

TABLE II—THE RISK OF HISTORY OF TRANSFUSION AND LIVER DISEASES FOR THYROID CANCER

	n	Person-years	Thyroid cancer	RR	95% CI	
History of transfusion						
No	29,169	291,920	58	Reference		
Yes	3,504	34,287	12	1.77	0.95	3.30
Unknown	5,310	52,928	9	0.91	0.45	1.84
History of liver disease						
No	31,363	315,766	64	Reference		
Yes	2,257	21,590	6	1.39	0.60	3.21
Unknown	4,363	41,780	9	1.13	0.55	2.30
Transfusion and liver disease						
Neither transfusion nor liver disease	26,088	262,190	50	Reference		
Transfusion and/or liver disease	5,357	52,061	18	1.84	1.07	3.16
Other <sup>1</sup>	6,538	64,885	11	0.95	0.49	1.84

<sup>1</sup>Subjects who did not have a transfusion history and whose history of liver disease was unknown, or subjects who did not have liver disease and whose transfusion history was unknown.

of thyroid cancer compared with those with no history of either. We propose that the combined category of individuals with a history of liver disease and transfusion captured more HCV-positive subjects, even if the sensitivity of HCV detection was relatively low. In addition, an HCV-negative reference group, comprising individuals with a history of neither transfusion nor liver disease, might have been more inclusive than only those with no history of transfusion, as blood transfusion is not the exclusive route of HCV transmission.<sup>22</sup>

A potential limitation of our study is that the participants reported their own blood transfusion history. However, a previous report<sup>26</sup> calculated the sensitivity and specificity of self-reported transfusion histories as 93% and 78%, respectively. In addition, misclassification would tend to weaken any association between a history of transfusion and thyroid cancer; therefore, the actual risk might be greater than that reported here.

This prospective cohort study indirectly supports the association between HCV and thyroid cancer suggested by a recent series of case-control studies in southern Italy. In addition, our results raise a new hypothesis: the association between blood transfusions and thyroid cancer is facilitated by transfusion-associated immunomodulation. Detailed epidemiological studies will be necessary to further examine the interactions between thyroid cancer, HCV and blood transfusion, including immunomodulation effects.

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# Sodium Intake and Risk of Death From Stroke in Japanese Men and Women

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**Background and Purpose**—Despite the evidence for a positive association of dietary salt and blood pressure, the few prospective studies that have assessed the association between dietary salt and stroke have reported inconsistent results. The purpose of this study was to examine the relation between sodium intake and death from stroke in a population-based cohort of Japanese men and women.

**Methods**—In 1992, usual diet including sodium intake was determined in 13 355 men and 15 724 women in Takayama City, Gifu, with the use of a validated food frequency questionnaire.

**Results**—There were 269 stroke deaths (137 men and 132 women) between baseline and 1999. In men, the highest compared with the lowest tertile of sodium intake was significantly positively associated with death from total stroke after controlling for covariates (hazard ratio [HR]), 2.33; 95% CI, 1.23 to 4.45). Significantly positive associations were also observed between sodium intake and death from ischemic stroke (HR, 3.22; 95% CI, 1.22 to 8.53) as well as death from intracerebral hemorrhage (HR, 3.85; 95% CI, 1.16 to 12.7). A positive association between sodium intake and death from stroke in women was suggested, although the associations for total stroke and ischemic stroke were of borderline significance (HR, 1.70; 95% CI, 0.96 to 3.02 and HR, 2.10; 95% CI, 0.96 to 4.62, respectively).

**Conclusions**—These prospective data support the hypothesis that dietary salt increases the risk of death from stroke. (*Stroke*. 2004;35:1543-1547.)

**Key Words:** diet ■ sodium ■ stroke ■ epidemiology

Several epidemiological and clinical studies have demonstrated that a low or reduced intake of salt is associated with lower blood pressure.<sup>1</sup> Because blood pressure is a major contributor to stroke, it would be reasonable to expect that dietary salt could increase the risk of stroke. Etiological studies investigating the relation between salt intake and stroke have generally produced positive associations.<sup>2,3</sup> There has been a suggestion that high salt intake may exert an adverse effect on the risk of stroke independent of blood pressure.<sup>4</sup> However, data from prospective cohort studies on salt intake and stroke are few and the results have been inconsistent.<sup>5-7</sup> To further evaluate the potential effect of salt intake on stroke, we examined the association of sodium intake with death from stroke in a cohort study of Japanese men and women (the Takayama Study).

## Subjects and Methods

The Takayama Study is a population-based cohort study conducted in Takayama City, Gifu, Japan. The methodology of the study design has been described previously.<sup>8</sup> Eligible participants were all the nonhospitalized residents of Takayama, aged 35 years and older. In 1992, 14 427 men and 17 125 women completed a baseline self-administered questionnaire that included questions on demographic characteristics, smoking and drinking habits, diet, exercise, and medical and reproductive histories, yielding a participation rate of

85.3% after excluding incomplete or unreliable responses to the dietary questionnaire (criteria shown in <sup>8</sup>). Dietary history was assessed using a 169-item semiquantitative food frequency questionnaire. For each food, participants were asked to indicate the average frequency with which food was consumed in the previous year and specified the usual serving size. Use of table salt was also asked. Intake of sodium and other foods and nutrients were estimated from frequency of intake and portion size using the *Standard Tables of Food Composition in Japan*, published by the Science and Technology Agency of Japan.<sup>9</sup> The validity of this questionnaire was assessed by comparison with other dietary assessment methods, including 3-day diet record, 4 diet recalls over 1 year, and 12 daily diet records over 1 year. Detailed information on the questionnaire, including validity and reproducibility tests, has been described elsewhere.<sup>10</sup> However, we subsequently revised our method of estimating sodium intake based on the use of seasonings. We included independent items for use of soy sauce, sauce, vinegar, and ketchup in the questionnaire, but the use of these seasonings had been also taken account of when we estimated nutrient intakes from dishes and menus. Therefore, such an overlap was corrected. The validity test results were updated according to the revision of the Japanese food composition data. The Spearman correlation coefficients comparing the estimates of sodium intake between the questionnaire and 12 daily diet records over 1 year were 0.53 in men and 0.54 in women. Corresponding figures for total energy, protein, vitamin E, and potassium were 0.45, 0.47, 0.44, and 0.50, respectively, in men and 0.53, 0.54, 0.36, and 0.67, respectively, in women.

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TABLE 1. Baseline Characteristics of Study Subjects According to Tertile of Sodium Intake

Basic Characteristics	Men				Women			
	Tertile of Sodium Intake*			P	Tertile of Sodium Intake			P
	Low	Middle	High		Low	Middle	High	
Sodium intake, mg/d	4082	5699	7194	<0.001	3970	5180	6478	<0.001
Age, y	51.0	53.2	57.7	<0.001	53.3	54.3	57.8	<0.001
Body mass index, kg/m <sup>2</sup>	22.6	22.5	22.5	0.08	21.9	22.0	22.1	0.003
Alcohol intake, mL/day	50.2	42.1	33.6	<0.001	9.7	7.9	5.6	<0.001
Exercise, METs† h/wk	28.0	27.2	25.9	0.02	18.0	19.7	18.8	0.15
Energy intake, kJ/d	10 703	11 230	10 836	0.41	8954	8954	8753	0.009
Protein intake, g/d	79.3	96.1	104.4	<0.001	73.7	82.3	88.7	<0.001
Vitamin E intake, mg/d	8.4	11.0	13.0	<0.001	8.7	10.7	12.2	<0.001
Potassium intake, mg/d	2756	3507	4217	<0.001	2817	3377	4061	<0.001
Married, %	90.5	92.1	91.8	0.02	75.1	75.9	74.6	0.32
Years of education ≥15 y, %	10.7	11.9	11.9	<0.001	4.6	5.4	4.1	<0.001
Current smokers, %	59.2	55.4	50.4	<0.001	16.0	12.7	10.6	<0.001
Former smokers, %	25.1	28.4	31.2	<0.001	4.6	4.2	4.3	0.35
Hypertension, %	17.6	18.1	21.0	<0.001	15.8	17.0	19.3	<0.001
Diabetes, %	4.6	5.5	7.7	<0.001	2.0	2.5	3.6	<0.001

Values are means (crude) or percentages. P values are for linear trend for continuous variables.

\*Based on energy-adjusted value.

†Metabolic equivalent.

Exercise was assessed by asking the average hours per week spent performing various kinds of activities during the past year. The details are described elsewhere.<sup>11</sup>

Registration of death is required under the Family Registration Law in Japan and is implemented throughout the country. Deaths and their causes occurring in Takayama City during the follow-up period (1992 to 1999) were confirmed with data from National Vital Statistics. The Statistics and Information Department of the Japanese Ministry of Health and Welfare obtains information on deaths and codes the causes of death using the International Classification of Diseases (ICD). The specified endpoint of this study was death from stroke (ICD-9 codes 430 to 448 and ICD-10 codes I60-I69). Stroke was classified as subarachnoid hemorrhage (ICD-9 codes 430 and ICD-10 codes I60 and I69.0), intracerebral hemorrhage (ICD-9 codes 431 and ICD-10 codes I61 and I69.1), ischemic strokes (ICD-9 codes 434 and ICD-10 codes I63 and I69.3), and stroke of undetermined type. Permission to review the data regarding dates and causes of deaths was obtained from the Management and Coordination Agency, Japan. Information concerning subjects who moved away from Takayama City during the course of the study was obtained from the residential registers. During the study period, 666 (4.6%) men and 506 (3.0%) women moved out of Takayama City. This study was approved by the local institutional review board.

For this analysis, we excluded subjects who reported having stroke (255 men and 154 women), ischemic heart disease (636 men and 707 women), or cancer (181 men and 540 women). Hence, the analytic population at baseline consisted of 29 099 (13 355 men and 15 724 women).

The associations of sodium intake with death from stroke were examined using Cox proportional hazard models. For each subject, person-years of follow-up were calculated from the study entry (September 1, 1992) to the date of death from stroke and any other cause, the date on which the person moved out of Takayama City, or the end of the study (December 31, 1999), whichever came first. Intakes of foods and nutrients including sodium were adjusted for total energy after log-transformation by using the residual method proposed by Willett.<sup>12</sup> Energy-adjusted sodium intake were categorized by tertile based on the distribution among the study population at baseline. The hazard ratios (HRs) and their 95% CIs for death from stroke for each category of sodium intake were computed in

comparison with the lowest intake category. Selection of potential confounders was based primarily on priori consideration of their association with both sodium intake and stroke as well as the change in risk estimates before and after adjustment. Variables adjusted for in the multivariate included age, level of education, marital status, body mass index, smoking status, alcohol consumption, histories of diabetes and hypertension, and energy-adjusted intake of protein, potassium, and vitamin E. Additional adjustment for menopausal status, use of aspirin or hormone replacement therapy, and other dietary intakes such as fat, fish oil, soy, dietary fiber, folate, calcium, carotene, vitamins B6, B12, and C, which have been reported to be associated with risk of stroke, did not substantially alter the results; therefore, these variables were not included in the final model. Statistic testing for linear trend was performed on continuous variables using the median value of the categories. All the statistical analyses were performed using SAS programs.<sup>13</sup> Because early symptoms related to stroke could result in change in dietary habits, we repeated the analyses described after excluding deaths from stroke (n=24 in men and n=36 in women) occurring during the first 2 years of follow-up.

## Results

Baseline characteristics of the study population according to levels of sodium intake are given in Table 1. Participants with the highest intake of sodium tended to be older, less likely to be smokers, more likely to consume the nutrients listed, and more likely to have hypertension and diabetes.

A total of 269 cohort members (137 men and 132 women) died from stroke during the 7-year follow-up. These strokes included 43 subarachnoid hemorrhages, 59 intracerebral hemorrhages, and 137 ischemic strokes. Table 2 shows the HRs of total stroke and subtypes of stroke according to sodium intake. In men, sodium intake had a marginally significant positive association with death from total stroke after controlling for nondietary variables. However, after additional adjustment for dietary variables, this association attained

TABLE 2. Hazard Ratios and 95% Confidence Intervals of Mortality From Total Stroke and Subtype According to Sodium Intake

	Men			P Trend	Women			P Trend
	Tertile of Sodium Intake*				Tertile of Sodium Intake			
	Low	Middle	High		Low	Middle	High	
Median intake,* mg/d	4070	5209	6613		3799	4801	5930	
N of person-years	30 670	30 779	29 587		36 719	36 874	36 530	
Total stroke, N of deaths	23	40	74		40	39	53	
HR (95% CI)								
Age- and energy-adjusted	1.00	1.23 (0.74–2.06)	1.45 (0.90–2.33)	0.12	1.00	0.94 (0.61–1.46)	0.94 (0.62–1.42)	0.77
Adjusted for nondietary variables†	1.00	1.33 (0.78–2.19)	1.58 (0.97–2.55)	0.06	1.00	0.99 (0.64–1.55)	1.00 (0.66–1.51)	0.99
Multivariate adjusted‡	1.00	1.60 (0.92–2.80)	2.33 (1.23–4.45)	0.009	1.00	1.33 (0.80–2.21)	1.70 (0.96–3.02)	0.07
Hemorrhagic stroke, N of deaths	13	19	23		16	15	16	
HR (95% CI)								
Age- and energy-adjusted	1.00	1.25 (0.62–2.54)	1.24 (0.62–2.50)	0.57	1.00	0.88 (0.44–1.78)	0.75 (0.37–1.49)	0.41
Adjusted for nondietary variables†	1.00	1.31 (0.65–2.67)	1.32 (0.65–2.69)	0.46	1.00	0.95 (0.47–1.66)	0.82 (0.41–1.66)	0.58
Multivariate adjusted‡	1.00	1.76 (0.79–3.91)	2.27 (0.85–6.02)	0.11	1.00	1.25 (0.56–2.82)	1.28 (0.49–3.37)	0.62
Subarachnoid hemorrhage, N of deaths	5	6	6		9	8	9	
HR (95% CI)								
Age- and energy-adjusted	1.00	1.06 (0.32–3.51)	0.92 (0.27–3.12)	0.88	1.00	0.85 (0.33–2.20)	0.84 (0.33–2.14)	0.72
Adjusted for nondietary variables†	1.00	1.10 (0.34–3.64)	0.94 (0.28–3.20)	0.91	1.00	0.97 (0.37–2.53)	0.95 (0.37–2.44)	0.92
Multivariate-adjusted‡	1.00	1.01 (0.27–3.82)	0.77 (0.14–4.27)	0.76	1.00	1.39 (0.47–4.13)	1.73 (0.48–6.27)	0.40
Intracerebral hemorrhage, N of deaths	8	13	17		7	7	7	
HR (95% CI)								
Age- and energy-adjusted	1.00	1.37 (0.57–3.32)	1.44 (0.61–3.40)	0.43	1.00	0.98 (0.34–2.78)	0.71 (0.25–2.01)	0.51
Adjusted for nondietary variables†	1.00	1.47 (0.61–3.58)	1.59 (0.66–3.83)	0.31	1.00	0.99 (0.34–2.83)	0.71 (0.25–2.03)	0.51
Multivariate-adjusted‡	1.00	2.41 (0.89–6.56)	3.85 (1.16–12.7)	0.03	1.00	1.21 (0.36–4.05)	0.92 (0.22–3.89)	0.89
Ischemic stroke, N of deaths	8	19	43		21	15	31	
HR (95% CI)								
Age- and energy-adjusted	1.00	1.49 (0.65–3.41)	1.86 (0.87–3.99)	0.10	1.00	0.72 (0.37–1.39)	1.06 (0.61–1.84)	0.77
Adjusted for nondietary variables†	1.00	1.67 (0.73–3.83)	2.06 (0.96–4.45)	0.06	1.00	0.76(0.39–1.48)	1.10 (0.63–1.93)	0.68
Multivariate-adjusted‡	1.00	2.07 (0.86–5.00)	3.22 (1.22–8.53)	0.02	1.00	1.09 (0.51–2.32)	2.10 (0.96–4.62)	0.05

\*Adjusted for total energy.

†Adjusted for age, total energy, marital status, years of education, body mass index, smoking status, alcohol intake, exercise, and histories of hypertension and diabetes.

‡Adjusted for age, total energy, marital status, years of education, body mass index, smoking status, alcohol intake, exercise, histories of hypertension and diabetes, and intake of protein, potassium, and vitamin E.

HR indicates hazard ratio; CI, confidence interval.

statistical significance. Sodium intake was also significantly positively associated with intracerebral hemorrhage and ischemic stroke. In the multivariate models, protein intake contributed greatly as a confounder; after controlling for nondietary variable and protein intake, the HRs of total stroke, intracerebral hemorrhage, and ischemic stroke for the highest tertile of sodium intake were 2.26 (95% CI, 1.25 to 4.08), 3.62 (95% CI, 1.21 to 10.8), and 2.80 (95% CI, 1.14 to 6.91), respectively.

In women, the associations of sodium intake with total stroke and ischemic stroke were of borderline significance after controlling for dietary variables. Actually, adjustment for potassium intake had great impacts on HR estimates; after controlling for nondietary variable and potassium intake, the HRs of total stroke and ischemic stroke for the highest tertile

of sodium intake were 1.69 (95% CI, 0.98 to 2.91) and 2.19 (95% CI, 1.04 to 4.61), respectively.

Obese persons are thought to be more sensitive to the effects of sodium on blood pressure than nonobese persons.<sup>14</sup> Reanalyses restricting the subjects to those with a body mass index of  $\geq 23$  revealed that the associations were somewhat strengthened; the HRs of total stroke for the highest tertile of sodium intake were 4.84 (95% CI, 1.10 to 21.3,  $P=0.04$  for trend) in men and 2.26 (95% CI, 0.67 to 7.57,  $P=0.17$  for trend) in women after controlling for the covariates.

We repeated the analyses after excluding the deaths from stroke that occurred during the first 2 years. The results were similar in men (for the highest compared with the lowest tertile of sodium intake, HR, 2.40; 95% CI, 1.16 to 4.94;  $P=0.02$  for trend). In women, somewhat strengthened asso-

ciation of sodium intake with total stroke (HR, 1.98; 95% CI, 1.02 to 3.84,  $P=0.04$  for trend) was observed.

### Discussion

We found a 2.4-fold increased risk of death from stroke associated with high sodium intake in men. In women, the association of sodium intake with stroke mortality was weaker and of marginal significance. Considering that the exclusion of cases during the first 2 years strengthened the HRs in women, the observed weaker association in women may be partially explained by the fact that women were more likely to have reduced sodium intake than men because of early symptoms leading to stroke death. Sodium intake was significantly positively associated with death from 2 major types of stroke, intracerebral hemorrhage and ischemic stroke in men. However, there was no association between sodium intake and intracerebral hemorrhage in women. The discrepancy for our findings between men and women may be caused by the difference in distributions of subtypes of intracerebral hemorrhage and ischemic stroke. Intracerebral hemorrhage and ischemic stroke are heterogeneous stroke types and their etiopathologies are poorly understood.<sup>15</sup> The subtypes of each major type may have different etiologies. Although we could not obtain information concerning subtype, recent brain and vessel imaging techniques have prompted a need for a reevaluation of the standard procedure for defining subtypes of stroke.<sup>16</sup> The small number of cases in the present study also precluded drawing conclusions concerning dietary sodium and type of stroke.

To our knowledge, there have been 3 prospective studies of dietary sodium in relation to the risk of stroke.<sup>5-7</sup> The present study is the first prospective investigation of this topic in the Japanese population living in Japan. The strengths of the present study include the prospective design, use of a general population, relatively low proportion of loss of follow-up, and adjustment for various potential confounders.

A significantly positive association between sodium intake and stroke was reported in overweight adults in the US (relative risk [RR], 2.2 for the highest quintile of sodium-to-energy ratio).<sup>6</sup> However, the remaining 2 studies found no significant positive association. In a cohort of people of Japanese ancestry living in Hawaii, no relation was found between sodium intake and stroke incidence.<sup>5</sup> In a study of Finnish men and women, urinary sodium excretion was significantly positively associated with mortality from cardiovascular disease but not with mortality from stroke (RR=1.3 in men).<sup>7</sup> In another prospective study that examined the relationship of dietary sodium to cardiovascular disease as a whole,<sup>17</sup> dietary sodium intake was significantly inversely associated with mortality from cardiovascular disease in the participants in the National Health and Nutrition Examination Survey.

Most of the subjects in the present study were not obese, but the observed magnitude of association between sodium intake and stroke mortality was similar to that reported in the study among overweight US adults (with a body mass index of  $\geq 27.8$ ). We could not include blood cholesterol level as a covariate, which may have resulted in an overestimation of the risk. However, in our previous study of a subsample from

this cohort,<sup>18</sup> salt intake was not associated with serum cholesterol level. In addition, 2 of the 3 prospective studies on dietary salt and stroke<sup>6,7</sup> showed that adjustments for nondietary risk factors, including blood cholesterol, had little effect on the HRs associated with dietary sodium. (The effect of adjustment was not referred to in the other study.<sup>5</sup>) In our study, adjustments for dietary variables strengthened the association between sodium intake and stroke mortality. The lack of a significant positive association in some of the previous studies<sup>5,7</sup> may be caused by the confounding effects of dietary variables. Still, we cannot eliminate the possibility that sodium intake is a marker for other unmeasured factors related to stroke. It is also possible that a positive association can be detected in a population with a relatively high intake of sodium, such as this Japanese population.

In the present study, adjustment for a history of hypertension did not substantially alter the magnitude of the association between sodium intake and stroke mortality. This result suggests that dietary sodium may be associated with the risk of stroke independently of the effect of hypertension. High salt intake can increase vascular oxidative stress in a rat model, possibly by reducing nitric oxide bioavailability.<sup>19</sup> This oxidative stress may be directly associated with vascular damage leading to stroke. Structural changes of the cerebral arteries or the carotid artery have been reported in spontaneous hypertensive rats with a high-salt diet without any change in blood pressure,<sup>20,21</sup> suggesting the potential deleterious effects of sodium intake excluding blood pressure. Because of the lack of data on blood pressure from each participant, we cannot deny the possibility that the effect of dietary sodium on the risk of stroke is mediated by blood pressure levels. It is also possible that some people on a high-salt diet developed hypertension during the follow-up. However, adjustment for blood pressure did not alter the association between dietary salt and stroke in previous studies.<sup>6,7</sup>

The use of mortality data instead of incidence data is also one of the limitations of the present study. We could not distinguish the effect of dietary sodium on incidence, survival, or both. Although the widespread use of computed tomography scans in Japanese local hospitals since the 1980s has probably made a death certificate data sufficiently accurate for diagnosis of stroke and differentiation of major stroke types,<sup>22</sup> we have no available data concerning the sensitivity and specificity of these diagnoses. However, it is unlikely that misclassification of the diagnoses is dependent on sodium intake.

We did not measure urinary sodium excretion. Urinary sodium is a good marker of short-term, but not long-term, sodium intake.<sup>23</sup> Some previous studies on dietary sodium and stroke or cardiovascular disease included urinary sodium measurements, but none of them repeated 24-hour urine collection.<sup>7,24</sup> The other studies were based on a single 24-hour dietary recall. The food frequency questionnaire, like all methods of dietary assessment, is subject to measurement error. However, in the present study, the questionnaire has been validated in comparison with daily 12 diet records over 1 year and estimates well the dietary intake of sodium.

Our findings provide support for dietary guidelines that advocate the reduction of salt intake for protection from

cardiovascular disease. Given the aforementioned limitations, our results cannot be considered definitive. Nevertheless, our findings do contribute additional significant evidence regarding this important public health issue.

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# Soy, fat and other dietary factors in relation to premenstrual symptoms in Japanese women

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**Objective** To evaluate the relations of intakes of soy, fat and other dietary components to premenstrual symptoms.

**Design** Cross sectional study.

**Setting** Three colleges and two nursing schools.

**Population** One hundred and eighty-nine Japanese women aged 19 to 34 years.

**Methods** Intakes of nutrients and foods, including soy products and isoflavones, were estimated by a semiquantitative food frequency questionnaire. Change in menstrual cycle symptoms were assessed by the Moos Menstrual Distress Questionnaire (MDQ).

**Main outcome measures** Spearman rank correlation of soy and other dietary factors with changes in MDQ scores between the follicular and the premenstrual phases after controlling for age, marital status, exercise, smoking status, age at menarche and number of days of bleeding.

**Results** Neither soy product nor isoflavone intake was significantly associated with change in MDQ score in the premenstrual phase. Intakes of total, saturated and monounsaturated fats were significantly correlated with change in scores for total MDQ and subscale 'pain' in the premenstrual phase after controlling for the covariates. Intake of cereals/potatoes/starches was significantly inversely correlated with a change in total MDQ score in the premenstrual phase.

**Conclusions** High intake of fats and low intake of foods with high concentration of carbohydrate may be associated with premenstrual symptoms.

## INTRODUCTION

Premenstrual syndrome is characterised by a wide variety of symptoms, emotional and physiologic, occurring during the last part of the luteal phase and subsiding after the beginning of the menstrual period.

Dietary modification and physical activity are traditionally the first lines of therapy for premenstrual syndrome. A diet rich in grains, vegetables, fruits, vitamins and minerals has been encouraged. Limited intake of fat, salt and caffeine-containing beverages has been recommended.<sup>1</sup> However, the evidences supporting such recommendations have been equivocal.

The hypothalamic–pituitary–adrenal system and central neurotransmitters have been implicated in premenstrual symptoms,<sup>2</sup> although the underlying mechanism is not clear. Isoflavonic phytoestrogens, which are present in large amounts in soy products, have structural and functional similarity to 17 $\beta$ -estradiol and either mimic or antagonise the actions of oestrogens.<sup>3</sup> Studies have indicated

that isoflavones can affect oestrogen metabolism in premenopausal women.<sup>4,5</sup> Changes in hormone patterns are complicated by a tightly linked hypothalamic–pituitary–ovarian system. Additionally, isoflavones have been suggested to alter adrenocortical function.<sup>6</sup> Consumption of soy may influence premenstrual symptoms. Dietary fat has also been suggested to affect oestrogen metabolism in humans.<sup>7</sup> In the present cross sectional study, we examined the relationship between intakes of soy, fat and other foods and nutrients and the severity of symptoms related to the menstrual cycle in Japanese women.

## METHODS

Between 1998 and 2001, 356 female students at colleges and nursing schools were invited to participate in the study. A total of 315 women aged 18 to 48 agreed to participate and responded to a self-administered questionnaire which asked about menstrual history, demographic characteristics, smoking and drinking habits, diet, exercise and past medical and reproductive histories. The response rate was 88.5%. This study was approved by the institutional review board.

We assessed menstrual cycle symptoms using Magos's modification of the retrospective version of Moos Menstrual Distress questionnaire (MDQ)<sup>8</sup> translated into Japanese.

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The MDQ consists of 47 symptom items across three menstrual cycle phases (during menses, the week before menses and over the remainder of the menstrual cycle). The symptoms were grouped into eight complexes: pain, concentration, behavioural change, autonomic reactions, water retention, negative affect, arousal and non-specific adverse symptoms designed to detect complainers (control). Each symptom was scored from 1 to 6, with 1 being 'no experience of the symptom' and 6 being 'disabling or incapacitating'. Magos *et al.*<sup>9</sup> modified the MDQ by deleting one item 'lowered motor coordination'. Scores were calculated for each symptom group (subscale) and the total MDQ excluding 'arousal' and 'control' for each cycle phase. Each woman reported whether her menstrual cycle was regular or not, and if regular, what her usual menstrual cycle length was. The women also reported their number of births, age at menarche, number of days of bleeding and use of oral contraceptives and steroid hormones.

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.<sup>10</sup>

A previously validated, 169-item semi-quantitative food frequency questionnaire was used to assess diet, including alcohol intake, during the past year.<sup>11</sup> The questionnaire asked participants how often on average they consumed each of the food item listed and what the usual serving size of each item was. 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). These nine items and some other dishes including soy products as ingredients were taken into account to obtain the estimates for total amount (g) of soy products and isoflavone intake. Isoflavone intake (mg/day) from soy products was estimated using isoflavone concentration in these soy foods.<sup>12</sup> The intakes of foods and nutrients were estimated from the frequency of ingestion and portion size using the Japanese Standard Tables of Food Composition, fourth and fifth editions, published by the Science and Technology Agency of Japan.<sup>13</sup> Fatty acid composition was evaluated using data published by Sasaki *et al.*<sup>14</sup> Detailed information on the questionnaire including its validity and reproducibility has been described elsewhere.<sup>11,15</sup> For example, the Spearman correlation coefficient comparing estimates of soy product intake from this questionnaire with the estimates from 12 daily diet records kept over a one year period was 0.68. The corresponding figures for fat and cereals/potatoes/starches were 0.52 and 0.49, respectively.

Complete data for age, diet and MDQ were available on 217 women; we could not assess diet for 40 women because of incomplete or unreliable responses to the dietary questionnaire (criteria shown in Ref. [8]); the total MDQ score was missing for 58 women. Therefore, the ultimate response rate was 61.0%. The percentage of non-respondents to each MDQ question ranged from 3.6% to 7.6%. There were no

significant differences between the women who completed the MDQ and those who did not in terms of age, marital status, parity, age at menarche, exercise, smoking status, regularity of menstrual cycle, usual cycle length and number of days of bleeding.

Women who were aged 40 or over ( $n = 4$ ) and had taken steroid hormones during last six months ( $n = 7$ ) were excluded from the present study. We also limited the analysis to women who reported that her last menstruation was within 35 days before the study. Thus, 189 women were available for analysis. Their age ranged from 19 to 34 years [mean (SD) = 21.0 (2.2)]. None of them were users of oral contraceptives. No one reported a history of endometabolic diseases such as diabetes and thyroid diseases.

For statistical analyses, percentage change in total and subscale scores between the follicular phase and the menstrual and premenstrual phases was calculated. These percentage change scores were computed to assess fluctuations in symptom reporting, allowing for differences in follicular reporting levels, as recommended by Van den Akker *et al.*<sup>16</sup> and Marván and Escobedo.<sup>17</sup> Spearman correlation coefficients were used to examine the associations between dietary variables and change in total or subscale MDQ scores. Adjustment for potential confounders of these associations was accomplished by regressing the MDQ and dietary values separately upon confounders. Spearman correlation coefficients were then calculated. Intakes of soy products and the individual nutrients were log-transformed and adjusted for total energy using the method proposed by Willett.<sup>18</sup> Initially, age-adjusted correlation coefficients between change in MDQ scores and variables in interest were computed. Several non-dietary factors including weight, height, body mass index, smoking, exercise, age at menarche, menstrual cycle, days of bleeding, number of births or pregnancies were examined in relation to total and subscale MDQ scores. Age at menarche, marital status and number of days of bleeding were included in the models for diet and changes in MDQ scores because these variables were significantly or marginally significantly correlated with change in MDQ scores. Smoking and exercise, which were previously reported to be associated with premenstrual symptoms,<sup>19-21</sup> were also included as covariates in the models. All statistical analyses were performed using SAS.

## RESULTS

The mean scores for all subscales except for 'arousal' had statistically significant variations by menstrual phase ( $P < 0.001$ ) (Table 1).

Table 2 shows the correlations between non-dietary factors and change in scores for total MDQ after controlling for age (the correlations for subscales of MDQ were omitted). The correlation between age at menarche and a change in

**Table 1.** Mean MDQ scores according to menstrual cycle phase. Values are expressed as mean (SD).

Scale	Premenstrual	Menstrual	Follicular	F <sup>a</sup>
Pain	10.0 (3.5)	12.8 (4.0)	7.5 (2.1)	121.0 <sup>b</sup>
Concentration	8.9 (3.4)	10.5 (4.3)	7.6 (1.9)	36.5 <sup>b</sup>
Behavioural change	6.9 (3.1)	8.7 (3.8)	5.5 (1.3)	53.9 <sup>b</sup>
Autonomic reactions	4.7 (1.5)	5.7 (2.5)	4.2 (0.9)	36.5 <sup>b</sup>
Water retention	7.1 (2.9)	6.9 (2.6)	4.5 (1.2)	70.5 <sup>b</sup>
Negative affect	11.4 (5.1)	12.4 (4.7)	8.7 (2.1)	398 <sup>b</sup>
Total	49.0 (15.7)	57.0 (17.9)	38.0 (7.8)	81.7 <sup>b</sup>
Arousal	5.6 (1.7)	5.6 (1.7)	5.7 (1.9)	0.24
Control	6.4 (1.5)	5.5 (1.5)	5.2 (0.7)	43.1 <sup>b</sup>

<sup>a</sup> ANOVA for three groups.<sup>b</sup>  $P < 0.001$ .

total MDQ score was significant in the premenstrual phase ( $r = -0.16$ ,  $P = 0.04$ ) and marginally significant in the menstrual phase ( $r = -0.14$ ,  $P = 0.06$ ). Age at menarche was significantly correlated with change in scores for pain ( $r = -0.16$ ,  $P = 0.04$ ) and concentration ( $r = -0.20$ ,  $P = 0.008$ ) in the premenstrual phase and these correlations were also statistically significant in the menstrual phase. Marital status was significantly correlated with a change in score for pain ( $r = -0.15$ ,  $P = 0.04$ ) in the menstrual phase. Number of days of bleeding was marginally significantly correlated with a change in score for pain ( $r = 0.13$ ,  $P = 0.08$ ) in the menstrual phase. Neither smoking nor exercise was significantly correlated with a change in total or any subscale of MDQ in the premenstrual phase.

Soy product as well as soy isoflavone intake was not significantly correlated with a change in total MDQ score in any menstrual phase, after controlling for age, marital status, smoking status, exercise, age at menarche and

**Table 2.** Spearman correlation coefficients between non-dietary variables and change in total MDQ score after controlling for age.

Variables	Mean (SD)	r	
		Premenstrual	Menstrual
BMI (kg/m <sup>2</sup> )	20.5 (2.4)	0.07	-0.08
Age at menarche (years)	12.1 (1.1)	-0.16 <sup>a</sup>	-0.14 <sup>a</sup>
Days of bleeding (days)	5.9 (1.2)	0.02	0.13
Exercise (METs h/week)	27.5 (41.8)	-0.01	-0.11
Married <sup>b</sup> (%)	2.7	-0.03	-0.05
Current smokers <sup>c</sup> (%)	14.3	0.006	0.04
Ex-smokers <sup>c</sup> (%)	3.2	-0.02	0.06
With regular menstrual cycle (%)	75.6	0.04	0.04
Cycle length <sup>d</sup> (days)	29.4 (3.3)	-0.12	-0.09

METs = metabolic equivalents.

<sup>a</sup> Correlation is significant at the 0.05 level.<sup>b</sup> Correlation is based on dummy variable (coded as 0 if not married and 1 if married).<sup>c</sup> Correlation is based on two dummy variables (coded as 0 and 1 if never-smokers, 1 and 0 if current smokers and 0 and 1 if ex-smokers).<sup>d</sup> Limited to women with regular menstrual cycle.**Table 3.** Spearman correlation coefficients between food and nutrient intakes and change in total MDQ score.

Variables	Mean (SD)	Premenstrual		Menstrual	
		r <sub>1</sub> <sup>a</sup>	r <sub>2</sub> <sup>b</sup>	r <sub>1</sub> <sup>a</sup>	r <sub>2</sub> <sup>b</sup>
Total energy (kcal)	2083 (807)	0.08	0.10	0.13	0.19 <sup>c</sup>
Soy product (g)	60.6 (62.4)	-0.02	-0.05	-0.004	-0.04
Soy isoflavone (mg)	26.9 (26.6)	-0.003	-0.04	-0.008	-0.03
Protein (g)	76.9 (35.3)	0.11	0.12	0.004	0.02
Fat (g)	63.4 (29.6)	0.16 <sup>c</sup>	0.17 <sup>c</sup>	0.05	0.04
Saturated fat (g)	19.3 (9.5)	0.15 <sup>c</sup>	0.17 <sup>c</sup>	0.02	0.03
Monounsaturated fat (g)	22.2 (10.5)	0.14 <sup>c</sup>	0.15 <sup>c</sup>	0.02	0.007
Polyunsaturated fat (g)	14.4 (7.1)	0.01	-0.001	-0.06	-0.13
Carbohydrate (g)	288 (102)	-0.12	-0.12	-0.03	0.001
Cholesterol (mg)	397 (190)	0.16 <sup>c</sup>	0.16 <sup>c</sup>	0.10	0.10
Sodium (mg)	4570 (2213)	0.03	0.03	0.01	0.007
Potassium (mg)	2996 (1518)	0.07	0.08	0.002	0.006
Calcium (mg)	747 (473)	0.13	0.14	0.03	0.04
Magnesium (mg)	304 (145)	0.07	0.07	-0.004	0.001
Vitamin B6 (mg)	1.4 (0.6)	0.06	0.08	-0.02	-0.02
Vitamin C (mg)	155 (117)	-0.08	-0.07	-0.07	-0.07
Vitamin E (mg)	10.1 (4.8)	0.07	0.08	0.05	0.04
Cereals/potatoes/starches (g)	286 (93)	-0.15 <sup>c</sup>	-0.16 <sup>c</sup>	-0.07	-0.05
Vegetables (g)	291 (191)	0.04	0.05	-0.04	-0.04
Fruits (g)	160 (150)	-0.10	-0.10	-0.05	-0.07
Seaweeds (g)	14.2 (14.5)	-0.10	-0.12	-0.12	-0.10
Alcohol (mL)	8.2 (32.0)	0.07	0.06	0.09	0.07
Caffeine (mg)	132 (101)	0.09	0.09	0.13	0.14

<sup>a</sup> Adjusted for age and total energy except for total energy.<sup>b</sup> Adjusted for age, total energy, marital status, smoking status, exercise, age at menarche and number of days of bleeding.<sup>c</sup> Correlation is significant at the 0.05 level.

number of days of bleeding (Table 3). Total fat and saturated and monounsaturated fat intakes were significantly correlated with a change in total MDQ score in the premenstrual phase after controlling for the covariates ( $r = 0.17$ ,  $P = 0.03$ ,  $r = 0.17$ ,  $P = 0.02$  and  $r = 0.15$ ,  $P = 0.04$ , respectively). Cholesterol intake was also significantly correlated with a change in total MDQ score in the premenstrual phase ( $r = 0.16$ ,  $P = 0.03$ ). Intake of cereals/potatoes/starches was significantly inversely correlated with a change in total MDQ score in the premenstrual phase ( $r = -0.16$ ,  $P = 0.04$ ). Intakes of total fat, saturated and monounsaturated fats, and cereals/potatoes/starches were still significantly correlated with a change in total MDQ score in the premenstrual phase after additional adjustment for a change in total MDQ score in the menstrual phase ( $r = 0.17$ ,  $P = 0.02$ ,  $r = 0.18$ ,  $P = 0.01$ ,  $r = 0.17$ ,  $P = 0.02$  and  $r = -0.16$ ,  $P = 0.04$ , respectively).

Total fat and saturated and monounsaturated fat intakes were significantly correlated with a change in score for pain in the premenstrual phase ( $r = 0.21$ ,  $P = 0.005$ ,  $r = 0.16$ ,  $P = 0.03$  and  $r = 0.20$ ,  $P = 0.007$ , respectively) (Table 4). Saturated fat intake was also significantly correlated with water retention and negative affect in the premenstrual phase ( $r = 0.16$ ,  $P = 0.04$  and  $r = 0.15$ ,  $P = 0.04$ ,

**Table 4.** Spearman correlation coefficients<sup>a</sup> between selected dietary factors and changes in scores for MDQ subscales in the premenstrual phase.

Variables	P	C	B	Au	W	N	Ar
<b>Fat</b>	0.21 <sup>b</sup>	0.09	0.08	0.06	0.07	0.10	-0.03
Saturated fat	0.16 <sup>c</sup>	0.03	0.01	0.07	0.15 <sup>c</sup>	0.15 <sup>c</sup>	-0.07
Monounsaturated fat	0.20 <sup>b</sup>	0.10	0.07	0.09	0.08	0.06	-0.06
Polyunsaturated fat	0.06	0.04	0.02	-0.001	-0.007	-0.07	0.01
<b>Cereals/potatoes/starches</b>	-0.17 <sup>c</sup>	-0.06	-0.09	-0.07	-0.08	-0.16 <sup>c</sup>	-0.08

P = pain; C = concentration; B = behavioral change; Au = autonomic reactions; W = water retention; N = negative affect; Ar = arousal.

<sup>a</sup> Adjusted for age, total energy, marital status, smoking status, exercise, age at menarche and number of days of bleeding.

<sup>b</sup> Correlation is significant at the 0.01 level.

<sup>c</sup> Correlation is significant at the 0.05 level.

respectively). Intake of cereals/potatoes/starches was significantly inversely correlated with changes in scores for pain and negative affect in the premenstrual phase ( $r = -0.17$ ,  $P = 0.02$  and  $r = -0.16$ ,  $P = 0.03$ , respectively).

Additional adjustments for the scores of 'arousal' and 'control' or change in these scores in any menstrual phase did not alter the results substantially; for example, the correlation coefficients of change in total MDQ score at premenstrual phase with total, saturated and monounsaturated fats and cereals/potatoes/starches were 0.17 ( $P = 0.03$ ), 0.17 ( $P = 0.02$ ), 0.15 ( $P = 0.04$ ) and  $-0.17$  ( $P = 0.03$ ) after controlling for a change in score for arousal in the premenstrual phase. Corresponding figures after controlling for a change in score for control were 0.19 ( $P = 0.01$ ), 0.20 ( $P = 0.009$ ), 0.19 ( $P = 0.01$ ) and  $-0.17$  ( $P = 0.03$ ), respectively.

## DISCUSSION

We found moderate, but significant, positive associations between intake of total and saturated fats and changes in MDQ scores. Studies have shown that a high intake of fat increases blood oestrogen levels in women,<sup>7</sup> suggesting that dietary fat affects the oestrogen status of women. Although there has been no consistent evidence of abnormal circulating levels of gonadal steroids in women with premenstrual symptoms,<sup>2</sup> it is possible that dietary fat may be related to premenstrual symptoms, which could involve modulation by gonadal steroids. As reviewed by Kurzer,<sup>22</sup> a high intake of soy isoflavones has been shown to decrease blood oestrogen levels in premenopausal women. In contrast to the results concerning fat intake, however, there was no significant association between soy or isoflavone intake and changes in MDQ scores. This discrepancy in the results may suggest that the reproductive endocrine factor is not sufficient to trigger premenstrual symptoms. Additional factors may explain the positive associations between intake of total and saturated fats and changes in MDQ scores. Soy intake among the women studied may have been too low to affect the hormonal axis which could lead to change in menstrual cycle symptoms.

To our knowledge, there has been no other cross sectional study on usual diet and premenstrual symptoms in which nutrient intakes were estimated quantitatively. Our results do not contradict those of an intervention study of Barnard *et al.*,<sup>23</sup> who reported that a low-fat vegetarian diet was associated with a short duration of premenstrual symptoms. Jones<sup>24</sup> observed no significant differences in self-reported symptoms measured by MDQ between diets with high and low ratios of polyunsaturated to saturated fatty acids ( $P/S = 1.0$  and  $P/S = 0.3$ , respectively). However, in their study, a low-fat diet (20% of energy from fat) compared with a high-fat diet (40% of energy from fat) decreased symptoms associated with water retention during menses and the premenstrual week. In our study, intake of saturated fatty acid was marginally significantly associated with water retention in the premenstrual phase. There have been no intervention studies on effects of dietary soy on premenstrual symptoms.

Intake of cereals/potatoes/starches was inversely significantly associated with MDQ scores in the premenstrual phase. It has been hypothesised that carbohydrate ingestion affects mood by increasing the availability of tryptophan, a precursor of serotonin, thereby, enhancing the release of serotonin.<sup>25</sup> Carbohydrate-rich beverages have been reported to alleviate PMS symptoms.<sup>26,27</sup> Carbohydrate intake was not significantly associated with a change in total or any subscale of MDQ. Intake of foods with high concentration of carbohydrates may be relevant to premenstrual symptoms.

We used MDQ,<sup>8</sup> one of the most well-cited questionnaires. There are a variety of measurement instruments available, most of which draw on aspects of this well-known retrospective questionnaire. However, retrospective questionnaires have been criticised for providing an inflated estimation of symptom severity and being heavily reliant on participants' memory of past menstrual-related symptoms. Prospective diaries, while less reliant on memory, are demanding for participants and lead to biased samples through nonadherence.<sup>28</sup> Our finding may be explained by the possibility that women who had high intakes of fat or low intakes of cereals/grains/potatoes were more concerned about or exaggerated the changes in symptoms related to

the menstrual cycle. It is also possible that women who had greater changes in menstrual symptoms reported higher than actual fat intake and lower than actual cereals/grains/starches intake. However, considering that the observed association of polyunsaturated fat with change in total MDQ was almost null, it is unlikely that such biases have affected the results substantially. In addition, adjustment for 'control' and 'arousal' did not alter the results substantially.

We used a food frequency questionnaire to assess average long term diet rather than intake on a few specific days. Our food frequency questionnaire is subject to measurement error, like all methods of dietary assessment. However, in the present study, the questionnaire had been validated in comparison with daily 12 diet records over one year. The correlation coefficients between the two dietary assessment methods for soy and fat intakes were comparable to those reported for well-established questionnaires.<sup>29,30</sup> 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 over-estimated because the mean of soy product intake estimated from the questionnaire was 40% higher than that estimated from the 12 daily diet records. The means of estimates for fat and cereals/potatoes/starches were about 4% higher in the validation study.

The score for symptoms related to 'arousal' did not show a cyclic fluctuation in the present study. Similar findings have been reported,<sup>16,31,32</sup> supporting the validity of our study.

We controlled for several potential confounders to assess the association between diet and change in MDQ scores. The confounding effects of age and the other covariates were not great in the present study; crude correlations of change in total MDQ score at premenstrual phase with total fat and cereals/potatoes/starches were  $r = 0.15$ ,  $P = 0.03$ , and  $r = -0.15$ ,  $P = 0.04$ , respectively. However, we cannot deny residual confounding effects. Confounding from unknown factors might exist.

Complete response to the MDQ was unavailable for 18.4% of the women who initially agreed to participate. However, the respondents and non-respondents were similar in the other measured variables. It is unlikely that the relationships between diet and premenstrual symptoms differed between respondents and non-respondents.

Our data suggest that consumption of fats and foods with high concentration of carbohydrate may be associated with premenstrual symptoms. It should be noted that these associations were modest and the clinical significance is yet to be known. Intervention studies might be able to elucidate the effects of dietary fats and carbohydrate on premenstrual symptoms.

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## ORIGINAL COMMUNICATION

# Associations of menstrual pain with intakes of soy, fat and dietary fiber in Japanese women

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**Objective:** Intakes of soy, fat, and dietary fiber may be associated with the symptoms of dysmenorrhea through their biological effects on estrogens or prostaglandin production. The present study was to examine the relationships between intakes of soy, fat, and dietary fiber and the severity of menstrual pain.

**Design:** Cross-sectional study.

**Setting:** Three colleges and two nursing schools.

**Subjects:** A total of 276 Japanese women aged 19–24 y.

**Methods:** Intakes of nutrients and foods including soy products, isoflavones, fats and dietary fiber were estimated by a validated semiquantitative food frequency questionnaire. Severity of menstrual pain was assessed by the multidimensional scoring system reported by Andersch and Milson.

**Results:** Intake of dietary fiber was significantly inversely correlated with the menstrual pain scale ( $r = -0.12$ ,  $P = 0.04$ ) after controlling for age, smoking status, age at menarche and total energy intake. Neither soy nor fat intake was significantly correlated with menstrual pain after controlling for the covariates.

**Conclusions:** The cross-sectional difference in dietary fiber intake across the level of menstrual pain was small in magnitude but warrants further studies.

**Sponsorship:** None.

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Dysmenorrhea, or painful menses, is a common gynecological disorder among women in the reproductive age groups. Several theories regarding the causes of primary dysmenorrhea have been presented over the years (Deligeoroglou, 2000). Since elevated levels of prostaglandins have been found in the endometrium and menstrual fluid of dysmenorrheic women (Pickles *et al*, 1965), abundant evidence linking prostaglandins to dysmenorrhea has been accumulated. Increased prostaglandin production is now the most accepted theory to explain the etiology of primary dysmenorrhea

(Deligeoroglou, 2000). Prostaglandin F<sub>2a</sub> (PGF<sub>2a</sub>) and PGE<sub>2</sub> stimulate uterine contractions and cervical narrowing and increase vasopressin release, leading to ischemia and pain. Isoflavones, the phytoestrogens found mainly in soybeans, inhibit PGE<sub>2</sub> production (Yamaki *et al*, 2001) and cyclooxygenase activity (Liang *et al*, 1999). Isoflavones also can reduce the responsiveness to PGF<sub>2a</sub> of rat uterine muscle (Picherit *et al*, 2000) and inhibit contractions of several types of smooth muscle (Steusloff *et al*, 1995). Dietary soy may have a beneficial effect on symptoms of dysmenorrhea by affecting the cyclooxygenase pathway. Estrogen has been suggested to modify PGE<sub>2</sub> production (Miyagi *et al*, 1993; Pavan *et al*, 2001). A high intake of soy isoflavones has been shown to decrease blood estrogen levels in premenopausal women (Kurzer, 2002). Dietary fat and fiber have been also indicated to alter estrogen status (Rose *et al*, 1997; Wu *et al*, 1999). These dietary components may be associated with symptoms of dysmenorrhea through hormonal influence.

Strom *et al* (2001) reported that infant exposure to soy formula vs cow milk formula was not associated with

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menstrual cramps in young adult women. To our knowledge, no other studies have described the association of soy intake and dysmenorrhea. Epidemiological data on dysmenorrhea and intakes of fat and dietary fiber are also scanty. In the present cross-sectional study, we examined the relationships between intakes of soy, fat, and dietary fiber and the severity of menstrual pain among premenopausal Japanese women.

## Methods

The study subjects were female students at three colleges and two nursing schools between 1998 and 2001. A total of 362 women agreed to participate in the present study and responded to a self-administered questionnaire that asked about menstrual history, demographic characteristics, smoking and drinking habits, diet, exercise, and past medical and reproductive histories. The response rate was 90.0%. The present study was approved by the institutional review board.

The severity of menstrual pain was measured using the verbal multidimensional scoring system reported by Andersch and Milson (1982). This scoring system grades pain as none, mild, moderate, or severe and takes into account the effect of pain on daily activity, systemic symptoms, and analgesic requirements. Each woman was asked to report the date of the beginning of her last menses, the length of her usual menstrual cycle, and the number of days of bleeding. For woman who reported irregular menstrual cycles, we asked the range of the length of cycles and allotted the median as her cycle length.

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 (Suzuki *et al*, 1998).

Diet including soy, fat, and dietary fiber intakes was assessed by a semiquantitative food-frequency questionnaire. 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). These nine items and some other dishes including soy products as ingredients were taken account for to obtain the estimates for total amount (g) of soy products and isoflavone intake. Isoflavone intake (mg/day) from soy products was estimated using isoflavone concentration in these soy foods (Wakai *et al*, 1999). The intakes of foods and nutrients were estimated from the frequency of ingestion and portion size using the Japanese Standard Tables of Food Composition, 4th and 5th editions, published by the Science and Technology Agency of Japan (2001). Fatty acid composition was evaluated using data published by Sasaki *et al* (1999). Detailed information on the questionnaire including its validity and reproducibility has been described elsewhere

(Shimizu, 1996; Shimizu *et al*, 1999; Nagata *et al*, 2001). 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 year period was 0.68. The corresponding figures for total fat and dietary fiber were 0.52 and 0.60.

Because of incomplete or unreliable responses to the dietary questionnaire (criteria shown in the reference by Shimizu, 1996), we did not assess the diets of 44 women. The response to the menstrual pain scale was missing for six women. One woman did not report her age. Therefore, the ultimate response rate was 77.4%. We restricted study subjects to women aged 24 y or less, because the frequency of secondary dysmenorrhea is likely to be higher in the elder women (Wentz, 1988). Therefore, 29 women were excluded. We further excluded women who had been taking steroid hormones during the previous 6 months ( $n=9$ ) or who had a history of thyroid diseases ( $n=1$ ) or other endocrine diseases ( $n=2$ ). No one reported ovariectomy or use of oral contraceptives. The remaining 276 women aged 19–24 y consisted of the present study. Age distribution of the study subjects were 81 (29.3%), 106 (38.4%), 70 (25.4%), 11 (3.9%), and 8 (2.9%) for 19, 20, 21, 22, 23 + y of age, respectively.

Spearman's correlation coefficients were used to examine the associations of severity of menstrual pain with study variables. Dietary values were log-transformed and adjusted for total energy using the method proposed by Willett (1990). Adjustment for potential confounders of the associations between dietary variables and the severity of menstrual pain was accomplished by regressing the menstrual pain scale and dietary values separately upon confounders. Spearman's correlation coefficients were then calculated. Several nondietary factors including weight, height, body mass index, smoking, exercise, marital status, age at menarche, menstrual cycle, days of bleeding, and number of births or pregnancies and intakes of macro- and micro-nutrients were examined as potential confounders. Age was always included in the model as a covariate to calculate the partial correlation coefficients. All statistical analyses were performed using SAS programs (Version 8, SAS Institute, Cary, NC, USA).

## Results

The distribution of menstrual pain scores among the study subjects was 46 (16.7%), 111 (40.2%), 95 (34.4%), and 24 (8.7%) for grades 0–3 (none, mild, moderate, and severe), respectively. Characteristics of subjects according to menstrual pain scale are shown in Table 1. Group comparison for any variable except age at menarche did not reveal a significant association with menstrual pain scale.

Table 2 shows the correlation coefficients between selected nondietary variables and the menstrual pain scale. Age at menarche was significantly inversely correlated with the menstrual pain scale. Smoking status was positively asso-

**Table 1** Characteristics of study subjects according to menstrual pain score

Variables	Score 0	Score 1	Score 2	Score 3	P-value <sup>a</sup>
Age (y)	20.6	20.5	20.7	20.8	0.52
BMI (kg/m <sup>2</sup> )	20.0	20.7	20.0	20.3	0.12
Age at menarche (y)	12.4	12.2	12.0	12.0	0.04
Menstrual cycle length (days)	30.3	31.4	30.3	28.5	0.38
Days of bleeding (days)	5.5	5.7	5.9	6.1	0.25
Exercise (METs h/week)	25.9	20.1	24.0	39.0	0.23
Alcohol (ml/day)	11.0	5.4	4.4	7.3	0.09
Married (%)	0.4	0.4	0.0	0.0	0.56
Current smokers (%)	8.9	8.1	16.8	16.7	0.20
Ex-smokers (%)	0.0	5.4	7.4	4.2	0.28
<i>Daily dietary intakes</i>					
Total energy (kcal)	2056	2090	1934	1870	0.29
Soy products (g)	57.5	60.8	59.2	55.3	0.50
Isoflavones (mg)	25.6	27.7	21.6	24.4	0.20
Dietary fiber (g)	13.9	14.1	12.4	11.5	0.13
Total fat (g)	59.8	63.2	59.2	56.1	0.55
Saturated fat (g)	17.8	19.5	18.3	15.6	0.20
Monounsaturated fat (g)	21.0	22.0	20.6	20.2	0.68
Polyunsaturated fat (g)	13.8	14.1	13.0	14.1	0.61

METs = metabolic equivalents.

<sup>a</sup>For differences between the groups by ANOVA or Fisher's exact test.

**Table 2** Correlations of selected nondietary variables with menstrual pain scale

Variables	Mean (s.d.)	Range	Spearman r	P-value
Age (y)	20.6 (1.0)	19–24	0.05	0.37
BMI (kg/m <sup>2</sup> )	20.3 (2.2)	15.8–33.7	-0.04	0.51
Age at menarche (y)	12.1 (1.1)	9–16	-0.17	0.005
Menstrual cycle length (days)	30.6 (7.6)	10–103	-0.03	0.61
Days of bleeding (days)	5.8 (1.2)	3–11	0.10	0.09
Exercise (METs h /week)	24.0 (41.8)	0–323	-0.03	0.60
Alcohol (ml/day)	6.2 (17.6)	0–201	-0.03	0.57
Married <sup>a</sup> (%)	0.7		-0.09	0.15
Current smokers <sup>b</sup> (%)	12.0		0.11	0.06
Exsmokers <sup>b</sup> (%)	5.1		0.08	0.18

METs = metabolic equivalents.

<sup>a</sup>Correlation is based on dummy variable (coded as 0 if not married and 1 if married).

<sup>b</sup>Correlation is based on two dummy variables (coded as 0 and 0 if never-smokers, 1 and 0 if current smokers and 0 and 1 if exsmokers).

**Table 3** Correlation coefficients between dietary intakes and menstrual pain scale

Variables	Mean (s.d.)	Range	r1 <sup>a</sup>	P-value	r2 <sup>b</sup>	P-value
Total energy (kcal)	2,012 (696)	704–6060	-0.11	0.08	-0.08	0.17
Soy product (g)	55.8 (54.3)	3.1–539	-0.03	0.67	-0.05	0.39
Soy isoflavone (mg)	25.0 (20.6)	1.6–155	-0.06	0.29	-0.08	0.22
Dietary fiber (g)	13.3 (6.5)	3.6–51	-0.13	0.03	-0.12	0.04
Fat (g)	60.6 (26.1)	15.2–208	0.07	0.30	0.08	0.19
Saturated fat (g)	18.5 (8.6)	4.1–56	0.08	0.23	0.11	0.08
Monounsaturated fat (g)	21.2 (9.2)	5.6–78	0.04	0.53	0.06	0.37
Polyunsaturated fat (g)	13.7 (6.1)	3.7–49	0.10	0.10	0.07	0.22

<sup>a</sup>Adjusted for total energy except for total energy.

<sup>b</sup>Adjusted for age, total energy, smoking status, and age at menarche.

ciated with the menstrual pain scale, but this association was of borderline significance ( $P = 0.06$ ).

Dietary fiber was significantly inversely correlated with the menstrual pain scale after controlling for age, smoking status and age at menarche ( $r = -0.12$ ,  $P = 0.04$ ) (Table 3). There were no significant correlations between the menstrual pain scale and intakes of soy product or isoflavone as well as any type of fat. The positive association between saturated fat intake and the menstrual pain scale was of borderline significance ( $P = 0.08$ ). The additional adjustment for marital status and numbers of days of bleeding did not alter the results substantially (for example, the correlation coefficient between dietary fiber and the menstrual pain scale was  $-0.13$ ,  $P = 0.03$ ). Reanalysis restricting the subjects to those who reported a regular menstrual cycle with length of 25–35 days ( $n = 156$ ) did not attenuate the association between dietary fiber intake and the menstrual pain scale ( $r = -0.14$ ,  $P = 0.10$ ).

### Discussion

In spite of the relatively low intake levels of dietary fiber in our study subjects, we found a moderate but significant inverse association between dietary fiber intake and menstrual pain. It is well known that primary dysmenorrhea occurs only in ovulatory cycles (Friederich, 1983), indicating that adequate uterine exposure to estrogen and then to progesterone is necessary. Studies have suggested that fiber intake decreases blood estrogen levels in women (Kaneda et al, 1997; Rose et al, 1997). Although fat intake has been associated with increased estrogen levels (Wu et al, 1999), we failed to find a significant positive association between fat intake and menstrual pain. Neither soy product nor isoflavone intake was associated with menstrual pain. We expected that dietary soy would be inversely associated with menstrual pain through its effects on estrogens or on the cyclooxygenase pathway. However, such effects did not appear to be clinically relevant regarding dysmenorrhea. It is also possible that a limited range of soy intake as well as fat intake among the study subjects may have obscured a real association. Additional findings on smoking and age at



menarche in relation to menstrual pain were consistent with previous results from other studies (Klein & Litt, 1981; Sundell *et al*, 1990; Parazzini *et al*, 1994; Harlow & Park, 1996; Hornsby *et al*, 1998).

So far, to our knowledge, five studies have assessed the relationship between diet and menstrual pain (Deutch, 1995; Harel *et al*, 1996; Di Cintio *et al*, 1997; Balbi *et al*, 2000; Barnard *et al*, 2000). One of them (Harel *et al*, 1996) was based on dietary intervention using supplementation of n-3 fatty acids. In two other studies (Di Cintio *et al*, 1997; Balbi *et al*, 2000), dietary fiber as well as fat intake could not be estimated because the questionnaires used for measuring diet, which were apparently not validated, included a limited number of food items. Barnard *et al* (2000) reported that a low-fat vegetarian diet with a change of total fiber from 26.7 to 31.3 g was associated with an increase in sex hormone-binding globulin levels and with reductions in dysmenorrhea duration and intensity. Their findings are not contradictory with our results. In the remaining study reported by Deutch (1995), diet was measured by a 4-day diet record, and fat and dietary fiber intakes were not significantly associated with menstrual pain after controlling for covariates.

One of the limitations of our study is that we could not perform physical imaging and surgical examinations, such as uterasonography and laparoscopy, to rule out secondary cause of dysmenorrhea. The frequency of secondary dysmenorrhea is much lower than that of primary dysmenorrhea in this age group (Balbi *et al*, 2000). However, we cannot deny the possibility that our findings from a study with a small number of subjects were due to the inclusion of secondary dysmenorrhea.

The lack of endocrinologic measures of ovarian activity was another limitation of the present study. Women with anovulatory cycles do not experience menstrual pain. We could not determine whether each woman was ovulatory or not. Thus, there might be a concern that dietary fiber intake may be associated with anovulation rather than menstrual pain. However, when we reanalyzed data restricted to subjects with normal cycle lengths of 25–35 days, whom we thought to be ovulatory (Harlow & Ephross, 1995), the association between dietary fiber and the menstrual pain scale was not altered.

We employed a widely used scaling system to assess menstrual pain. However, pain is difficult to measure because it cannot be confirmed by any instrumental or clinical evaluation. Therefore, measurement error may have affected the results. However, it seems unlikely that women who had a lower intake of dietary fiber reported their pain more inaccurately or perceived more pain than those with a higher intake of dietary fiber. The food-frequency questionnaire, like all methods of dietary assessment, is subject to measurement error. 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 overestimated because soy product intake estimated from the questionnaire was 40%

higher than that estimated from the 12 daily diet records. The estimate for dietary fiber was 8% higher than that from the diet records. However, again, it is likely that this measurement error was unrelated to menstrual pain and led to an underestimation of the true associations.

Owing to the cross-sectional study design, we can only infer associations. Neuroendocrine functions of the body, mental attitude, and food choice may be mutually related. It is possible that the decreased intake of dietary fiber might be a consequence of menstrual pain. However, if this is true, intakes of other nutrients should also have been affected. None of the other measured nutrients or food groups was associated with the menstrual pain scale. Although the cross-sectional differences in dietary fiber intake across the level of menstrual pain was small in magnitude, more attention should be paid to the role of diet, including soy, fat, and dietary fiber, in the etiology of dysmenorrhea cases that are amenable to public health intervention.

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