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Association of blood pressure with intake of soy products and other food groups in Japanese men and women☆

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Abstract

Background. Soy diet has been suggested to have antihypertensive effect in animal studies. The present study examined the cross-sectional relationship between blood pressure and intake of soy products and other food groups in Japanese men and women.

Methods. Blood pressure was measured in Japanese 294 men and 330 women (246 premenopausal and 84 peri- and postmenopausal women) who participated in a health check-up program provided by a general hospital. Intake of various food groups and nutrients was estimated from a validated semiquantitative food frequency questionnaire.

Results. In men, soy product intake was inversely significantly correlated with diastolic blood pressure ($r = -0.12$, $P = 0.04$) after controlling for age, total energy, smoking status, body mass index, and intake of alcohol, salt and seaweeds. The correlation of soy product intake with systolic blood pressure was of borderline significance ($r = -0.10$, $P = 0.09$). Systolic blood pressure was inversely correlated with intake of vegetables ($r = -0.12$, $P = 0.04$) and dairy products ($r = -0.12$, $P = 0.05$). There were no significant correlations between soy product intake and diastolic blood pressure in women.

Conclusion. These results indicate a mild effect of soy intake on blood pressure reduction in men.

Keywords: Soy; Diet; Blood pressure; Japanese

Introduction

Recent studies on diet and blood pressure have tried to look at foods instead of emphasizing single nutrients [1]. The Dietary Approaches to Stop Hypertension (DASH) study demonstrated that diets rich in dairy foods, fruits, and vegetables reduced blood pressure [2]. In animal studies, soy beans or soy products have been suggested to have antihypertensive effect [3,4]. A soy-based diet attenuated the development of hypertension in rats compared to a casein diet [5].

A number of intervention studies have examined the effect of soy or isoflavone intake on blood pressure, but the results have been inconsistent. Washburn et al. [6] found a decline in diastolic blood pressure in perimenopausal women after a soy diet compared with a carbohydrate placebo diet for 6-week period. Teede et al. [7] observed a decline in systolic and diastolic blood pressure in men and postmenopausal women after a soy diet for 3 months, compared with a casein placebo diet. Jenkins et al. [8] reported a decline in systolic blood pressure in hyperlipidemic men after a soy diet for 3 months, compared with a low-fat dairy food control diet. Rivas et al. [9] found that soymilk consumption significantly reduced systolic and diastolic blood pressure after 3 months in men and women with mild to moderate essential hypertension, compared with cow's milk. Two other studies noted improved arterial compliance in menopausal women after isoflavone supplementation,

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although arterial blood pressure was unaffected [10,11]. The other studies found no reduction in blood pressure after a soy or isoflavone diet compared with a control diet [12–19].

Most of these intervention studies limit the power to find associations of moderate magnitude. Furthermore, a person's usual soy intake over a longer period than the relatively short duration studied in the trials may affect blood pressure. Thus, cross-sectional studies of blood pressure in relation to usual soy intake, which can be done on a larger number of subjects, may also provide useful information. However, there have been few such studies. We therefore examined the relationships between blood pressure and intake of soy products and other food groups in Japanese men and women. It is useful to study the association between soy product intake and blood pressure among Japanese because they consume significant amounts of soy products and there is a considerable variation in intake.

Methods

Subjects were participants in a health check-up program provided by a general hospital in Gifu, Japan, between September 1996 and August 1997. A total of 394 men and 400 women completed a self-administered questionnaire which asked about demographic characteristics, smoking and drinking habits, diet, exercise, and past medical and reproductive histories. The response rate was 97.3%. To obtain complete data, a nurse epidemiologist interviewed those who returned questionnaire with incomplete information.

Diet was assessed by a validated semiquantitative food-frequency questionnaire. Respondents were asked to indicate how often, on average, they had consumed 169 food items during the year prior to the study and the usual serving size of each item. The intake of foods and nutrients was estimated from the frequency of ingestion and portion size using the Japanese Standard Tables of Food Composition, 4th edition, published by the Science and Technology Agency of Japan. Fatty acid composition was evaluated using data published by Sasaki et al [20]. We included nine food items for soy products (miso soup, tofu, deep-fried tofu, fried bean curd, dried bean curd, fermented soy beans, houbamiso, soymilk, and boiled soy beans). The total intake of soy products was calculated as the sum of these nine food items. The other food groups included cereals, potatoes, and starches; fishes and shellfishes; flesh and processed meats; dairy products (including milk); fruits; vegetables; and seaweeds. Detailed information on the questionnaire including its validity and reproducibility have been described elsewhere [21]. For example, the Spearman correlation coefficients comparing estimates of soy product intake from this questionnaire with the estimates from 12 daily dict records kept over a 1-year period were 0.71 in both men and women.

Exercise was assessed by asking the average hours per week spent performing various kinds of activities during the past year. The details including its validity are described elsewhere [22].

Blood pressures were measured in the early morning, between 8 AM and 9 AM by a same observer throughout the study using a digital recorder (UDEX-II, Ueda Electronics Works, ltd., Tokyo, Japan). All blood pressure measurements were taken on the right arm after a 5-min rest period. This study was approved by the local institutional review board.

For statistical analysis, we excluded subjects who used antihypertensives (50 men and 18 women), oral contraceptives (2 women), or hormone replacement therapy (6 women). Furthermore, those who had history of cancer (6 men and 23 women), angina/myocardial infarction (10 men and 5 women), or diabetes mellitus (32 men and 16 women) were excluded. Consequently, the study comprised 296 men and 330 women. Analyses were conducted separately for premenopausal (n = 246) and peri/postmenopausal (n = 84) women. Women who had had a menstrual period within the past 3 months were defined as premenopausal. The rest of the women were considered peri- or postmenopausal women.

Spearman correlation coefficients were used to examine the associations of blood pressure levels with intake of soy products and other food groups and nutrients. Intake of foods and nutrients was log-transformed and adjusted for total energy using the method proposed by Willett [22]. Age, body mass index (BMI), smoking status, and intake of alcohol, salt, and seaweeds were included in models as covariates. We further examined the effects of potential confounders that included marital status, exercise, age at menarche, and number of births. (the latter two for women only), as well as intake of other foods and nutrients. Significant difference was declared at P = 0.05.

Results

The characteristics of the study subjects are described in Table 1. The variations in systolic and diastolic blood pressure were small in premenopausal as well as peri- and postmenopausal women compared with men.

In men, soy product intake was moderately but significantly inversely correlated with diastolic blood pressure after controlling for age, total energy, BMI, smoking status, and intake of alcohol, salt, and seaweeds (Table 2). Intake of vegetables was significantly inversely correlated with systolic blood pressure. The correlation of dairy product intake with systolic blood pressure was of borderline significance (P = 0.05). The correlation coefficients of systolic blood pressure with intake of soy products, vegetables, and dairy products were −0.06 (P = 0.32), −0.10 (P = 0.10), and −0.10 (P = 0.09), respectively, in the model including these food groups simultaneously.

In premenopausal women, the correlations between

Table 1
Selected characteristics of subjects

Variable	Men (n = 296)	Premenopausal women (n = 246)	Peri- and postmenopausal women (n = 84)
Age (years)	50.5 ± 7.9 (21–71)	42.1 ± 5.2 (20–53)	53.2 ± 6.0 (38–68)
Body mass index (kg/m^2)	23.3 ± 2.8 (16.9–31.2)	21.6 ± 2.5 (16.7–28.6)	22.5 ± 2.9 (17.5–31.3)
Exercise (METs^a · h/week)	17.5 ± 23.8 (0–152)	21.7 ± 29.4 (0–256)	14.7 ± 18.9 (0–90)
Alcohol (mL/day)	34.0 ± 41.2 (0–318)	5.4 ± 10.5 (0–83.6)	6.2 ± 13.1 (0–74)
Smoking (%)			
Current	43.6	6.1	8.3
Past	30.4	2.8	7.1
Blood pressure (mmHg)			
Systolic	122.8 ± 19.0 (81–250)	113.6 ± 13.4 (74–151)	120.7 ± 15.2 (90–161)
Diastolic	78.2 ± 12.1 (50–143)	71.5 ± 8.8 (44–94)	76.3 ± 10.5 (55–105)
Food intake per day			
Soy products (g)	59.0 ± 48.2 (5.0–271)	49.9 ± 34.4 (4.9–240)	64.3 ± 44.2 (4.9–222)
Soy isoflavones (mg)	28.5 ± 22.6 (2.1–170)	24.0 ± 15.9 (3.0–114)	28.6 ± 17.9 (1.9–87.7)
Cereals, potatoes, and starches (g)	368 ± 141 (108–914)	328 ± 110 (103–906)	321 ± 119 (137–707)
Fishes and shell fishes (g)	124 ± 93 (83–770)	86 ± 54 (12–421)	105 ± 65 (16.5–377)
Fresh and processed meats (g)	88.6 ± 53.1 (6.6–306)	84.9 ± 52.0 (6.9–365)	73.6 ± 51.0 (9.4–276)
Dairy products (g)	227 ± 237 (1.4–2,035)	297 ± 349 (4.3–3,095)	256 ± 191 (9.9–1,074)
Vegetables (g)	369 ± 220 (44.2–1,614)	395 ± 267 (97–2,039)	482 ± 301 (114–1,525)
Fruits (g)	172 ± 179 (1.4–1,538)	147 ± 123 (7.6–791)	164 ± 153 (9.0–742)
Seaweeds (g)	4.4 ± 3.6 (0.6–29.2)	4.5 ± 3.2 (0.4–18.0)	5.7 ± 4.4 (1.0–19.4)
Nutrient intake per day			
Energy (kcal)	2,645 ± 949 (706–6,136)	2,322 ± 845 (824–7,547)	2,247 ± 752 (903–4,044)
Total protein (g)	101.8 ± 43.2 (21.5–307)	92.5 ± 37.0 (26.1–298)	95.8 ± 37.5 (35.3–191)
Total fat (g)	71.0 ± 31.5 (10.7–182.3)	70.9 ± 32.0 (13.6–278)	65.3 ± 27.6 (21.8–148)
Saturated fat (g)	20.0 ± 9.5 (3.0–59.5)	21.2 ± 11.3 (4.2–109)	18.7 ± 8.0 (5.9–55.9)
Monounsaturated fat (g)	25.4 ± 11.7 (3.2–68.2)	25.2 ± 11.7 (3.9–45.1)	22.8 ± 10.3 (6.7–54.5)
Polyunsaturated fat (g)	18.1 ± 8.1 (2.8–45.1)	17.2 ± 7.3 (3.9–45.1)	17.3 ± 8.1 (5.9–55.9)
Carbohydrates (g)	344 ± 128 (111–796)	314 ± 111 (104–943)	304 ± 99 (136–564)
Crude fiber (g)	5.4 ± 2.8 (1.0–21.2)	5.4 ± 3.0 (1.8–24.0)	6.2 ± 3.2 (1.9–15.5)
Calcium (mg)	788 ± 422 (145–3,235)	834 ± 517 (227–4,624)	867 ± 399 (297–1,968)
Phosphorus (mg)	1,580 ± 670 (370–4,535)	1,487 ± 676 (472–6,058)	1,522 ± 580 (542–3,005)
Retinol (μ g)	541 ± 584 (24.0–5,862)	506 ± 598 (43.0–5,014)	516 ± 498 (47.0–2,893)
Carotene (μ g)	4,294 ± 2,822 (555–17,864)	4,622 ± 3,113 (1,026–25,207)	5,834 ± 4,561 (1,413–31,159)
Vitamin B1 (mg)	1.2 ± 0.5 (0.3–3.3)	1.1 ± 0.5 (0.4–4.5)	1.2 ± 0.5 (0.4–2.4)
Vitamin B2 (mg)	1.6 ± 0.8 (0.3–5.1)	1.6 ± 0.9 (0.4–7.6)	1.6 ± 0.7 (0.5–3.7)
Vitamin C (mg)	146 ± 103 (21.0–951)	145 ± 116 (29.0–1,244)	181 ± 133 (39.0–773)
Vitamin E (mg)	9.6 ± 4.5 (1.6–28.2)	9.1 ± 4.3 (2.6–32.5)	9.8 ± 4.4 (3.6–22.8)
Sodium (mg)	5,898 ± 2,566 (1,086–15,490)	5,536 ± 2,270 (1,267–15,088)	5,844 ± 2,300 (2,065–11,461)
Potassium (mg)	3,923 ± 1,834 (855–12,219)	3,756 ± 1,904 (1,196–14,935)	4,149 ± 1,929 (1,697–9,996)
Salt (g)	14.7 ± 6.4 (2.7–38.8)	13.7 ± 5.6 (3.1–37.4)	14.5 ± 5.7 (5.1–28.5)

Note. Values represent means ± SD and range in parentheses unless otherwise specified.
[a] Metabolic equivalents.

soy product intake and systolic and diastolic blood pressure were of borderline significance ($r = -0.11$, $P = 0.08$, for systolic blood pressure; $r = -0.12$, $P = 0.06$, for diastolic blood pressure) after controlling for age and total energy. Additional adjustment for BMI, smoking status, and alcohol, salt, and seaweed intake did not substantially alter the correlation between soy product intake and blood pressure. Intake of cereals, potatoes and starches was significantly positively correlated with both systolic and diastolic blood pressure. An additional adjustment for intake of cereals, potatoes, and starches did not alter the correlations of soy product intake with systolic ($r = -0.08$, $P = 0.19$) and diastolic ($r = -0.10$, $P = 0.13$) blood pressure.

Soy product intake was positively correlated with both systolic and diastolic blood pressure in peri- and postmenopausal women, but the correlations were not statistically significant.

The correlation coefficients of diastolic blood pressure with soy product intake were significantly different between men and peri- and postmenopausal women ($P = 0.01$).

Table 3 shows the correlations between individual nutrients and blood pressure. In men, significant correlations were observed for the nutrients rich in vegetables, soy products, or dairy products. There was no significant correlation between blood pressure and any nutrients measured in premenopausal as well as peri- and postmenopausal women after controlling for covariates.

Table 2
Correlation coefficients for blood pressure with soy products and other food groups

Food group	Men				Premenopausal women				Peri- and postmenopausal women			
	Systolic		Diastolic		Systolic		Diastolic		Systolic		Diastolic	
	r1	r2	r1	r2	r1	r2	r1	r2	r1	r2	r1	r2
Soy products	−0.10	−0.08	−0.12*	−0.12*	−0.11	−0.10	−0.12	−0.11	0.16	0.20	0.15	0.19
Cereals, potatoes, and starches	−0.06	0.07	−0.06	0.08	0.14*	0.15*	0.16*	0.15*	0.08	0.09	0.04	0.03
Fishes and shell fishes	0.02	0.04	0.04	0.04	0.02	0.03	0.03	0.05	−0.20	−0.12	−0.25*	−0.19
Fresh and processed meats	−0.02	0.002	0.01	0.03	−0.02	−0.02	0.02	0.03	−0.12	−0.17	−0.18	−0.18
Dairy products	−0.13*	−0.12	−0.07	−0.06	−0.03	−0.04	−0.07	−0.08	0.15	0.10	0.06	0.004
Vegetables	−0.14*	−0.12*	−0.07	−0.05	0.003	0.02	0.04	0.06	0.03	0.09	−0.01	0.05
Fruits	−0.08	−0.05	0.01	0.06	−0.10	−0.12	−0.10	−0.11	−0.09	−0.04	−0.12	−0.10
Seaweeds	−0.05	—	−0.08	—	−0.04	—	0.003	—	−0.02	—	−0.07	—

Note. r1, partial correlation coefficients after controlling for age and total energy; r2, partial correlation coefficients after controlling for age, total energy, smoking status, body mass index, and intake of alchohol, salt, and seaweeds.
* $P < 0.05$.

Discussion

We found a significant inverse correlation between soy product intake and diastolic blood pressure in men, but this correlation was not strong. A weak inverse association between soy product intake and diastolic blood pressure was also noted in premenopausal women but not in peri- and postmenopausal women. Although these observations did not strongly support the hypothesis that dietary soy may reduce blood pressure, they indicate a mild effect of soy intake on blood pressure reduction in men. Considering the effect of measurement error from the dietary food-frequency questionnaire, the observed correlations between soy product intake and blood pressure may be underestimated. We also observed that vegetable intake as well as dairy product intake was inversely correlated with blood pressure. The magnitudes of these correlations were similar to that of the correlation for soy product intake in men. A diet rich in vegetables and dairy foods was demonstrated to reduce blood pressure in the DASH study. The observed association of blood pressure with even usual intake of soy products may suggest a greater effect of higher intake of soy products on blood pressure. However, we must mention that the relationship of dosage to the effect on blood pressure is

Table 3
Correlation coefficients for blood pressure with nutrient intake

Nutrient	Men				Premenopausal women				Peri- and postmenopausal women			
	Systolic		Diastolic		Systolic		Diastolic		Systolic		Diastolic	
	r1	r2	r1	r2	r1	r2	r1	r2	r1	r2	r1	r2
Energy	−0.001	−0.06	0.02	−0.04	−0.06	−0.07	−0.11	−0.11	−0.03	−0.02	−0.02	−0.05
Total protein	−0.15†	−0.10	−0.09	−0.05	0.01	0.04	0.02	0.06	0.01	0.05	−0.08	−0.02
Total fat	−0.11	−0.07	−0.07	−0.03	−0.06	−0.07	−0.09	−0.10	−0.18	−0.18	−0.21	−0.18
Saturated fat	−0.11	−0.07	−0.05	0.001	−0.06	−0.08	−0.11	−0.12	−0.14	−0.14	−0.17	−0.16
Monounsaturated fat	−0.09	−0.05	−0.11	−0.02	−0.04	−0.06	−0.06	−0.06	−0.20	−0.21	−0.22*	−0.20
Polyunsaturated fat	−0.11	−0.08	−0.11	−0.08	−0.03	−0.04	−0.05	−0.04	−0.12	−0.11	−0.14	−0.08
Carbohydrates	−0.09	0.03	−0.12*	0.01	0.04	0.03	0.07	0.04	0.07	0.03	0.12	0.07
Crude fiber	−0.15*	−0.10	−0.10	−0.06	−0.02	−0.003	−0.005	0.01	0.09	0.13	0.06	0.12
Calcium	−0.18†	−0.15†	−0.11	−0.08	−0.004	−0.006	−0.06	−0.06	0.08	0.07	0.05	0.05
Phosphorus	−0.20†	−0.16†	−0.11	−0.06	0.02	0.02	−0.001	0.01	0.09	0.07	0.04	0.06
Retinol	−0.09	−0.11	−0.03	−0.05	0.04	0.04	−0.03	−0.01	−0.14	−0.21	−0.14	−0.17
Carotene	−0.13*	−0.12*	−0.09	−0.07	−0.02	−0.01	−0.03	−0.03	0.07	0.13	0.08	0.14
Vitamin B1	−0.18†	−0.11	−0.15*	−0.08	0.03	0.06	0.05	0.07	0.10	0.11	0.05	0.08
Vitamin B2	−0.18†	−0.18†	−0.11	−0.12*	0.002	0.01	−0.02	−0.01	0.08	0.06	0.03	0.03
Vitamin C	−0.12*	−0.11	−0.02	0.003	−0.02	−0.02	−0.02	−0.01	0.09	0.15	0.09	0.14
Vitamin E	−0.16†	−0.11	−0.13*	−0.09	0.03	0.05	0.002	0.02	−0.03	0.05	−0.06	0.02
Sodium	−0.04	−0.02	−0.01	−0.01	−0.02	0.11	−0.03	0.09	−0.08	0.11	−0.11	0.18
Potassium	−0.20†	−0.19†	−0.12*	−0.09	−0.02	−0.008	−0.04	−0.02	0.04	0.09	0.004	0.06

Note. r1, partial correlation coefficients after controlling for age and total energy; r2, partial correlation coefficients after controlling for age, total energy, smoking status, body mass index, and intake of alchohol, salt, and seaweeds.
* $P < 0.05$.
† $P < 0.01$.

not clear based on results from previous intervention studies using soy supplementation. Reduction of blood pressure was reported in four studies [6–9] in which 34, 118, 10, and 143 mg of isoflavones were used daily, respectively but not in the other studies in which the dose of isoflavones ranged from 47 to 165 mg [12–19]. Although we cannot deny the possibility that the variation in soy product intake in our subjects was not large enough to assess the relationship between soy product intake and blood pressure, additional intervention studies are needed to elucidate the dose–effect relationship.

We failed to observe a significant inverse association between blood pressure and soy product intake in women. In particular, the results for peri- and postmenopausal women were unexpected considering the possibility that the soy isoflavone might act like estrogens, especially in peri- and postmenopausal women whose endogenous estrogen levels are low. A relatively small variation in blood pressure in peri- and postmenopausal women as well as premenopausal women may have distorted the results. In addition, the average blood pressures for men and women were better than normal (<120/80 mmHg). The observed weak effects of soy and other food groups may have been influenced by the fact that the average blood pressure was already normal to low.

To our knowledge, only one previous cross-sectional study reported a relationship between soy intake and blood pressure in men. Takashima et al. [24] observed no association between frequency of soy product intake and blood pressure in 473 middle-age Japanese men. None of the previous three cross-sectional studies among women showed a significant association [25–27]. Arai et al. [25] reported no significant association between blood pressure and isoflavone intake estimated from a 3-day dietary record in 115 Japanese women ages 29–78. The other two studies of postmenopausal U.S. women found no significant association between blood pressure and isoflavone intake estimated from a standardized food frequency questionnaire [26,27].

We observed a significant association between blood pressure and a food group of cereals, potatoes, and starches in premenopausal women. A significant positive association between starch intake and blood pressure was also noted in the Multiple Risk Factor Intervention Trial [28]. This may be ascribed to salt and water retention and subsequent blood pressure increase after ingestion of sugar [29]. However, we must mention that the observed positive association between blood pressure and this food group was attributable to the positive association between blood pressure and rice intake ($r = 0.13$, $P = 0.04$, and $r = 0.11$, $P = 0.10$, for systolic and diastolic blood pressure, respectively). Intake of the other cereals was inversely correlated with blood pressure in premenopausal women ($r = -0.11$, $P = 0.10$, and -0.12, $P = 0.06$, for systolic and diastolic blood pressure, respectively). Positive association between blood pressure and rice intake was also observed in men ($r = 0.14$, $P = 0.02$, and $r = 0.08$, $P = 0.15$, for systolic and diastolic blood pressure, respectively) and peri- and postmenopausal women ($r = 0.13$, $P = 0.04$, and $r = 0.11$, $P = 0.10$, for systolic and diastolic blood pressure, respectively).

The recent report from the Framingham Heart Study indicated that diastolic blood pressure was negatively related to coronary heart disease risk in people 60 years of age and older [30]. Most of our study subjects were younger than 60 years of age. When we reanalyzed the data after excluding 33 men and 15 peri- or postmenopausal women who were age 60 or over, the correlations for soy product intake and diastolic blood pressure were not altered substantially ($r = -0.09$, $P = 0.14$, in men; $r = 0.16$, $P = 0.23$, in peri- and postmenopausal women after controlling for the covariates).

Our questionnaire was designed to measure an individual's relative intakes of foods and nutrients rather than absolute values. The data presented for soy products may have been underestimated by the questionnaire, because in the validity study, these estimates were about 30% lower based on the questionnaire than the estimates based on the diet records. On the other hand, the intakes of vegetables and dairy products may have been overestimated because the estimates based on the questionnaire were 30–45% higher than those based on the diet records. However, it is unlikely that these measurement errors were dependent on blood pressure level.

Although we examined the relationships between individual nutrients and blood pressure, we could not distinguish the effects of components contained in soy products as well as other food groups in blood pressure. The results concerning blood pressure and nutrients reflected the correlations of blood pressure with food groups in men. Crude fiber, calcium, potassium, and vitamin B1, which were significantly inversely correlated with blood pressure, are rich in soy products. Some laboratory studies have suggested that soy isoflavones affect blood pressure through their estrogenic actions, antioxidative effects, or inhibition of tyrosine kinase activity [4,31]. It is also known that soy protein inhibits angiotensin-converting enzyme [32]. Soy protein or soy isoflavones may be responsible for the inverse association between soy product intake and blood pressure. In our study, correlations of blood pressure with soy protein or soy isoflavone intake were similar to those with soy product intake (data not shown).

Given the limitation of the diet assessment, the cross-sectional study design, and the possible confounding effects of unmeasured lifestyle factors, our results cannot be considered definitive. Nonetheless, these results suggest a mild effect of soy intake on blood pressure, although the effect may be limited to men. If the association is real, it could have considerable public health implications.

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Dietary Soy and Fats in Relation to Serum Insulin-Like Growth Factor-1 and Insulin-Like Growth Factor-Binding Protein-3 Levels in Premenopausal Japanese Women

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Abstract: *Circulating levels of insulin-like growth factor-1 (IGF-1) and insulin-like growth factor-binding protein-3 (IGFBP-3) have each been associated with premenopausal breast cancer risks. We analyzed data from a cross-sectional study of 261 premenopausal Japanese women aged 20–54 yr with adequate nutritional status to evaluate the relationships between concentrations of IGF-1 and IGFBP-3 in serum and dietary intakes of soy, fats and other nutrients. Diet was assessed by a semiquantitative food frequency questionnaire. There was no significant correlation between soy product as well as soy isoflavone intake and serum IGF-1 or IGFBP-3 levels after controlling for age, total energy, percent body fat, and education level. Total fat intake was significantly inversely correlated with serum IGFBP-3 level (*$r = -0.13$*,* $P = 0.04$*). The correlations of saturated and monounsaturated fats with serum IGFBP-3 were of borderline significance (*$r = -0.12$*,* $P = 0.06$ *and* $r = -0.11$*,* $P = 0.07$*, respectively).*

Introduction

Laboratory and experimental studies have shown that insulin-like growth factor-1 (IGF-1) has mitogenic and antiapoptotic effects on breast cancer cells (1,2), suggesting its role in the development of breast cancer. Elevated circulating IGF-1 levels have been associated with an increased risk of premenopausal breast cancer (3–6). A large majority of circulating IGF-1 is bound with high affinity to IGF-binding protein (BP)-3 (7). A low level of IGFBP-3 and a high IGF-1/IGFBP-3 ratio are also associated with an increased risk of premenopausal breast cancer (3,6). If the strong association between serum IGF-1 or IGF-1/IGFBP-3 level and risk of breast cancer is confirmed, IGF-1 may be useful to identify subjects with an increased risk and to monitor the change in risk when it is used in the practice of intervention. Studies identifying the factors that can manipulate IGF-1 would be warranted.

It is known that a very-low-calorie diet causes a drop in the circulating IGF-1 level (8). However, few studies have examined the relationship between diet and IGF-1 or IGFBP-3 in women with adequate nutritional status (9–12). We sought dietary factors that were associated with serum IGF-1 and IGFBP-3 levels in premenopausal Japanese women who were apparently healthy. In particular, we were interested in the relationships between soy product intake and serum IGF-1 and IGFBP-3 levels. Soybeans and soy products are rich in isoflavones. Soy isoflavones inhibit protein kinases, which are important in the signal transduction of several growth factors (13,14). The mitogenic action of IGF-1 in breast cancer cells is a tyrosine kinase-dependent phenomenon (15). Therefore, dietary soy may play a role in determining serum IGF-1 and IGFBP-3 levels.

Materials and Methods

Subjects for this study were participants in a health check-up program provided by a general hospital in Gifu, Japan, between September 1996 and August 1997. A total of 400 women agreed to participate in the present study and completed a self-administered questionnaire that asked about demographics, smoking and drinking habits, diet, exercise, and past medical and reproductive histories (the response rate was 95.7%). To obtain complete data, a nurse epidemiologist interviewed those who returned questionnaires with incomplete information. Of these women, 294 women reported that they had had menses within the past 12 mo. Among them, three women had experienced surgical menopause more than 3 mo before the study. The remaining 291 women were regarded to be premenopausal and were selected for the present study. Informed consent was obtained from each woman. The institutional review board approved this study, including use of their blood for IGF-1 measurement.

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Diet was assessed by a semiquantitative food-frequency questionnaire developed by us. We based our questionnaire format on the one designed for a multiethnic cohort study in Hawaii and Los Angeles (16). The women were asked to indicate the average frequency that they consumed 169 food items during the year prior to the study and the usual serving size of each item. We included nine food items for soy products (miso soup, tofu, deep-fried tofu, fried bean curd, dried bean curd, fermented soy beans, houba-miso, soymilk, and boiled soy beans). The total intake of soy products was calculated as the sum of these nine food items. Isoflavone intake from soy products was also estimated using isoflavone concentration in these soy foods (17). The intake of foods and nutrients was estimated from the frequency of ingestion and portion size using the *Japanese Standard Tables of Food Composition*, 4th ed., published by the Science and Technology Agency of Japan. Fatty acid composition was evaluated using data published by Sasaki and others (18). The validity of the questionnaire was evaluated by comparing the estimates from this questionnaire with those from 3-day diet records, four 24-h recalls, and 12 1-day diet records kept over a 1-yr period. Detailed information on the questionnaire including its validity and reproducibility has been described elsewhere (19,20). For example, the Spearman correlation coefficients comparing estimates of soy product intake from this questionnaire with the estimates from 12 daily diet records kept over a 1-yr period were 0.71.

Exercise was assessed by asking the average hours per week spent performing various kinds of activities during the past year. The details including its validity are described elsewhere (21).

A fasting blood sample was collected from each subject between 9:00 and 10:00 in the morning. The samples were stored at −80°C until assayed. Serum IGF-1 and IGFBP-3 were measured by radioimmunoassay using kits from TFB, Inc., Tokyo, and Cosmic Corp., Tokyo, respectively. The intra- and interassay coefficients of variations (CVs) were 3.9% and 5.5% for IGF-1 and 5.8% and 6.3% for IGFBP-3, respectively.

Percent body fat was measured by bioelectrical impedance analysis using a TBF-102BIA system (Tanita, Tokyo).

For statistical analysis, we excluded women who were taking hormone replacement therapy or other hormones ($n = 11$) and who had history of cancer ($n = 10$) or diabetes mellitus ($n = 9$). Of the 264 eligible women, 261 had sufficient sera available for IGF-1 assays. Their age ranged from 20 to 54 yr old.

Spearman correlation coefficients were used to examine the associations of dietary variables with serum IGF-1 and IGFBP-3 levels. Intakes of soy products and the individual nutrients were log-transformed and adjusted for total energy using the method proposed by Willett (22). Adjustments were also made for age and nondietary factors that were significantly associated with serum IGF-1 or IGFBP-3 level. We examined a number of potential confounders, which included age, weight, height, body mass index (BMI), percent body fat, smoking status, exercise, age at menarche, number of births or pregnancies, age at first and last births, lactation, intake of macro- and micronutrients, and use of medications. Serum albumin was measured for 197 women who chose program courses including this measurement. We used this variable as a surrogate of nutritional status as well as a confounder.

Results

The mean (SD) age of the study subjects was 42.7 (5.3) yr. The correlation coefficients of age with serum IGF-1 and IGFBP-3 levels were −0.28 ($P = 0.0001$) and −0.04 ($P = 0.52$), respectively. Table 1 shows selected nondietary variables and their correlations with serum IGF-1 and IGFBP-3 levels after controlling for age. Weight and percent body fat were significantly positively correlated with serum IGF-1 level after controlling for age. The positive correlation between BMI and serum IGF-1 level was of borderline significance ($r = 0.11$, $P = 0.07$). Years of education was significantly positively correlated with serum IGF-1 level ($r = 0.12$, $P = 0.04$). Seventeen (6.5%) women were current smokers and six (2.3%) women were ex-smokers. Smoking status was not significantly associated with serum IGF-1 level ($P = 0.81$). None of the nondietary factors measured was significantly correlated with serum IGFBP-3 level.

Table 2 shows that the correlations of soy product intake with serum IGF-1 and IGFBP-3 levels were nearly null after controlling for age and total energy ($r = -0.01$ and 0.03, respectively). Additional adjustment for percent body fat and years of education did not alter the results. Similarly, isoflavone intake was not significantly correlated with serum IGF-1 and IGFBP-3 levels after controlling for the covariates. Among the nutrients or foods measured, only vitamin D was significantly positively correlated with serum IGF-1 level ($r = 0.16$, $P = 0.01$) after controlling for the covariates. Total fat intake was significantly inversely correlated with serum IGFBP-3 level ($r = -0.13$, $P = 0.04$). The correlations of saturated and monounsaturated fat intake with serum IGFBP-3 level were of borderline significance ($r = -0.12$, $P = 0.06$ and $r = -0.11$, $P = 0.07$, respectively).

Serum albumin levels among the subjects were within the expected normal range of 3.8–5.3 g/dl. Serum IGF-1 level was significantly positively correlated with serum albumin level after controlling for age, percent body fat, and years of education ($r = 0.22$, $P = 0.002$). The association between saturated fat intake and serum IGFBP-3 level was strengthened after additional adjustment for serum albumin levels ($r = -0.17$, $P = 0.02$). The correlations between total fat intake and serum IGFBP-3 and between vitamin D intake and serum IGF-1 were not changed substantially after additional adjustment for serum albumin level ($r = -0.19$, $P = 0.009$ and $r = 0.15$, $P = 0.03$, respectively).

Discussion

We found no association between soy intake and serum IGF-1 and IGFBP-3 levels. To our knowledge, there is one

Table 1. Means of Selected Nondietary Variables and Their Age-Adjusted Correlations With Serum IGF-1 and IGFBP-3 Levels Among 261 Premenopausal Japanese Women[a,b]

Variables	Means ± SD (Range)	Correlation Coefficients	
		IGF-1	IGFBP-3
Height (cm)	156.9 ± 4.9 (142.9–170.0)	0.01	0.01
Weight (kg)	53.3 ± 6.7 (39.0–73.4)	0.13*	–0.005
BMI (kg²/m)	21.7 ± 2.5 (16.6–28.6)	0.11	–0.008
Percent body fat (%)	25.5 ± 5.2 (15.6–39.9)	0.17†	0.06
Years of education (yr)	13.0 ± 2.1 (6.0–22.0)	0.12*	0.08
Age at menarche (yr)	13.0 ± 1.1 (10–17)	–0.03	–0.003
Number of births	2.0 ± 0.9 (0–6)	–0.008	–0.04
Age at first birth (yr)	25.0 ± 2.5 (20–32)	0.05	–0.03
Exercise, METs (h/wk)[c]	3.0 ± 4.1 (0–4.4)	–0.06	–0.04
Alcohol (ml/day)	5.3 ± 10.4 (0–83.6)	–0.04	–0.04
Serum concentration			
IGF-1 (ng/ml)	210.8 ± 57.3 (84–430)	—	—
IGFBP-3 (ng/ml)	2,414.0 ± 460 (1,300–3,900)	—	—
Albumin (g/dl)[d]	4.3 ± 0.21 (3.8–4.8)	0.22†	0.09

a: Abbreviations are as follows: IGF, insulin-like growth factor; IGFBP, IGF binding protein; BMI, body mass index.
b: Statistical significance is as follows: *, $P < 0.05$; †, $P < 0.01$.
c: METs, metabolic equivalents.

Table 2. Means of Daily Intake of Foods and Nutrients and Their Correlations With Serum IGF-1 and IGFBP-3 Levels[a]

Variables	Means ± SD (Range)	IGF-1		IGFBP-3	
		r1[b]	r2[c]	r1	r2
Total energy (kcal)	2,315.0 ± 846 (824–7,547)	0.05	0.06	0.03	0.04
Soy product (g)	50.4 ± 35.1 (4.9–240)	–0.01	–0.01	0.03	0.03
Soy isoflavone (mg)	24.2 ± 15.9 (3.0–113.6)	0.01	–0.003	0.06	0.05
Protein (g)	92.4 ± 37.4 (26.1–298)	0.07	0.06	–0.05	–0.05
Animal protein (g)	47.3 ± 24.4 (6.8–202)	0.10	0.09	–0.04	–0.05
Vegetable protein (g)	45.0 ± 16.7 (17.7–120)	0.004	0.01	0.06	0.06
Fat (g)	70.2 ± 31.4 (13.6–278)	–0.01	–0.02	–0.12*	–0.13*
Saturated fat (g)	20.9 ± 10.9 (4.2–109)	–0.05	–0.04	–0.11	–0.12
Monounsaturated fat (g)	24.9 ± 11.5 (4.1–98.2)	–0.04	–0.05	–0.11	–0.11
Polyunsaturated fat (g)	17.2 ± 7.5 (3.9–45.1)	–0.01	–0.01	–0.05	–0.05
Carbohydrate (g)	314.0 ± 112 (104–943)	–0.00	0.08	0.07	0.08
Cholesterol (mg)	362.0 ± 171 (60–1,290)	0.05	0.02	–0.08	–0.10
Crude fiber (g)	5.4 ± 2.9 (1.4–24.0)	–0.04	–0.05	0.01	0.01
Calcium (mg)	830.0 ± 507 (227–4,624)	0.05	0.05	–0.01	–0.01
Vitamin C (mg)	146.0 ± 119 (20–1,244)	–0.07	–0.09	–0.06	–0.07
Carotene (μg)	604.0 ± 3,140 (1,014–25,207)	–0.05	–0.05	–0.01	–0.01
Vitamin D (IU)	228.0 ± 137 (28–979)	0.17†	0.16*	–0.04	–0.05
Salt (g)	13.7 ± 5.8 (3.1–37.4)	0.09	0.08	–0.01	–0.01

a: Statistical significance as as follows: *, $P < 0.05$; †, $P < 0.01$.
b: Age-adjusted correlation coefficient.
c: Correlation coefficient adjusted for age, total energy, percent body fat, and years of education.

other study of dietary soy in relation to circulating IGF-1 in healthy women (12). A small increase in IGF-1 level (by 10%) was observed in premenopausal women with diet including about 65 mg/day of isoflavones for 3 mo compared with a control diet containing 8 mg/day of isoflavones.

Although in vitro studies demonstrated that isoflavones can suppress IGF-1 signaling in cell cycle progression (13,14), such a reduction in activity may not be reflected in circulating IGF-1 levels but rather in a reduction in the phosphorylated receptor or other downstream intermediates. However, one animal study showed that soy protein feeding resulted in a decreased serum IGF-1 in the pcy mouse, the model mouse of polycystic kidney disease (23). Soy intake among our study subjects may have been too low to affect serum IGF-1 level.

We observed a significant inverse association between serum IGFBP-3 level and total fat and saturated fat intake, although these associations were not strong. Because of the cross-sectional study design, a cause-and-effect relationship between fat intake and IGFBP-3 level can only be inferred. A similar finding was reported by Kaklamani et al. (11). In their study, serum IGFBP-3 level was significantly inversely associated with saturated fat intake (r = –0.24) among 115 healthy Greek subjects after controlling for age, sex, and other covariates. A significant positive association between fat intake and serum IGF-1 level was also observed in their study. Allen et al. (24) found that mean serum IGF-1 level was significantly lower in vegan men compared with meat eaters. Results from these studies support a potential effect of dietary fat on the IGF-1 system. Previous studies (9–11) including our study have failed to find a significant association between serum IGF-1 level and total energy or protein intake.

Intake of animal protein, rich in essential amino acids, is suggested to increase IGF-1 level (25). We observed that vitamin D intake was significantly correlated with serum IGF-1 level. Vitamin D intake was strongly correlated with animal protein intake (r = 0.58). Our finding concerning vitamin D intake may reflect the association between animal protein intake and serum IGF-1 level.

Our dietary questionnaire was designed to measure an individual's relative intakes of foods and nutrients rather than absolute values. The data presented for soy products may have been underestimated by the questionnaire because, in the validity study, the soy product intake estimated from the questionnaire was 20% lower than that estimated from the 12 daily diet records over 1 yr. On the other hand, the intake of total energy and total fat may have been overestimated because these estimates from the questionnaire were about 10% higher than those from the 12 daily diet records.

We could not measure serum albumin levels for some women. However, considering that their total energy and percent body fat were within the ranges observed for women whose serum albumin levels were measured, it is likely that the entire study population was in adequate nutritional status. Reanalysis restricted to women with measured serum albumin levels did not alter the results substantially. Serum IGF-1 level was associated with serum albumin level even in this normal range. It is interesting that our findings concerning diet and serum IGF-1 and IGFBP-3 levels were not altered substantially after adjustment for serum albumin level.

BMI has not been associated with circulating IGF-1 level in previous studies conducted in other countries (26,27). An inverse correlation of BMI or adiposity with IGF-1 level has been reported among obese subjects (28). There has been a suggestion that there may be a threshold effect of body fat below which its inhibitory effects on IGF-1 level are not apparent. Our study population was less obese than that in other studies, and a similar finding (positive correlation r = 0.16 for % body fat) was reported from another study of a Japanese population (29).

We could not obtain blood samples according to the menstrual cycle. Little variation in IGF-1 level over the menstrual cycle has been reported (30). However, a recent study reported by Jernström et al. (31) showed that IGF-1 level varied during the menstrual cycle. Although adjustment for the day at blood draw according to the menstrual cycle did not alter the results (e.g., r = –0.13, P = 0.04 between fat intake and serum IGFBP-3 level and r = 0.16, P = 0.01 between vitamin D intake and serum IGF-1 level), it had been desirable that IGF-1 levels were measured repeatedly at different times because notable interindividual variation in serum IGF-1 may exist. Following the definition used in the study by Hankinson et al. (4), women who had had at least one menstrual cycle in the previous 12 mo were regarded as premenopausal in the present study. However, some women were perimenopausal and their hormonal status might differ from that of the others. The exclusion of 16 women whose previous menses were more than 3 mo before did not change the results substantially (r = –0.10, P = 0.10 between fat intake and serum IGFBP-3 level and r = 0.16, P = 0.01 between vitamin D intake and serum IGF-1 level). As the IGF-1 system has been thought to be involved in the development of breast cancer, our finding on dietary fat and serum IGFBP-3 may have preventive implications. Because IGF-1 is partially regulated by estrogens (7) and because dietary fat and soy isoflavone may affect endogenous estrogen level (32), further studies should incorporate estrogen measurements. However, we must mention that some studies have failed to confirm the association between dietary fat and breast cancer risk or the association between dietary fat and endogenous estrogen level (33,34). We also must keep in mind that data concerning IGF-1 and health, especially cancer, are still at a preliminary level and IGF-1 itself has not been accepted as a marker of overall health (35). Tamoxifen has been shown to increase the expression of IGFBPs and reduce the effect of IGF-1 (36). The present study would suggest indirectly that dietary soy does not exhibit a tamoxifen-like effect on IGFBP-3 and IGF-1.

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原著

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胆管・胆のうがんと食生活との関連

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抄録
目的：約12万人規模の大規模コホート研究のデータを利用し，食習慣および摂取品目と胆道がん発生との関連について調査した．方法：1986年から6年間で全国の約12万名から生活習慣に関連するデータを収集した．このデータを用い追跡調査を行い胆管・胆嚢がん死亡について食品摂取品目別にリスク比を算出した．結果：男性では胆管がんで脂肪摂取と，女性では胆嚢がんで脂肪摂取との間にリスクを増加させる関連が見られた．また男性の胆管がん，女性の胆嚢がんでは鮮魚の高摂取が予防的因子として認められた．結論：男性では胆管がんに，女性では胆嚢がんに対して共通のリスク因子と予防因子を持つことが明らかになった．
■キー・ワード：胆道がん，疫学，栄養

Eating Habits Associated with Bile Duct and Gallbladder Cancers: Matsuba T[*1], Inaba H[*1], Kurosawa M[*1], Yagyu S[*2], Hayashi O[*2], Kikuchi S[*2], Tamagoshi A[*3] and JACC Study Group ([*1]Dept of Hygiene, Juntendo Univ, School of Med, [*2]Dept of Public Health, Aichi Medical Univ, School of Med, [*3]Dept of Preventive Medicine, Nagoya Univ Graduate School of Med)

Objective: This study was conducted to evaluate the relationship between bile tract cancer and diet. Method: Data about lifestyle was collected from surveys of 120,000 subjects from 1986 to 1992. We calculated the risk ratio of each food items for death due to bile tract cancer from these data. Results: A relationship between dietary fat in take and bile duct cancer in males was recognized, while gallbladder cancer and fat were implicated in females. Fresh fish intake was revealed as a preventive factor for bile duct cancer in males and gallbladder cancer in females. Conclusion: It was clarified that the bile duct cancer in males and gallbladder cancer in females havecommon risk and preventive factors.
Key words: Bile tract cancer, Epidemiology, Nutrition
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はじめに

肝外胆管がん（以下胆管がん）および胆嚢がんはわが国の全悪性新生物死亡の約5%を占めるが，特徴的な地域集積性を示すことから疫学的にその発生要因については注目されている．胆管・胆のうがんの食生活と関連するリスク要因としては，これまでに多量飲酒，脂肪・牛乳の過剰摂取，野菜・果物不足など報告されているが，世界的に多発地域とされているわが国において，食生活と当疾患に関する調査はあまり行われていない．今回，約12万人規模の大規模コホート研究のデータを利用し，食習慣および摂取品目と胆管・胆のうがん発生との関連について調査を行った．

1. 方法

JACC Study (Japan Cooperative Cohort Study，文部科学省がん特定疫学研究領域大規模コホート研究）のデータ（1986年から1992年

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表1　胆道がんと食事に関するリスク比

摂取品目		男性			女性		
		リスク比	95%CI		リスク比	95%CI	
チーズ	低摂取	1.00			1.00		
	高摂取	**1.67**	1.09	2.57	**1.63**	1.08	2.47
バター	低摂取	1.00			1.00		
	高摂取	1.36	0.89	2.09	**1.52**	1.01	2.29
マーガリン	低摂取	1.00			1.00		
	高摂取	**1.60**	1.02	2.50	**1.72**	1.11	2.67
フライ	低摂取	1.00			1.00		
	中等度摂取	1.46	0.91	2.33	**1.94**	1.24	3.02
	高摂取	**1.79**	1.00	3.18	**2.02**	1.15	3.54
鮮魚	低摂取	1.00			1.00		
	中等度摂取	1.18	0.70	1.97	1.26	0.78	2.03
	高摂取	**0.58**	0.37	0.90	0.73	0.47	1.12
ホウレンソウ	低摂取	1.00			1.00		
	中等度摂取	**1.85**	1.09	3.14	1.04	0.66	1.65
	高摂取	1.05	0.67	1.64	0.99	0.64	1.57
キャベツ	低摂取	1.00			1.00		
	中等度摂取	1.64	0.95	2.83	1.00	0.62	1.62
	高摂取	0.77	0.48	1.24	0.93	0.57	1.51
煮豆	低摂取	1.00			1.00		
	中等度摂取	1.21	0.71	2.08	0.90	0.44	1.84
	高摂取	1.22	0.72	2.06	**0.50**	0.26	0.98

まで全国24施設で自記式問診票を用い，男性54,032名，女性73,445名から既往歴，家族歴のほか，食習慣，運動習慣，嗜好品等生活習慣に関連するデータを収集，追跡）のうち1988年より1997年まで観察を行った段階でのデータを用い，この間の胆管・胆のうがん死亡例（胆管がん男70名，女70名，胆のうがん男46名，女66名）を，食品摂取品目別にリスク比（オッズ比で近似）を算出した．食品摂取頻度は食品により低摂取・高摂取の2群，または低摂取・中等度摂取・高摂取の3群に分類された．リスク比は全て低摂取群を参照群として算出している．そのうち有意差を認めた食品に関してはCoxの比例ハザードモデルを用い年齢を調整したうえでハザード比（リスク比）を求めた．ただし男性の胆のうがんについては例数が少なく，比例ハザードモデルの適応が不能であった．統計学的分析には統計分析パッケージSPSSを用いた．

2. 結　果

胆道がん（胆管がん＋胆嚢がん）および胆管，胆嚢の各部位で死亡数の性比を見ると，男女比はそれぞれ0.85, 1.00, 0.70で，胆管がんでは性差は見られないが胆嚢がんでは女性が多い．

次に部位別に単回帰によるリスク比が統計学的に有意であったものについて結果をまとめる．

1) 胆道がん

男性ではチーズ1.67（1.09～2.57）（括弧内は95％信頼区間，以下同じ），マーガリン1.60（1.02～2.50），フライ高摂取1.79（1.00～3.18），ホウレンソウ中等度摂取1.85（1.09～3.14）でリスク比が有意に1を越え鮮魚0.58（0.37～0.90）は1以下の値を示した（表**1**）．

女性ではチーズ1.63（1.08～2.47），バター1.52（1.01～2.29），マーガリン1.72（1.11～2.67），フライ中等度摂取1.94（1.24～3.02），フライ高摂取2.02（1.15～3.54）でリスク比は有意に1を超えた値を示し，煮豆高摂取0.50（0.26～

表2　胆管がんと食事に関するリスク比

摂取品目		男性			女性		
		リスク比	95%CI		リスク比	95%CI	
チーズ	低摂取	1.00			1.00		
	高摂取	**2.00**	1.13	3.54	1.26	0.73	2.20
バター	低摂取	1.00			1.00		
	高摂取	1.57	0.90	2.75	1.31	0.74	2.30
マーガリン	低摂取	1.00			1.00		
	高摂取	**1.76**	1.00	3.08	1.76	0.95	3.28
フライ	低摂取	1.00			1.00		
	中等度摂取	1.86	1.02	3.38	1.83	1.00	3.35
	高摂取	1.70	0.86	3.38	1.80	0.85	3.79
鮮魚	低摂取	1.00			1.00		
	中等度摂取	0.99	0.53	1.85	1.49	0.79	2.85
	高摂取	**0.53**	0.30	0.94	1.27	0.66	2.47
ホウレンソウ	低摂取	1.00			1.00		
	中等度摂取	1.79	0.92	3.50	1.52	0.77	3.00
	高摂取	1.03	0.59	1.81	0.98	0.55	1.78
キャベツ	低摂取	1.00			1.00		
	中等度摂取	1.20	0.64	2.24	1.10	0.55	2.20
	高摂取	0.79	0.43	1.46	0.99	0.50	1.98
煮豆	低摂取	1.00			1.00		
	中等度摂取	1.80	0.91	3.57	1.20	0.46	3.15
	高摂取	1.41	0.75	2.64	0.57	0.24	1.35

0.98）では1以下の値を示した（表**1**）.

2）胆管がん

男性ではチーズ2.00（1.13～3.54），マーガリン1.76（1.00～3.08）で有意に1を越える値を示し，鮮魚高摂取0.53（0.30～0.94）では1以下の値を示した（表**2**）.

女性ではフライ中等度摂取1.83（1.00～3.35）が有意な値を示した．リスク比が1以下のいわゆる予防的因子は認められなかった.

3）胆嚢がん

男性ではキャベツの中等度摂取3.85（1.13～13.10）で高い値を示したほかは統計学的に有意な値を示した因子はなかった（表**3**）.

女性ではチーズ2.23（1.18～4.22），フライ中等度摂取2.08（1.08～4.00）でリスク比が1を越え，鮮魚高摂取0.43（0.24～0.79）で1以下の値を示した（表**3**）.

さらに，単回帰で有意な値を示した変数だけを用い調整因子として年齢を加えて回帰モデルを作成しCoxの比例ハザードモデルにてハザード比（リスク比）を計算した.

（1）胆道がん

男女ともにではフライ中等度摂取2.58（1.08～6.16）（男性），2.96（1.28～6.86）（女性）にて統計学的に有意な値を示した（表**4**）.

（2）胆管がん

男女ともに統計学的に有意なハザード比を有する因子は認められなかった（表**5**）.

（3）胆嚢がん

男性では例数が少なく，比例ハザードモデルの適応が不能であった.

女性ではフライ中等度摂取3.15（1.03～9.59），ホウレンソウ高摂取3.72（1.38～10.10）で1以上の有意な値を呈し，鮮魚中等度摂取0.38（0.16～0.95）で1以下の値を呈した（表**6**）.

3. 考　察

わが国は世界的に南米チリに並んで胆道がんの多発地域として知られている．胆道がんは全がん死亡の中で5%を占めるに過ぎないが，予後が悪

表3 胆嚢がんと食事に関するリスク比

摂取品目		男性			女性		
		リスク比	95%CI		リスク比	95%CI	
チーズ	低摂取	1.00			1.00		
	高摂取	1.30	0.67	2.52	**2.23**	1.18	4.22
バター	低摂取	1.00			1.00		
	高摂取	1.10	0.56	2.16	1.80	0.99	3.27
マーガリン	低摂取	1.00			1.00		
	高摂取	1.35	0.64	2.83	1.69	0.91	3.12
フライ	低摂取	1.00			1.00		
	中等度摂取	0.99	0.46	2.14	**2.08**	1.08	4.00
	高摂取	2.01	0.69	5.88	2.33	0.99	5.51
鮮魚	低摂取	1.00			1.00		
	中等度摂取	1.65	0.65	4.15	1.01	0.50	2.07
	高摂取	0.65	0.31	1.35	**0.43**	0.24	0.79
ホウレンソウ	低摂取	1.00			1.00		
	中等度摂取	1.95	0.82	4.63	0.73	0.38	1.40
	高摂取	1.09	0.53	2.24	1.02	0.51	2.04
キャベツ	低摂取	1.00			1.00		
	中等度摂取	**3.85**	1.13	13.1	0.91	0.47	1.79
	高摂取	0.74	0.35	1.57	0.88	0.44	1.74
煮豆	低摂取	1.00			1.00		
	中等度摂取	0.64	0.25	1.63	0.65	0.22	1.94
	高摂取	0.88	0.34	2.32	0.43	0.15	1.23

表4 胆道がんと食事に関するハザード比

摂取品目		男性			女性		
		ハザード比	95%CI		ハザード比	95%CI	
チーズ	低摂取	1.00			1.00		
	高摂取	1.37	0.71	2.70	1.19	0.61	2.30
バター	低摂取	1.00			1.00		
	高摂取	0.77	0.40	1.50	0.87	0.46	1.67
マーガリン	低摂取	1.00			1.00		
	高摂取	1.64	0.86	3.08	1.27	0.69	2.32
フライ	低摂取	1.00			1.00		
	中等度摂取	**2.58**	1.08	6.16	**2.96**	1.28	6.86
	高摂取	1.82	0.78	4.23	1.26	0.53	3.00
鮮魚	低摂取	1.00			1.00		
	中等度摂取	0.55	0.29	1.05	0.83	0.44	1.54
	高摂取	0.76	0.39	1.47	0.51	0.24	1.06
ホウレンソウ	低摂取	1.00			1.00		
	中等度摂取	1.34	0.67	2.63	1.67	0.82	3.41
	高摂取	0.99	0.47	2.07	1.73	0.87	3.43
キャベツ	低摂取	1.00			1.00		
	中等度摂取	0.66	0.34	1.29	0.62	0.31	1.25
	高摂取	0.48	0.22	1.05	0.92	0.47	1.81
煮豆	低摂取	1.00			1.00		
	中等度摂取	0.78	0.75	2.68	0.57	0.25	1.32
	高摂取	2.09	0.40	1.51	0.67	0.36	1.21

表5　胆管がんと食事に関するハザード比

摂取品目		男性			女性		
		ハザード比	95%CI		ハザード比	95%CI	
チーズ	低摂取	1.00			1.00		
	高摂取	1.54	0.68	3.47	1.12	0.42	2.92
バター	低摂取	1.00			1.00		
	高摂取	0.88	0.40	1.97	0.72	0.28	1.81
マーガリン	低摂取	1.00			1.00		
	高摂取	1.34	0.63	2.85	1.66	0.68	4.05
フライ	低摂取	1.00			1.00		
	中等度摂取	1.92	0.78	4.74	2.72	0.76	9.77
	高摂取	0.94	0.37	2.36	1.52	0.42	5.52
鮮魚	低摂取	1.00			1.00		
	中等度摂取	0.74	0.34	1.61	1.76	0.70	4.43
	高摂取	0.84	0.37	1.91	0.41	0.11	1.63
ホウレンソウ	低摂取	1.00			1.00		
	中等度摂取	1.36	0.59	3.15	1.28	0.50	3.25
	高摂取	1.11	0.46	2.69	0.66	0.22	1.98
キャベツ	低摂取	1.00			1.00		
	中等度摂取	0.74	0.33	1.70	0.50	0.18	1.33
	高摂取	0.63	0.25	1.57	0.86	0.32	2.27
煮豆	低摂取	1.00			1.00		
	中等度摂取	1.53	0.74	3.14	0.80	0.31	2.48
	高摂取	0.47	0.19	1.15	0.55	0.22	1.35

いことや地域集積性が認められることからリスク因子の解明について関心がもたれてきた[1,2]．当研究での胆道がん死亡の性比は女性に多く，国内や海外での調査結果と一致する[2,3]．また部位別に見ると胆嚢がんは女性に多く胆管がんでは性差は認められなかった．

胆管・胆のうがんの食事に関するリスク要因としては，過去に脂肪・牛乳の過剰摂取多食，野菜・果物不足が報告されている[4~6]．野菜・果物摂取に関して当研究では有意な関連性は認められなかった．脂肪摂取に関連しては，男性の胆道がんでチーズ，マーガリン，フライ高摂取，ホウレンソウ中等度摂取などがリスク因子として有意なリスク比を示した．ただし部位別に分けると胆道がんではチーズ，マーガリンがリスク因子として一致するものの，胆嚢がんではキャベツの中等度摂取のみがリスク因子として有意な値を示すという結果になった．このことから男性では胆管がんは脂肪摂取との関連は見られるものの胆嚢がんではその他の因子の影響が考えられる．女性では胆道がんでチーズ，バター，マーガリン，フライの中等度および高摂取がリスク因子として認められ，胆嚢がんにおいてもチーズ，フライ中等度摂取，ホウレンソウ高摂取と脂肪摂取に関するリスク因子が重なっている．ただし男性の場合と異なり胆管がんでは脂肪摂取に関する因子のみならず，食生活によるリスク因子は認められなかった．鮮魚の高摂取は男性の胆道がん，胆管がんで，女性の胆嚢がんで予防的因子として有意なリスク比を呈した．また女性の胆道がんで煮豆が予防的因子としてのリスク比の値を呈しているが，海外での研究において豆の摂取が同様に影響しているという報告がみられる[5]．海外の報告ではその他砂糖の過剰摂取やとうがらしの摂取との関連が報告されている．砂糖の摂取や当研究におけるバター，マーガリン，フライ等の脂肪摂取は高カロリー食を反映しているのかもしれない．このことから，今後食生活を反映した食品群としてまとめた形でリスク比について分析を行う予定である．また，胆石のリスク因子がそのまま胆道がん

表6 胆嚢がんと食事に関するハザード比

摂取品目		女性		
		ハザード比	95%CI	
チーズ	低摂取	1.00		
	高摂取	1.26	0.51	3.09
バター	低摂取	1.00		
	高摂取	1.04	0.43	2.53
マーガリン	低摂取	1.00		
	高摂取	1.00	0.44	2.26
フライ	低摂取	1.00		
	中等度摂取	**3.15**	1.03	9.59
	高摂取	1.04	0.32	3.41
鮮魚	低摂取	1.00		
	中等度摂取	**0.38**	0.16	0.95
	高摂取	0.52	0.21	1.25
ホウレンソウ	低摂取	1.00		
	中等度摂取	2.32	0.76	7.09
	高摂取	**3.72**	1.38	10.1
キャベツ	低摂取	1.00		
	中等度摂取	0.79	0.29	2.12
	高摂取	1.02	0.40	2.65
煮豆	低摂取	1.00		
	中等度摂取	0.31	0.07	1.36
	高摂取	0.79	0.36	1.71

のリスク因子であるという報告もあり[7]，胆石の既往を調整したかたちでの分析が必要である．

まとめ

当研究において胆道がん，胆嚢がん死亡は女性に多く今までの研究と一致した．胆管がんは性差がみられず，両部位では発生に関する因子が異なることが示唆された．食事との関連では，男性では胆管がんで脂肪摂取と，女性では胆嚢がんで脂肪摂取との間にリスクを増加させるような関連が見られた．同様に男性の胆管がん，女性の胆嚢がんでは鮮魚の高摂取が予防的因子として認められる．

当研究は文部科学省大規模コホート研究の一部として行われた．

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千葉県立東金病院における女性専用外来の歩みと今後の課題について

竹尾愛理*・平井愛山**

abstract

平成13年9月，千葉県立東金病院は，総合的な女性の医療サービスの提供と，gender-specific medicineの実践を目的に，女性専用外来を開設した．開設にあたっては，千葉県の保健医療政策の基本方針である「健康ちば21」が大きな役割を果たした．ゆとりのある診療を行うため，初診時30分の診療時間を設定し，女性特有の疾患の診療の場であるとともに身体と心を総合的に診療する個の医療の可能性をもたらしたことから，受診者にはこれまでにない医療と好評である．また，受診に抵抗のあるデリケートな疾患の早期治療の場の可能性を与えた．多岐にわたる疾患の診療の場である当外来の今後の課題としては，他科との連携と，コメディカルスタッフとの協力体制の確立が挙げられる．

I はじめに

このわずか1～2年の間に，女性の総合的な医療を目的とした，女性専用外来あるいは女性総合診療科と名づけられる診療科が，日本全国に急速に広がってきた．性差に基づく医療（gender-specific medicine）の実践と個の医療を目指したこれまでにない新しい医療として，女性医療は大きな話題をよんでいる．本稿では，都道府県立病院としては全国で初めて女性専用外来を設置した千葉県立東金病院での開設に至るこれまでの経緯および診療の実際，そしてこれまでの成果と今後の課題について述べる．

II 開設の経緯

平成13年9月，千葉県立東金病院（以下当院と略）は堂本暁子知事の強い要請を受け，女性特有の疾患に対応するため，総合的な女性の医療サービスの提供を目的として，女性専用外来を開設した．ここでは，今後10年間の千葉県の保健医療政策の基本方針である「健康ちば21」[1] が女性専用外来の開設にあたり大きな役割を果たしたことが特徴である[2]．「健康ちば21」において「根拠に基づいた保健医療行政（医政）」の構築と実践を目指して，千葉県の保健医療に関する現状分析を行い，今後行政が取り組むべき課題を明示し，これが女性専用外来を開設する際の要となった．

III 女性専用外来開設の目的

当院における女性専用外来開設の目的は以下の通りである．

①女性特有の疾患に配慮した医療の実践

女性と男性にはそれぞれ特有の疾患や病態があるという「性差に基づく医療」（gender-specific

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medicine）の概念が，1990年代よりアメリカを中心に急速に広がってきた．日本では天野恵子千葉県衛生研究所所長が先駆けとして啓蒙した．当院では，gender-specific medicineの考え方に基づき，「健康ちば21」による千葉県の女性の健康と医療におけるエビデンスを中心に，女性の健康についての問題点に対応しつつ，女性特有の疾患の診断，治療を行う．

②女性医師が担当することで，医療受診に対する抵抗を少なくする．

診療は女性医師が担当し，話しやすい雰囲気づくりに留意しつつデリケートで女性特有な症状，希望に対応し，診療をより抵抗なくスムーズに進めることによって，疾患の早期発見，早期治療を図る．

③個の医療の実践

初診時1人当たり30分の診察時間を設定し，十分に傾聴することから疾患の背景に対する配慮を行い，身体と精神を分離せず総合的な医療を行う．人間の身体は個々の分離した臓器ではなくすべてが集まって一人の人間を構成するという考え方に基づき，個人に合った医療を実践する．

④他の専門外来との連携

当院が開設している専門外来である乳腺外来，高脂血症外来，骨粗鬆症外来，婦人科外来などとの連携を図るとともに，地域の他の診療科および女性医師との連携を行い，各専門分野の視点から診療する．

⑤自治体病院としての役割

千葉県における女性専用外来の先駆けとして，開設以後，県内各地の病院に外来を広げ，定着させる．

Ⅳ 女性専用外来開設にあたっての準備

女性専用外来開設にあたり，当院の平井愛山院長によりさまざまな準備が行われた．カーテンで仕切られていた内科の診察室の入り口にスライド式ドアを設置し，窓をスリガラスに換えることでプライバシーへの配慮を行った．また，上述のように「健康ちば21」で明らかにされた千葉県の女性の医療・健康問題の課題にかんがみ，女性に特有な疾患に対応するため，X線骨密度測定装置および乳癌X線撮影器（マンモグラフィー）を導入した．また，女医に

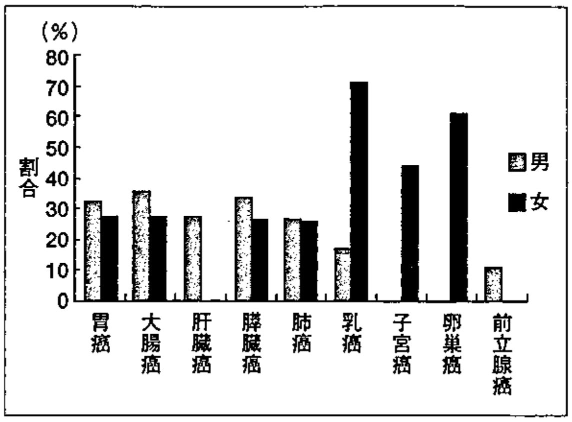

図1　千葉県民の各癌の65歳未満における死亡率早世係数（%）　〔文献1）より引用〕

よる女性専用外来を核として乳腺外来，骨粗鬆症外来，高脂血症外来などの専門外来がサポートし，病院を挙げて女性の全身を診る診療体制を整えた．

平井院長および担当医は，一足早く女性のための女医外来を開設した鹿児島大学医学部第一内科を視察し，温かい指導を受けた．診療の担当は千葉大学大学院医学研究院細胞治療学（第二内科）齋藤康教授の全面的な協力により当該科の女性医師が非常勤としてあたったが，受診希望者が殺到したことから，担当日が増設され，平成14年4月より整形外科でも女性専用外来が開設された．担当医は天野恵子千葉県衛生研究所所長により丁寧な指導を受けた．また，ウイメンズヘルスフォーラム21（WHF21）コーディネーターの薬剤師宮原富士子氏からは地域の調剤薬局薬剤師への啓蒙普及活動が行われた．

県民へのPR方法などについては，県民だよりや各市町村の広報を活用した．

Ⅴ 「健康ちば21」について

東金病院では女性特有の疾患に対応するにあたり，「健康ちば21」策定の基礎となったエビデンスのなかから女性専用外来の基礎となる重要な事実を見出した．

①千葉県の働き盛り（65歳未満）の女性の死亡原因の半分は癌であり，なかでも乳癌が最も多い（図1）．

②千葉県の女性は乳癌の死亡率（標準化死亡比：

表1　千葉県における癌死亡の全国の位置づけ

	性別	年齢調整死亡率	順位	SMR	順位
胃癌	男	50	4	107.1	13
	女	18.4	19	103.5	19
肺癌	男	39.7	44	90.2	41
	女	12.1	20	95.2	23
大腸癌	男	24.7	19	102.9	14
	女	13.6	24	102.1	17
乳癌	男女	10.5	10	107.9	4
子宮癌	女	5.2	23	101	23

〔文献1）より引用〕

SMR）は全国4位ときわめて悪い状況にある（表1）.
③千葉県の若年女性のCa摂取量は著しく低下しており，骨粗鬆症の予防の観点からきわめて大きな問題である.
④動脈硬化性疾患の死亡原因に占める割合は女性が男性よりもかなり高い.
⑤千葉県の女性は閉経後高コレステロール血症が急増する.

これらのエビデンスに基づき，平井院長は当院の女性専用外来の開始にあたって乳癌と骨粗鬆症が最も重要と思われたことから，乳癌の早期診断のために高精度のマンモグラフィーを，また骨粗鬆症の診断に精密度の高い最新のX線骨密度測定装置を導入した.

VI 女性専用外来の診療の流れ

心と身体のゆとりのある診療を行うため，初診時には一人30分の診察時間を設定した．受診希望者はまず，電話で担当の看護師に簡単な症状を伝え，予約する．受診日は再度看護師からの連絡により決定する.

受診日には，問診表をもとにしながら詳細な問診を行い，必要であれば，背景の家庭的，社会的な状況も含めて聞いていく．基本的には口を挟まず，まずは訴えを十分に傾聴する．これだけで体調が改善することもある．その後，診察し，身体所見を取り，必要であれば血液検査などを実施，投薬などを行うことになる点は一般外来と大きな差異はない．必要があれば院内外の他科医に紹介する.

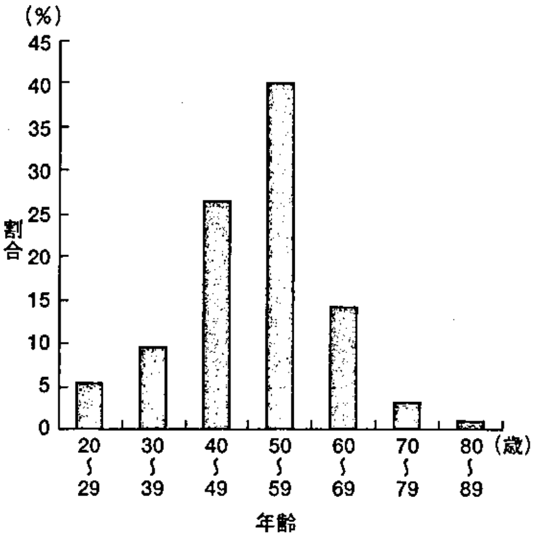

図2　受診者の年齢分布　〔千葉県立東金病院調べ，2002〕

VII 女性専用外来の受診者について

平成13年9月から平成14年5月までに当院を受診した199名についての概要についてまとめた.

まず，来院者の年齢は，40歳，50歳代の閉経前後の受診者が多く，全体の3分の2を占めた（図2）．年齢層は10歳代から80歳代まで広く分布していた．受診者のこれまでの医療機関通院歴については，全く初診である者は全体の17%にすぎず，複数の医療機関を受診していた者も多く，これまでの説明や治療に納得できなかった者が受診したものと思われた．受診科については，内科，産婦人科，精神科・心療内科が多かった.

受診者の疾患分類について述べる．当院の受診者は，更年期障害が43.6%と最も多く，精神神経疾患が13.2%，産婦人科疾患や，それらのセカンドオピニオンを求める者が12.3%，狭心症，プロラクチン産生下垂体腫瘍などの器質的疾患が11.3%，冷え，肩こりなどの不定愁訴が5.4%であった．その他，乳腺疾患，骨粗鬆症，など多岐にわたった（図3）.

治療については，当院では，傾聴やカウンセリング，漢方薬，抗不安薬，ホルモン補充療法など，個々の病態に合わせて用いている.

特に，更年期障害や，西洋医学的に器質的な疾患