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Relationships Between Types of Fat Consumed and Serum Estrogen and Androgen Concentrations in Japanese Men

Chisato Nagata, Naoyoshi Takatsuka, Norito Kawakami, and Hiroyuki Shimizu

Abstract: *The relationships between types of fat consumed and serum concentrations of estrone, estradiol, total and free testosterone, dihydrotestosterone, and sex hormone-binding globulin were examined in 69 Japanese men aged 43–88 years. Diet was assessed by a semiquantitative food frequency questionnaire. Intake of saturated, monounsaturated, and polyunsaturated fats was inversely correlated with serum total testosterone after controlling for age, total energy, body mass index, alcohol intake, and smoking status, but the correlation was statistically significant only for polyunsaturated fat (*r = *−0.29,* p = *0.02). Intakes of eicosapentanoic and docosahexaenoic acids, n–3 fatty acids from fish, were significantly inversely correlated with total testosterone (*r = *−0.25,* p = *0.04 and* r = *−0.32,* p = *0.01, respectively). Serum estrone, estradiol, and free testosterone were not significantly correlated with any type of fat studied. The correlations of total testosterone with n–3 fatty acids from fish remained significant after additional adjustment for the other categories of fat (*r = *−0.27,* p = *0.03 for eicosapentanoic acid and* r = *−0.32,* p = *0.01 for docosahexaenoic acid), while the correlations with saturated and monounsaturated fats became nearly null after the adjustment.*

Introduction

Laboratory studies have suggested a role of androgens in the etiology of prostate cancer (1). Several epidemiological studies have demonstrated higher serum or plasma testosterone concentrations in prostate cancer patients than in controls (2–4). In addition, a possible role of estrogens in the development of prostate cancer has been postulated (5).

Previous studies have investigated the determinants of circulating levels of estrogens and androgens. Diet, especially dietary fat, has been given attention in relation to blood levels of estrogens and androgens. The effect of fat intake on these hormone levels has been examined in some dietary intervention studies (6–9). However, data on any relationships between specific types of fat and serum estrogen and androgen levels have been insufficient. Negative associations between seafood intake and risk of prostate cancer have been reported in some studies (10,11). There is a possibility that fat from fish may affect one's prostate cancer risk by modulating the estrogen or androgen mechanism. To our knowledge, however, there is no study on the effect of fat from fish on serum estrogen and androgen levels.

The incompleteness of the Japanese food composition table in regard to fatty acid composition has presented problems in determining fatty acid content in the diet. However, a recently developed fatty acid composition table (12) has enabled us to study the relationships between the types of fat consumed and serum concentrations of estrogens and androgens in Japanese men. It is considered worthwhile to examine these relationships in Japanese men, because a relatively high average and a large range of fat intake from fish are expected in this population. Although there is a limitation to assessing the causal effect in this cross-sectional study, the results should reflect the association of hormonal status with the usual diet of subjects over longer periods than those described in the intervention studies.

Materials and Methods

The study population is a subset of the Takayama Study (13), which was designed to evaluate the role of diet and lifestyle in the subsequent development of cancer. The cohort for the Takayama Study was established in 1992 when ~92% of all residents aged ≥35 years in Takayama City, Japan, completed self-administered questionnaires.

In 1995, a total of 256 men, randomly selected from the 14,427 male participants in the Takayama Study, were invited to join a comprehensive study investigating the relationships between lifestyle and several biomarkers. The study included urine-sample collection as well as a validation study of the dietary questionnaire, factors that may have decreased the rate of participation. A written informed consent to participate in the study was obtained from each of 97 men. The results of soy product intake and hormone status in these men have been published elsewhere (14), but the results referring to fat and other nutrients are new data.

The authors are affiliated with the Department of Public Health, Gifu University School of Medicine, Gifu 500-8705, Japan.

A blood sample was collected from each subject. Samples were centrifuged within three hours, and the serum was separated and stored at −80°C. Radioimmunoassay kits were used to measure serum concentrations of estradiol and total and free testosterone (Diagnostic Products, Chiba, Japan), estrone (Eiken Chemical, Tokyo, Japan), dihydrotestosterone (DHT; Medical System Service, Kanagawa, Japan), and sex hormone-binding globulin (SHBG; Pharmacia & Upjohn, Tokyo, Japan). The intra-assay coefficients of variation, derived from routine quality control procedures, were 10.8% for estrone, 15.4% for estradiol, 6.1% for total testosterone, 4.9% for free testosterone, 11.7% for DHT, and 7.8% for SHBG.

The information on height and weight, smoking status, and past histories of cancer, cardiovascular disease, and metabolic and endocrine disease was obtained during an interview at the time of blood collection in 1995.

In the present study, we used information on diet and exercise obtained from the 1992 questionnaire. Diet was assessed by a semiquantitative food frequency questionnaire. The men were asked to indicate the average frequency of consumption of 169 food items during the year before the study and the usual serving size of each item. In total, 16 items of fish or fish dishes were included. Individual nutrient intake was estimated from the frequency of intake and portion size using the Standard Tables of Food Composition in Japan (14a). Fatty acid composition was evaluated using data published by Sasaki and others (12). Detailed information about the questionnaire, including the results of the validity test, is described elsewhere (15). We additionally validated the estimates of various types of fat for the present study. The Spearman correlation coefficients comparing estimates of n–3 and n–6 fatty acids, as well as eicosapentanoic and docosahexaenoic acids, from this questionnaire with the estimates from 12 daily diet records kept over a one-year period were 0.40, 0.29, 0.58, and 0.52, respectively.

We excluded from the present analysis men who reported a history of prostate surgery ($n = 2$), prostate enlargement ($n = 4$), diabetes mellitus ($n = 8$), chronic liver disease ($n = 1$), and cardiovascular diseases (ischemic heart diseases and thrombosis, $n = 6$), inasmuch as these conditions may affect testosterone or estrogen levels (16–18). In addition, we excluded seven men with an insufficient blood volume for taking hormone measurements. After these exclusions, 69 men aged 43–88 years were available.

Spearman correlation coefficients were calculated to assess the associations between dietary variables and hormone concentrations. Adjustment for potential confounders was done by regressing the hormone and nutrient values separately on the confounders. The Spearman correlation coefficients between these residuals were then calculated. The nutrient intake was logarithmically transformed and adjusted for total energy using the method proposed by Willett (19). Associations of categorical variables and hormone concentrations were assessed by analysis of variance. The mean hormone concentrations within each category were calculated after controlling for potential confounders. To men with undetectable levels (<10 pg/ml) of estrone ($n = 14$) or estradiol ($n = 11$), minimum values (i.e., 10 pg/ml) were allotted. Serum androgens and SHBG were detectable in all the subjects. All statistical analyses were performed using SAS programs (20). This study was approved by the local institutional review board.

Results

The means ± SD for nonnutritional factors and hormone concentrations are shown in Table 1 along with correlation coefficients between these variables. The estrone and estradiol concentrations were 21.8 ± 8.7 and 18.4 ± 6.1 (SD) pg/ml, respectively, after the subjects with undetectable levels

Table 1. Spearman Correlation Coefficients Between Serum Hormone Concentrations and Demographic Characteristics and Other Nonnutritional Factors[a–c]

	Serum Hormones[d]						
Factors[d]	E1[e] (19.4 ± 9.2 pg/ml)	E2[f] (17.1 ± 6.4 pg/ml)	T (432 ± 137 ng/dl)	Free T (14.3 ± 4.3 pg/ml)	SHBG (49.7 ± 20.3 nmol/l)	DHT (75 ± 28 ng/dl)	DHT/T (1.8 ± 0.5)
Age (60.5 ± 10.7 yr)	−0.04	−0.16	0.13	−0.42	0.46	0.20	0.09
Height (163.3 ± 6.5 cm)	−0.13	−0.13	0.08	0.15	−0.21	−0.10	−0.23
Weight (60.4 ± 9.8 kg)	0.01	−0.04	−0.21	0.03	−0.46†	−0.20	−0.04
BMI (22.6 ± 3.0 kg^2/m)	0.05	0.01	−0.30*	−0.06	−0.42†	−0.17	0.09
Exercise (25.2 ± 37.1 METs·h/wk)	0.18	0.16	0.06	0.15	0.10	0.08	0.13
Alcohol intake (37.6 ± 36.0 ml/day)	0.35†	0.20	−0.15	0.14	−0.27*	0.03	0.20

a: Adjusted for age, except for age.

b: Abbreviations are as follows: E1, estrone; E2, estradiol; T, testosterone; SHBG, sex hormone-binding globulin; DHT, dihydrotestosterone; BMI, body mass index; METs, metabolic equivalents.

c: Statistical significance is as follows: *, $p < 0.05$; †, $p < 0.01$.

d: Values are means ± SD.

e: 10 pg/ml was allotted to 14 men with undetectable level (<10 pg/ml).

Table 2. Spearman Correlation Coefficients Between Nutrient Intakes[a]

Nutrients[b]	Energy	TP	TF	SF	MF	PF	n–6	n–3	EPA	DHA	CH	Cho	CF
Energy (2,421 ± 616 kcal)	1.00												
TP (89.3 ± 26.0 g)	0.92	1.00											
TF (57.7 ± 20.8 g)	0.79	0.89	1.00										
SF (16.2 ± 7.0 g)	0.76	0.85	0.92	1.00									
MF (20.0 ± 7.8 g)	0.77	0.87	0.99	0.90	1.00								
PF (15.0 ± 5.2 g)	0.75	0.84	0.91	0.79	0.90	1.00							
n–6 (12.0 ± 4.1 g)	0.73	0.82	0.90	0.79	0.90	1.00	1.00						
n–3 (3.0 ± 1.1 g)	0.74	0.86	0.86	0.73	0.84	0.95	0.92	1.00					
EPA (349 ± 173 mg)	0.53	0.60	0.45	0.39	0.43	0.51	0.46	0.69	1.00				
DHA (591 ± 275 mg)	0.54	0.62	0.48	0.41	0.46	0.55	0.50	0.73	0.99	1.00			
CH (328 ± 84 g)	0.87	0.78	0.59	0.60	0.58	0.56	0.56	0.56	0.43	0.41	1.00		
Cho (337 ± 141 mg)	0.63	0.76	0.79	0.68	0.77	0.75	0.77	0.77	0.49	0.57	0.41	1.00	
CF (4.6 ± 1.6 g)	0.55	0.64	0.49	0.45	0.48	0.65	0.64	0.63	0.43	0.43	0.56	0.49	1.00

a: Abbreviations are as follows: TP, total protein; TF, total fat; SF, saturated fat; MF, monounsaturated fat; PF, polyunsaturated fat; n–6, n–6 fatty acids; n–3, n–3 fatty acids; EPA, eicosapentanoic acid; DHA, docosahexaenoic acid; CH, carbohydrate; Cho, cholesterol; CF, crude fiber.
b: Values are means ± SD.

were excluded. Weight, body mass index (BMI), and alcohol were inversely correlated with SHBG, while BMI was inversely correlated with total testosterone, and alcohol was positively correlated with estrone. Smoking status was marginally significantly ($p = 0.08$) associated with estrone concentrations; the age-adjusted means of estrone were 20.4, 15.2, and 17.2 pg/ml in current smokers ($n = 28$), former smokers ($n = 28$), and lifelong nonsmokers ($n = 13$), respectively.

Table 2 presents the means and correlation coefficients among fats and other major nutrients. The intakes of fish, shellfish, dried fish, and boiled fish paste were 74.0 ± 36.6, 9.4 ± 6.7, 1.0 ± 0.5, and 15.1 ± 12.2 (SD) g/day, respectively.

We assessed the associations between energy-adjusted nutrient intake and individual hormone concentrations after controlling for age, BMI, alcohol intake, and smoking status (Table 3). Intake of total fat was significantly inversely correlated with SHBG and DHT. The inverse correlation with total testosterone was of borderline significance ($p = 0.06$). Intake of saturated fat was significantly inversely correlated with DHT. Intake of monounsaturated fat was significantly inversely correlated with SHBG and DHT. Intakes of polyunsaturated fat and n–6 fatty acids were significantly inversely correlated with total testosterone, SHBG, and DHT. The n–3 fatty acids from fish, eicosapentanoic and docosahexaenoic acids, were significantly inversely correlated with total testosterone and SHBG. None of the estrogens nor free testosterone was significantly correlated with any type of fat studied.

Blood samples were drawn before 10 AM ($n = 20$), between 10 AM and 2 PM ($n = 27$), and after 2 PM ($n = 22$). Additional adjustment for the time of blood drawing did not affect the results; after controlling for this variable, for example, the correlation coefficients of total testosterone with eicosapentanoic and docosahexaenoic acids were –0.25 and –0.32, respectively.

Table 3. Spearman Correlation Coefficients Between Serum Hormone Concentrations and Selected Nutrient Intakes[a,b]

	E1[c]	E2[d]	T	Free T	SHBG	DHT	DHT/T
Energy (kcal)	–0.06	0.01	0.05	0.02	0.03	–0.05	–0.19
Total protein	0.05	–0.04	–0.09	0.06	–0.15	–0.16	–0.22
Total fat	0.21	0.18	–0.24	–0.003	–0.31*	–0.33†	–0.23
Saturated fat	0.22	0.22	–0.19	–0.02	–0.14	–0.27*	–0.22
Monounsaturated fat	0.22	0.21	–0.24	–0.03	–0.31*	–0.36†	0.24
Polyunsaturated fat	0.15	0.07	–0.29*	–0.10	–0.38†	–0.30*	–0.12
n–6 Fatty acids	0.14	0.08	–0.27*	–0.11	–0.36†	–0.31*	–0.15
n–3 Fatty acids	0.13	0.003	–0.34†	–0.08	–0.42†	–0.23	0.0003
Eicosapentanoic acid	–0.05	–0.11	–0.25	–0.04	–0.29*	–0.16	0.04
Docosahexaenoic acid	–0.09	–0.15	–0.32†	–0.08	–0.34†	–0.22	0.03
Carbohydrate	–0.17	–0.08	0.32†	0.10	0.29*	0.32	0.12
Cholesterol	–0.03	–0.07	–0.33†	–0.08	–0.40†	–0.36†	–0.11
Crude fiber	–0.22	–0.11	0.09	–0.03	0.11	0.06	–0.12

a: Adjusted for age, BMI, smoking status, alcohol intake, and total energy, except for energy intake.
b: Statistical significance is as follows: *, $p < 0.05$; †, $p < 0.01$.
c: 10 pg/ml was allotted to 14 men with undetectable level (<10 pg/ml).
d: 10 pg/ml was allotted to 11 men with undetectable level (<10 pg/ml).

Table 4. Spearman Correlation Coefficients Between Fat Intake and Serum Hormone Concentrations[a,b]

	E1[c]	E2[d]	T	Free T	SHBG	DHT	DHT/T
Saturated fat	0.08	0.05	–0.09	–0.04	0.06	–0.02	–0.04
Monounsaturated fat	0.07	0.15	0.04	0.09	–0.06	–0.14	–0.15
Polyunsaturated fat	–0.01	–0.14	–0.18	–0.13	–0.20	–0.03	0.10
n–6 Fatty acids	–0.03	–0.04	–0.04	–0.12	–0.06	–0.07	–0.07
n–3 Fatty acids	0.02	–0.14	–0.23	–0.03	–0.23	0.04	0.22
Eicosapentanoic acid	–0.04	–0.12	–0.27*	–0.04	–0.29*	–0.15	0.05
Docosahexaenoic acid	–0.10	–0.17	–0.32*	–0.09	–0.31*	–0.18	0.07

a: Saturated, monounsaturated, and polyunsaturated fats were mutually adjusted for each other. n–6 Fatty acid was adjusted for saturated and monounsaturated fats and n–3 fatty acid. n–3 Fatty acid was adjusted for saturated and monounsaturated fats and n–6 fatty acid. Eicosapentanoic and docosahexaenoic acids were adjusted for saturated and monounsaturated fats, n–6 fatty acid, and n–3 fatty acid, other than eicosapentanoic and docosahexaenoic acids. Values were adjusted for age, energy, BMI, smoking status, and alcohol intake.

b: Statistical significance is as follows: *, $p < 0.05$.

c: 10 pg/ml was allotted to 14 men with undetectable level (<10 pg/ml).

d: 10 pg/ml was allotted to 11 men with undetectable level (<10 pg/ml).

Correlations of total testosterone with saturated and monounsaturated fats became nearly null after additional adjustment for the other categories of fats (Table 4). Eicosapentanoic and docosahexaenoic acids were still significantly inversely correlated with total testosterone after adjustment for saturated and monounsaturated fats, n–6 fatty acids, and n–3 fatty acids excluding eicosapentanoic and docosahexaenoic acids.

Discussion

We found that intake of eicosapentanoic and docosahexaenoic acids was significantly inversely correlated with total testosterone and that these correlations were not altered after controlling for the other categories of fat. Saturated fat intake was not associated with total testosterone after controlling for the other types of fat. These findings suggest that the association between fat intake and testosterone concentration may be dependent on the type of fat and that the higher intake of n–3 fatty acids from fish may be associated with lower total testosterone concentrations. High intake of n–3 fatty acids has been reported to reduce testosterone synthesis by altering the lipid composition of rat testicular plasma membranes (21). For estrogens, positive correlations were not significant, being identical for saturated and monounsaturated fat and slightly lower for polyunsaturated fat.

Few studies have investigated the relationship between specific types of fat and testosterone concentration. Key and co-workers (22) observed a positive association between polyunsaturated fatty acid and serum testosterone ($r = 0.38$). Dorgan and associates (9) compared the effect of a diet containing different ratios of polyunsaturated to saturated fats (1.3 vs. 0.6) and found 13% higher total testosterone among men consuming a diet with a low polyunsaturated-to-saturated fat ratio. In their study, however, fiber intake greatly differed between the diets.

DHT is believed to be the principal intraprostatic androgen (23). In the present study, the correlations of DHT with the specific types of fat were similar to those of total testosterone, although the correlations were somewhat weaker for DHT. A significantly positive, but not strong, association between DHT and vegetable fat ($r = 0.08$) was observed in the cross-sectional study reported by Field and others (24). Free testosterone, the biologically active form of testosterone, was not significantly correlated with any of the nutrient intakes studied. The correlation of DHT-to-testosterone ratio with n–3 fatty acids from fish was nearly null. Although we used this ratio as an indirect measure of 5α-reductase activity, which converts testosterone to DHT in prostate tissue, androstanediol glucuronide should be a better marker (25). In previous epidemiological studies, neither serum DHT nor DHT-to-testosterone ratio has been associated with a risk of prostate cancer.

The information on diet was obtained three years before the blood samples were collected. In another group of men, we assessed subjects' change in dietary intake over this period by again administering the dietary questionnaire three years after the original was given. The correlation coefficients for the reproducibility of nutrient intakes measured ranged from 0.48 for carbohydrate to 0.92 for animal fat. Those for eicosapentanoic and docosahexaenoic acids were 0.74 and 0.84, respectively. In the present study, change in diet during the three years might not have been great.

Our dietary questionnaire enabled us to estimate the intake of a wide scope of nutrients; therefore, we could take into account the confounding effects of various nutrients and foods. Additional adjustments for carbohydrate, cholesterol, crude fiber, vitamins, and soy products did not substantially alter the results on types of fat and hormone concentrations substantially.

Although we had only a single serum sample, sex steroid levels in men are relatively stable for a long interval (26). Wu and associates (27) studied serum androgens in older Japanese-Americans. They found significant inverse associations of BMI with total testosterone and SHBG, which agrees with our results. Our results concerning nonnutritional factors, such as BMI, smoking, and alcohol intake, are also compatible with the findings reported in previous studies (28–30). Such compatibility seems to support the validity of our data, although the possibility that the nondietary vari-

ables changed little between the time of questionnaire assessment and the time of blood draw may have helped us confirm the results regarding nondietary variables.

Acknowledgments and Notes

This study was supported in part by grants from the Science Promotion Foundation of Gifu University School of Medicine. Address correspondence to Chisato Nagata, Dept. of Public Health, Gifu University School of Medicine, 40 Tsukasa-machi, Gifu 500-8705, Japan. Phone: +81 58 267 2247. FAX: +81 58 265 9020.

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