(Hamburg, Germany). The sensitivity and the intra-assay and interassay coefficients of variation were 1.7 ng/mL, 9.8%, and 15.3%, respectively. The value of assay sensitivity was assigned for a woman (n = 1) who had an undetectable level. To adjust for variation in the diluteness of urine, urinary aMT6-s levels were expressed as urine aMT6-s/urine creatinine.

We excluded 31 women from analyses because of incomplete or unreliable responses to the dietary questionnaire (criteria shown in ref. 7). Women who reported having cancer (n = 6) or heart disease (n = 10) were excluded. As exogenous estrogen may suppress melatonin level (9), women using hormone replacement therapy (n = 6) or contraceptive pills (n = 1) were excluded from the study. Because it was not possible to obtain information on the use of diuretics and β-blockers, which can affect urinary aMT6-s levels (10), we further excluded 55 women with the diagnosis of hypertension. The urine samples from 34 women were insufficient for the measurement. Hence, the remaining 289 women were the focus of this report.

Urinary aMT6-s level was transformed into logarithmic values for statistical analysis. Intakes of vegetables and other foods and nutrients were adjusted for total energy after log transformation by using the residual method proposed by Willett (11). The relationship between vegetable intake and urinary aMT6-s level was assessed by linear regression models. Geometric means of urinary aMT6-s levels according to the quartile of vegetable intake were provided using analysis of covariance models. Potential confounders, such as age, body mass index, alcohol intake, menopausal status, and day length (the number of hours of daylight between dawn and dusk), of the day before urine collection were included into models as covariates.

Results

The characteristics of the study subjects were shown in Table 1.

Table 2 shows the geometric means of urinary aMT6-s according to the quartile of vegetable intake. The mean urinary aMT6-s was 15.9% higher in women with the highest quartile of vegetable intake than it was in those with the lowest quartile of intake after controlling for age, total energy, body mass index, smoking status, alcohol intake, menopausal status, and day length. There was a significant trend between urinary aMT6-s and intake of vegetables after controlling for the covariates. A similar tendency was observed for the association of aMT6-s with green and yellow vegetables as well as other vegetables, although the association with other vegetables was of borderline significance.

Table 1. Basic characteristics of 289 women

Variables	
Age (y)	48.1 (8.7)
Body mass index (kg/m^2)	22.8 (2.8)
Alcohol intake (mL/d)	5.4 (13.4)
Dietary intake	
Total energy (kcal/d)	2,252 (782)
Vegetables (g/d)	440 (315)
Green and yellow vegetables (g/d)	162 (151)
Other vegetables (g/d)	279 (180)
Fruits (g/d)	138 (116)
Total protein (g/d)	90.3 (34.8)
Total fat (g/d)	64.5 (27.5)
Carbohydrate (g/d)	318 (110)
Current smokers (%)	2.1
Ex-smokers (%)	7.7
Postmenopausal (%)	39.8
Family history of breast cancer* (%)	3.5

Values are means (SD) or percentage.
*Among first-degree relatives.

Table 2. Geometric means of urinary aMT6-s according to quartile of vegetable intake

Quartile (g)	Median (g)	Urinary aMT6-s (ng/mg creatinine)	
		Age and energy-adjusted	Adjusted*
Vegetables (total)			
Q1 (<272)	223	31.1 (26.7-36.3)	32.1 (28.0-36.8)
Q2 (272-367)	319	31.9 (27.4-37.2)	32.4 (28.3-37.1)
Q3 (368-498)	414	34.2 (29.4-40.0)	34.8 (30.4-39.9)
Q4 (>498)	593	38.8 (33.2-45.4)	37.2 (32.3-42.7)
P_{trend}†		0.02	0.04
Green and yellow vegetables			
Q1 (<83)	68	32.2 (27.6-37.6)	32.7 (28.5-37.6)
Q2 (83-20)	101	30.7 (26.4-35.8)	32.7 (28.5-37.4)
Q3 (120-184)	154	34.1 (29.2-39.7)	32.9 (28.7-37.6)
Q4 (>184)	232	39.1 (33.4-45.7)	38.3 (33.3-44.0)
P_{trend}		0.01	0.04
Other vegetables			
Q1 (<178)	147	29.5 (25.3-34.3)	30.6 (26.7-35.0)
Q2 (178-231)	207	34.6 (30.0-40.3)	34.7 (30.3-39.8)
Q3 (232-313)	271	37.5 (32.2-43.7)	35.9 (31.3-41.2)
Q4 (>313)	374	34.5 (29.6-40.2)	35.2 (30.7-40.4)
P_{trend}		0.06	0.07

*Adjusted for age, total energy, body mass index, alcohol intake, menopausal status, and the day length of the day before urine collection.
†The values for trend were from linear regression models.

Table 3 shows the association of fruit intake with urinary aMT6-s. Fruit intake was positively associated with urinary aMT6-s but this association was not statistically significant. There was no significant association of urinary aMT6 with total energy and other food groups and nutrients, such as grains, potatoes, meats, fishes, dairy foods, protein, fat, and carbohydrate. Carotene, dietary fiber, and vitamins, which are abundant in vegetables, were marginally significantly associated with urinary aMT6-s (data not shown).

As exposure to light at night may affect the urinary aMT6-s levels (12), an additional survey was conducted 3 years after to obtain information on sleeping habits around the time when the urine sampling had been conducted. Out of the 289 women, 204 responded to the second survey. Further adjustment for the frequency of being awake around 1:00 and 2:00 a.m. (the approximate time of the melatonin peak) did not substantially alter the results; the mean urinary aMT6-s was 20.7% higher in women with the highest quartile of vegetable intake than it was in those with the lowest quartile of intake after controlling for the covariates (P_{trend} = 0.05).

When we analyzed data separately for premenopausal and postmenopausal women, the association of vegetable intake with urinary aMT6-s level was weak in postmenopausal women; mean aMT6-s levels in the lowest and the highest quartiles of vegetable intake was 32.8 and 37.3 ng/mg creatinine, respectively, in postmenopausal women. The corresponding values for premenopausal women were 31.9 and 41.0 ng/mg creatinine, respectively.

Table 3. Geometric means of urinary aMT6-s according to quartile of fruit intake

Quartile (g)	Median (g)	Urinary aMT6-s (ng/mg creatinine)	
		Age and energy-adjusted	Adjusted*
Fruits			
Q1 (<69)	47	30.3 (26.0-35.3)	31.9 (27.8-36.6)
Q2 (69-107)	88	33.1 (28.4-38.6)	35.0 (30.6-40.1)
Q3 (108-157)	127	33.2 (28.5-38.7)	31.8 (27.7-36.4)
Q4 (>157)	228	39.6 (33.9-46.2)	37.8 (33.0-43.3)
P_{trend}†		0.04	0.11

*Adjusted for age, total energy, body mass index, alcohol intake, menopausal status, and day length.
†The values for trend were from linear regression models.

Discussion

To our knowledge, this is the first report on vegetable intake and melatonin levels in humans. Vegetable intake was moderately but significantly associated with urinary aMT6-s level. We speculate that this association may be explained by the melatonin contained in vegetables. Hattori et al. (3) reported that feeding chicks a diet containing plant products rich in melatonin increased blood melatonin levels.

Urinary specimens were not collected over a long period (12 or 24 hours). However, the validity of the use of the first-void morning urine has been previously reported. Urinary aMT6-s level in morning urine is strongly correlated with total nocturnal plasma melatonin output and peal nocturnal melatonin value (13). Sufficient reproducibility of measurement of aMT6-s in morning urine over 5 years (intraclass correlation coefficient = 0.58; ref. 14) has been also reported.

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 vegetables may have been overestimated because vegetable intake estimated from the questionnaire was 46% higher than that estimated from the 12 daily diet records. Our questionnaire included 13 items for specific vegetables, such as tomato, pumpkin, spinach, Japanese radish, cabbage, carrot, etc. Besides these food items, we took into account some dishes that include vegetables as ingredients, which may have yielded higher intake compared with the diet records. However, it is likely that this measurement error was unrelated to urinary aMT6-s levels and led to an underestimation of the true associations.

As data for melatonin concentration are available only for a few plants, it is not possible to estimate the dietary melatonin intake from vegetables or from the entire diet. Hattori et al. (3) measured the melatonin concentrations in plants commonly consumed as vegetables among the Japanese. In their study, melatonin concentrations ranged from 24.6 pg/g tissue for cucumber to 657.2 pg/g tissue for white radish sprouts. Serum melatonin levels in normal humans are very low during most of the day but increase significantly to a mean of 80 pg/mL (range, 0-200) between 2:00 and 4:00 a.m., and remain elevated during the normal hours of sleep, falling sharply to daytime values around 9:00 a.m. (15). Even 10 μg of melatonin infusion raises serum melatonin concentration ~40 times more at 5 minutes after administration (from 12 ± 5 to 487 ± 377 pg/mL; ref. 16). However, consumption of 400 g of white radish sprouts should provide only 0.3 μg of melatonin. We cannot rule out the possibility that melatonin in vegetables may not be sufficient to affect blood melatonin or urinary aMT6-s levels. In such a case, vegetable intake may be merely a correlate of certain factors, which are associated with urinary aMT6-s.

Cagnacci et al. (17) suggested that the effects of melatonin on some biological functions, such as hypothermic response, are reduced in aged women, which may partially explain the observed weak association of urinary aMT6-s with vegetable intake in postmenopausal women.

Thus far, melatonin has been identified in some grains, nuts, and fruits, but we did not observe significant associations of urinary aMT6-s with intakes of these food groups. In these food groups, the number of foods that contain melatonin may be very limited or the concentration of melatonin may vary greatly in different foods belonging to the same food group. Folate deficiency decreases melatonin secretion in rats (18). Although folate intake itself was nonsignificantly associated with urinary aMT6-s levels (P = 0.10), it is possible that the association of vegetable intake with urinary aMT6-s may be attributable to melatonin together with folate in vegetables. Fruits are also rich in folate. Like vegetables, high intake of fruits has been associated with reduced risks of cancer and cardiovascular disease (1). Our data did not deny the possibility that melatonin contained in fruits may be implicated in these associations.

Clearly, more extensive studies to determine the melatonin concentrations in a wider variety of vegetables, as well as other foods, will be necessary before our results are thoroughly understood. In addition, evidences for the beneficial effects of melatonin on cancer and other diseases is mainly based on laboratory data and must be confirmed in epidemiologic studies. Nonetheless, our findings might stimulate studies investigating the role of dietary melatonin in health.

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Short Communication

Leanness, Smoking, and Enhanced Oxidative DNA Damage

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Abstract

An increased risk of some forms of cancer, including lung cancer, among lean individuals has been consistent; however, there is a paucity of biological evidence supporting this relation. Subjects analyzed were 177 healthy Japanese workers who participated in a lifestyle intervention study. The levels of urinary 8-hydroxydeoxyguanosine (8-OHdG), a marker of oxidative DNA damage, were measured using an automated high-pressure liquid chromatography and urinary creatinine levels were adjusted for before statistical analysis. A clear inverse association was found between body mass index (BMI) and 8-OHdG levels among smokers [Pearson correlation coefficient (r) = −0.48], and the association did not materially change after adjustment for potential confounding factors. In contrast, no apparent relation was observed between BMI and 8-OHdG levels among nonsmokers (r = −0.12), although lean nonsmokers had a slightly higher mean of 8-OHdG levels compared with nonlean nonsmokers. The interaction of smoking and BMI reached statistical significance (P = 0.04). Leanness may enhance oxidative DNA damage induced by smoking and thus serve as a marker of host susceptibility to smoking-related cancers. (Cancer Epidemiol Biomarkers Prev 2006;15(3):582–5)

Introduction

Obesity has been admitted as a risk factor of cancer (1); however, little attention has been paid to the role of leanness in carcinogenesis. Epidemiologic studies have shown an inverse association between body mass index (BMI) and total cancer risk (2) or the risk of several cancer forms, including cancer of the lungs (3) and esophagus (4). Several studies (2-4) reported a stronger association among smokers than among nonsmokers. Leanness is thus hypothesized to represent a host susceptibility to these smoking-related cancers. However, controversy continues regarding causal role of leanness in carcinogenesis due to a potential bias in epidemiologic studies (5). For instance, the effect of preclinical cancer on weight loss cannot be completely ruled out. Moreover, because smoking is related to lower BMI levels (6), the inverse association between BMI and cancer risk may merely reflect smoking-induced weight loss.

Oxidative DNA stress is thought to play a major role in carcinogenesis (7), and increased levels of 8-hydroxydeoxyguanosine (8-OHdG), a reliable marker of oxidative DNA damage, have been detected in urine of smokers (8, 9) or in lung cancer tissue (10). However, the association between BMI and urinary 8-OHdG levels has been inconsistent; two studies (8, 9) reported an inverse association, whereas others (11, 12) failed to detect such association. Moreover, there is limited evidence suggesting a modifying effect of smoking on BMI and 8-OHdG levels (8). We therefore investigated whether leanness modulates the relation of smoking to oxidative DNA damage among healthy working employees, using an automated high-pressure liquid chromatography (HPLC; ref. 13).

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Materials and Methods

Data were obtained from the baseline survey of a worksite lifestyle intervention study, in which 179 volunteers ages 28 to 57 years of a Japanese city office participated. A written informed consent was obtained. The study protocol has been approved by the ethics committee of Kyushu University.

Health-related lifestyles were ascertained using a detailed questionnaire. Ever smokers were defined as those who smoked 100 cigarettes or more in their lifetime. Current smokers consuming cigarettes on a daily basis were asked about cigarette consumption a day, whereas current smokers consuming less than daily basis were defined as occasional smokers. Regular alcohol drinkers were defined as those who consumed alcohol beverage on a weekly basis over the recent 1-month period, and they were asked about the frequency and quantity per occasion of consumption for each type of five alcohol beverages—shochu, beer, sake, wine, and whisky/liquor. Those who engaged in any leisure-time physical activities during the past month were asked about the names, frequencies, and minutes or hours engaged per occasion of each activity.

Casual urine samples, collected mostly between 5 to 6 p.m. before super, were kept in tubes stored in a cooler box overnight and then frozen at −80°C until analysis. Urinary samples were analyzed for 8-OHdG using an automated HPLC system composed of two columns and an electrochemical detector (13). In short, the urinary 8-OHdG level was determined using an apparatus in which the pump 1 (Shiseido Nanospace SI-2), the sampling injector (Gilson 231XL), the guard column for the HPLC-1 (valve 1, pump 3), the HPLC-1 column, the UV detector (Toso UV-8020, microcell), the HPLC-2 column (valve 2, loop, pump 2), and the EC detector (ESA Coulochem 2) were connected. Urine samples were defrosted and 50 μL of each was mixed with the same volume of a dilution solution containing the ribonucleoside marker 8-hydroxyguanosine (120 μg/mL) and 4% acetonitrile in a solution of 130 mmol/L sodium acetate (pH 4.5) and 0.6 mmol/L H_2SO_4. The urine solutions were centrifuged at 13,000 rpm for 5 minutes. A 20 μL aliquot of each supernatant was injected into the first HPLC (MCI

GEL CA08F, 7 μm, 1.5 × 150 mm, 2% acetonitrile in 0.3 mmol/L sulfuric acid, 37 μL/min) from the sampling injector, via the guard column, and the chromatogram was recorded by the UV detector (254 nm). A aliquot of the fraction containing 8-OHdG was automatically injected into the second HPLC column [Shiseido, Capcell Park C18, 5 μm, 4.6 × 250 mm, 10 mmol/L sodium phosphate buffer (pH 6.7), 5% methanol, plus an antiseptic Reagent MB (100 μL/L), 1 mL/min]. Finally, the 8-OHdG was detected by an EC detector with a guard cell (5020) and an analytic cell (5011). The accuracy of the measurement, estimated from the recovery of an added 8-OHdG standard, was 90% to 98%. When the same urine sample was analyzed thrice, the variation of the data was within 7%. Urinary creatinine levels of the same urine sample were simultaneously measured by using anion exchange chromatography in the HPLC-1 step.

8-OHdG levels were adjusted for urinary creatinine levels and then log-transformed before analysis. Subjects were divided into either nonsmokers, including past smokers, or current smokers, including occasional smokers. Weight was measured in a light cloth and information about height was obtained from record of the latest checkup. BMI was calculated as body weight in kilograms divided by the square of height in meters. Ethanol consumption was estimated by multiplying the frequency of consumption and amount consumed per occasion for each of five alcohol beverages and summed. Intensity of each leisure-time physical activity was determined in terms of metabolic equivalent (MET) according to the literature (14). MET hours per week for a specific activity was calculated by multiplying weekly hours spent in that activity and the corresponding intensity, and weekly MET hours of total activity was estimated by summing the MET hours for each type of activity. The association between BMI and 8-OHdG levels was assessed by Pearson correlation coefficient (r). Multiple regression and analysis of covariance were used to estimate regression coefficients and means, respectively, while adjusting for sex, age (continuous), alcohol consumption (<3.0, 3.0-22.9, or ≥23.0 g/d), and physical activities (<1.0, 1.0-9.9, or ≥10.0 MET-h/wk). Effect modification was tested by adding a cross-product term of smoking status and BMI (continuous) in the model. Preliminary analysis indicated that data for two smokers who had extremely high BMI (over the mean value plus 3 SD) were outliers, and thus these were excluded. All statistical tests were two-tailed and were considered to be statistically significant at the 0.05 level. All analyses were done with SAS (15).

Results

Characteristics of the study subjects were shown in Table 1. Of 177 subjects, 38 (21%) were female and 49 (28%) were current smokers. Only three women were current smokers, and they were all occasional smokers. Among men, means of BMI were 24.7 and 24.3 kg/m^2 for smokers and nonsmokers, respectively. BMI was not significantly associated with the number of cigarette consumption among daily smokers (r = 0.11).

The levels of 8-OHdG ranged from 1.2 to 11.4 μg/g creatinine, with median of 3.9 μg/g creatinine. The geometric means of 8-OHdG levels were 3.70, 4.50, and 4.52 μg/g creatinine for nonsmokers, occasional smokers, and daily smokers, respectively. A weak positive association was observed among daily smokers between the number of cigarette smoked a day and 8-OHdG levels (r = 0.21). Among nonsmokers, geometric means of 8-OHdG levels were 3.68 and 3.74 μg/g creatinine for men and women, respectively.

As shown in Fig. 1, a clear inverse association emerged among 49 current smokers (r = −0.48; P = 0.0004). Adjustment for daily cigarette consumption, with 0.5 assigned to occasional smokers, slightly strengthened the association (partial r = −0.51), whereas analysis excluding occasional smokers somewhat attenuated the association (r = −0.41). Regression coefficient of log-transformed 8-OHdG on BMI (−0.069 μg/g creatinine per unit BMI) did not materially change after adjustment for age, sex, alcohol consumption, and physical activities (−0.070 μg/g creatinine per unit BMI). In contrast, 8-OHdG levels did not apparently correlate with BMI among 128 nonsmokers (r = −0.12; P = 0.18), although a marginally significant inverse correlation was observed among nonsmoking men (r = −0.19; P = 0.06).

Table 1. Characteristics of study subjects by gender

	Men (n = 139)	Women (n = 38)
Age (y)	42 (7)	39 (8)
Current smokers (%)	33	8
Occasional smokers among current smokers (%)	13	100
No. cigarettes smoked a day among daily smokers	19 (10)	—
Past smokers among nonsmokers (%)	40	3
Height (cm)	171 (5)	159 (5)
Weight (kg)	71 (9)	54 (7)
Body mass index (kg/m^2)	24.4 (2.8)	21.5 (2.4)

NOTE: Values were mean and standard deviation (in parenthesis) unless otherwise stated.

Subjects were divided into six groups by smoking status and BMI category (tertiles of BMI among smokers: <23.1, 23.1-25.1, and ≥25.2 kg/m^2). Multivariate adjusted mean of 8-OHdG levels was statistically significantly higher among smokers than among nonsmokers in the lowest tertile of BMI (geometric mean: 5.22 μg/g creatinine for smokers versus 4.03 μg/g creatinine for nonsmokers; P = 0.03), whereas 8-OHdG levels did not materially differ according to smoking status in the highest tertile of BMI (geometric mean: 3.56 μg/g creatinine for smokers versus 3.56 for nonsmokers μg/g creatinine; P = 0.90). Among nonsmokers, mean of 8-OHdG levels in the lowest tertile of BMI was slightly higher than those in upper categories of BMI (geometric mean: 4.03, 3.47, and 3.50 μg/g creatinine for the lowest, medium, and highest tertile, respectively). The interaction of smoking and BMI (continuous) reached statistical significance ($P_{interaction}$ = 0.04).

Discussion

The source of urinary 8-OHdG may be the hydrolysis of 8-OH-dGTP by the nucleotide sanitization enzyme MTH1, the mucleotide excision repair of DNA, and the apoptosis of oxidatively damaged cells (16, 17). Urinary excretion of 8-OHdG is a useful biomarker reflecting general average risk of a promutagenic oxidative adduct in DNA, and thus carcinogenesis of all tissues and organs (16). Using an automated HPLC method, we investigated the association of smoking, BMI, and levels of urinary 8-OHdG among a healthy working population and found a clear inverse association between BMI and urinary 8-OHdG levels among smokers.

Most HPLC methods developed thus far have not been suitable for the analysis of 8-OHdG in epidemiologic studies because of complicated manual procedures involved (reviewed in ref. 13). ELISA method is simple and cost-efficient, but it produced two to four times higher values compared with those obtained using HPLC, probably due to cross-reactions to substances having similar structure to 8-OHdG (18). The method we used is able to analyze large samples with reasonable reproducibility (13). In addition, the urinary 8-OHdG level was unchanged, even when urine samples were kept at room temperature for 24 hours (9).

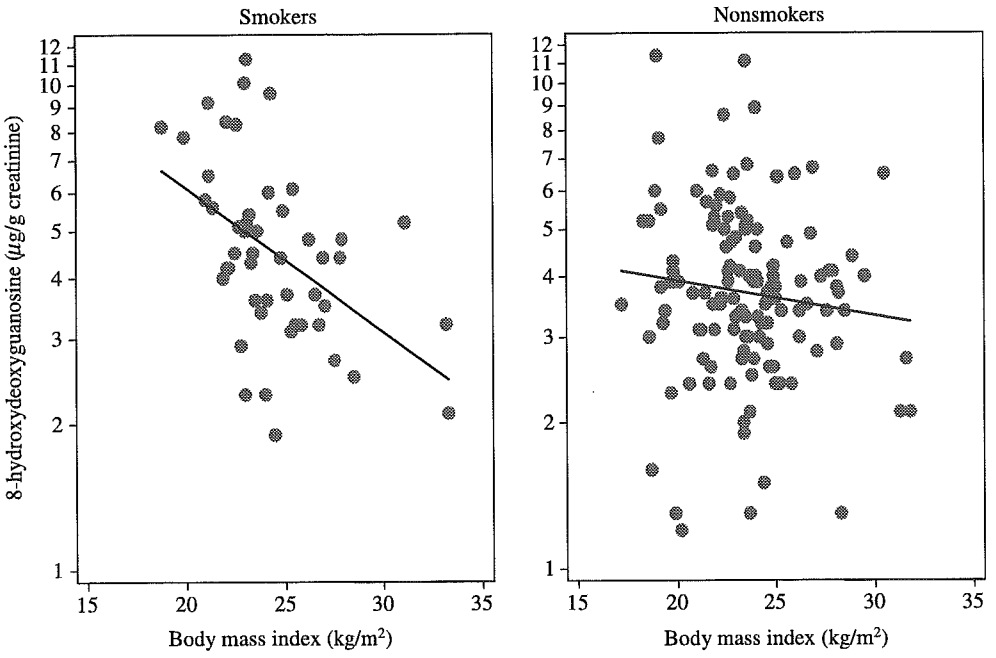

Figure 1. Body mass index and urinary 8-OHdG levels by smoking status.

Of two studies showing an inverse association between BMI and urinary 8-OHdG levels (8, 9), Loft et al. (8) found that the association among smokers was stronger than that among nonsmokers, a finding consistent with ours. The finding suggests that leanness is related to increased oxidative DNA damage, especially among smokers. Furthermore, a pilot investigation among smokers (19) showed that leanness was associated with high DNA adducts levels, an indication for the net outcome of carcinogen exposure, bioactivation, and DNA repair. Findings from these biomarker studies indicate that leanness-cancer association found in numerous epidemiologic studies (2-4) is biologically plausible, not a mere confounding effect.

The mechanism by which leanness enhances smoking-related oxidative DNA stress is not clear. Lean individuals may have low levels of antioxidants due to insufficient nutritional status. However, increased levels of 8-OHdG were not confined to subjects with very low BMI, but 8-OHdG levels constantly decreased as BMI increased up to BMI of 28 kg/m^2 among smokers (Fig. 1). Therefore, nutritional deficiency is not a plausible explanation. The mechanism of oxidative stress from tobacco smoking may involve not only the presence of ROS and ROS-generating compound in the smoke but also an increased metabolic rate with an increase in mitochondrial production of ROC in the cells (16). Thus, leanness may be related to either or both of these ROC-producing pathways, leading to an enhancement of smoking-induced oxidative stress. A lack of an apparent association between BMI and 8-OHdG levels among nonsmokers suggests that leanness itself may not have significant effect on oxidative DNA damage in the absence of carcinogens. However, because 8-OHdG levels among lean nonsmokers were slightly elevated compared with those among nonlean nonsmokers, we do not deny the possibility that leanness enhances oxidative DNA damage among nonsmokers.

We should discuss methodologic issues. First, the sample size was not large and the majority of smokers were male. However, a study including greater number of smoking women (8) exhibited result similar to ours, indicating the consistency of our finding. Second, there is a concern about the use of creatinine-adjusted 8-OHdG levels in assessing their relation to BMI, because creatinine levels reflect muscle mass and may vary according to sex and age. However, the present study did not include elderly persons and analysis including only men showed similar results. We thus believe that the effect of bias associated with the creatinine adjustment is minimal. Third, because smoking influences body weight (6), whether the magnitude of weight change after smoking initiation or cessation, irrespective of the initial BMI, determines 8-OHdG levels needs to be clarified in a longitudinal study.

In conclusion, the present result of increased 8-OHdG levels among lean smokers provides mechanistic insight into epidemiologic finding of an increased risk of smoking-related cancers associated with low BMI. Leanness may represent decreased biological functions against oxidative DNA stress induced by smoking and thus could be used as a marker of host susceptibility to smoking-related cancer. Because smoking cessation leads to a substantial decline of 8-OHdG levels (20), it is expected that lean smokers may have large health benefit from smoking cessation. It remains uncertain, however, whether leanness itself or factor related to leanness modulates the carcinogenic effect of smoking, and this point deserves further investigations, including a search for genetic profiles regarding metabolism of tobacco smoke or repair of DNA damage.

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Dietary Patterns and Colorectal Adenomas in Japanese Men

The Self-Defense Forces Health Study

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The role of dietary patterns in colorectal carcinogenesis remains unclear in Asian populations. Using 1999–2002 data, the authors investigated the association between dietary patterns and colorectal adenomas in 1,341 Japanese men who underwent total colonoscopy. Information about diet was obtained using a 74-item food frequency questionnaire prior to the colonoscopy. Three dietary patterns were generated by factor analysis: 1) a high-dairy, high-fruit and -vegetable, high-starch, low-alcohol pattern; 2) an "animal food" pattern; and 3) a Japanese pattern. Logistic regression analysis was used to estimate the odds ratio of having colorectal adenomas with the adjustment for potential confounding variables including body mass index, smoking, alcohol, and leisure-time physical activities. A significant inverse association was found for the high-dairy, high-fruit and -vegetable, high-starch, low-alcohol pattern; the odds ratios for the second, third, and fourth quartiles were 0.97 (95% confidence interval: 0.70, 1.36), 0.71 (95% confidence interval: 0.50, 1.01), and 0.62 (95% confidence interval: 0.43, 0.90), respectively, compared with the lowest (p_{trend} = 0.003). Similar associations were observed for larger adenomas or for each subsite of the colorectum. The Japanese and "animal food" patterns were not clearly associated with colorectal adenomas. A dietary pattern including greater consumption of dairy products and fruits and vegetables with low alcohol consumption may be associated with decreased risk of colorectal adenomas.

adenoma; cross-sectional studies; diet

Abbreviation: DFSA, high-dairy, high-fruit and -vegetable, high-starch, low-alcohol (dietary pattern).

Colorectal cancer is a major cause of cancer deaths in developed countries. Geographic and time-trend analyses, as well as migrant studies, strongly suggest that environmental factors, especially diet, play an important role in the pathogenesis of colorectal cancer (1–3). However, analytical epidemiologic studies have yielded conflicting findings; for example, a body of evidence suggesting a protective role of vegetables or dietary fiber (4) has been either challenged (5–8) or supported (9, 10) by recent large-scale studies. In Japan, colorectal cancer mortality has markedly increased over the last several decades (11) and is now among the highest levels in the world (12). Time-trend analysis has suggested that decreased consumption of dietary fibers (13) or grains (14) may account for the increase in mortality. Yet it is largely unknown which lifestyle changes associated with Westernization or modernization have contributed to the rapid increase of colorectal cancer in Japan, or whether the traditional Japanese diet protects against this type of cancer.

Analysis of dietary patterns has recently drawn a great deal of attention as a method of investigating the role of foods or nutrients in studies of chronic diseases. Approaches of this sort, dealing with a combination of several foods, can overcome problems arising from close intercorrelation and potential effect modifications among numerous foods or nutrients (15). Factor-analysis studies of Western populations have suggested that a certain dietary pattern may be

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predictive of colorectal cancer risk (16–18). Dietary patterns generated by factor analysis, however, are sample specific and may not be applicable to populations having different dietary cultures. While having adopted a Western-style diet, many Japanese still consume large amounts of traditional foods, including rice, fish, and soybean products (19). Thus, dietary patterns among Japanese may differ considerably from those among Western populations.

The aim of the present study was therefore to investigate dietary patterns in relation to the risk of colorectal adenoma, a precursor of colorectal cancer (20, 21), using data from preretirement check-ups among male Self-Defense Forces officials in Japan.

MATERIALS AND METHODS

Study setting

The data used were derived from the Self-Defense Forces Health Study, a cross-sectional survey of male Self-Defense Forces officials who participated in a preretirement health examination at two hospitals (Fukuoka and Kumamoto) in Japan. The study procedure has been described elsewhere (22, 23). In short, all officials undergo a comprehensive health examination before retirement; total colonoscopy is included as a routine procedure. Study questionnaires about health-related lifestyles were distributed prior to colonoscopy to male examinees on the first day of hospital admission for examination. Research assistants checked the questionnaire for unanswered questions and apparently inconsistent answers and, if necessary, sought clarification from the study subjects.

Results of laboratory tests and colonoscopic findings, including histologies for polyp, were extracted from clinical reports. Written informed consent was obtained from study participants. The study protocol has been approved by the ethics committee of Kyushu University.

Study subjects

The present study used data from April 1999 through March 2002. Among 2,390 male Self-Defense Forces officials who underwent the examination, 2,370 (99 percent) agreed to participate in the present study. After excluding men with histories of cancer, stroke, myocardial infarction, coronary revascularization, inflammatory bowel diseases, colorectal surgery, or diabetes mellitus, we kept 2,141 men in the analysis of dietary patterns. Of these, we excluded men who did not receive colonoscopy (n = 57), who underwent partial or unsuccessful colonoscopy (n = 177), or who had colorectal polyp removal prior to the examination (n = 148). Of the remaining 1,759 subjects who completed total colonoscopy, 764 men were identified as having colorectal polyps including hyperplastic nodules. Of these, 476 men had their polyps histologically confirmed: cancer (n = 1), carcinoid (n = 1), adenoma (n = 346), and other histologies (n = 128). Only 29 men had adenomas of 10 mm or larger, and nine had tubulovillous or villous adenomas. The data for the 346 men who had adenoma (case group) and 995 men who were free from any colorectal polyp and cancer (referent group) were analyzed to assess the association between dietary patterns and colorectal adenomas.

Dietary assessment

Information about diet was collected using a food frequency questionnaire designed to assess the average intakes of 74 food items, food groups, and food preparations over the previous year. The questionnaire was an expanded version of a 45-item food frequency questionnaire that was developed on the basis of a published questionnaire (24) and was validated against the 28-day dietary record (25). The expansion of food items was done with reference to food consumption in the National Nutrition Survey (19) and a dietary questionnaire developed elsewhere in Japan (26). Participants were asked to choose from seven response options for most dietary items, ranging from "never/less than one per month" to "two to three times per day." Different response schemes were used for green tea, coffee, and rice (five options) and for alcoholic beverages (six options). Daily consumers of green tea, coffee, or rice were asked about the number of cups or bowls consumed per day. Current drinkers, defined as those who have consumed alcoholic beverages weekly for at least 1 year in their lifetime and who were drinking at the time of the survey, were asked about the frequency of consumption and the amount of consumption per occasion of five alcoholic beverages, that is, sake (a Japanese wine), shochu (a Japanese distilled beverage), beer, whiskey, and wine. The amount of consumption per occasion was used in the estimation of total ethanol intake from these alcoholic beverages, but only the frequency of consumption for each alcoholic beverage was used in the analysis of dietary patterns.

Grouping of food factors

Before the analysis of dietary patterns, intakes of green tea, coffee, or rice were converted into units of cups or bowls per day, while those of other dietary items were quantified in terms of frequency per week. Five dietary questions that overlapped with or were duplicated by others (collective consumption of cooked vegetables, apples, mandarin oranges, other oranges, watermelons) and three questions about food spreads (butter, margarine, and jam/honey) were not used. Furthermore, some foods or food groups similar in nutritional content or culinary use were combined, leaving 39 food items for the purposes of the present study.

Statistical analysis

Dietary patterns were generated by factor analysis (principal components) using SAS PROC FACTOR statistical software (27). Factor analysis is a technique to reduce a number of variables into fewer independent factors. To make interpretation easier, a linear transformation called a "rotation" is normally performed on the initial factor solution. We used an orthogonal rotation procedure (varimax rotation), which maintains the uncorrelated nature of the factors and tries to get the original variables to load high on one of the factors and low on the rest. When factor scores are used as

independent variables in a subsequent regression analysis, this procedure has the advantage over oblique rotation that the analysis is less subject to problems of collinearity. In determining the number of factors to retain, we consider eigenvalue, the scree test, and interpretability. Eleven factors satisfied the criteria for eigenvalues greater than one, and the scree plot showed small breaks in the eigenvalues after factor 5, suggesting three or four factors to retain. Post-rotated factor loadings revealed that three factors well describe distinctive dietary patterns of the study population.

We thus retained the three dietary patterns and designated them as 1) a high-dairy, high-fruit and -vegetable, high-starch, low-alcohol (DFSA) pattern; 2) an "animal food" pattern; and 3) a Japanese pattern, according to the food items showing high loading (absolute value) with respect to each dietary pattern. We confirmed that these three dietary factors emerged when all 74 food items in our questionnaire were simply included in factor analysis. A factor score for each dietary pattern was calculated by weighting consumption of each food item by the corresponding factor loading and summing the resulting values. This score ranks individuals in terms of how closely they conform to the dietary pattern.

The potential confounding variables considered were hospital (Fukuoka or Kumamoto), age (treated as a continuous variable), parental history of colorectal cancer (absent or present), occupational rank (three categories), body mass index (<22, 22–23.9, 24–25.9, and ≥26 kg/m^2), smoking (lifetime nonsmoker, former smoker, and current smoker using <15, 15–24, or ≥25 cigarettes/day), and leisure-time physical activity, expressed as the sum of metabolic equivalents for each activity multiplied by the corresponding hours of such activity per week (none, <20, 20–39.9, and ≥40 metabolic equivalent-hours). Quartiles of factor scores of each dietary pattern among controls were used for cutoff values. Multiple logistic regression that included terms for the above-mentioned variables was performed to estimate the odds ratio and 95 percent confidence interval of colorectal adenomas according to quartiles of scores for each dietary pattern, taking the lowest quartile group as the referent group. Analyses were repeated for adenomas of 5 mm or larger (n = 140) or according to the location of the lesion (proximal colon including the cecum, ascending colon, liver flexure, transverse colon, and splenic flexure; distal colon including the descending colon and sigmoid colon; and the rectum). Logistic regression analysis was performed using SAS PROC LOGISTIC software (27).

RESULTS

Table 1 shows factor loadings, which are equivalent to simple correlations between the food items and the dietary patterns. A positive loading indicates that the food item is positively associated with the dietary pattern, and a negative loading indicates an inverse association with the dietary pattern. The DFSA dietary pattern was characterized by frequent intake of fermented dairy products, milk, confectionaries, bread, fruits, and vegetables and infrequent intake of shochu, a local alcoholic beverage in the study areas. The "animal food" dietary pattern was characterized by various kinds of animal foods, including red meat, poultry, seafood excluding fish, processed meat and fish products, and fried or broiled foods. The Japanese dietary pattern was characterized by traditional foods in Japan (soybean products, seaweed, pickles, and green tea), vegetables, and fish. The proportion of the total variance explained by the three factors was 24 percent.

TABLE 1. Factor-loading matrix for dietary patterns, Self-Defense Forces Health Study, Japan, 1999–2002*

	DFSA† dietary pattern	"Animal food" dietary pattern	Japanese dietary pattern
Fermented dairy products	0.61	–	–
Confectionaries	0.55	0.18	–
Canned fruits	0.52	–	–
Bread	0.47	–	–0.39
Fruits (not canned)	0.47	–	0.21
Fruit juices	0.47	–	–
Vegetable juice	0.41	–	0.17
Milk	0.40	–	–
Oil dressing	0.33	0.19	0.26
Soda, cola	0.30	0.20	–0.18
Shochu (alcoholic beverage)	–0.40	0.15	0.24
Red meat	–	0.68	–
Poultry	–	0.63	–
Fried foods	0.25	0.49	0.29
Broiled fish/meat	–	0.48	0.32
Seafood (except fish)	–	0.47	0.18
Processed meat	0.17	0.46	–
Processed fish	–	0.41	0.18
Gyoza‡	–	0.40	–
Liver	–	0.38	–
Eggs	–	0.34	0.22
Noodles	–	0.34	–
Soybean products	–	–	0.64
Cooked vegetables	0.36	0.23	0.56
Seaweed	0.27	–	0.55
Raw vegetables	0.45	–	0.52
Pickles	0.19	–	0.51
Green tea	–	–0.15	0.46
Fish	–	0.27	0.38
Potatoes	0.33	0.24	0.35
Garlic	0.20	–	0.32
Variance explained (%)	8.5	7.9	7.7

* Factor loadings are equivalent to simple correlations between the food items and the dietary patterns. Factor loadings less than ±0.15 were indicated by a dash; food items with factor loadings less than ±0.30 for all dietary patterns (rice, mayonnaise, nuts, coffee, wine, beer, whiskey, sake) were omitted.

† DFSA, high-dairy, high-fruit and -vegetable, high-starch, low-alcohol (dietary pattern).

‡ Dumpling with minced pork and vegetable stuffing.

TABLE 2. Dietary patterns in relation to potential confounding variables and alcohol intake among referents, Self-Defense Forces Health Study, Japan, 1999–2002

Dietary patterns	Hospital (% Kumamoto)	Age (mean years)	Rank (% highest)	Parental history of colorectal cancer (%)	Body mass index (mean kg/m^2)	Smoking (% current smokers)	Physical activity (median metabolic equivalent-hours)	Alcohol (median ml/day)*
DFSA† dietary pattern								
Quartile 1 (low)	28	52.4	10	6	23.7	45	15	62
Quartile 2, 3	27	52.4	14	4	24.0	38	16	32
Quartile 4 (high)	18	52.4	19	5	23.5	40	16	14
p_{trend}‡	0.01	0.49	<0.01	0.66	0.46	0.26	0.84	<0.01
"Animal food" dietary pattern								
Quartile 1 (low)	30	52.5	15	4	23.6	40	16	14.5
Quartile 2, 3	24	52.4	14	4	23.8	42	16	34
Quartile 4 (high)	22	52.3	13	6	23.9	37	15	49
p_{trend}	0.05	0.23	0.43	0.52	0.15	0.56	0.87	<0.01
Japanese dietary pattern								
Quartile 1 (low)	21	52.4	17	5	23.7	48	9.5	21
Quartile 2, 3	25	52.3	13	4	23.8	39	16	40
Quartile 4 (high)	29	52.5	14	4	23.9	36	19	38
p_{trend}	0.02	0.58	0.51	0.66	0.51	<0.01	<0.01	<0.01

* Estimated from the consumption of five alcoholic beverages: beer, sake, shochu, wine, and whiskey.
† DFSA, high-dairy, high-fruit and -vegetable, high-starch, low-alcohol (dietary pattern).
‡ Mantel-Haenszel chi-squared test for categorical variables and linear regression analysis for continuous variables, assigning to categories of each dietary pattern their median scores (physical activity and alcohol consumption were log transformed).

Table 2 shows the association of dietary patterns with potential confounding variables and alcohol consumption among men free from colorectal polyp or cancer (referent group). Examinees at the Kumamoto hospital had a higher score for the Japanese dietary pattern but lower scores for the DFSA and "animal food" dietary patterns than those at the Fukuoka hospital. This reflects the geographic characteristics of dietary patterns; the southern parts of Kyushu Island, including Kumamoto, are less urbanized than the northern parts, including Fukuoka. Men with a high score for the DFSA dietary pattern tended to have higher occupational positions and consumed smaller amounts of alcohol. Men with high scores for the "animal food" dietary pattern tended to consume greater amounts of alcohol. Men in the upper quartiles of the Japanese dietary pattern tended to be nonsmokers and engaged in higher levels of leisure-time physical activity, and they consumed greater amounts of alcohol.

As shown in table 3, the DFSA dietary pattern was inversely associated with the risk of colorectal adenomas, showing a 40 percent reduced odds ratio among men in the highest quartile of the dietary pattern compared with those in the lowest. This association was slightly more evident for adenomas with a diameter of 5 mm or larger. No apparent association was observed for either the "animal food" dietary pattern or the Japanese dietary pattern.

The DFSA dietary pattern was inversely associated with adenomas at all subsites of the colorectum (table 4). The association was slightly stronger for the proximal colon in terms of the odds ratio of 0.5 for the highest quartile of the dietary pattern score and test for the trend association ($p_{trend} = 0.003$), but the confidence intervals of odds ratios for this site overlapped substantially with those for other sites. The Japanese and "animal food" dietary patterns were not measurably associated with colon adenomas. However, a nonsignificant positive association with rectal adenomas was observed for the Japanese pattern, while a nonsignificant inverse association was found for the "animal food" pattern. The odds ratios for the upper three quartiles combined compared with the lowest were 1.64 (95 percent confidence interval: 0.83, 3.25) and 0.64 (95 percent confidence interval: 0.36, 1.13) for the Japanese pattern and "animal food" pattern, respectively.

DISCUSSION

We investigated the association between major dietary patterns and colorectal adenomas among middle-aged Japanese men. Of the three dietary patterns we identified, the DFSA dietary pattern showed a significant, inverse association with the risk of colorectal adenomas.

Strengths and limitations

Our study had several strengths. Selection bias in terms of study participation was unlikely because of nonselective

TABLE 3. Logistic regression results for the association between dietary patterns and colorectal adenoma, Self-Defense Forces Health Study, Japan, 1999–2002

Dietary pattern	Quartile*							p_{trend}
	1 (low)	2		3		4 (high)		
		Odds ratio†	95% confidence interval	Odds ratio	95% confidence interval	Odds ratio	95% confidence interval	
DFSA‡ dietary pattern								
Adenoma of any size	1.00	0.97	0.70, 1.36	0.71	0.50, 1.01	0.62	0.43, 0.90	0.003
Adenoma of 5 mm or larger	1.00	0.84	0.52, 1.34	0.68	0.41, 1.12	0.59	0.35, 0.996	0.04
"Animal food" dietary pattern								
Adenoma of any size	1.00	0.87	0.61, 1.23	0.91	0.64, 1.28	0.86	0.60, 1.23	0.49
Adenoma of 5 mm or larger	1.00	1.05	0.64, 1.72	0.84	0.50, 1.41	0.98	0.59, 1.63	0.75
Japanese dietary pattern								
Adenoma of any size	1.00	0.96	0.67, 1.38	1.13	0.79, 1.61	1.18	0.83, 1.69	0.26
Adenoma of 5 mm or larger	1.00	1.00	0.59, 1.70	1.11	0.66, 1.86	1.24	0.75, 2.08	0.36

* Among referents.
† Adjusted for hospital, age, parental history of colorectal cancer, occupational rank, body mass index, smoking, and leisure-time physical activity.
‡ DFSA, high-dairy, high-fruit and -vegetable, high-starch, low-alcohol (dietary pattern).

recruitment for the preretirement health examination, which included total colonoscopy as a routine procedure, and high study participation rate. The questionnaire was distributed and collected prior to colonoscopy, and thus recall bias associated with adenoma status was also unlikely. The control series consisted of only subjects who were confirmed via total colonoscopy to be free from any colorectal polyp and cancer, leading to a more valid assessment compared with studies

TABLE 4. Logistic regression results for the association between dietary patterns and colorectal adenoma according to the location of the lesion, Self-Defense Forces Health Study, Japan, 1999–2002

Dietary pattern	Quartile*							p_{trend}
	1 (low)	2		3		4 (high)		
		Odds ratio†	95% confidence interval	Odds ratio	95% confidence interval	Odds ratio	95% confidence interval	
Colon adenoma (n = 299)								
DFSA‡ dietary pattern	1.00	0.93	0.66, 1.32	0.70	0.48, 1.01	0.59	0.40, 0.87	0.003
"Animal food" dietary pattern	1.00	0.93	0.64, 1.35	0.97	0.67, 1.40	0.95	0.65, 1.38	0.85
Japanese dietary pattern	1.00	0.93	0.64, 1.37	1.09	0.76, 1.59	1.11	0.77, 1.62	0.45
Proximal colon adenoma (n = 158)								
DFSA dietary pattern	1.00	1.00	0.64, 1.54	0.67	0.41, 1.09	0.50	0.30, 0.85	0.003
"Animal food" dietary pattern	1.00	0.84	0.51, 1.39	1.08	0.68, 1.73	0.94	0.57, 1.53	0.95
Japanese dietary pattern	1.00	0.87	0.53, 1.42	0.92	0.56, 1.49	1.08	0.67, 1.74	0.70
Distal colon adenoma (n = 171)								
DFSA dietary pattern	1.00	1.00	0.64, 1.54	0.77	0.48, 1.23	0.68	0.42, 1.11	0.08
"Animal food" dietary pattern	1.00	1.01	0.63, 1.62	0.95	0.59, 1.52	1.01	0.63, 1.62	0.97
Japanese dietary pattern	1.00	1.10	0.67, 1.79	1.43	0.90, 2.28	1.21	0.74, 1.96	0.35
Rectal adenoma (n = 63)								
DFSA dietary pattern	1.00	0.94	0.48, 1.84	0.64	0.30, 1.36	0.71	0.34, 1.48	0.26
"Animal food" dietary pattern	1.00	0.66	0.33, 1.34	0.64	0.31, 1.32	0.62	0.30, 1.28	0.22
Japanese dietary pattern	1.00	1.58	0.71, 3.51	1.56	0.70, 3.47	1.79	0.82, 3.92	0.18

* Among referents.
† Adjusted for hospital, age, parental history of colorectal cancer, occupational rank, body mass index, smoking, and leisure-time physical activity.
‡ DFSA, high-dairy, high-fruit and -vegetable, high-starch, low-alcohol (dietary pattern).

based on partial colonoscopy. We controlled for major known or suspected confounding factors. The uniform background of the study subjects in terms of occupation, sex, and age was also advantageous in maintaining comparability between cases and controls, although this uniformity limits the extent to which we may generalize from the present findings.

The present study also features some limitations. For one, the dietary questionnaire has not been validated. However, the former version, including questions and response options similar to those of the present questionnaire, has been validated against 7-day, year-round dietary records (25). Most nutrients and foods demonstrated fairly good correlation between the dietary record and questionnaire; relatively high correlation coefficients of 0.80, 0.77, 0.58, and 0.58 were observed for bread, fruits, dairy products, and pickled vegetables, respectively. Nondifferential misclassification in our dietary assessment could distort risk estimates toward the null. Such a bias may be minimal for the analysis of the DFSA dietary pattern, composed of food items showing good correlation between the dietary record and questionnaire, but this bias could be the reason for the lack of an apparent association with the "animal food" or Japanese dietary pattern.

Limitations of factor analysis arise from the arbitrary decisions (15) involved in selecting and grouping foods for analysis from the questionnaire, in determining the number of factors to retain, in choosing the method of rotation of the initial factors to increase the interpretability of the dietary pattern, and in labeling dietary patterns according to their factor loadings. Masaki et al. (28) identified four major dietary patterns using baseline data of a cohort of male employees in Tokyo. Similar to our study, their study identified a "Western breakfast" dietary pattern and an "animal" dietary pattern, suggesting the existence of dietary patterns common to the Japanese. Our derived dietary patterns accounted for 24 percent of the total variance, which is comparable with a figure observed in a previous study (17) but less than that reported in a Japanese study (28). Caution needs to be exercised when comparing the variance explained across studies, which is determined by various factors including the number of variables in analysis.

Interpretation of findings

A dietary pattern characterized by frequent intakes of dairy products, confectionaries, and fruits and vegetables, as well as by infrequent consumption of shochu, a local alcoholic beverage, was inversely associated with the risk of colorectal adenomas. This dietary pattern seems to consist of relatively healthy selections of foods found in Western countries and includes foods of probably low consumption in Japan. According to the food balance sheet (29), per capita supplies of dairy products in Japan and among developed countries in the year 2001 were 66 kg (181 g/day) and 197 kg (540 g/day), respectively; the corresponding values for fruits were 53 kg (145 g/day) and 83 kg (227 g/day). Although the associations between these foods and colorectal cancer have been inconsistent, the present results are in agreement with the existing body of evidence, including findings from recent studies, indicating that high consumption of dairy products or calcium (30–34) and high consumption of fruits, fruit juices, or fruit fiber (10, 35–38) are each associated with reduced risk of colorectal cancer or adenoma. A positive association of alcohol consumption and colorectal adenomas or cancer has been reported in many studies, including those in Japan (23, 39). In addition to independent effects, there may be complex interactions among food factors constituting the DFSA dietary pattern. For example, fruit juices may enhance calcium absorption (40), and reduced alcohol intake increases the bioavailability of folate (41). The glycemic effects of a high-starch or a high-sugar diet and their contribution to increased risk of colorectal cancer have been suspected, but epidemiologic findings are inconsistent on this point (42, 43). Our finding of an inverse association between the DFSA dietary pattern and colorectal adenomas provides the following suggestions: that a high-starch diet may inhibit, rather than promote, the formation of colorectal adenomas and that the adverse effects of a high-starch diet, if any, may not be so strong as to negate the protective effects of other foods contributing to this dietary pattern on adenoma risk. The inverse association of this dietary pattern with adenoma risk was somewhat stronger for the proximal colon than for other sites. Random error could be an explanation. Alternatively, the dietary pattern may be more closely involved in the formation of adenomas in the proximal colon.

The Japanese dietary pattern was characterized by high consumption of many plant foods, including traditional Japanese foods (soybean products, seaweed, pickles) and vegetables. A diet rich in various plant foods could potentially reduce cancer risk because of their many biologically active chemicals (44). However, the Japanese dietary pattern was not apparently associated with colonic adenomas. In studies of Western populations, inverse associations between similar dietary patterns (designated "prudent" or "healthy" patterns) and colorectal cancer have been unclear (18) or limited to subgroups (17). The lack of such an association in our study may contradict a body of evidence supporting an inverse association between vegetables and colorectal cancer (4) but agree with results of recent prospective, but not all (10, 37), studies reporting no association between vegetables or fiber and colorectal cancer or adenoma (5–8). As most of the adenomas in the present study were small in size and less malignant in nature, the present finding is in line with a hypothesis that vegetables are inversely associated with the progression of colorectal adenomas to cancer but not with the initial appearance of adenomas (38). We found a nonsignificant positive association between the Japanese dietary pattern and the risk of rectal adenomas. Studies in Japan (45–49) have consistently shown that frequent consumption of preserved foods including pickled vegetables and dried/salted fish, typical of the Japanese diet, is associated with increased risk of colorectal cancer; of these studies, three documented a significant association specifically for the rectum (46–48). These preserved foods contain *N*-nitroso compounds (50), which are potent carcinogens (51). Among other foods characterizing the Japanese pattern, broiled fish is a potential source of exposure to carcinogenic heterocyclic amine (52), although we are not aware of any epidemiologic

findings suggesting a relation between broiled fish and colorectal cancer risk.

Meat, especially red meat, processed meat, or meat broiled at high temperature, has been associated with colorectal cancer (53, 54) or adenoma (55). A study in Japan found a significant positive association between intake of animal protein and the risk of colorectal adenoma (56). However, we find no increase in the risk of colorectal adenomas associated with the "animal food" dietary pattern. Besides possible bias due to misclassification in the dietary assessment (as discussed above), the lack of such an association for colon adenomas in our study may be attributable to the moderate consumption of meat in Japan (mean daily intake of total meat: 96 g for men aged 40–49 years (19)). In addition, poultry has contributed to the healthy or prudent dietary patterns in Western populations (16–18). The diversity of animal food sources may dilute the potential carcinogenic effects of a specific animal food. Furthermore, it is possible that moderate intake of animal foods prevents carcinogenesis because these foods provide nutrients such as methionine and folate, which are beneficial in DNA synthesis and DNA methylation (57). In this context, our finding showing an increased risk of rectal adenomas associated with the lowest quartile of the "animal food" pattern may be of note and is consistent with results of certain studies relating to colorectal cancer in Japan (45, 48, 58).

In conclusion, the present results indicate that a dietary pattern characterized by frequent consumption of dairy products, confectionaries, bread, fruits, and vegetables but low intake of local alcoholic beverages is associated with a reduced risk of colorectal adenomas in Japanese men. Nonsignificant associations for rectal adenomas, based on an analysis including only 63 men with adenomas in the rectum, should set a limit to causal inference. However, since the incidence of rectal cancer in Japan has been high among industrial countries (12), the question as to whether a Japanese-style diet or a diet low in animal foods promotes carcinogenesis of the rectum warrants further investigation.

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Note

ECOLOGICAL STUDY OF SOLAR RADIATION AND CANCER MORTALITY IN JAPAN

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Abstract—**Geographic observation of the increased mortality of some cancers at higher latitudes has led to a hypothesis that vitamin D produced after exposure to solar radiation has anti-carcinogenic effects. However, it is unclear whether such association would be observed in countries like Japan, where fish consumption, and therefore dietary vitamin D intake, is high. Pearson correlation coefficients were calculated between averaged annual solar radiation levels for the period from 1961 through 1990 and cancer mortality in the year 2000 in 47 prefectures in Japan, with adjustments for regional per capita income and dietary factors. A moderate, inverse correlation with solar radiation was observed for cancers of the esophagus, stomach, colon, rectum, pancreas, and gallbladder and bile ducts in both sexes (correlation coefficient, ranging from −0.6 to −0.3). The results of this study support the hypothesis that increased exposure to solar radiation reduces the risk of cancers of the digestive organs.**
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Key words: cancer; radiation, cosmic; mortality; exposure, population

INTRODUCTION

Studies of the geographical distribution of cancers have shown that certain types of cancer mortality increase with decreasing intensity of solar radiation, including cancers of the colon (Garland and Garland 1980; Gorham et al. 1989; Grant 2002), breast (Gorham et al. 1989; Garland et al. 1990; Grant 2002), prostate (Hanchette and Schwartz 1992; Grant 2002), and ovary (Lefkowitz and Garland 1994; Grant 2002). Since the association is not fully explained by known risk factors, including diet, one hypothesis that has been proposed is that increased exposure to solar radiation helps to prevent cancers through the augmented synthesis of vitamin D (Garland and Garland 1980). This hypothesis is biologically plausible, since vitamin D analogs are reported to affect cell proliferation and differentiation (Lointier et al. 1987; Brehier and Thomasset 1988).

Previous studies in Japan have detected increased mortality from cancers of certain digestive organs at high latitudes (Kato et al. 1985; Watanabe and Arimoto 1990). These findings suggest the existence of an association between solar radiation and cancer, even in countries like Japan where fish consumption, and therefore dietary vitamin D intake, is high (FAOUN 1996). Geographically, Japan extends across a wide region from north to south, with major cities in its 47 prefectures ranging from 26°N to 43°N latitude. Its islands feature mountain ranges running through their center. Together, these two characteristics result in significant meteorological variations. The present study sought to investigate whether levels of solar radiation at various sites in Japan over the past 30 y are associated with cancers of the digestive organs and sex-hormone-related organs. The potential confounding effect of diet was assessed using data from a national nutritional survey.

MATERIALS AND METHODS

We chose the prefecture (n = 47) as the unit of ecological observation. Sex-specific age-standardized mortality rates according to prefecture for the year 2000 (SID 2002) were obtained for cancers of the colon, rectum, prostate, breast (female), and ovary (Appendix A1), for which a relation with solar radiation or latitude has been suggested; and cancers of the esophagus, stomach, pancreas, and gallbladder and bile ducts, for which higher mortality has been reported in northern regions or in regions of Japan with cloudy and snowy winters.

We obtained data of average annual hours of solar radiation received from 1961 to 1990 for the central city of each prefecture (Japan Meteorological Agency 2001), except for two prefectures, for which data on solar radiation was available for another major city (Saitama: Kumagai City, Shiga: Hikone City). The mean average annual solar radiation during 1961–1990 for the prefectures was 3.59 KWh h d^{-1} (range: 3.29–4.01).

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We regarded income and nutritional factors as potential confounding factors. Prefectural income per person was obtained from the 1990 Report on Prefectural Economic Calculation (The Cabinet Office 1990). Data on nutrition were obtained from the 1990 National Nutritional Survey (Bureau of Public Health, Ministry of Health and Welfare 1992), in which subjects were selected at random from the general population. Mean intake of food groups and nutrients was available only for 12 geographical districts, each composed of one to six prefectures (Appendix B1). Therefore, dietary intake for a district was assigned to prefectures that compose the district. The dietary factors initially considered included animal protein, total fat, and fish of any kind (excluding processed food) for cancers of the colon, breast, and prostate; and salt for stomach cancer. Soy products in relation to hormone-related cancers and fiber in relation to colon cancer were not considered because recent ecological studies in Japan have not detected significant associations for these factors (Nagata 2000; Nakaji et al. 2003). Among dietary factors considered, intakes of fat and salt, which were inversely associated with solar radiation (correlation coefficient, −0.49 and −0.26, respectively), were adjusted in the analysis, while intakes of fish and animal protein, which were materially unrelated to solar radiation (correlation coefficient, 0.09 and 0.08, respectively), were not adjusted.

The Pearson correlation coefficient between solar radiation and cancer mortality was calculated for all prefectures ($n = 47$). Partial correlation coefficient was estimated by including terms of income and fat intake in the analysis of cancers of the colon, rectum, prostate, breast, and ovary; and for income and salt intake in the analysis of stomach cancer. The analysis was then repeated while excluding prefectures with large metropolitan areas (Kanto area: Saitama, Tokyo, Chiba, Kanagawa; Hanshin area: Kyoto, Osaka, Hyogo; Aichi; Fukuoka). This exclusion was made to account for the potential effects of large migration from other prefectures and reduced exposure to sunlight due to the shadows cast by buildings. Low levels of serum 25-hydroxyvitamin D concentrations in elderly persons, especially those who are sun-deprived, have been reported, suggesting a reduced sun exposure in cities (Gloth et al. 1995). Further analysis excluded Okinawa prefecture at 26°N, which is situated 5 degrees latitude south of the prefecture with the second southern-most latitude in Japan. The reasons for excluding this prefecture included unique dietary and disease patterns in Okinawa. For example, so-called westernized foods including bread, beef, and coffee were consumed more heavily, while the frequency of salted food intake was remarkably low in Okinawa (Tsugane et al. 2001). The importance of such dietary factors is further suggested by the observation that the mortality of stomach cancer is only half of the average mortality in Japan (SID 2002).

RESULTS

In men, a significant inverse association was observed between solar radiation and age-adjusted mortality rates from cancers of the digestive organs: the esophagus, stomach, colon, rectum, pancreas, gallbladder and bile ducts (Table 1). In women, significant associations were also observed for these sites, although the strength of the associations was generally weaker than in men (Table 2). In both sexes, the associations for cancers of the colon, rectum, and stomach remained significant after controlling for income and the above-mentioned dietary factors. In contrast, there was virtually no association between solar radiation and mortality for cancers of the prostate, breast, and ovary. Excluding prefectures with major urban areas and Okinawa prefecture did not materially change the results, except for cancers of the stomach and pancreas in women, for which the correlation coefficients became non-significant after these exclusions.

DISCUSSION

We found a moderate, inverse relation between solar radiation and cancer mortality involving cancers of the digestive organs. The findings for colon cancer are consistent with previous ecological analyses (Garland and Garland 1980; Gorham et al. 1989; Grant 2002). Increased mortality from cancers of the esophagus, stomach, and pancreas in areas of Japan with low solar radiation is also consistent with previous spatial observations, including those in Japan (Kato et al. 1985; Watanabe and Arimoto 1990). The present study also

Table 1. Correlation coefficient (r) between solar radiation (1961–90) and cancer mortality (2000) in men, Japan.

Cancer site	Age-adjusted yearly mortality (min, max) per 100,000 person	r	r^a	r^b
Esophagus	10.4 (6.0, 16.5)	−0.42[c]	−0.45[c]	
Stomach	39.1 (21.7, 51.5)	−0.50[c]	−0.48[c]	−0.44[c]
Colon	14.4 (10.8, 19.2)	−0.55[c]	−0.53[c]	−0.41[c]
Rectum	9.3 (6.7, 11.7)	−0.54[c]	−0.53[c]	−0.40[c]
Colorectum	23.7 (18.0, 29.6)	−0.63[c]	−0.61[c]	−0.49[c]
Pancreas	12.4 (7.0, 17.2)	−0.51[c]	−0.53[c]	
Gallbladder and bile duct	8.2 (6.6, 12.6)	−0.31[d]	−0.55[c]	
Prostate	8.6 (5.9, 11.6)	−0.04	−0.01	−0.07

[a] Adjusted for income.
[b] Additionally adjusted for fat intake (colon, rectum, prostate) or salt intake (stomach).
[c] $p < 0.01$.
[d] $p < 0.05$.

Table 2. Correlation coefficient (r) between solar radiation (1961–90) and cancer mortality (2000) in women, Japan.

Cancer site	Age-adjusted yearly mortality (min, max) per 100,000 person	r	r^a	r^b
Esophagus	1.3 (0.5, 1.8)	−0.45[c]	−0.41[c]	
Stomach	15.3 (7.7, 19.2)	−0.37[d]	−0.32[d]	−0.35[d]
Colon	9.5 (7.3, 12.3)	−0.51[c]	−0.46[c]	−0.33[d]
Rectum	4.1 (2.7, 5.3)	−0.47[c]	−0.47[c]	−0.39[c]
Colorectum	13.6 (10.4, 17.6)	−0.58[c]	−0.54[c]	−0.42[c]
Pancreas	7.2 (4.0, 9.9)	−0.32[d]	−0.31[d]	
Gallbladder and bile duct	6.3 (4.7, 8.5)	−0.44[c]	−0.50[c]	
Breast	10.7 (7.1, 13.4)	−0.20	−0.09	−0.06
Ovary	4.3 (2.1, 5.4)	−0.17	−0.06	−0.04

[a] Adjusted for income.
[b] Additionally adjusted for fat intake (colon, rectum, breast, ovary) or salt intake (stomach).
[c] $p < 0.01$.
[d] $p < 0.05$.

suggests that cancers of the gallbladder and bile ducts are associated with levels of solar radiation. In contrast, cancers of the prostate, breast, and ovary did not significantly correlate with solar radiation.

As previously hypothesized, one plausible explanation for the present inverse association is that exposure to solar radiation reduces the risk of cancer through photoinitiation of vitamin D production. Vitamin D is synthesized in skin on exposure to ultraviolet B, then metabolized in the liver and kidney to vitamin 1,25-D_3. The synthesis of 1,25-D_3 from the precursor 25-D_3 also occurs at tissue levels (Schwartz et al. 1998). 1,25-D_3 not only promotes cell differentiation and reduces proliferation (Lointier et al. 1987; Brehier and Thomasset 1988) but also inhibits tumor growth in xenografts (Eisman et al. 1987) and induces apoptosis of various cancer cells, including colon (Vandewalle et al. 1995). Furthermore, there is evidence, although not always consistent, that elevated levels of serum vitamin D analog are associated with reduced risk of cancer or cancer precursors (Garland et al. 1989; Platz et al. 2000). These findings suggest that vitamin D may be involved in several stages of carcinogenic process.

The Japanese consume large amounts of fish, a food source rich in vitamin D. Although fish consumption in the present data set was relatively equal among regional populations subject to different levels of solar radiation intensity, the intake of fatty fish, which are especially rich in vitamin D, tends to be greater in northern regions (Bureau of Public Health, Ministry of Health and Welfare 1992). Consistent with this observation, recent national nutritional survey estimated greater intake of vitamin D for Japan's northern districts (The Study Circle for Health and Nutrition Information 2003); the mean dietary intakes of vitamin D were 11.4 mg and 6.5 mg for the most northern district and the most southern district, respectively. Without this gradient in dietary intake of vitamin D opposite to that of solar radiation, the effects of the latter may well have been greater. However, without population data showing serum vitamin D levels across the nation, we can neither refute nor adopt the proposed hypothesis involving vitamin D.

Other factors may account for the present association. Mortality rates from suicide, more frequent among those who are clinically depressed, are inversely associated with intensity of solar radiation in Japan (Terao et al. 2002). Depression has been suggested to cause immune suppression (Miller et al. 1993) and has been proposed as a predisposing condition for diseases that develop more easily under decreased surveillance activity of the immune system, including cancer. Several, but not all, epidemiological studies have reported an increased risk of cancer among those who are depressed (Penninx et al. 1998). Thus, it is possible that the exposure to solar radiation may indirectly reduce cancer risks through positive effects on mood that intensify immune surveillance systems. However, since there is no direct evidence linking digestive cancers to immune suppression, further research is required to judge the plausibility of this mechanism as an explanation for the inverse association between solar radiation and digestive cancers.

The present study found no association between solar radiation and sex hormone-related cancers (prostate, breast, and ovary), a finding at odds with previous ecological studies (Gorham et al. 1989; Garland et al. 1990; Hanchette and Schwartz 1992; Lefkowitz and Garland 1994; Grant 2002). Although these cancers have steadily increased in Japan over recent decades, their resulting incidence rates remain at the lowest levels among developed countries (Parkin et al. 2002). Studies have indicated that intake of soy products (rich in isoflavones) and fish (rich in ω-3 fatty acid), staples of the traditional Japanese diet, are associated with reduced risk of cancers of the breast and prostate, respectively (Terry et al. 2001; Yamamoto et al. 2003). High consumption of these foods among the Japanese may mask the effects of solar radiation on these cancers. Alternatively, since hormone-related cancers tend to originate early in life (Swerdlow et al. 2002), an adequate study might require information on lifetime exposure to solar radiation. The increasing gap between cancer incidence and mortality has been observed especially for hormone-related cancers. If people living in northern prefectures have a greater availability of medical care service than those living in southern prefectures, it is possible that an association between solar radiation and these cancers would be masked due to a better prognosis of cancer patients in northern areas. In reality, however, medical care cost tends to be higher in southwest districts than

northeast districts in Japan (MHLW 1999), indicating that such bias is a less likely explanation for the lack of the association for these cancers.

Ecological studies are apt to suffer from the ecological fallacy. We adjusted for fat intake in our analysis for colon and rectal cancers and for salt intake in our analysis for stomach cancer. The results indicate that these dietary factors do not fully explain the inverse relationship with solar radiation. Smoking, a possible risk factor of some digestive cancers (Mizoue et al. 2000), did not show a latitudinal gradient in Japan (Bureau of Public Health, Ministry of Health and Welfare 1992). Internal migration or large population increase in some prefectures may dilute the association between solar radiation and cancer. The amount of time that people spend indoors may affect the result. If a snowy winter confines people inside the home, the difference in exposure to solar radiation across the nation would be enhanced. Women showed a slightly weaker association between solar radiation and cancer mortality than men. One possible reason is that women, who may stay longer hours indoors than men, and whose clothing habits may further restrict exposure of the skin, have a smaller geographical difference in exposure levels to solar radiation than men. We used mean solar radiation levels for the period from 1961 through 1990 and mortality data in 2000. Not knowing the minimum exposure period and latent period for the development of cancer, we cannot assess the validity of these periods. An analysis using appropriate exposure and lag periods should yield a stronger association between solar radiation and cancer risk.

CONCLUSION

The present study adds evidence to the hypothesis that solar radiation reduces mortality from cancers of the digestive organs. The lack of association found in this study between solar radiation and sex-hormone-dependent cancers warrants further investigation.

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APPENDIX A1. Solar radiation, income, and age-standardized cancer mortality by prefecture in Japan. Abbreviations: M, male; F, female.

	Name of prefecture	Solar radiation[b] (KWh/ hour-day)	Income[c] (thousand yen/person)	Age-standardized cancer mortality[a] (/100,000)																
				esophagus		stomach		colorectum		colon		rectum		pancreas		gall bladder and bile duct				
				M	F	M	F	M	F	M	F	M	F	M	F	M	F	breast	ovary	prostate
01	Hokkaido	3.45	2382	11.8	1.3	36.9	13.4	26.4	14.3	16.9	9.9	9.5	4.4	15.8	8.2	9.9	6.7	11.7	4.1	8.8
02	Aomori-ken	3.36	2217	13.2	1.4	45.8	16.2	28.7	14.8	17.0	10.1	11.7	4.7	17.2	8.0	10.5	6.4	11.5	3.5	9.7
03	Iwate-ken	3.44	2239	11.3	1.8	35.6	12.9	24.8	15.4	14.6	10.5	10.2	4.9	11.7	6.3	10.2	5.8	8.8	5.2	10.7
04	Miyagi-ken	3.38	2549	12.8	1.7	37.9	15.2	26.4	13.6	15.7	9.9	10.7	3.7	13.0	8.1	8.9	6.5	12.8	4.4	8.7
05	Akita-ken	3.29	2278	16.5	1.7	51.5	19.2	29.6	17.6	19.2	12.3	10.4	5.3	13.5	7.9	12.6	7.3	10.1	3.7	8.2
06	Yamagata-ken	3.41	2333	11.6	1.7	50.4	18.5	23.1	16.4	13.0	11.6	10.1	4.8	13.9	7.9	9.2	7.7	9.8	3.6	9.1
07	Fukushima-ken	3.44	2474	10.6	0.7	38.5	17.0	23.6	12.2	14.1	8.9	9.5	3.4	13.2	5.8	9.4	8.3	9.0	4.4	10.2
08	Ibaraki-ken	3.47	2938	10.6	1.3	43.8	16.6	21.9	13.0	13.0	9.1	9.0	3.8	11.7	8.0	8.6	7.4	10.2	4.5	9.4
09	Tochigi-ken	3.44	2894	10.7	1.6	47.2	15.6	23.2	14.0	13.7	9.9	9.5	4.1	13.0	6.6	7.6	7.1	8.7	4.8	7.9
10	Gumma-ken	3.54	2811	10.1	1.1	40.2	14.3	21.1	13.2	12.0	8.7	9.1	4.5	12.3	6.5	8.2	7.6	10.8	3.8	10.0
11	Saitama-ken	3.58	3008	10.6	1.5	42.1	17.1	24.8	14.1	15.2	10.2	9.5	3.9	12.3	6.8	8.1	6.6	11.9	4.9	7.8
12	Chiba-ken	3.55	3129	10.2	1.4	40.4	15.4	24.4	14.2	14.4	10.1	10.0	4.1	11.5	7.1	7.8	5.6	11.5	5.3	8.8
13	Tokyo-to	3.34	4452	13.3	1.7	38.2	15.2	26.0	15.0	15.9	10.6	10.1	4.4	11.6	7.4	6.6	6.1	13.4	5.4	9.0
14	Kanagawa-ken	3.50	3210	12.4	1.5	39.2	14.5	26.3	14.3	16.0	10.0	10.4	4.4	11.9	6.9	6.8	5.4	12.0	5.1	9.3
15	Niigata-ken	3.32	2576	14.4	1.3	47.1	15.4	23.8	14.9	14.1	9.9	9.7	5.0	14.0	7.3	9.2	7.7	9.8	4.3	7.4
16	Toyama-ken	3.33	2855	8.6	1.0	41.7	15.2	22.8	12.9	13.6	8.3	9.2	4.6	14.3	6.3	7.3	7.5	10.0	3.3	5.9
17	Ishikawa-ken	3.44	2757	6.5	1.2	42.1	15.0	22.4	13.0	15.0	8.4	7.4	4.7	14.7	7.9	10.1	7.0	10.6	3.8	8.2
18	Fukui-ken	3.35	2598	6.5	0.7	30.7	16.1	24.9	10.9	16.2	7.9	8.7	3.0	11.4	8.4	8.7	8.5	10.5	2.1	7.0
19	Yamanashi-ken	3.76	2726	10.2	1.1	36.5	13.4	21.4	10.5	13.1	7.3	8.4	3.2	10.8	7.6	7.4	5.2	11.0	2.9	7.0
20	Nagano-ken	3.58	2888	8.1	1.1	34.5	12.3	20.4	12.3	12.8	8.3	7.6	4.0	12.7	7.1	8.4	5.2	9.4	4.5	10.0
21	Gifu-ken	3.80	2791	6.9	0.6	39.9	18.8	24.3	14.3	14.7	10.6	9.5	3.8	13.4	8.1	6.8	6.8	10.7	3.9	8.5
22	Shizuoka-ken	3.66	2920	8.2	1.0	34.0	13.8	22.9	12.7	12.6	8.6	10.3	4.1	12.1	7.1	8.0	6.2	9.9	4.0	8.9
23	Aichi-ken	3.65	3496	7.4	1.0	37.8	18.3	22.4	14.7	13.6	10.4	8.8	4.3	12.1	7.2	7.6	6.0	10.5	4.2	8.1
24	Mie-ken	3.72	2777	7.3	0.5	40.7	16.4	20.8	13.6	12.9	10.0	7.9	3.6	14.0	6.1	7.6	5.2	11.2	4.1	9.1
25	Shiga-ken	3.55	2979	7.6	0.9	37.3	16.1	20.1	14.2	11.5	10.2	8.7	4.0	12.0	8.2	7.8	6.3	8.9	2.9	7.2
26	Kyoto-fu	3.41	2812	8.4	1.7	38.1	17.3	23.5	14.6	13.9	10.9	9.6	3.8	12.9	7.2	8.5	6.4	8.9	3.8	8.1
27	Osaka-fu	3.58	3346	11.3	1.6	43.2	16.7	26.0	14.4	16.4	10.4	9.6	4.0	12.1	7.6	7.9	6.3	10.8	4.3	7.8
28	Hyogo-ken	3.66	2776	11.2	1.6	42.4	15.9	23.6	13.3	14.1	8.6	9.5	4.7	12.6	7.8	7.2	5.6	10.4	4.4	6.9
29	Nara-ken	3.66	2709	7.5	1.1	46.1	15.3	20.4	13.2	13.1	10.0	7.3	3.2	13.2	6.6	7.7	4.8	8.8	3.3	9.5
30	Wakayama-ken	3.77	2182	8.6	1.5	45.7	18.0	23.7	14.0	14.5	9.4	9.1	4.6	11.5	9.9	8.0	5.0	7.6	4.2	8.1
31	Tottori-ken	3.44	2393	10.6	0.7	43.0	19.1	22.6	13.7	12.3	9.5	10.2	4.2	12.0	7.7	8.7	8.2	7.8	4.0	8.0
32	Shimane-ken	3.52	2202	10.5	1.0	40.7	14.5	26.0	13.0	14.8	8.4	11.2	4.6	13.8	8.4	7.1	4.8	7.5	2.6	8.2
33	Okayama-ken	3.69	2688	8.6	1.4	32.0	16.3	20.5	11.7	11.6	8.3	8.9	3.4	12.1	6.3	8.7	5.6	9.7	4.8	8.1
34	Hiroshima-ken	3.88	2893	8.1	1.0	36.2	14.1	23.0	12.2	14.8	8.5	8.2	3.6	10.7	6.5	7.6	4.7	9.3	3.7	9.0
35	Yamaguchi-ken	3.66	2532	9.9	1.6	37.6	16.8	21.4	12.7	14.6	8.3	6.8	4.4	11.8	7.2	8.1	6.5	9.1	4.0	9.0
36	Tokushima-ken	3.74	2440	8.4	1.1	37.0	12.6	21.7	11.9	11.9	7.9	9.8	4.0	9.5	7.2	7.2	7.1	9.9	3.3	6.7
37	Kagawa-ken	3.80	2582	6.6	1.1	37.5	17.2	18.4	11.6	10.9	8.1	7.5	3.5	13.7	6.9	7.4	6.6	10.5	3.2	9.2
38	Ehime-ken	3.80	2251	6.0	0.9	40.2	15.5	20.9	12.0	12.8	7.9	8.1	4.1	11.6	6.4	8.2	4.9	11.0	4.1	7.0
39	Kochi-ken	3.85	2051	9.2	0.5	35.0	13.9	18.8	10.8	10.9	8.0	7.8	2.8	11.9	7.5	8.2	6.0	9.4	3.5	6.2
40	Fukuoka-ken	3.54	2445	10.8	1.1	37.6	14.8	23.0	13.8	15.3	9.9	7.7	4.0	11.3	7.3	7.9	6.7	11.2	3.7	9.1
41	Saga-ken	3.62	2208	8.6	1.2	39.2	14.3	22.6	11.6	13.2	8.9	9.4	2.7	13.4	7.3	9.5	7.6	10.2	4.2	10.9
42	Nagasaki-ken	3.67	2060	10.1	1.1	37.3	16.0	24.2	11.4	14.1	7.3	10.1	4.1	11.7	7.1	9.2	7.1	11.0	3.7	8.3
43	Kumamoto-ken	3.72	2319	7.1	0.9	26.8	11.6	18.0	11.2	11.3	8.0	6.7	3.3	11.2	8.3	8.4	6.3	9.7	3.1	9.7
44	Oita-ken	3.61	2317	6.2	1.4	31.2	11.8	22.0	11.5	13.3	7.5	8.7	3.9	11.2	6.1	10.0	5.6	7.1	3.5	8.3
45	Miyazaki-ken	3.85	1996	11.4	0.9	33.5	12.9	18.9	13.7	10.8	9.1	8.1	4.6	13.4	6.0	9.7	5.9	8.4	3.6	11.6
46	Kagoshima-ken	3.69	2060	12.5	0.8	28.4	11.6	20.4	11.7	11.9	7.7	8.5	4.0	12.2	5.8	8.9	7.4	9.9	4.2	9.2
47	Okinawa-ken	4.01	1984	12.1	0.9	21.7	7.7	20.6	10.4	12.8	7.5	7.9	3.0	7.0	4.0	9.2	7.1	9.3	3.6	9.0

[a] Age-adjusted death rates by prefecture, Special Report on Vital Statistics 2000.
[b] Japan Meteorological Table (the mean average annual values during 1961–1990).
[c] Prefectural Economic Calculation (1990).