

A case-control study of diet and prostate cancer in Japan: possible protective effect of traditional Japanese diet

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The age-adjusted incidence of prostate cancer is low in Japan, and it has been suggested that the traditional Japanese diet, which includes many soy products, plays a preventive role against prostate cancer. We performed a case-control study on dietary factors and prostate cancer in order to assess the hypothesis that the traditional Japanese diet reduces the risk of prostate cancer. Four geographical areas (Ibaraki, Fukuoka, Nara, and Hokkaido) of Japan were selected for the survey. Average daily intake of food from 5 years before the diagnosis was measured by means of a semi-quantitative food frequency questionnaire. We studied 140 cases and 140 individually age (± 5 years)-matched hospital controls for analysis. Estimates of age-adjusted odds ratios (ORs) and linear trends were calculated by conditional logistic regression models with adjustment for cigarette smoking and total energy intake as confounding factors. Consumption of fish, all soybean products, tofu (bean curds), and natto (fermented soybeans) was associated with decreased risk. ORs of the fourth vs. first quartile and 95% confidence intervals (95% CIs) were 0.45 (0.20–1.02) for fish, 0.53 (0.24–1.14) for all soybean products, 0.47 (0.20–1.08) for tofu, and 0.25 (0.05–1.24) for natto. Consumption of fish and natto showed significantly decreasing linear trends for risk ($P < 0.05$). Consumption of meat was significantly associated with increased risk (the OR of the second vs. first quartile was 2.19, 95% CI 1.00–4.81). Consumption of milk, fruits, all vegetables, green-yellow vegetables, and tomatoes showed no association. Our results provide support to the hypothesis that the traditional Japanese diet, which is rich in soybean products and fish, might be protective against prostate cancer. (*Cancer Sci* 2004; 95: 238–242)

The age-standardized incidence of prostate cancer is low in Japan (10.0 per 100,000), being approximately one-tenth of that in the United States.¹ Among Japanese immigrant in Hawaii, age-standardized incidence of prostate cancer is approximately ten times that in Japan.² It is suggested that environmental factors such as dietary habits play a major role in causation of prostate cancer. A number of case-control studies have indicated that high intake of fat, especially saturated fat, increases the risk of prostate cancer.³ In contrast, high intake of isoflavone, which is mainly found in soybeans and soy products, may reduce the risk of prostate cancer.^{4,5} The traditional Japanese diet which includes many soy products is richer in isoflavone,^{6,7} and contains less fat than the Western diet. However, an epidemiological study of prostate cancer in Kyoto in 1988⁸ yielded no evidence that fat or soybeans were associated with the risk of prostate cancer.

Recently in Japan, the incidence rate of prostate cancer has been increasing concomitantly with the westernization of dietary habits. We carried out a case-control study on dietary factors

and prostate cancer to assess the hypothesis that the traditional Japanese diet reduces the risk of prostate cancer. In this article, we report the results of an analysis of whether intake of soy products and other foods is related to the risk of prostate cancer.

Materials and Methods

Subjects. Surveys on diet in this case-control study were performed mainly in Ibaraki and Hokkaido prefectures. Eighty-four cases were obtained from the Department of Urology of Tsukuba University Hospital in Ibaraki and 56 cases from the Department of Urology of Sapporo Medical University Hospital in Hokkaido.

These 140 cases, who had a confirmed histological diagnosis of adenocarcinoma made between January 1996 and September 2002, were used for analysis. The age range was 59–73 years. The stage distribution was as follows: 2 cases of stage I, 86 cases of stage II, 36 cases of stage III and 16 cases of stage IV.

Controls were selected from the Department of Oral Surgery, Ophthalmology, or Dermatology of the same hospitals as cases and matched to each case by age (± 5 years). Disease categories were as follows: oral diseases, cataract, benign kidney disorder, and dermatosis. Exclusion criteria for controls were having other prostatic diseases or malignant tumors, being under dietary restriction and having a PSA value of more than 5.0 ng/ml.

This study was approved by the ethical committee of each university. Informed consent was given by all subjects.

Questionnaire. Both cases and controls were interviewed in hospital. Average daily intake of 102 foods and 4 beverages during 5 years before diagnosis were measured by means of a semi-quantitative food frequency questionnaire based on the questionnaire of Takayama Study in Gifu prefecture, with their permission. The validity of the questionnaire in the Takayama Study was confirmed by Nagata *et al.*⁹ The Pearson correlation coefficient for men between macronutrients from the questionnaire and 3-day records was from 0.45 to 0.51.⁹ The intake of the following food groups was calculated: rice, meat, fish, eggs, milk, dairy products, all vegetables, green-yellow vegetables, fruits, all soybean products, alcohol, coffee, black tea, and green tea. The intake of all soybean products was estimated from Japanese food items, such as tofu (bean curd), natto (fermented soybeans), miso soup (soybean paste soup), aburaage (fried bean curd), kinako (soy flour), yuba (dried bean curd), tonyu (soybean milk), soy sauce, green soybeans, and bean sprouts. The average intake of each food group per day was calculated by adding the intake of food items obtained by multiplying the gram-portion size by food frequency per day.

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Table 1. Odds ratios (ORs) and 95% confidence intervals (95% CIs) of food intake for prostate cancer

Food	Cases (n=140)	Controls (n=140)	OR	95%CI	P for trend
Energy (kcal/day)					
≤1419.3	23	34	1.00		
1419.3–1718.1	39	37	1.57	0.79–3.11	
1718.1–2123.9	45	36	1.81	0.91–3.62	
≥2123.9	33	33	1.44	0.69–3.02	0.43
Rice (g/day)					
≤110 (1cup)	16	28	1.00		
220 (2cups)	53	48	1.59	0.75–3.34	
≥330 (3cups)	71	64	1.57	0.79–3.14	0.27
Meat (g/day)					
≤21.1	22	35	1.00		
21.1–37.7	40	35	2.19	1.00–4.81	
37.7–62.8	39	35	2.19	0.94–5.07	
≥62.8	39	35	1.80	0.81–3.98	0.46
Fish (g/day)					
≤47.3	37	35	1.00		
47.3–75.7	41	35	1.04	0.53–2.02	
75.7–130.7	37	35	0.79	0.39–1.59	
≥130.7	25	35	0.45	0.20–1.02	0.04
Egg (g/day)					
≤16.9	22	35	1.00		
16.9–33.1	43	35	1.96	0.95–4.06	
33.1–55.6	40	35	2.15		
≥55.6	35	35	1.69	0.73–3.90	0.41
Milk (ml/day)					
≤6.6	30	33	1.00		
6.6–100.0	37	41	0.98	0.48–2.00	
100.0–200.0	66	52	1.21	0.62–2.35	
≥200.0	7	14	0.33	0.10–1.10	0.39
Dairy products (g/day)					
≤6.0	21	35	1.00		
6.0–19.5	40	35	1.65	0.80–3.38	
19.5–53.9	42	35	1.62	0.81–3.24	
≥53.9	37	35	1.37	0.69–2.71	0.70
Fruits (g/day)					
≤78.7	31	35	1.00		
78.7–153.0	46	35	1.40	0.70–2.78	
153.0–239.9	40	35	1.19	0.61–2.33	
≥239.9	23	35	0.63	0.29–1.38	0.13
All vegetables (g/day)					
≤151.7	37	35	1.00		
151.7–220.8	32	35	0.73	0.34–1.58	
220.8–300.0	36	35	0.74	0.36–1.53	
≥300.0	35	35	0.65	0.28–1.48	0.35
Green-yellow vegetables (g/day)					
≤68.2	38	35	1.00		
68.2–108.4	23	34	0.58	0.29–1.16	
108.4–188.8	40	36	0.80	0.40–1.60	
≥188.8	39	35	0.82	0.40–1.69	0.98
Tomatoes (g/day)					
≤28.5	39	34	1.00		
28.5–42.7	21	23	0.76	0.36–1.63	
42.7–100.0	60	67	0.66	0.35–1.26	
≥100.0	20	16	0.86	0.37–2.01	0.87
All soy products (g/day)					
≤77.0	39	35	1.00		
77.0–125.0	37	35	0.75	0.36–1.52	
125.1–187.2	34	35	0.61	0.28–1.35	
≥187.2	30	35	0.53	0.24–1.14	0.11
Tofu (g/day)					
≤19.7	36	28	1.00		
19.7–42.7	33	39	0.57	0.27–1.20	
42.7–96.4	45	38	0.81	0.38–1.75	
≥96.4	26	35	0.47	0.20–1.08	0.16
Natto (g/day)					
≤5.7	34	32	1.00		
5.7–13.2	45	37	1.10	0.53–2.30	
13.2–40.0	58	65	0.66	0.33–1.32	
≥40.0	3	6	0.25	0.05–1.24	0.03

ORs and 95% CIs were calculated by conditional logistic regression models with adjustment for cigarette smoking and energy intake.

Data analysis. Estimates of age-adjusted odds ratios (ORs), 95% confidence intervals (95% CIs) and linear trend of foods and beverages for prostate cancer were calculated by conditional logistic regression models with adjustment for cigarette smoking and total energy intake as potential confounding factors. Because some controls were selected from patients with smoking-related diseases, such as cataracts^{10,11} and oral diseases,^{12–14} we adjusted for cigarette smoking in the analyses. Energy adjustment was performed by a logistic regression model that used total energy as a confounding factor, since food groups were analyzed instead of nutrients in this report.¹⁵ Alcohol intake, BMI (data not shown), a family history of prostate cancer (data not shown) were not considered as potential factors, because no association with prostate cancer risk was observed. Food and green tea consumption were classified into quartiles or other suitable categories on the basis of their distribution among control subjects. Coffee and black tea consumption was categorized as shown in Table 2, because consumption was low. Alcohol consumption was classified into four categories (see Table 2) according to the Healthy Japan 21 plan. The lowest category, with an OR of 1.00, was the reference category throughout the analysis. Median values of food consumption in each category were entered into models for linear trend test. Analyses were performed with SPSS release 10.0.

Results

ORs for food intake are shown in Table 1. Consumption of fish, all soybean products, tofu, and natto was associated with decreased risk. ORs of the fourth vs. first quartile and 95% CIs were 0.45 (0.20–1.02) for fish, 0.53 (0.24–1.14) for all soybean products, 0.47 (0.20–1.08) for tofu, and 0.25 (0.05–1.24) for natto. Fish and natto showed significantly decreasing linear trends for risk ($P < 0.05$). Consumption of meat was significantly associated with increased risk (the OR of the second vs. first quartile was 2.19, 95% CI 1.00–4.81). Eggs did not show a significant association with increased risk (the OR of the third vs. first quartile was 2.15, 95% CI 0.94–4.90). Total energy, rice, and dairy products showed a modest increase in risk. ORs of the fourth vs. first quartile were 1.44 (0.69–3.02) for total energy, 1.57 (0.79–3.14) for rice, and 1.37 (0.69–2.71) for dairy products. Milk, fruits, all vegetables, green-yellow vegetables, and tomatoes showed no association.

ORs of beverages are shown in Table 2. Consumption of alcohol did not show a significant association with increased risk. Green tea showed a modest reduction in risk (the OR of the fourth vs. first category was 0.67, 95% CI 0.28–1.66). Coffee and black tea showed no association.

Discussion

The traditional Japanese diet is notably high in phytoestrogens (isoflavones), chiefly from soybean products. Isoflavones have been suggested to be preventive against cancer. Growth inhibition and induction of apoptosis of prostate cancer cells by isoflavones were indicated in several experimental reports.^{16–25} Tofu and natto are rich in isoflavones (tofu 509 $\mu\text{g/g}$ and natto 1273 $\mu\text{g/g}$ ²⁶). In fact, Japanese have higher phytoestrogen concentrations in serum than men and women of Western countries (for example, the mean concentration of genistein in phytoestrogen in Japanese men is 492.7 nmol/liter, compared with 33.2 nmol/liter in men from the UK),²⁷ and have very high urinary excretion of phytoestrogens.²⁸ These reports suggested that the low incidence of prostate cancer in Japanese men might be related to higher intake of isoflavones. A cohort study of people of Japanese ancestry in Hawaii reported that tofu might reduce the risk of prostate cancer.²⁹ A case-control study in Kyoto^{8,30} did not report on soybean products with regard to risk of prostate cancer. Our results suggest that natto and tofu might be protective factors against prostate cancer. Natto is especially rich in phytoestrogens and we found that it had a significant protective effect against prostate cancer.

Furthermore, the traditional Japanese diet is rich in fish. Various studies have indicated significant^{31–33} or nonsignificant^{34–36} inverse associations of fish consumption with prostate cancer, although the study in Hawaii found that fish intake was not associated with decreased risk.²⁹ Marine fatty acids in fish, particularly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DPA) among the ω -3-fatty acids, have been consistently shown to inhibit the proliferation of prostate cancer cell lines *in vitro* and to reduce the risk and progression of these tumors *in vivo*.³⁷

Energy intake is positively associated with levels of insulin-like growth factor I and this growth factor has been associated with increased prostate cancer risk in several studies.^{38–40} Several epidemiologic studies have suggested that total energy in-

Table 2. Odds ratios (ORs) and 95% confidence intervals (95% CIs) of beverage intake for prostate cancer

Drink	Cases (n=140)	Controls (n=140)	OR	95% CI	P for trend
Green tea (cups/day)					
≤1	34	32	1.00		
2–4	48	42	0.99	0.48–2.03	
5–9	42	45	0.79	0.38–1.63	
≥10	16	21	0.67	0.27–1.64	0.30
Coffee (cups/day)					
0	43	49	1.00		
1–2	82	69	1.42	0.82–2.47	
≥3	15	22	0.92	0.40–2.11	0.66
Black tea (cups/day)					
0	84	98	1.00		
≥1	56	42	1.51	0.89–2.56	
Alcohol (g/day)					
0	31	39	1.00		
≤20	46	30	1.16	0.83–3.12	
20–60	51	47	1.01	0.58–2.04	
≥60	12	24	0.53	0.21–1.33	0.09

ORs and 95% CIs were calculated by conditional logistic regression models with adjustment for cigarette smoking and energy intake.

take is positively associated with prostate cancer,⁴¹⁻⁴⁷ though some case-control studies have suggested no association between energy intake and prostate cancer.⁴⁸⁻⁵² In this study, energy intake increased the risk of prostate cancer to some extent.

Saturated fats from animal meat have been shown to have clear tumor-promoting effects.⁵³⁻⁵⁶ In a review, 11 of 14 case-control study trials yielded a significant correlation between fat consumption and prostate cancer risk.² These observations are further supported by studies reporting a correlation between obesity and prostate cancer risk.^{2,57-59}

Green-yellow vegetables have been indicated to have protective effects against prostate cancer. β -Carotene, in particular, has received the most attention among carotenoids, which are prevalent in green-yellow vegetables, because of its antioxidant effect. Ohno *et al.* reported protective effects of dietary β -carotene and vitamin A against prostate cancer in Japan.³⁰ Giovannucci *et al.* reported on the relationship between lycopene, present in tomatoes and tomato products, and prostate cancer.^{60,61} Some cohort studies reported that lycopene significantly decreased prostate cancer risk.^{58,62,63} A case-control study in Canada suggested that intake of tomatoes and higher intakes of green and cruciferous vegetables reduced prostate cancer risk.⁶⁴ In contrast, epidemiological studies in Italy,⁶⁵ the United States,⁶⁶ and Canada,⁶⁷ as well as our study, found no association with vegetables. In summary, there is insufficient evidence to draw a conclusion regarding a protective effect of vegetables against prostate cancer. A considerable number of epidemiologic studies have suggested a role of alcohol drinking as a risk factor for prostate cancer. Acetaldehyde, which is a

metabolite of alcohol, is a carcinogen, and alcohol is known to affect cell membrane integrity, to enhance production of free radicals, to impair immune function and to reduce levels of DNA repair enzymes.⁶⁸ On the other hand, several studies, like our study, have found no association between alcohol and prostate cancer.^{43,69-74} A recent experimental study showed a direct inhibitory effect of low concentrations of antioxidant wine polyphenols on the proliferation of human prostate cancer cell lines, and suggested potential beneficial effects of wine and other phenol-containing foods or drinks for the control of prostate cancer cell growth.⁷⁵ However, we could not examine this effect because too few subjects drank wine (9.7%).

Experimental studies have shown prostate cancer-preventive effects of epigallocatechin 3-gallate (EGCG) in green tea.⁷⁶⁻⁷⁹ A phase II trial of androgen-independent metastatic prostate cancer showed that green tea had limited antineoplastic activity.⁸⁰ In this study, green tea showed no significant reduction in risk. No associations between the consumption of coffee or black tea and prostate cancer have been reported consistently.^{31,70,71,81-83}

Although a case-control study of food intake with a semi-quantitative food frequency questionnaire is susceptible to recall bias, trained staff conducted face-to-face interviews, spending more than 1 h per subject.

In conclusion, the traditional Japanese diet may be protective against prostate cancer, because soybean products and fish were found to be associated with reduced risk. We intend to continue with this case-control study.

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