and Intake Levels	OR/RR/HR (95% CI) ¹ (Highest vs. Lowest)	Major Findings
Huang (2000)	Prognostic analysis (1988-1998), self-administered questionnaire.	Participants: 877 post-surgery patients of gastric adenocarcinoma, Ages: 40-79 yrs, Japanese/Japan	Age, gender, and pathological and stage of cancer.	Bean curd >3-4 times/wk vs. ≤3 times/wk	0.65 (0.42-0.98)	Frequent intake of tofu is related to a significantly lower death rate of stomach cancer in post-surgery gastric cancer patients compared with the less frequent intake (<i>P</i> <0.05).

Table 15. Epidemiological studies on soy consumption and stomach and esophageal cancer in humans (continued).

Nutritional Survey						
Reference	Design, Dietary Assessment Methods	Description of Subjects, Race, and Study Site	Confounding Factors Adjusted	Soy Products Assessed and Intake Levels	OR/RR/HR (95% CI) ¹ (Highest vs. Lowest)	Major Findings
Nagai (1982)	Nationwide nutritional survey (1969-1976)	A correlation analysis of data from a nationwide nutrition survey with the mortality data of stomach and esophageal cancer in Japan, Japanese/Japan		Tofu 31.3 ± 11.4 g/* (mean ± SD) *Time unit not presented.	Stomach: Men: $r^* = -0.094$ Women: $r^* = -0.091$ Esophagus: Men: $r^* = -0.03$ Women: $r^* = 0.02$	Intake of tofu is correlated with a significantly lower stomach cancer mortality in men ($P \leq 0.01$) and women ($P \leq 0.01$), but not correlated to esophageal cancer mortality in either sex. *Regression coefficient.
Ecological Studies						
Reference	Design, Dietary Assessment Methods	Description of Subjects, Race, and Study Site	Confounding Factors Adjusted	Soy Products Assessed and Intake Levels	OR/RR/HR (95% CI) ¹ (highest vs. lowest)	Major Findings
Nagata (2000)	Ecological study	Correlation analysis using data from National Nutritional Survey Report 1980-1985 and National Vital Statistics 1995, Japanese/Japan.	Mean age, proportion of current smokers, and intake of alcohol and salt.	Soy protein* 6.5 ± 0.8 g/d (mean ± SD) *Standardized from soyfoods – miso, tofu, fried tofu, soybeans, soy milk, and yuba.	Men: $r^* = -0.31$ Women: $r^* = -0.10$ *Correlation coefficient.	Intake of soy protein is correlated with a significantly lower mortality of stomach cancer in men ($P < 0.04$), but not in women.

Table 15. Epidemiological studies on soy consumption and stomach and esophageal cancer in humans (continued).

Ecological Studies						
Reference	Design, Dietary Assessment Methods	Description of Subjects, Race, and Study Site	Confounding Factors Adjusted	Soy Products Assessed and Intake Levels	OR/RR/HR (95% CI) ¹ (highest vs. lowest)	Major Findings
Takezaki (1999)	Comparative ecological study in people residing in a low-risk and a high-risk area of stomach cancer (1995-1996), questionnaire (interview)	Participants: 414 from a high-risk area, 425 from a low-risk area, Ages: 30-79 yrs, Chincsc/China	Age.	Soybean products ≥ 3 times/wk vs. less	N/A	People living in the low-risk area consume soy at significantly greater frequencies than those in the high-risk area. For example, 60% of men and 57% of women in the low-risk area eat soybean products at ≥ 3 times/wk, whereas only 5% of men and 4% of women in the high-risk area are at the same intake frequencies ($P < 0.001$ for both sexes).

¹OR/RR/HR (95% CI) = odds ratio/relative risk/hazard ratio (95% confidence interval).

B.3.3 (2). Epidemiological Studies – Colorectal Cancer

Summary

There are 11 publications available to date that relate soy consumption to colorectal cancer in humans (one short-term intervention study, eight case-control studies, one cross-national analysis, and one ecological investigation)(see Table 16 for summary and Table 17 for details). A thorough review of these studies shows that consumption of soyfoods is associated with a lower risk of colorectal cancer in humans. This relationship is supported by a meta-analysis of these studies that yields a pooled estimate of 0.78 (95% CI = 0.64 –0.96; $P = 0.02$)(Figure 8).

Results of the intervention study show that an intake of isolated soy protein at 39 g/d for one year significantly reduces colon mucosa cell proliferation compared with an intake of casein at 39 g/d in an “at risk” population (Bennink, 2001). The “at risk” population is defined as participants with a history of colon polyps or colon cancer. For the eight case-control studies, Witte et al (1996) reported that tofu intake is related to a significantly lower incidence of adenomatous polyps (adjusted OR = 0.48). Hoshiyama et al (1993) showed that intake of soy foods is related to a lower risk of colon (adjusted RR = 0.4) and rectal cancer (adjusted RR = 0.6). Nishi et al (1997) reported that tofu intake is associated with a lower risk of colon cancer (OR = 0.79), but not related to rectal cancer (OR = 1.02). Seow et al (2002) found that soy intake is not related to colorectal cancer risk (adjusted OR = 1.3), and Tajima et al (Tajima & Tominaga, 1985) showed that bean curd is not associated with colon cancer (RR = 1.08), but related to the risk of rectal cancer (RR = 1.63). Le Marchand et al (1997) found that consumption of soy products and legumes is related to a lower risk of colorectal cancer in women (adjusted OR = 0.5) and men (adjusted OR = 0.8), but results are statistically significant only in women. Hu et al (1991) reported that bean curd is related to a significantly lower risk of rectal cancer in men (estimated ORs are 0.33 and 0.27 for data collected in 1985 and 1966), but not in women nor to colon cancer in either sex. Inoue et al (1995) found that bean curd intake is related to a lower risk of distal colon cancer but not related to proximal and rectal cancer in women, and bean curd intake is not associated with proximal and rectal cancer but related to the risk of distal cancer in men. Results of the cross-national analysis show

that soy availability is not related to the risk of colorectal cancer in men (McKeown-Eyssen & Bright-See, 1984). Results of the ecological study show that intake of soy products is correlated with the mortality of colorectal cancer risk in both sexes (Nagata, 2000). Results of a meta-analysis of the studies that provide adequate data for a pooled analysis show a pooled estimate of odds ratio/relative risk 0.78 (95% CI = 0.64 – 0.96, $P = 0.02$).