

# Ecological study of the association between soy product intake and mortality from cancer and heart disease in Japan

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<b>Background</b>	The anticarcinogenic and antiatherogenic properties of soy have been demonstrated in experimental studies. To evaluate the relationship between soy product intake and mortality from several types of cancer and heart disease, an ecological analysis was performed in 47 prefectures in Japan.
<b>Methods</b>	Age-standardized mortality rates for heart disease and stomach, colorectal, lung, breast and prostate cancer were obtained from the National Vital Statistics, 1995. Information on major nutrient and soy product intake was obtained from the National Nutritional Survey Report 1980–1985. In this survey, dietary habits were surveyed annually by 3-day diet record in about 6000 randomly selected households.
<b>Results</b>	Soy protein intake was significantly correlated with stomach cancer mortality rate in men after controlling for total energy, alcohol and salt intake, and the mean age and proportion of current smokers in the prefecture ( $r = -0.31$ , $P = 0.04$ ). Soy product intake estimated as total amount as well as isoflavone and soy protein intake were significantly positively correlated with colorectal cancer mortality rates in both sexes (for total amount, $r = 0.32$ , $P = 0.03$ in men and $r = 0.44$ , $P = 0.001$ in women) after controlling for covariates. The inverse correlation between soy product intake (as total amount or soy protein) and heart disease mortality rate was statistically significant in women after controlling for covariates ( $r = 0.32$ , $P = 0.04$ and $r = -0.31$ , $P = 0.045$ , respectively).
<b>Conclusion</b>	The present study provides modest support for the preventive role of soy against stomach cancer and heart disease death.
<b>Keywords</b>	Soy, mortality, ecological study, cancer, heart diseases
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Soybeans contain high quantities of the isoflavones, daidzein and genistein.<sup>1</sup> These compounds have been shown to possess oestrogenic and anticarcinogenic activity.<sup>2</sup> It has also been shown that soy protein or/and isoflavones exert antiatherogenic effects,<sup>3</sup> and decrease low-density lipoprotein cholesterol.<sup>4</sup> The low incidence of, and mortality from, heart disease and some types of cancer (e.g. breast and prostate) in Japan have been attributed to the high consumption of soy products. However, the relation between soy product intake and risk of heart disease has not been elucidated and epidemiological studies on soy product intake and cancer risk have produced inconclusive results.<sup>5</sup>

In analytical studies, large intra-individual variability in the measurement of exposure will attenuate associations. Ecological studies may be less subject to the effects of random error in the measurement of exposure.<sup>6</sup> Two cross-national studies examined the association between dietary soy and mortality from certain cancers (colon and prostate cancer, respectively).<sup>7,8</sup> The association was significantly inverse for prostate cancer but not for colon cancer. However, it is difficult to evaluate these studies because few countries consume amounts of soy likely to be physiologically meaningful. It is interesting to study ecologically the association between soy intake and cancer mortality and heart disease in Japan as significant amounts of soy products are consumed and there is a considerable variation in consumption. The uniformity of the data sources on mortality and dietary habits for all the geographical units within Japan is also advantageous. We examined ecological correlations between soy product intake and mortality rates from several types of cancer and heart disease in 47 Japanese prefectures.

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## Materials and Methods

The cancers studied were stomach (ICD-10 02103), colorectal (ICD-10 02104–2105), lung (ICD-10 02110), breast (female only ICD-10 02112) and prostate (ICD-10 02115). These are relatively common and have been suggested as being associated with soy product intake in previous studies.<sup>9</sup> Information concerning age-standardized mortality rates from these types of cancer and heart disease (ICD-10 09200) and mid-year population by prefecture were obtained from the Special Report on Vital Statistics, 1995<sup>10</sup> and the 1995 Population Census of Japan.<sup>11</sup>

Soy product and major nutrient intake were obtained from National Nutritional Survey Reports<sup>12</sup> between 1980 and 1985. In the National Nutritional Survey, dietary habits were surveyed annually by 3-day diet records in about 6000 randomly selected households in 12 geographical districts covering 47 prefectures. Nutrient and food intake, including alcohol, were estimated using the Standard Tables of Food Composition in Japan. The means of total energy and intake of soy products and several nutrients according to district are presented in the annual report. The survey included four items for soy products; miso, tofu, fried tofu, and soybeans, and the rest of soy products such as soy milk and yuba. For each district, we calculated the means of total amount (g) of soy products and isoflavone and soy protein intake from soy products 1980–1985, weighted by the number of households studied in each year. To estimate isoflavone intake, we used isoflavone content data summarized by Wakai *et al.*<sup>13</sup> Estimation of soy protein intake was based on the food table used in the survey.<sup>12</sup> These mean values were assigned to the prefectures forming the district.

The associations between soy product intake and mortality rates were assessed by Pearson correlation coefficients weighted by a factor proportional to the square root of population of each prefecture. The mortality rates and intake of soy products and nutrients were log-transformed. Adjustment for total energy was performed using the method proposed by Willett.<sup>14</sup> We considered the potential confounding effects of major nutrient intake and prefecture characteristics (e.g. mean age, proportion of smokers, income index, total fertility rate, age at first marriage, education level, number of hospitals, proportion of one-person households and distribution of three broad industry groups), by including them as covariates in the model. However, the sample size was small and we had to minimize the number of variables included simultaneously in the model. Sources of these non-dietary data were the 1985 Population Census of Japan,<sup>11</sup> the Latest Demographic Statistics, 1986–1995,<sup>15</sup> and the Report on Comprehensive Survey of Living Conditions of People on Health and Welfare, 1985 and 1995.<sup>16</sup> Information on the age of participants according to district was not available in the National Nutritional Survey and so we used the mean age of the population of each prefecture in 1985 as a covariate. The proportion of current smokers in each prefecture was based on data from the National Nutritional Survey 1986–1988.<sup>12</sup>

## Results

Summary statistics for soy product intake and the age-standardized mortality rates from heart disease and stomach, colorectal, lung, breast and prostate cancers are presented in

Table 1. The variation in soy product intake across prefecture was greater than that for listed nutrients.

Stomach cancer mortality rate in men was significantly ( $P = 0.03$ ) inversely correlated with total amount of soy products and marginally ( $P = 0.06$ ) inversely correlated with isoflavone intake (Table 2). Similar correlations were observed for women in crude analysis. Adjustment for mean age, total energy intake, proportion of current smokers, and alcohol and salt intake did not alter the results substantially in men, although the correlations were statistically significant for soy protein ( $r = 0.31$ ,  $P = 0.04$ ) and marginally significant for total soy product and isoflavone intake ( $r = -0.28$ ,  $P = 0.07$  and  $r = -0.26$ ,  $P = 0.08$ , respectively). The adjustment changed the correlations towards the null in women.

Significant positive correlations were observed between colorectal cancer mortality rates and soy product intake (total amount as well as isoflavone intake) in men and women after controlling for mean age, total energy, proportion of current smokers, and animal fat and alcohol intake.

The significantly inverse correlation between total amount of soy products and breast cancer mortality rate ( $r = -0.32$ ,  $P = 0.03$ ) was altered to be nearly null after controlling for mean age, total energy, and total fertility rate. Additional adjustment for mean age at first marriage, and animal fat intake did not alter the results substantially.

Adjustment for mean age, total energy, proportion of current smokers, and alcohol intake decreased the positive correlations between soy product intake and prostate cancer mortality rate.

The inverse correlation of heart disease mortality rate with total amount of soy products and soy protein intake remained statistically significant after controlling for covariates in women ( $r = -0.32$ ,  $P = 0.04$ , and  $r = -0.31$ ,  $P = 0.045$ , respectively) but not in men (Table 3). Additional adjustment for animal fat and alcohol intake did not alter the results substantially.

Additional adjustment for income index and proportion of those with 10 years or more education did not affect the results.

## Discussion

We found an inverse correlation between soy product intake and stomach cancer mortality rate in men, although the correlation in terms of total amount or isoflavone intake was of borderline significance. The correlation with colorectal cancer mortality rate was significantly positive in men and women after controlling for covariates.

Previous epidemiological studies on soy product intake and stomach or colorectal cancer, most of which were conducted in Japan, have produced conflicting results.<sup>17–23</sup> These studies focused on certain types of soy foods and did not estimate total intake of soy products or isoflavone intake. The increase in colorectal mortality found in the present study was unexpected as an anticarcinogenic role for soy. However, a significantly increased risk of colon cancer was reported among Japanese-born Issei in Hawaii who had a high intake of fermented soybeans.<sup>17</sup> An experimental study has shown that administration of genistein resulted in increased adenocarcinomas in rats.<sup>24</sup> The relation between soy intake and colorectal cancer should be elucidated.

The role of soy or soy isoflavone in cancer prevention initially focused on hormone-related cancers. However, soy product

**Table 1** Summary statistics for mortality rates from cancer and heart disease and food and nutrient intake in 47 prefectures in Japan

Variable	Mean (SD)	Minimum	Maximum
<b>Mortality rate, 1995 (per 100 000)</b>			
Stomach cancer			
Male	44.3 (5.9)	24.9	57.4
Female	18.5 (2.9)	7.9	24.7
Colon cancer			
Male	23.8 (2.7)	18.1	29.3
Female	13.7 (1.6)	10.8	16.0
Lung cancer			
Male	47.2 (5.0)	36.0	58.8
Female	11.9 (1.7)	8.7	16.3
Breast cancer, female	9.3 (1.4)	6.8	12.8
Prostate cancer	7.7 (1.2)	5.3	10.5
Heart disease			
Male	97.7 (8.9)	74.5	123.0
Female	57.1 (5.8)	41.7	67.9
<b>Diet, 1980–1985</b>			
Soy products			
Total amount (g)	66.8 (7.7)	52.3	81.0
Isoflavones (mg)	28.7 (4.1)	21.3	35.7
Soy protein (g)	6.5 (0.8)	5.1	8.0
Total energy (kcal)	2110 (39.3)	2061	2188
Total protein (g)	79.2 (1.9)	76.6	83.0
Animal protein (g)	39.7 (1.4)	37.5	44.1
Total fat (g)	55.4 (2.2)	52.1	60.7
Animal fat (g)	27.1 (1.2)	25.3	30.1
Carbohydrate (g)	308 (9.3)	295	323
Salt (g)	12.6 (1.2)	11.0	14.6
Vitamin A (IU)	1980 (72)	1818	2080
Vitamin C (mg)	124 (4.4)	118	130
Alcohol (mg)	4.7 (0.8)	2.7	5.8
<b>Other variables</b>			
Mean age (years)	36.5 (1.5)	32.2	39.0
Total fertility rate	1.8 (0.12)	1.4	2.3
Income index <sup>a</sup>	88.6 (16.7)	56.9	139.3
Population of first industry (%)	13.1 (6.4)	0.6	25.4
Number of hospitals <sup>b</sup>	8.8 (3.4)	4.5	19.0
Current male smokers (%)	57.2 (2.5)	51.4	61.7
Current female smokers (%)	7.8 (2.8)	4.6	18.0

<sup>a</sup> All Japan = 100.<sup>b</sup> Per 100 000.

intake was not inversely associated with breast cancer or prostate cancer mortality rate in the present study.

We found a significant inverse correlation between soy protein intake and heart disease mortality rate in women, although the correlations were modest in men. Numerous epidemiological and clinical studies have indicated that soy product intake should improve heart disease risk factors.

In nutritional ecological studies, estimates of nutrient intake are often based on so-called 'food appearance' data, which may be a poor reflection of actual individual consumption. We obtained data on soy product intake based on diet records from a large sample (36 447 households) of the Japanese population. However, sample selection in the nutritional survey was based

on household units and information on the participants' characteristics such as age, sex, and family were not available, which could have biased some of the results.

Substantial changes in the results after adjustment for covariates may indicate the possibility that associations are still subject to ecological confounding. Aggregating dietary data by district may have diluted the true association. These weakness are an inherent limitation of the ecological approach.

Previous epidemiological studies investigating the role of soy have focused on breast cancer and prostate cancer. The present study emphasizes that the associations of soy product intake with stomach cancer and heart disease should be evaluated using various study designs including the full range of soy products.

**Table 2** Pearson correlation coefficients between soy product intake and mortality rates from various types of cancer

	Crude			Adjusted <sup>a</sup>		
	Total amount	Isoflavone <sup>b</sup>	Soy protein	Total amount	Isoflavone	Soy protein
<b>Stomach cancer</b>						
Male	-0.32*	-0.28	-0.24	-0.28	-0.27	-0.31*
Female	-0.28	-0.30*	-0.25	-0.15	-0.13	-0.10
<b>Colorectal cancer</b>						
Male	-0.08	0.04	0.06	0.32*	0.32*	0.36*
Female	-0.004	0.10	0.12	0.44**	0.51**	0.51**
<b>Lung cancer</b>						
Male	-0.23	-0.35*	-0.31*	0.05	-0.15	-0.06
Female	-0.39**	-0.44**	-0.42**	0.05	-0.12	-0.04
<b>Breast cancer</b>	-0.32*	-0.22	-0.23	-0.01	-0.09	-0.08
<b>Prostate cancer</b>	0.41**	0.46**	0.44**	0.20	0.24	0.19

<sup>a</sup> Adjusted for the following variables: Stomach cancer: the mean age, proportion of current smokers and intake of alcohol and salt; Colorectal cancer: the mean age, proportion of current smokers, and intake of alcohol and animal fat; Lung cancer: the mean age and proportion of current smokers; Prostate cancer: the mean age, proportion of current smokers and alcohol intake; Breast cancer: the mean age and total fertility rate. Amount of soy products as well as isoflavone intake are adjusted for total energy.

<sup>b</sup> Genistein plus daidzein.

Statistically significant: \* $P < 0.05$ ; \*\* $P < 0.01$ .

**Table 3** Pearson correlation coefficients between soy product intake and mortality rates from heart diseases

	Crude			Adjusted <sup>a</sup>		
	Total amount	Isoflavone <sup>b</sup>	Soy protein	Total amount	Isoflavone	Soyprotein
Male	-0.32*	-0.27	-0.25	-0.08	-0.03	0.07
Female	-0.57**	-0.52**	-0.48**	-0.32*	-0.31*	-0.27

<sup>a</sup> Male: adjusted for the mean age, percentage of population with first industry, proportion of current smokers and intake of animal fat and salt; female: adjusted for the mean age, percentage of population with first industry, proportion of current smokers and intake of salt. Amount of soy products and soy protein are adjusted for total energy.

<sup>b</sup> Genistein plus daidzein.

Statistically significant: \* $P < 0.05$ ; \*\* $P < 0.01$ .

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