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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 (kg^2/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	
		*r*1[b]	*r*2[c]	*r*1	*r*2
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 asso-

ciated 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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