



APPENDIX III

### ***Appendix III. Scientific Evidence—Other Cancers***

#### **Summary**

This section reviews scientific evidence from epidemiological studies that relate soy consumption to the risk of endometrial/ovarian, thyroid, lung, pancreas, liver, nasopharyngeal, and urinary bladder cancer in humans. It includes three case-control studies on endometrial/ovarian cancer, three case-control studies on thyroid cancer, seven case-control and one ecological study on lung cancer, one case-control study on pancreatic cancer, one case-control study on hepatic cancer, and one cohort and one case-control study each on nasopharyngeal cancer and urinary bladder cancer. Results from these studies generally reflect a trend that consumption of soyfoods is related to a lower risk of cancerous diseases. However, the number of studies is limited and findings are not consistent in certain types of cancers.

Findings from the studies on endometrial/ovarian cancer demonstrate that consumption of soy protein-containing foods is related to a lower risk of endometrial (adjusted ORs range, 0.46 – 0.59)(Goodman et al., 1997; Horn-Ross et al., 2003) and ovarian cancer (adjusted OR = 0.4, 95% CI = 0.2 – 0.7)(Zhang et al., 2002). Results are statistically significant in all of these three studies.

Three studies are available on thyroid cancer. Two population-based case-control studies reveal that soy consumption is associated with a lower risk of thyroid cancer (adjusted ORs range, 0.52 – 0.65) (Haselkorn et al., 2003; Horn-Ross et al., 2002). Results of a hospital-based case-referent study show that tofu intake is related to the risk of the disease (adjusted OR = 1.4, 95% CI = 0.7 – 2.8) (Takezaki et al., 1996). None of these results is statistically significant.

Of the seven case-control studies on lung cancer, six show that consumption of soyfoods is associated with a low risk of lung cancer (adjusted RRs/ORs range, 0.44 – 0.68) (Hu et al., 1997; Koo, 1988; Seow et al., 2002; Swanson et al., 1992; Takezaki et al., 2001; Wakai et al., 1999). Results are statistically significant in four studies (Seow et al., 2002;

Takezaki et al., 2001)\*(Wakai et al., 1999)\*\*(Swanson et al., 1992). Results of one case-control study (adjusted OR = 1.0, 95% CI = 0.8 – 1.3) (Wu-Williams et al., 1990) and an ecological study (Nagata, 2000) show that soy consumption is not associated with lung cancer. One study shows that bean curd intake is related to the risk of squamous cell and small cell carcinoma in men (adjusted OR = 3.0, 95% CI = 0.72-12.6) (Takezaki et al., 2001)\*. (\*Takezaki et al (2001) analyzed data on the basis of sub-types of lung cancer. Bean curd intake is related to a significantly lower risk of adenocarcinoma in women, but not in men. Intake of bean curd is related to the risk of squamous cell and small cell carcinoma in men, but not in women. \*\*Wakai et al (1999) reported that intake of tofu and soybeans is related to a significantly lower risk of lung cancer in men, but not in women.)

Results of a case-control study on pancreatic cancer show that soy consumption is related to a lower risk of pancreatic cancer (Ohba et al., 1996). The RR is 0.75 (95% CI = 0.56 – 1.01) for tofu and 0.76 (95% CI = 0.60 – 0.97) for deep-fried tofu.

Findings from a case-control study on phytoestrogen intake and hepatic cancer show that patients with hepatocellular carcinoma have a significantly lower intake of genistein compared with cirrhotic patients ( $P = 0.001$ ) (Lei et al., 2002). There is no difference in daidzein intake between the groups.

Two studies are available on soy and nasopharyngeal cancer. Results of a cohort study show that tofu intake is related to a lower risk of upper aero-digestive tract cancer (adjusted RR = 0.49, 95% CI = 0.07 – 3.54)(Chyou et al., 1995). Findings from a case-control study show that consumption of soybean products during childhood (at ages 3 and 10) is related to a lower risk of nasopharyngeal cancer (Ward et al., 2000). The adjusted OR is 0.4 (95% CI = 0.2 – 1.0) for soy consumption at age 10, and 0.7 (95% CI = 0.3 – 1.7) for the intake at age 3.

Two studies are available on soy and urinary bladder cancer. Results of a cohort study show that consumption of soyfoods is related to the risk of urinary bladder cancer

(adjusted RR = 2.34, 95% CI = 1.07 – 5.09) (Sun et al., 2002). Findings from a case-control study show that intake of soy juice is not related to urinary bladder cancer (adjusted RR = 0.95, 95% CI = 0.43 – 2.12) (Lu et al., 1999).

## I. Endometrial and Ovary Cancer

### Summary

There are three case-control studies that assess the association of soy consumption and the risk of endometrial and ovary cancer in women (please see Table 1 for summary and Table 2 for details). Results of these studies show that consumption of soy protein-containing foods is related to a lower risk of endometrial (adjusted ORs range, 0.46 – 0.59) (Goodman et al., 1997; Horn-Ross et al., 2003) and ovary cancer in women (adjusted OR = 0.4) (Zhang et al., 2002). Results are statistically significant in all of these three studies.

Table 1. Summary of epidemiological studies on soy intake and endometrial and ovary cancer in women.

Reference	Soy Products Assessed	OR (95% CI) <sup>1</sup> (Highest vs. Lowest Intake)	P trend
<b>Case-Control Studies</b>			
Horn-Ross (2003)	Isoflavones	0.59 (0.37 – 0.93)	0.02
Zhang (2002)	Soybean products	0.4 (0.2 – 0.7)	0.01
Goodman (1997)	Tofu	0.53 (0.30 – 0.94)	0.04
	Tofu and other soy products	0.46 (0.26 – 0.83)	0.01

<sup>1</sup>OR (95% CI) = odds ratio (95% confidence interval).

### Case-Control Studies

Horn-Ross et al (2003) assessed the association of soy consumption and the risk of endometrial cancer in a non-Asian multi-ethnic population in the United States (500 cases, 470 controls). Soy isoflavone intake was derived from soy intake before data were analyzed. Isoflavone intake is related to a significantly lower risk of endometrial cancer in women ( $P$  trend = 0.02). The adjusted OR is 0.59 (95% CI = 0.37 – 0.93) when the highest quartile of intake ( $\geq 2,726$   $\mu\text{g}/\text{d}$ ) is compared with the lowest ( $< 1,159$   $\mu\text{g}/\text{d}$ ). When data are analyzed on the basis of menopausal status, isoflavone intake is related to a lower risk of endometrial cancer in postmenopausal (adjusted OR = 0.44, 95% CI =

0.26 – 0.77) and premenopausal women (adjusted OR = 0.68, 95% CI = 0.22 – 2.1). The difference is statistically significant in postmenopausal women but not in premenopausal women.

Zhang et al (2002) assessed diet in relation to ovarian cancer in a hospital-based case-control study in China. Cases were 254 patients with histologically confirmed epithelial ovarian cancer. Controls (n = 652) comprised 340 hospital visitors, 261 non-neoplasm outpatients, and 51 community controls. Consumption of soybean products is associated with a significantly lower risk of ovarian cancer (adjusted OR = 0.4, 95% CI = 0.2-0.7) when the highest quartile of intake ( $\geq 82$  g/d) is compared with the lowest ( $\leq 21$  g/d). The test for trend is statistically significant ( $P < 0.01$ ).

Goodman et al (1997) investigated the relationship between soy consumption and the risk of endometrial cancer in a population-based multi-ethnic case-control study in Hawaii, the United States (332 cases, 511 controls). Tofu was analyzed separately or in combination with other soy products. Consumption of tofu is associated with a significantly lower risk of endometrial cancer ( $P$  trend = 0.04). The adjusted OR is 0.53 (95% CI = 0.30-0.94) when the highest quartile of intake ( $> 23.4$  g/d) is compared with the lowest (no tofu consumed). Consumption of soy products (tofu included) is related to a significantly lower risk of endometrial cancer ( $P$  trend = 0.01). The adjusted OR is 0.46 (95% CI = 0.26-0.83).

Table 2. Epidemiological studies on soy consumption and endometrial and ovarian cancer in women.

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 (95% CI) <sup>f</sup> (Highest vs. Lowest Intake)	Major Findings
Horn-Ross (2003)	Population-based case-control study (1996-1999), food frequency questionnaire (in-person interview).	Cases: 500, Controls: 470, Ages: 35-79 yrs, Non-Asian multi-ethnic population (African American, Latina, and White)/U.S.A.	Age, race/ethnicity, daily caloric intake, age at menarche, parity, use of oral contraceptives and hormone replacement therapy, and body mass index.	Isoflavones* Q4: $\geq 2,726$ $\mu\text{g}/\text{d}$ Q1: $< 1,150$ $\mu\text{g}/\text{d}$  *Driven from tofu, soy milk, and foods with added soy flour or soy protein.	0.59 (0.37-0.93)  Data assessed on menopausal status Postmenopausal: 0.44 (0.26-0.77) Premenopausal: 0.68 (0.22-2.1)	Consumption of isoflavone-containing foods is related to a significantly lower risk of endometrial cancer ( $P$ trend = 0.02).  When data are assessed on the basis of menopausal status, isoflavone consumption is related to a significantly lower risk of endometrial cancer in postmenopausal women ( $P$ trend = 0.001), but not in premenopausal women.
Zhang (2002)	Hospital-based case-control study, food frequency questionnaire (in-person interview).	Cases: 254, Controls: 652, Ages: $48 \pm 13$ yrs, Chinese/China	Age at interview, education, living area, body mass index (5 years old), smoking, alcohol drinking, tea drinking, family income, marital and menopause status, parity (full-term pregnancy), tubal ligation, oral contraceptive use, physical activity, family history of ovarian cancer, energy intake, etc.	Soybean products Q4: $\geq 82.2$ g/d Q1: $\leq 21.0$ g/d	0.4 (0.2-0.7)	Consumption of soybean products is related to a significant lower risk of ovarian cancer in women ( $P$ trend = 0.01).

Table 2. Epidemiological studies on soy consumption and endometrial and ovarian 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 (95% CI) <sup>1</sup> (Highest vs. Lowest Intake)	Major Findings
Goodman (1997)	Population-based case-control study, food frequency questionnaire and in-person interview.	Cases: 332, Controls: 511, Ages: 18-84 yrs, Multi-ethnic population (Japanese, Caucasian, Native Hawaiian, Filipino, and Chinese)/USA	Age, pregnant history, birth control pill use, history of diabetes mellitus, Quetelet's index (kg/m <sup>2</sup> ), and total calories.	Tofu Q4: >23.4 g/d Q1: 0  Tofu and other soy products* Q4: >45.4 g/d Q1: <0.05 g/d  *Included soy-beans and miso.	Tofu 0.53 (0.30-0.94)  Tofu and other soy products 0.46 (0.26-0.83)	Consumption of tofu is associated with a significantly lower risk of endometrial cancer ( <i>P</i> trend = 0.04).  Consumption of soy products (including tofu) is related to a significantly lower risk of endometrial cancer ( <i>P</i> trend = 0.01).

<sup>1</sup>OR (95% CI) = odds ratio (95% confidence interval).

## II. Thyroid Cancer

There are three case-control studies that examine the relationship between soy consumption and thyroid cancer in humans (please see Table 3 for summary and Table 4 for details). Findings from the most recently published population-based case-control studies in the United States show that consumption of soy protein-containing foods is associated with a lower occurrence of thyroid cancer (Haselkorn et al., 2003; Horn-Ross et al., 2002). Results from a hospital-based case-referent study in Japan show that tofu intake is related to the risk of thyroid cancer (Takezaki et al., 1996). None of these results are statistically significant.

Table 3. Summary of epidemiological studies on soy consumption and thyroid cancer in humans.

Reference	Soy Products Assessed	OR (95% CI) <sup>1</sup> (Highest vs. Lowest Intake)	P trend
<b>Case-Control Studies</b>			
Haselkorn (2003)	Isoflavones	0.59 (women <50 years of age) 0.52 (women ≥50 years of age)	
Horn-Ross (2002)	Isoflavones	0.65 (0.41 – 1.0)	0.13
Takezaki (1996)	Tofu	1.4 (0.7 – 2.8)	0.44

<sup>1</sup>OR (95% CI) = odds ratio (95% confidence interval).

### Case-Control Studies

The incidence of thyroid cancer among Southern Asian (SA) women living in the United States is 2-3 fold higher than that among Northern Asian (NA) women residing in the same country. Haselkorn et al (2003) conducted a population-based case-control study (515 cases, 486 controls) aimed at determining causes of such a difference. Southern Asian women included Filipino, Vietnamese, Thai, Indonesian, and Pacific Islander, and Northern Asian women included Chinese, Japanese, and Korea. Intake of isoflavones (derived from soy food intake) is associated with a lower risk of thyroid cancer in women. The estimated OR is 0.59 for younger women (<50 years of age) and 0.53 for older women (≥50 years of age) when the high intake of isoflavones (3,725 µg/d) is compared with the low intake (<1,517 µg/d). A lower consumption of isoflavones from soy-based foods explains 36% of the difference in the incidence between younger SA and NA women and 21% of the difference between older SA and NA women.

Horn-Ross et al (2002) investigated phytoestrogen intake in relation to thyroid cancer in a population-based multiethnic case-control study in the United States (608 cases, 608 controls). Isoflavone intake was derived from intake of isoflavone-containing foods, including soy. Consumption of soy-based foods is associated with a lower risk of thyroid cancer. The adjusted OR is 0.65 (95% CI = 0.41-1.0) when the highest quintile of intake ( $\geq 7.8$  mg/d) is compared with the lowest ( $< 1$  mg/d). The test for trend is  $P = 0.13$ . The adjusted OR is 0.5 (95% CI = 0.3-0.84) for tofu, 0.81 (95% CI = 0.44-1.5) for soymilk, 0.63 (95% CI = 0.37-1.1) for soyburgers and meat substitutes, and 0.59 (95% CI = 0.31-1.1) for soybean sprouts when the high intake is compared with non-users. The high intake is  $\geq 50$  g/d for tofu and soymilk,  $\geq 4$  g/d for soy-burgers and meat substitutes, and  $\geq 15$  g/d for soybean sprouts.

Takezaki et al (1996) examined risk factors of thyroid cancer in women in a hospital-based case-referent study in Japan. Ninety-four cases of thyroid cancer were compared with 22,666 non-cancer outpatients as referents. Tofu was one of the food items assessed. Tofu intake is related to the risk of thyroid cancer in this study population. The adjusted OR is 1.4 (95% CI = 0.7-2.8) when the highest tertile of intake is compared with the lowest. The intake frequency of each tertile was not presented in this publication.

Table 4. Epidemiological studies on soy consumption and thyroid cancer in humans.

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 (95% CI) <sup>1</sup> (Highest vs. Lowest Intake)	Major Findings
Haselkorn (2003)	Population-based case-control study (1992-1998), standardized, structured questionnaire (in-person interview).	Cases: 515, Controls: 486, Age: 20-74 yrs, Multiethnic women (Southern Asian: Filipino, Vietnamese, Thai, Indonesian, and Pacific Islander; Northern Asian: Chinese, Japanese, and Korean; and non-Latino Caucasian) /U.S.A.	Age and race/ethnicity. Dietary variables were additionally adjusted for average daily caloric intake.	Isoflavones* High: >3,725 µg/d Low: <1,517 µg/d  *Standardized from intake of soy-based foods.	Younger women (<50 yrs of age) 0.59*  Older women (≥50 yrs of age) 0.53*  *Estimated OR based on the data presented.	The incidence of thyroid cancer in Southern Asian (SA) women living in the United States is 2-3 fold higher than that in Northern Asian (NA) women residing in the United States. Consumption of isoflavones is related to a lower risk of thyroid cancer in younger and older women. A lower consumption of isoflavones among SA women explains 36% of the difference in thyroid cancer incidence between younger SA and NA women (<50 years of age) and 21% of the difference between the older SA and NA women (>50 years of age).

Table 4. Epidemiological studies on soy consumption and thyroid 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 (95% CI) <sup>1</sup> (Highest vs. Lowest Intake)	Major Findings	
Horn-Ross (2002)	Population-based case-control study (1992-1998), standardized, structured questionnaire (in-person interview).	Cases: 608, Controls: 608, Age: 20-74 yrs, Multiethnic women (white, African-American, Latino, Asian, and Native Americans) /U.S.A.	Age, race/ethnicity, daily caloric intake, goiter or thyroid nodules, radiation to the head or neck, and family history of proliferative thyroid disease.	Total isoflavones*	0.65 (0.41-1.0)	Isoflavone consumption is related to a lower risk of thyroid cancer in this study population when the highest intake is compared with the lowest ( <i>P</i> trend = 0.13).	
				Q5: ≥7,826 µg/d Q1: <1,046 µg/d			
				Tofu High: ≥50 g/d Low: nonconsumers	0.50 (0.30-0.84)		Consumption of tofu is related to a significantly lower risk of thyroid cancer.
				Soymilk High: ≥50 g/d Low: nonconsumers	0.81 (0.44-1.50)		Consumption of soymilk, soyburgers and meat substitutes, and soybean sprouts is associated with a 19%, 37%, and 41% reduction in thyroid cancer risk when the highest intake was compared with the non-users, but these results are not statistically significant.
				Soy-burgers and meat substitutes High: ≥4 g/d Low: nonconsumers	0.63 (0.37-1.10)		
				Soybean sprouts High: ≥15 g/d Low: nonconsumers	0.59 (0.31-1.1)	*Derived from intake of soyfoods.	

Table 4. Epidemiological studies on soy consumption and thyroid 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 (95% CI) <sup>1</sup> (Highest vs. Lowest Intake)	Major Findings
Takezaki (1996)	Hospital-based case-referent study (1988-1993), self-administered questionnaire.	Cases: 94, References: 22,666 non-cancer outpatients, Ages: 20-79 yrs, Japanese women/Japan	Age and years of visit.	Tofu T3:* T1:*  *Intake frequency not presented.	1.4 (0.7-2.8)	Tofu intake is associated with the risk of thyroid cancer ( <i>P</i> trend = 0.44), and these results are not statistically significant.

<sup>1</sup>OR (95% CI) = odds ratio (95% confidence interval).

### III. Lung Cancer

There are seven case-control studies and one ecological study available to date that examine the relationship between soy consumption and the risk of lung cancer in humans (please see Table 5 for summary and Table 6 for details). Of the seven case-control studies, six show that consumption of soy protein-containing foods is associated with a low risk of lung cancer (adjusted ORs/RRs range, 0.44 – 0.68) (Hu et al., 1997; Koo, 1988; Seow et al., 2002; Swanson et al., 1992; Takezaki et al., 2001; Wakai et al., 1999). Results are statistically significant in four studies (Seow et al., 2002; Takezaki et al., 2001)\*(Wakai et al., 1999)\*\*(Swanson et al., 1992). Results of one case-control study (Wu-Williams et al., 1990) and the ecological study (Nagata, 2000) show that soy consumption is not associated with lung cancer. (\*Takezaki et al (2001) analyzed data on the basis of types of lung cancer. Bean curd intake is related to a significantly lower occurrence of adenocarcinoma in women, but not in men. Bean curd intake is related to the risk of squamous cell and small cell carcinoma in men, but not in women. \*\*Wakai et al (1999) reported that intake of tofu and soybeans is related to a lower risk of lung cancer in men, but not in women.)

Table 5. Summary of epidemiological studies on soy consumption and lung cancer in humans.

Reference	Soy Products Assessed	OR/RR (95% CI) <sup>1</sup> (Highest vs. Lowest Intake)	P trend
Case-Control Studies			
Seow (2002)	Soyfoods	0.53 (0.34 – 0.81) (non-smokers) 1.53 (0.76 – 3.11) (smokers)	0.01 0.2
Takezaki (2001)	Soybean curds	Adenocarcinoma: 0.52 (0.30 – 0.91) (women) 1.24 (0.83 – 1.85) (men)  Squamous and small cell carcinoma: 3.00 (0.72 – 12.6) (women) 1.23 (0.84 – 1.81) (men)	0.02 0.48  0.52 0.34
Wakai (1999)	Tofu	0.72 (0.5 – 1.04) (men) 1.0 (0.54 – 1.84) (women)	0.10
	Soybeans	0.63 (0.40 – 0.98) (men) 1.09 (0.49 – 2.39) (women)	0.05 0.92
Hu (1997)	Soya bean products	0.6 (0.4 – 1.1)	0.10
Swanson (1992)	Bean curd	0.44	0.01
Wu-Williams (1990)	Soya bean products	1.0 (0.8 – 1.3)	
Koo (1988)	Tofu	0.68	0.52
Ecological Study			
Nagata (2000)	Soy protein	$r = -0.06$ (men) $r = -0.04$ (women)	

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

### Case-Control Studies

Seow et al (2002) assessed dietary factors in relation to lung cancer risk in Chinese women (303 cases, 765 controls) in Singapore. Data from non-smokers and smokers were separately analyzed, and soyfoods were analyzed as one category of food in this study. A higher soy intake is associated with a significantly lower risk of lung cancer in non-smokers ( $P$  trend = 0.01), but not in smokers. The adjusted OR is 0.53 (95% CI = 0.34-0.81) when the highest tertile of intake ( $\geq 5.4$  servings/wk) is compared with the lowest ( $< 2.2$  servings/wk). The trend persists in non-smokers after further adjustment for fruit intake ( $P$  trend = 0.01). The adjusted OR is 0.58 (95% CI = 0.37-0.91). When adenocarcinoma is separately analyzed from other types of lung cancer, soy intake is related to a significantly lower incidence of adenocarcinoma in non-smokers ( $P$  trend = 0.01). The adjusted OR is 0.47 (95% CI = 0.29-0.76) when the highest intake is compared with the lowest.

Takezaki et al (2001) investigated dietary factors in relation to lung cancer in a hospital-based case-control study in Japan (1,045 cases, 4,143 controls). Soybean curd was one of the food items assessed. Adenocarcinoma and squamous cell and small cell carcinomas were separately analyzed, and smoking status (never, former, and current smokers) was adjusted as a confounding factor in this study. Consumption of soybean curd is associated with a significantly lower risk of adenocarcinoma in women ( $P$  trend = 0.02), but not in men. The adjusted OR is 0.52 (95% CI = 0.30-0.91) for women and 1.24 (0.83-1.83) for men when the highest quartile of intake ( $\geq 5$  times/wk) is compared with the lowest ( $< 1$  time/wk). Soybean curd intake is related to the risk of squamous cell and small cell carcinomas in women (adjusted OR = 3.0, 95% CI = 0.72-12.6), but not related to the disease in men (adjusted OR = 1.23, 95% CI = 0.84-1.81).

Wakai et al (1999) investigated the association of dietary factors with lung cancer in a population-based case-control study in Japan (333 cases, 666 controls). Tofu and soybeans were separately analyzed as two food items in this study. Consumption of tofu is related to a lower risk of lung cancer in men ( $P$  trend  $< 0.10$ ), but not in women. The adjusted OR is 0.72 (95% CI = 0.50-1.04) for men and 1.0 (95% CI = 0.54-1.86) for women when daily users are compared with weekly users ( $< 3-4$  times/wk). When data are analyzed on the basis of tumor sub-types, tofu intake is related to a significantly lower risk of squamous cell carcinoma in both men and women ( $P$  trend  $< 0.05$ ). The adjusted OR is 0.55 (95% CI = 0.34-0.89) for men and 0.14 (95% CI = 0.02-0.89) for women when the daily users are compared with the weekly users. A frequent consumption of tofu is associated with a lower risk of adenocarcinoma in men (adjusted OR = 0.68, 95% CI = 0.42-1.11), but not in women (adjusted OR = 1.01, 95% CI = 0.54-1.92).

Consumption of soybeans is related to a significantly lower risk of lung cancer in men (adjusted OR = 0.63, 95% CI = 0.40-0.98), but not in women (adjusted OR = 1.09, 95% CI = 0.49-2.39), when the upper level of intake ( $\geq 1-2$  times/wk) is compared with the lower level ( $< 1$  time/m). When data are analyzed on the basis of tumor sub-types, soybean intake is related to a lower incidence of squamous cell carcinoma and adenocarcinoma in men, but not in women. The adjusted OR is 0.69 (95% CI = 0.40-1.20) for squamous cell carcinoma and 0.83 (0.47 – 1.46) for adenocarcinoma in men,

and 0.92 (95% CI = 0.18-4.61) and 1.27 (95% CI = 0.55-2.93) for women respectively, when the upper level of intake is compared with the lowest.

Hu et al (1997) studied the relationship between diet and lung cancer in a hospital-based case-control study in China (227 cases, 227 controls). Soya bean products were analyzed as one category of food. Consumption of soya bean products is associated with a lower risk of lung cancer ( $P$  trend = 0.10). The adjusted OR is 0.6 (95% CI = 0.4-1.1) when the highest quartile of intake ( $\geq 8$  kg/yr) is compared with the lowest ( $< 2$  kg/yr).

Swanson et al (1992) investigated dietary determinants of lung cancer in men (428 cases, 1,011 controls) in a tin mining community in southern China. Cases and controls were tin mine workers and residents of an adjacent city. Bean curd was assessed in this study. Bean curd intake is associated with a lower risk of lung cancer ( $P$  trend  $< 0.01$ ). The adjusted RR is 0.44 when the highest quartile of intake ( $\geq 16$  times/m) is compared with the lowest ( $< 8$  times/m). Similar risk reduction exists when data from smokers are separately analyzed (data not presented). Dietary associations were not separately evaluated for non-smokers in this study because they were few in numbers.

Wu-Williams et al (1990) examined risk factors associated with lung cancer in women (965 cases, 959 controls) in Shenyang and Harbin, two major industrial cities in northern China. These two cities were among the cities with the highest incidence of lung cancer in China, and smoking was highly prevalent in women in these cities. Soya bean products were analyzed as one dietary factor, and smoking was adjusted as a confounding factor in this study. Consumption of soya bean products is not associated with lung cancer in this study population. The adjusted RR is 1.0 (95% CI = 0.8-1.3) when the upper level of intake ( $> 485$  times/yr) is compared with the lower level of intake ( $< 153$  times/yr).

Koo (1988) assessed dietary habits in relation to lung cancer in Chinese women (88 cases and 137 controls) in Hong Kong who never smoked (defined as smoked  $< 20$  cigarettes or pipes in the past). Tofu was one of the food items assessed. Consumption of tofu is

related to a lower risk of lung cancer (estimated RR = 0.68) when the high intake (>1-4 times/wk) is compared with the low intake (never or <1 time/m), but test for trend is not statistically significant ( $P = 0.52$ ). When data are analyzed on the basis of tumor subtypes, tofu intake is related to a significantly lower risk of adenocarcinoma and large cell tumors ( $P$  trend = 0.04). The estimated RR is 0.29 when the high intake is compared with the low intake. Tofu consumption is not related to squamous cell and small cell carcinomas in this study population.

### Ecological Study

Nagata et al (2000) investigated the correlation between soy intake and cancer mortality in an ecological study in Japan. Soy intake data from a National Nutritional Survey Report were correlated with cancer mortality data (lung, prostate, breast, stomach, colorectal 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 associated with the mortality of lung cancer in men ( $r = -0.04$ ) and women ( $r = -0.08$ ). This analysis also reveals that soy intake is correlated with a lower mortality of stomach cancer, not correlated with breast and prostate cancer, and positively correlated with the mortality of colorectal cancer (Please see the respective sections for details).

Table 6. Epidemiological studies on soy consumption and lung cancer in humans.

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) <sup>a</sup> (Highest vs. Lowest Intake)	Major Findings
Seow (2002)	Hospital-based case-control study (1996-1998), standardized questionnaire (in-person interview).	Cases: 303, Controls: 765. Ages: 20-89 yrs, Chinese women /Singapore	Age, birth place, and first degree relative with history of cancer. For smokers, further adjusted for duration and intensity of smoking. For non-smokers, further adjusted for passive smoking did not materially affect estimates.	Soy foods* >5.4 svgs/wk vs. <2.2 svgs/wk  *Yellow soy beans, soy bean milk, soy bean curd and cake, fried soy bean puff, soy bean sheet, and soy strips.	0.53 (0.34-0.81) (non-smokers)  1.53 (0.76-3.11) (smokers)  Adenocarcinoma: 0.47 (0.29-0.76) (non-smokers)	Consumption of soyfoods is associated with a significantly lower risk of lung cancer in non-smokers ( <i>P</i> trend = 0.01), but not in smokers ( <i>P</i> trend = 0.2). The statistical significance in non-smokers persists after further adjustment for fruits intake (adjusted OR = 0.58, 95% CI = 0.37-0.91), and the test for trend is <i>P</i> = 0.01.  Soy intake is related to a significantly lower incidence of adenocarcinoma in non-smokers ( <i>P</i> trend = 0.01) when adenocarcinoma is separately analyzed from other types of lung cancer.
Takezaki (2001)	Hospital-based case-control study (1988-1997), self-administered questionnaire.	Cases (adenocarcinoma and squamous cell and small cell carcinoma): 1,045, Controls: 4,143, Ages: 40-79 yrs, Japanese/Japan	Age, season and year of visit, occupation, prior lung diseases, smoking, passive smoking from husband, and consumption of green vegetables and meat.	Soybean curds ≥5 times/wk vs. <1 time/wk	Adenocarcinoma: 0.52 (0.30-0.91) (women)  1.24 (0.83-1.85) (men)  Squamous cell and small cell carcinomas: 3.00 (0.72-12.6) (women)  1.23 (0.84-1.81) (men)	Consumption of soybean curd is related to a significantly lower risk of adenocarcinoma in women ( <i>P</i> trend = 0.02), but in men ( <i>P</i> trend = 0.48).  Intake of soybean curd is related to the risk of squamous cell and small cell carcinomas in women ( <i>P</i> trend = 0.52), but not in men ( <i>P</i> trend = 0.34).

Table 6. Epidemiological studies on soy consumption and lung 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 (95% CI) <sup>1</sup> (Highest vs. Lowest Intake)	Major Findings
Wakai (1999)	Population-based case-control study (1988-1991), standardized questionnaire (in-person interview).	Cases: 333, Controls: 666, Ages: 40-89 yrs, Japanese/Japan	Age, residence, education, smoking, and medical history of lung cancer.	Tofu Daily vs. ≤3-4 times/wk	0.72 (0.50-1.04) (men)  1.0 (0.54-1.86) (women)  Squamous cell carcinoma: 0.55 (0.34-0.89) (men)  0.14 (0.02-0.89) (women)  Adenocarcinoma: 0.68 (0.42-1.11) (men)  1.01 (0.54-1.92) (women)	Consumption of tofu is associated with a lower risk of lung cancer in men ( <i>P</i> trend <0.10), but not in women.  When data are analyzed on the basis of tumor sub-types, tofu intake is related to a significantly lower risk of squamous cell carcinoma in both men ( <i>P</i> trend <0.05) and women ( <i>P</i> trend <0.05).  Tofu intake is related to a lower risk of adenocarcinoma in men, but in women.

Table 6. Epidemiological studies on soy consumption and lung cancer in humans (continued).

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) <sup>1</sup> (Highest vs. Lowest Intake)	Major Findings
Waiki (1999) (continued)	Population-based case-control study (1988-1991), standardized questionnaire (in-person interview).	Cases: 333, Controls: 666, Ages: 40-89 yrs, Japanese/Japan	Age, residence, education, smoking, and medical history of lung cancer.	Soybeans $\geq 1$ -2 times/wk vs. $< 1$ time/m	0.63 (0.40-0.98) (men) 1.09 (0.49-2.39) (women)  Squamous cell carcinoma: 0.69 (0.4-1.2) (men) 0.92 (0.18-4.61) (women)  Adenocarcinoma: 0.83 (0.47-1.46) (men) 1.27 (0.55-2.93) (women)	Soybean intake is related to a significantly lower risk of lung cancer in men ( $P$ trend $< 0.05$ ), but not in women ( $P$ trend = 0.92).  When data are analyzed on the basis of tumor sub-types, soybean intake is related to a lower risk of squamous cell carcinoma in men ( $P$ trend = 0.17), but not in women ( $P$ trend = 0.92).  Soybean intake is related to a lower risk of adenocarcinoma in men ( $P$ trend = 0.49), but not in women ( $P$ trend = 0.61).
Hu (1997)	Hospital-based case-control study (1985-1987), structured questionnaire (in-person interview).	Cases: 227, Controls: 227, Age (mean): 52 yrs, Chinese/China	Cigarettes per day, duration of smoking and family income.	Soya bean products Q4: $> 8$ kg/y Q1: $< 2$ kg/y	0.6 (0.4-1.1)	Consumption of soya bean products is associated with a lower lung cancer ( $P$ trend = 0.10).

Table 6. Epidemiological studies on soy consumption and lung 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 (95% CI) <sup>†</sup> (Highest vs. Lowest Intake)	Major Findings
Swanson (1992)	Population-based case-control study (1987-1990), standardized, structured questionnaire (in-person interview).	Cases: 428, Controls: 1,011, Ages: 35-74 yrs, Chinese men /China	Age group, respondent type, study site, education, and income.	Bean curd Q4: >16 times/m Q1: <8 times/m	0.44	Consumption of bean curd is associated with a significantly lower risk of lung cancer ( <i>P</i> trend <0.01).
Wu-Williams (1990)	Population-based case-control study (1985-1987), structured, pre-coded questionnaire (in-person interview).	Cases: 965, Controls: 959, Age (mean): 56 yrs, Chinese women/China	Age, education, personal smoking, and study area.	Soya bean products* Q4: >485 times/y Q1: <153 times/y  *Bean curd and fermented bean paste.	1.0 (0.8-1.3)	Consumption of soya bean products is not related to lung cancer in this study population.*  *The study was done in Shenyang and Harbin, two major industrial cities with the highest incidence of lung cancer in northern China. Smoking was highly prevalent in women in these cities. The level of air pollution in these cities was high. For example, the indoor and outdoor levels of benzopyrene from coal burning (a risk factor of lung cancer) in these cities were 60-fold greater than standards for cities in the United States.

Table 6. Epidemiological studies on soy consumption and lung 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 (95% CI) <sup>1</sup> (Highest vs. Lowest Intake)	Major Findings
Koo (1988)	Case-control study (1981-1983), questionnaire (in-person interview).	Cases: 88, Controls: 137, Age (mean): 59 yrs, Hong Kong women/ China	Age, number of live births, and schooling.	Tofu/soy products High: >1-4 times/wk Low: never to <1 time/wk	0.68*  Adenocarcinoma and large cell carcinoma: 0.29*  Squamous cell and small cell carcinoma: 1.54*	Consumption of tofu is related to a lower risk of lung cancer, but the test for trend is not statistically significant ( $P = 0.52$ ).  When data are analyzed on the basis of tumor sub-types, tofu intake is associated with a significantly lower risk of adenocarcinoma and large cell carcinoma ( $P$ trend = 0.04), but not related to squamous cell and small cell carcinomas ( $P$ trend = 0.37).  *Estimated RR from the data presented.
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) <sup>1</sup> (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)  *Standardized from soyfoods (miso, tofu, fried tofu, soybeans, soy milk, and yuba).	-0.06** (men)  -0.04** (women)  **correlation coefficient.	Consumption of soyfoods is not correlated with lung cancer in either sex.

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

#### IV. Pancreatic Cancer

Results of one case-control study show that consumption of tofu is related to a lower risk of pancreatic cancer in humans (Table 7).

##### Case-Control Study

Ohba et al (1996) examined eating habits in relation to pancreatic cancer in a community-based case-control study in Japan (141 cases, 282 controls). Tofu and deep-fried tofu were assessed in this study. Consumption of tofu or deep-fried tofu is associated with a 25% reduction in pancreatic cancer risk when frequent users (>3 times/wk) are compared with less-often users (<3 times/wk). The RR is 0.75 (95% CI = 0.56-1.01) for tofu and 0.76 (95% CI = 0.60-0.97) for deep-fried tofu.

## V. Hepatic Cancer

One case-control study examined the phytoestrogen intake in patients with hepatic diseases (Lei et al., 2002) (Table 8). It was found that patients with hepatocellular carcinoma have a significantly lower intake of genistein compared with cirrhotic patients.

### Case-Control Study

Lei et al (2002) assessed phytoestrogen intake in patients with hepatocellular carcinoma (n = 32) and cirrhosis (n = 92, served as controls). Patients were recruited to the study at the first diagnosis of their disease, and interviewed for their dietary practice during the past year. Phytoestrogen intake was derived from the food intake data collected. There is no difference in total calorie and nutrient intake between the groups. Patients with hepatocellular carcinoma have a significantly lower intake of genistein compared with cirrhotic patients ( $P = 0.001$ ), suggesting patients with hepatocellular carcinoma consumed less phytoestrogen-containing foods, including soy, than cirrhotic patients. There is no difference in daidzein intake between the groups. The quantity of phytoestrogen intake or food intake was not presented in this publication.

## VI. Nasopharyngeal Cancer

There are one cohort study and one case-control study that examine the relationship between soy intake and nasopharyngeal cancer in humans (please see Table 9 for summary and Table 10 for details). Results from these studies show that soy consumption is associated with a lower risk of nasopharyngeal cancer, although these results are not statistically significant.

Table 9. Summary of epidemiological studies on soy intake and nasopharyngeal cancer in humans.

Reference	Soy Products Assessed	OR/RR (95% CI) <sup>1</sup> (Highest vs. Lowest Intake)	P trend
<b>Cohort Study</b>			
Chyou (1995)	Tofu	0.49 (0.07 – 3.54)	0.091
<b>Case-Control Study</b>			
Ward (2000)	Fresh soybean products	0.4 (0.2 – 1.0) (at age 10) 0.7 (0.3 – 1.7) (at age 3) 1.1 (0.5 – 2.1) (during weaning) 0.6 (0.2 – 1.5) (mothers' soy intake during breast-feeding)	

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

### Cohort Study

Chyou et al (1995) conducted a cohort study on upper aero-digestive tract cancer with 7,995 Hawaii Japanese men in the United States. The upper aero-digestive cancer included oral/pharyngeal, esophageal, and laryngeal cancer. A food frequency questionnaire was provided to each participant at the time of interview during 1965 to 1968. Tofu was one of the food items assessed. After 24 years of follow-up, 92 histologically confirmed cases were identified. Intake of tofu is associated with a lower risk of upper aero-digestive tract cancer ( $P$  trend = 0.091). The adjusted RR is 0.49 (95% CI = 0.07-3.54) when the highest level of intake ( $\geq 5$  times/wk) is compared with the lowest ( $\leq 1$  time/wk).

### Case-Control Study

Ward et al (2000) examined the relationship between diet consumed during childhood and the risk of nasopharyngeal cancer later in life in a population-based case-control study in Taiwan (375 cases, 327 controls). Cases and controls were interviewed for their

dietary habits during childhood and adulthood. In addition, mothers of the participants were interviewed for their dietary history during breast feeding and their children's diet at ages 10, 3, and during weaning. Fresh soybean products (mainly tofu and its derivative products) were assessed as one group of food in this study. Consumption of fresh soybean products during childhood is related to a lower risk of nasopharyngeal cancer. The adjusted OR is 0.4 (95% CI = 0.2-1.0) for age 10 and 0.7 (95% CI = 0.3-1.7) for age 3. The highest and the lowest quartile of intake are >1.5 g/wk and <0.5 g/wk for age 10, and >1.0 g/wk and <0.04 g/wk for age 3, respectively. Intake of fresh soy products during weaning is not associated with the disease (adjusted OR = 1.1, 95% CI = 0.5-2.1) when users (>0 g/wk) are compared with non-users. Consumption of soy products by mothers during breast-feeding is related to a 40% reduction in nasopharyngeal cancer risk in offspring (adjusted OR = 0.6, 95% CI = 0.2-1.5), but results are not statistically significant.

Table 10. Epidemiological studies on soy consumption and nasopharyngeal cancer in humans.

Cohort 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) <sup>1</sup> (Highest vs. Lowest Intake)	Major Findings
Chyou (1995)	Cohort study (1965-1992), food frequency questionnaire (in-person interview).	92 incident cases identified from a study population of 7,995 Japanese American men during a 24-year follow-up period, Ages: 45-68 yrs, Hawaiian Japanese/ USA	Age, alcohol, number of cigarettes/d, and number of years smoked.	Tofu High: ≥5 times/wk Low: ≤1 time/wk	0.49 (0.07-3.54)	Consumption of tofu is associated with a lower risk of upper aerodigestive tract cancer* ( <i>P</i> trend = 0.091).  *Upper aerodigestive tract cancer included oral/pharyngeal, esophageal, and laryngeal cancer.

Table 10. Epidemiological studies on soy consumption and nasopharyngeal cancer in humans (continued).

Case-Control 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) <sup>1</sup> (Highest vs. Lowest Intake)	Major Findings
Ward (2000)	Population-based case-control study (1991-1994), questionnaire (in-person interview).	Cases: 375, Control: 327, Ages: <75 yrs, Chinese/Taiwan	Age, gender, and ethnicity.	<p>Fresh soybean products*</p> <p>At age 10: Q4: &gt;1.5 g/wk Q1: &lt;0.5 g/wk</p> <p>At age three: Q4: &gt;1.9 g/wk Q1: &lt;0.04 g/wk</p> <p>During weaning: Users vs. non-users</p> <p>Mothers' soy intake during breast-feeding: Not reported.</p>	<p>At age 10: 0.4 (0.2-1.0)</p> <p>At age 3: 0.7 (0.3-1.7)</p> <p>During weaning: 1.1 (0.5-2.1)</p> <p>Mothers' soy intake during breast-feeding: 0.6 (0.2-1.5)</p>	<p>Consumption of fresh soybean products during childhood (at ages 10 and 3) is associated with a lower risk of nasopharyngeal cancer in later life.</p> <p>Consumption of soy products during weaning is not related to nasopharyngeal cancer.</p> <p>Consumption of soybean products by mothers during breast-feeding is related to a lower risk of developing nasopharyngeal cancer in offspring.</p> <p>*Tofu, fried tofu, bean curd skin, dried bean strips, and other bean curd products, soybean milk, bean flowers, and soybeans.</p>

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

## VII. Urinary Bladder Cancer

There are one cohort study and one case-control study that assess soy intake in relation to urinary bladder cancer risk in humans (Lu et al., 1999; Sun et al., 2002) (please see Table 11 for summary and Table 12 for details). Sun et al (2002) reported that soyfood intake is related to the risk of urinary bladder cancer. Lu et al (1999) showed that consumption of soy juice is not related to urinary bladder cancer.

Table 11. Summary of epidemiological studies on soy intake and urinary bladder cancer in humans.

Reference	Soy Products Assessed	OR (95% CI) <sup>1</sup> (Highest vs. Lowest Intake)	P trend
<b>Cohort Study</b>			
Sun (2002)	Soyfoods	2.34 (1.07 – 5.09)	
<b>Case-Control Study</b>			
Lu (1999)	Soy juice	0.95 (0.43 – 2.12)	

<sup>1</sup>OR (95% CI) = odds ratio (95% confidence interval).

### Cohort Study

Sun et al (2002) investigated the relationship between soy intake and urinary bladder cancer in a population-based cohort study in Singapore. Sixty-one histologically confirmed incident cases of urinary bladder cancer were identified from 63,257 Chinese men and women during a six-year follow-up period (1993-1998). Intake of soyfoods is related to the risk of urinary bladder cancer. The adjusted RR is 2.34 (95% CI = 1.07-5.09) when the highest quartile of intake ( $\geq 92.5$  g/1,000 Kcal) is compared with the lowest ( $< 36.9$  g/1,000 Kcal). Similar results exist when data are analyzed as soy protein intake or soy isoflavone intake.

### Case-Control study

Lu et al (1999) studied beverage consumption in relation to urinary bladder cancer in a hospital-based case-control study in Taiwan (40 cases, 160 controls). Soy juice was one of the beverages assessed. Consumption of soy juice is not associated with urinary bladder cancer in this study population. The adjusted OR is 0.95 (95% CI = 0.43-2.12). Soy juice was not defined in this publication.

Table 12. Epidemiological studies on soy consumption and urinary bladder cancer in humans.

Cohort 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) <sup>1</sup> (Highest vs. Lowest Levels)	Major Findings
Sun (2002)	Population-based cohort study (1993-2000), structured questionnaire (in-person interview).	62 incident cases of urinary bladder cancer from 63,257 Chinese men and women, who participated in the Singapore Chinese Health Study, during a 6-year follow-up period (1993-1998) Chinese /Singapore	Age, year of recruitment, sex, dialect group, cigarette smoking status, and level of education.	Soyfoods* Q4: >92.5 g/1,000 Kcal Q1: ≤36.9 g/1,000 Kcal  *Plain tofu, taupok, taukwa, foopei, foojook, tofu-far, and soybean drinks)	2.34 (1.07-5.09)	Intake of soyfoods is related to the risk of urinary bladder cancer in this study population. Similar results exist when data are analyzed as soy protein intake or soy isoflavone intake.
Case-Control 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) <sup>1</sup> (Highest vs. Lowest Levels)	Major Findings
Lu (1999)	Hospital-based case-control study (1996-1997), structured questionnaire (in-person interview).	Cases: 40, Controls: 160, Chinese/Taiwan	Age, sex, date of admission, family history, ethnicity, and smoking status.	Soy juice Users vs. non-users	0.95 (0.43-2.12)	Consumption of soy juice is not associated with urinary bladder cancer.

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

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