sensitivity to change assessed with the Beck depression inventory—II in Japanese patients with depression. Psychiatry Res 2005;135:229–35.
38. Kimmel PL, Peterson RA, Weihs KL, Simmens SJ, Alleyne S, Cruz I, Veis JH. Multiple measurements of depression predict mortality in a longitudinal study of chronic hemodialysis outpatients. Kidney Int 2000; 57:2093–8.
39. Watnick S, Wang PL, Demadura T, Ganzini L. Validation of 2 depression screening tools in dialysis patients. Am J Kidney Dis 2005;46:919–24.
40. SPSS Advanced Models 12.0. Chicago, IL: SPSS Inc; 2006.
41. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychol 1960;23:56–62.
42. Goldberger AL, Amaral LA, Hausdorff JM, Ivanov PC, Peng CK, Stanley HE. Fractal dynamics in physiology: alterations with disease and aging. Proc Natl Acad Sci U S A 2002;99(Suppl 1):2466–72.
43. Chen HF, Ho CA, Li CY. Age and sex may significantly interact with diabetes on the risks of lower-extremity amputation and peripheral revascularization procedures: evidence from a cohort of a half-million diabetic patients. Diabetes Care 2006;29:2409–14.
44. Guasti L, Grimoldi P, Mainardi LT, Petrozzino MR, Piantanida E, Garganico D, Diolisi A, Zanotta D, Bertolini A, Ageno W, Grandi AM, Cerutti S, Venco A. Autonomic function and baroreflex sensitivity during a normal ovulatory cycle in humans. Acta Cardiol 1999;54:209–13.
45. Minson CT, Halliwill JR, Young TM, Joyner MJ. Sympathetic activity and baroreflex sensitivity in young women taking oral contraceptives. Circulation 2000;102:1473–6.
46. Beckers F, Verheyden B, Aubert AE. Aging and nonlinear heart rate control in a healthy population. Am J Physiol Heart Circ Physiol 2006; 290:H2560–H2570.
47. Yeragani VK, Meiri P, Balon R, Pohl R, Golec S. Effect of imipramine treatment on changes in heart rate and blood pressure during postural and isometric handgrip tests. Eur J Clin Pharmacol 1990;38:139–44.
48. Yeragani VK, Pohl R, Balon R, Ramesh C, Glitz D, Jung I, Sherwood P. Heart rate variability in patients with major depression. Psychiatry Res 1991;37:35–46.
49. Rechlin T, Weis M, Claus D. Heart rate variability in depressed patients and differential effects of paroxetine and amitriptyline on cardiovascular autonomic functions. Pharmacopsychiatry 1994;27:124–8.
50. Beck AT. Depression: Clinical, Experimental, and Theoretical Aspects. New York: Harper & Row; 1967.

COMMENTARY

Are There any Real *Helicobacter pylori* Infection-negative Gastric Cancers in Asia?

Shinkan Tokudome[1*], Ryosuke Ando[1], Reza Ghadimi[1], Tsutomu Tanaka[1], Nami Hattori[1], Zhao Yang[1], Mitsuhiro Marumoto[1], Hiroyuki Agawa[1], Kazuyuki Arakawa[1], Yuko Osaka[1], Hideyoshi Tanaka[1], Akihiro Hosono[1], Malcolm A Moore[2]

Abstract

The great variability in gastric cancer rates across Asia, with very high incidences in Japan and Korea, and exceedingly low incidences in ethnic Malays, whether in Malaysia or Indonesia, appears largely due to variation in *Helicobacter pylori* infection rates. While between 2% and 10.6% of gastric cancers in a recent Japanese survey were considered to be negative for bacterial infection on the basis of seropositivity and *H. pylori*-dependent mucosal atrophy, it is notoriously difficult to preclude past infection. The situation is greatly complicated by reported differences in the etiology of gastric cardia and non-cardia cancers. In the Western world there do appear to be tumours arising close to the esophageal-gastric junction which are not related to *H. pylori* and associated inflammation, but in most Asian populations these appear to be very rare. Therefore preventive efforts, and particularly screening, should be focused on markers of bacterial infection, with avoidance of unnecessary exposure to X-ray radiation.

Key words: Gastric cancer - cardia - non-cardia - *H. pylori* - inflammation

Asian Pacific J Cancer Prev, **8**, 462-463

Introduction

Although the incidence of stomach cancer is steadily declining in Japan, it is still a major cause of malignancy-associated death. Its prevention and control remain crucial. Recently, Kato et al. (2007) presented an important article indicating that the percentage of *Helicobacter pylori* (*H. pylori*) infection-negative gastric cancer ranged from 2.0% (minimum) to 10.6% (maximum), indicating that the bacterium is a major etiologic factor. The results seem compatible with our finding that the very low incidence of stomach malignancy in Yogyakarta (Tokudome et al., 2005) and Semarang (Tokudome et al., 2006), Indonesia, appears to be due to the rarity of infection. Similar results have been reported in Malaysia, whereby the incidence of gastric carcinoma was found to be much higher in Chinese in Penang compared to Malays in Kelantan, where the *H. pylori* infection rate is exceptionally low (Gurjeet et al., 2005).

A complicating factor is the existence of cardia and non-cardia cancers in the body of the stomach with differing etiologies (Palli et al. 2007). Furthermore, the current evidence indicates that cardia cancers are also of at least two distinct types in Western populations (Jonkers et al., 1999; Gonzalez et al., 2006), one resembling cancer of the more distal stomach (Type A), being a consequence of atrophic gastritis due to bacterial infection or more rarely autoimmune atrophic gastritis. The other type (Type B) resembles oesophageal adenocarcinoma and is likely to be a consequence of short-segment gastro-oesophageal reflux disease. Type A occurs in patients with evidence of atrophic gastritis whereas Type B is found in subjects with healthy acid-secreting stomachs (McColl, 2006). *H. pylori* appears to be a strong risk factor for non-cardia gastric cancer but is inversely associated with the risk of gastric cardia cancer. These findings bolster the hypothesis that decreasing *H. pylori* prevalence during the past century may have contributed to lower rates of non-cardia cancer and higher rates of cardia cancer in Western countries (Kamangar et al., 2006). In contrast, associations between *H. pylori* exposure and gastric cardia and non-cardia adenocarcinoma development in Linxian, China, were equally strong, in contrast to Western countries, perhaps due to the absence of Barrett's oesophagus and oesophageal adenocarcinomas, making all cardia tumours of gastric origin, rather than a mixture of gastric and oesophageal malignancies (Kamangar et al., 2007).

As has been suggested (Ekstrom et al., 2001; Huang et al., 1998; Malfertheiner et al., 2002), *H. pylori* may disappear from the stomach along with the progressive changes of gastric milieu from chronic inflammation/ atrophic gastritis, intestinal metaplasia, dysplasia to cancer. However, Kato et al (2007) found that the level of gastric atrophy detected by pepsinogen test (Miki et

[1]*Department of Public Health, Nagoya City University Graduate School of Medical Sciences, Mizuho-ku, Nagoya 467-8601 Japan* [2]*APJCP Editorial Office, UICC Asia Regional Office *For correspondence: tokudome@med.nagoya-cu.ac.jp*

al.,1993) did not necessarily correlate well with that diagnosed by Updated Sydney System Scores. Furthermore, testing of serum anti-*H. pylori* IgG antibodies according to ELISA would invariably yield false negative test, particularly in case-control study settings (Ekstrom et al., 2001; Huang et al., 1998). Thus, the maximum proportion (10.6%) of *H. pylori* infection-negative stomach malignancy appears to have been overestimated. The final judgment on the percentage of *H. pylori* infection-positive or -negative stomach cancer should be made according to prospective approaches, in which no gastric malignancy occurred among *H. pylori* infection-negative subjects and randomized controlled trials of the *H. pylori* eradication program (Ohata et al., 2004; Uemura et al., 2001).

Stomach cancer indeed appears to be an infectious disease caused by *H. pylori* infection (Kikuchi et al., 1995; Huang et al., 1998; Ekstrom et al., 2001; Uemura et al., 2001; Ohata et al., 2004; Tokudome et al., 2005; Tokudome et al., 2006; Egi et al., 2007). Thus, infection prevention, control and eradication of the bacterium seem crucial for primary prevention of gastric malignancy. For secondary prevention, instead of immediate application of photofluography/X-ray examination, we propose that non-invasive examinations for *H. pylori* infection, including urea breath test and assays for the bacterial antigen and antibodies, together with pepsinogen test should be first adopted to screen high-risk subjects. This will assure more effective use of personnel and monetary resources and reduce unnecessary exposure to X-ray radiation.

References

Egi Y, Ito M, Tanaka S, et al (2007). Role of *Helicobacter pylori* infection and chronic inflammation in gastric cancer in the cardia. *Jpn J Clin Oncol*, **37**, 365-9.

Ekstrom AM, Held M, Hansson LE, Engstrand L, Nyren O (2001). *Helicobacter pylori* in gastric cancer established by CagA immunoblot as a marker of past infection. *Gastroenterology*, **121**, 784-91.

Gonzalez CA, Pera G, Agudo A, et al (2006). Fruit and vegetable intake and the risk of stomach and oesophagus adenocarcinoma in the European Prospective Investigation into Cancer and Nutrition (EPIC-EURGAST). *Int J Cancer*, **118**, 2559-66.

Gurjeet K, Subathra S, Bhupinder S (2004). Differences in the pattern of gastric carcinoma between north-eastern and north-western peninsular Malaysia: a reflection of *Helicobacter pylori* prevalence. *Med J Malaysia*, **59**, 560-1.

Hansen S, Vollset SE, Derakhshan MH, et al (2007). Two distinct aetiologies of cardia cancer; evidence from premorbid serological markers of gastric atrophy and *Helicobacter pylori* status. *Gut*, **56**, 918-25.

Huang J-Q, Sridhar S, Chen Y, Hunt RH (1998). Meta-analysis of the relationship between *Helicobacter pylori* seropositivity and gastric cancer. *Gastroenterology*, **114**, 1169-79.

Jonkers D, Houben P, Hameeteman W, et al (1999). Differential features of gastric cancer patients, either *Helicobacter pylori* positive or *Helicobacter pylori* negative. *Ital J Gastroenterol Hepatol*, **31**, 836-41.

Kamangar F, Dawsey SM, Blaser MJ, et al (2006). Opposing risks of gastric cardia and noncardia gastric adenocarcinomas associated with *Helicobacter pylori* seropositivity. *J Natl Cancer Inst*, **98**, 1445-52.

Kamangar F, Qiao YL, Blaser MJ, et al (2007). *Helicobacter pylori* and oesophageal and gastric cancers in a prospective study in China. *Br J Cancer*, **96**, 172-6.

Kato S, Matsukura N, Tsukada K, et al (2007). *Helicobacter pylori* infection-negative gastric cancer in Japanese hospital patients: incidence and pathological characteristics. *Cancer Sci*, **98**, 790-4.

Kikuchi S, Wada O, Nakajima T, et al (1995). Serum anti-*Helicobacter-pylori* antibody and gastric carcinoma among young adults. *Cancer*, **75**, 2789-93.

Malfertheiner P, Megraud P, O'Morain C, et al (2002). Current concepts in the management of *Helicobacter pylori* infection – The Maastricht 2-2000 Consensus Report. *Aliment Pharmacol Ther*, **16**, 167-80.

Matsukura N, Yamada S, Kato S, et al (2003). Genetic differences in interleukin-1 beta polymorphisms among four Asian populations: an analysis of the Asian paradox between *H. pylori* infection and gastric cancer incidence. *J Exp Clin Cancer Res*, **22**, 47-55.

McColl KE (2006). Cancer of the gastric cardia. *Best Pract Res Clin Gastroenterol*, **20**, 687-96.

Miki K, Ichinose M, Ishikawa KB, et al (1993). Clinical application of serum pepsinogen I and II levels for mass screening to detect gastric cancer. *Jpn J Cancer Res*, **84**, 1086-90.

Ohata H, Kitauchi S, Yoshimura N, et al (2004). Progression of chronic atrophic gastritis associated with *Helicobacter pylori* infection increases risk of gastric cancer. *Int J Cancer*, **109**, 138-43.

Palli D, Masala G, Del Giudice G, et al (2007). CagA+ *Helicobacter pylori* infection and gastric cancer risk in the EPIC-EURGAST study. *Int J Cancer*, **120**, 859-67.

Tokudome S, Soeripto, Triningsih FXE, et al (2005). Rare *Helicobacter pylori* infection as a factor for the very low stomach cancer incidence in Yogyakarta, Indonesia. *Cancer Lett*, **219**, 57-61.

Tokudome S, Samsuria WD, Soeripto, et al (2006). *Helicobacter pylori* infection appears essential for stomach carcinogenesis - observations in Semarang, Indonesia. *Cancer Sci*, **96**, 873-5.

Uemura N, Okamoto S, Yamamoto S, et al (2001). *Helicobacter pylori* infection and the development of gastric cancer. *N Engl J Med*, **345**, 784-9.

NUTRITION AND CANCER, 57(2), 138–145

Dietary Habits and Risk of Ovarian Cancer Death in a Large-Scale Cohort Study (JACC Study) in Japan

Fumio Sakauchi, M.M.H. Khan, Mitsuru Mori, Tatsuhiko Kubo, Yoshihisa Fujino, Sadao Suzuki, Shinkan Tokudome, and Akiko Tamakoshi for the JACC Study Group

Abstract: *The Japan Collaborative Cohort (JACC) Study was established in 1988–1990 and consisted of 46,465 men and 64,327 women observed until the end of 2003. A self-administered food frequency questionnaire was used as a baseline survey, and associations of dietary habits with the risk of ovarian cancer death were evaluated, taking into consideration age, menstrual and reproductive, anthropometric, and lifestyle factors. During the observation period, 77 women died of ovarian cancer. Hazard ratios for dietary factors were calculated by Cox's proportional hazards model. Being adjusted only for age, high intakes of dried or salted fish and Chinese cabbage were positively associated with the risk of ovarian cancer death, and the risk increased dose-dependently. In contrast, intake of soybean curd (tofu) was inversely associated with the risk. After being adjusted for age and potential confounding factors, the results regarding the intakes of dried or salted fish and Chinese cabbage did not change. However, the significance relating to the intake of soybean curd (tofu) was attenuated.*

From the results of this cohort study, it was suggested that high intakes of dried or salted fish and Chinese cabbage were potential risk factors of ovarian cancer death. In contrast, however, a high intake of soy bean curd (tofu) might have preventive effects against the risk.

Introduction

Ovarian cancer is the leading cause of death from gynecological malignancies. Its prevalence is higher in Western countries due to environmental factors associated with modern lifestyles (1). The relations between ovarian cancer and menstrual, reproductive, anthropometric, and lifestyle factors have been discussed in many epidemiological studies (2). Estrogen exposure is strongly related to the development of ovarian cancer (3,4). Obesity and hypoactivity are also considered risk factors for ovarian cancer (5). However, the effects of other factors, including dietary habits, have not been sufficiently elucidated, although some epidemiological studies have shown that high consumption of vegetables reduces the risk of ovarian cancer (2). Recently, the protective qualities of soy-based foods against female malignancies such as breast cancer and endometrial cancer have been a main focus with regard to their anti-estrogenic effects (6–8). In addition, it has been reported that intake of soy and isoflavone is associated with a reduced risk of developing ovarian cancer (9).

The Japan Collaborative Cohort Study for Evaluation of Cancer Risk Sponsored by the Ministry of Education, Culture, Sports, Science, and Technology (JACC Study) was planned in the late 1980s as a large-scale cohort study surveying Japanese people comprehensively and detailing their lifestyles. This cohort consisted of persons in various areas of Japan, and follow-ups concerning morbidity continued until the end of 2003. In the present study, we examined the association of the risk of ovarian cancer death with dietary habits surveyed by a baseline questionnaire, taking into consideration some confounding factors.

Subjects and Methods

Study Population

The JACC Study is a large and prospective cohort study sponsored by the Ministry of Education, Culture, Sports, Science, and Technology of Japan. The methods adopted in the baseline survey and follow-up in this study were described in detail elsewhere (10). In brief, the cohort was established from 1988 to 1990, with 46,465 men and 64,327 women aged 40–79 years in 45 study areas throughout Japan. In almost all of the study areas, the participants who attended the municipal health screening program were enrolled as the basic cohort population; however, the subjects consisted of some

Fumio Sakauchi, M.M.H. Khan, and Mitsuru Mori are affiliated with the Department of Public Health, Sapporo Medical University School of Medicine. Tatsuhiko Kubo and Yoshihisa Fujino are affiliated with the Department of Clinical Epidemiology, University of Occupational and Environmental Health. Sadao Suzuki and Shinkan Tokudome are affiliated with the Department of Health Promotion and Preventive Medicine, Nagoya City University Graduate School of Medical Sciences. Akiko Tamakoshi is affiliated with the National Center for Geriatrics and Gerontology.

volunteers from the general population. Follow-up of the study subjects was subsequently conducted until the end of 2003.

Follow up Survey

The follow-up survey was annually conducted using population registries in local municipalities to determine the vital and residential status of the cohort. All deaths that occurred in the cohort were ascertained by death certificates from local public health centers in the study areas with the permission from the Director-General of the Prime Minister's Office (Ministry of Public Management, Home Affairs, Post, and Telecommunications). The causes of death were coded according to the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD10) by verifying computer-stored data in the Ministry of Health, Labour, and Welfare. Diagnosis of ovarian cancer was defined by code C56 in ICD10. Regarding the cancer site, diagnoses of cancer are usually confirmed according to pathological methods such as biopsy in Japan. Thus the completeness of the resident registration and the quality of death certificates for sites of ovarian cancer were substantially ascertained. All subjects who moved out of the study areas were treated as censored subjects. Although a total of 3,004 (4.7%) female subjects moved out of the study areas, we could not find any difference in ovarian cancer death among the study areas.

Questionnaire

In the baseline survey, a self-administered questionnaire was used to obtain past and family medical history, menstrual and reproductive history, sex hormone use, and lifestyles such as smoking, alcohol consumption, and physical activity. As for diet, the questionnaire elicited the intake frequency of 32 food items. The subjects were asked about daily intake frequencies of the foods at the baseline survey. The 32 items were pork, beef, chicken, ham and sausage, liver, eggs, fish (raw, grilled or boiled fish, excluding processed and preserved fish), boiled fish paste ('kamaboko' in Japanese), dried or salted fish, milk, cheese, butter, yogurt, margarine, fried foods, fried vegetables, cabbage and lettuce, Chinese cabbage, green leafy vegetables, carrots and squash, tomatoes, edible wild plants ('sansai' in Japanese), mushrooms, potatoes, seaweed, pickles, foods boiled down in soy sauce ('tsukudani' in Japanese), boiled beans, soybean curd (tofu), oranges, fruits other than oranges, and fruit juice. There were 5 categories pertaining to intake frequency (seldom, 1–2 times a month, 1–2 times a week, 3–4 times a week, and almost every day). Reproducibility of the food frequency questionnaire (FFQ) was evaluated by conducting it twice one year apart on 85 participants selected from the study areas and comparing the results. The intake frequencies of the two FFQs had good agreement, showing the Spearman's correlation coefficient ranging from 0.42 (edible wild plants) to 0.71 (liver) (11). We also asked about the use of vitamin supplementation in the questionnaire. However, in Japan it was not common at the baseline survey; thus, we did not include it in this examination.

Statistical Analyses

Among female subjects, the mean follow-up period was 13.3 years (standard deviation 2.9), and 77 women died of ovarian cancer during the observation period. At first, we assessed the potential confounding effects of several factors adjusting for age. These criteria included past and family medical history, menstrual and reproductive history, sex hormone use, lifestyle, and body mass index (BMI). Second, we selected some variables from the above-mentioned items as potential confounding factors to calculate hazard ratios (HRs) and 95% confidence intervals (95% CIs) for dietary habits, because cases of ovarian cancer death were so small that adequate HRs would not be obtainable if those items were all concomitantly considered. The selected variables were menopausal status, number of pregnancies, history of sex hormone use, BMI, physical activity, and education. These variables were either considered as possible risk factors of ovarian cancer in the previous epidemiological reports (2,3) or revealed significance in the first analyses assessing confounding potentiality. Unfortunately, the effect was not adjusted for total energy or for its surrogates because diet was measured by a simple food frequency method. The five categories of food frequency were integrated into three groups by considering a balance of person-years in each group. HRs of the highest and intermediate intakes compared with the lowest were calculated with Cox's proportional hazards model using the PHREG procedure in the SAS (Statistical Analysis System) package (12). Because there were substantial differences in the frequency of food intake among geographical areas, HRs were obtained by stratification of observed regions using the 'strata' statement of the procedure. These differences were attributable to accessibility to certain foods and local culture (13).

The dose-response trend was tested by evaluating the regression coefficient when the three intake categories were treated as equally spaced numeric variables in Cox's model. P values <0.05 were considered significant. The Ethics Boards from the Nagoya University School of Medicine approved this investigation.

Results

Subjects' Age and Characteristics

The distribution of subjects for this study according to age and individual characteristics is shown in Table 1. Increment of age was significantly associated with risk of ovarian cancer death. The number of pregnancies and one of childbirth showed significant inverse associations with the risk. BMI ≥25.0 and an adequate physical activity were also inversely associated with the risk, though their HRs did not reach the level of significance. Age at menarche, menopausal status,

Table 1. Age Distrbution and Age Adjusted Hazard Ratios and 95% Confidence Intervals of Ovarfan Cancer Death

Age at Baseline Survey	Category	Subjects[a]	Cases[a]	HR[b]	95% CI[c]	*P* value
57.8 ± 10.1 years	40–49	15.391 (24.2)	15 (19.5)	1.00		
(Mean ± standard deviation)	50–59	19.720 (31.0)	23 (29.9)	1.23	0.64–2.35	0.54
	60–69	19.391 (30.5)	25 (32.5)	1.45	0.77–2.76	0.25
	70–79	9.039 (14.2)	14 (18.2)	1.99	0.96–4.12	0.07
	Total	63.541 (100%)	77 (100%)			Trend *P* = 0.01
Items	**Categories**	**Subjects[a]**	**Cases[a]**	**HR[d]**	**95% CI**	***P* value**
Age at menarche	≤14	24,385 (42.6)	23 (35.9)	1.00		
	≥15	32,922 (57.4)	41 (64.1)	1.21	0.71–2.09	0.49
Menopausal status	No	24,424 (38.4)	27 (35.1)	1.00		
	Yes	39,117 (61.6)	50 (64.9)	0.88	0.54–1.42	0.59
Number of pregnancy	0	2,001 (3.5)	6 (9.0)	1.00		
	≥1	54,968 (96.5)	61 (91.0)	0.38	0.17–0.89	0.03
Number of childbirth	0	2,054 (3.7)	6 (9.0)	1.00		
	≥1	54,077 (96.3)	61 (91.0)	0.40	0.17–0.92	0.03
Age at first birth	≤24	26,284 (50.0)	29 (47.5)	1.00		
	≥25	26,299 (50.0)	32 (52.5)	1.08	0.65–1.79	0.76
History of sex hormone use	No	45,310 (95.1)	52 (92.9)	1.00		
	Yes	2,359 (4.9)	4 (7.1)	1.51	0.54–4.17	0.43
History of cancer in first-degree relatives	No	49,521 (77.9)	62 (80.5)	1.00		
	Yes	14,020 (22.1)	15 (19.5)	0.90	0.51–1.58	0.71
Body mass index (BMI)	<18.5	3,728 (6.3)	6 (9.1)	1.71	0.72–4.06	0.23
	18.5–25.0	42,143 (70.9)	39 (59.1)	1.00		
	≥25.0	13,545 (22.8)	21 (31.8)	1.69	0.99–2.87	0.054
Physical activity	Seldom	38,376 (76.1)	49 (86.0)	1.00		
	≥1–2 hours/week	12,032 (23.9)	8 (14.0)	0.51	0.24–1.07	0.08
Smoking	No	50,914 (92.7)	58 (95.1)	1.00		
	Yes	4,013 (7.3)	3 (4.9)	0.68	0.21–2.18	0.52
Alcohol consumption	No	42,442 (73.8)	53 (81.5)	1.00		
	Yes	15,044 (26.2)	12 (18.5)	0.65	0.35–1.23	0.19
Education	<15 years old	19,423 (38.4)	22 (42.3)	1.00		
	≤16 years old	31,202 (61.6)	30 (57.7)	1.01	0.57–1.78	0.98

[a]: Number (%).
[b]: Hazard ratio (unadjusted).
[c]: Confidence interval.
[d]: HR adjusted for age (category).

age at first birth, history of sex hormone use, history of cancer in first-degree relatives, smoking, alcohol consumption, and education were not associated with the risk. Unfortunately, we could not adopt all of the items as potential confounding factors to calculate the HRs for dietary habits because of the low number of ovarian cancer deaths.

Hazard Ratios Adjusted for Age

Hazard ratio 1 (HR1) in Table 2 shows major findings regarding the relation between risk of ovarian cancer death and intake frequencies of various kinds of foods after adjusting only for age. No significant associations were found between risk and intakes of pork, beef, chicken, ham and sausage, eggs, and fresh fish. However, the highest intake of dried or salted fish was significantly associated with the risk compared with the lowest, and the risk increased dose-dependently. No significant associations were found between the risk of ovarian cancer death and intakes of milk and dairy products (cheese, butter, and yogurt).

Regarding the consumption of vegetables, the highest and intermediate intakes of Chinese cabbage were significantly associated with the risk of ovarian cancer death. However, intakes of cabbage and lettuce, green leafy vegetables, carrots and squash, tomatoes, and potatoes were not associated the risk. The highest intake of soybean curd (tofu) was inversely associated with the risk of ovarian cancer death compared with the lowest, and the risk decreased dose-dependently. Intakes of oranges, fruits other than oranges, and fruit juice were not significantly associated with the risk. Regarding other foods which were not shown in Table 2, none of them was associated with the risk of ovarian cancer death in the present study.

Hazard Ratios Adjusted for Age and Selected Confounding Factors

Hazard ratio 2 (HR2) in Table 2 shows the relations between risk of ovarian cancer death and intake frequencies of various kinds of foods after adjusting for age and selected

Table 2. Hazard Ratios and 95% Confidence Itervals of Ovarian Cancer Dealh

Items	Categories	Cases[a]	HR1[b]	95% CI[c]	HR2[d]	95% CI
Pork	≤1–2 times/monlh	13 (25.5)	1.00		1.00	
	1–2 times/week	23 (45.1)	1.27	0.64–2.51	1.26	0.55–2.88
	≥3–4 times/week	15 (29.4)	1.72	0.81–3.65	1.59	0.62–4.08
			Trend $P = 0.16$		Trend $P = 0.34$	
Beef	Seldom	13 (28.9)	1.00		1.00	
	1–2 times/month	13 (28.9)	0.92	0.42–1.97	1.06	0.41–2.75
	≥1–2 times/week	19 (42.2)	1.12	0.55–2.27	1.24	0.50–3.05
			Trend $P = 0.73$		Trend $P = 0.63$	
Chicken	≤1–2 times/month	15 (28.3)	1.00		1.00	
	1–2 times/week	27 (50.9)	1.21	0.64–2.28	1.22	0.54–2.77
	≥3–4 times/week	11 (20.8)	1.05	0.48–2.29	1.13	0.40–3.17
			Trend $P = 0.84$		Trend $P = 0.77$	
Ham and sausge	≤1–2 times/monlh	27 (47.4)	1.00		1.00	
	1–2 tines/week	16 (28.1)	0.84	0.45–1.57	0.73	0.31–1.73
	≥3-4 times/week	14 (24.6)	1.47	0.77–2.83	0.91	0.30–2.76
			Trend $P = 0.38$		Trend $P = 0.68$	
Eggs	≤1–2 times/week	25 (34.7)	1.00		1.00	
	3–4 times/week	21 (29.2)	0.84	0.47–1.50	0.76	0.33–1.77
	Almost every day	26 (36.1)	0.71	0.41–1.23	0.65	0.30–1.41
			Trend $P = 0.22$		Trend $P = 0.27$	
Fresh fish	≤1–2 times/week	29 (45.3)	1.00		1.00	
	3–4 times/week	17 (26.6)	0.66	0.36–1.20	1.20	0.55–2.63
	Almost every day	18 (28.1)	0.91	0.51–1.65	1.33	0.59–2.98
			Trend $P = 0.63$		Trend $P = 0.48$	
Dried or salted fish	≤1–2 times/month	10 (20.8)	1.00		1.00	
	1–2 times/week	18 (37.5)	1.55	0.72–3.36	1.55	0.61–3.94
	≥3-4 tines/week	20 (41.7)	2.30	1.08-4.92*	2.80	1.14–6.89*
			Trend $P = 0.03$		Trend $P = 0.02$	
Milk	≤1–2 times/month	16 (22.9)	1.00		1.00	
	1–4 times/week	17 (24.3)	0.95	0.48–1.88	1.38	0.49–3.90
	Almost every day	37 (52.9)	1.27	0.71–2.29	1.67	0.66–4.23
			Trend $P = 0.35$		Trend $P = 0.27$	
Cheese	Seldom	24 (51.1)	1.00		1.00	
	1–2 times/month	12 (25.5)	1.04	0.52–2.10	1.36	0.55–3.34
	≥1–2 times/week	11 (23.4)	1.16	0.56–2.36	1.66	0.65–4.25
			Trend $P = 0.70$		Trend $P = 0.27$	
Butter	Seldom	24 (51.1)	1.00		1.00	
	1–2 times/month	10 (21.3)	0.91	0.43–1.90	0.81	0.29–2.27
	≥1–2 times/week	13 (27.7)	1.03	0.52–2.02	1.35	0.56–3.25
			Trend $P = 0.98$		Trend $P = 0.59$	
Yogurt	Seldom	24 (51.1)	1.00		1.00	
	1–2 times/month	9 (19.1)	1.02	0.47–2.19	1.53	0.59–3.93
	≥1–2 times/week	14 (29.8)	1.13	0.58–2.18	1.66	0.71–3.91
			Trend $P = 0.73$		Trend $P = 0.24$	
Cabbage and lettuce	≤1–2 times/week	26 (48.1)	1.00		1.00	
	3–4 times/week	11 (20.4)	0.50	0.25–1.02	0.70	0.29–1.68
	Almost every day	17 (31.5)	0.80	0.44–1.48	1.23	0.57–2.62
			Trend $P = 0.39$		Trend $P = 0.64$	
Chinese cabbage	≤1–2 times/month	4 (8.0)	1.00		1.00	
	1–2 times/week	21 (42.0)	3.22	1.10–9.36*	8.15	1.07–62.36*
	≥3–4 times/week	25 (50.0)	2.95	1.03–8.49*	10.28	1.38–76.84*
			Trend $P = 0.09$		Trend $P = 0.01$	
Green leafy vegetables	≤1–2 times/week	22 (39.3)	1.00		1.00	
	3–4 times/week	20 (35.7)	1.04	0.57–1.90	1.67	0.74–3.77
	Almost every day	14 (25.0)	0.62	0.32–1.22	0.87	0.34–2.22
			Trend $P = 0.18$		Trend $P = 0.82$	
Carrots and squash	≤1–2 times/week	27 (49.1)	1.00		1.00	
	3–4 times/week	19 (34.5)	1.02	0.57–1.83	1.40	0.66–2.98
	Almost every day	9 (16.4)	0.67	0.32–1.43	1.11	0.45–2.77
			Trend $P = 0.37$		Trend $P = 0.69$	
Tomatoes	≤1–2 times/month	23 (41.8)	1.00		1.00	
	1–2 times/week	15 (27.3)	0.69	0.36–1.33	0.67	0.26–1.70
	≥3–4 times/week	17 (30.9)	0.62	0.33-1.16	0.96	0.43–2.10
			Trend $P = 0.13$		Trend $P = 0.93$	

Table 2. Hazard Ratios and 95% Confidence Itervals of Ovarian Cancer Dealh (*Continued*)

Items	Categories	Cases[a]	HRI[b]	95% CI[c]	HR2[d]	95% CI
Potatoes	≤1–2 times/week	33 (46.5)	1.00		1.00	
	3–4 times/week	22 (31.0)	0.90	0.52–1.55	1.15	0.52–2.56
	Almost every day	16 (22.5)	1.04	0.57–1.89	1.54	0.66–3.61
			Trend P = 0.99		Trend P = 0.33	
Soybean curd (tofu)	≤1–2 times/week	28 (43.8)	1.00		1.00	
	3–4 times/week	22 (34.4)	0.72	0.41–1.26	0.90	0.42–1.92
	Almost every day	14 (21.9)	0.49	0.26–0.93*	0.61	0.26–1.45
			Trend P = 0.03		Trend P = 0.27	
Oranges	≤1–2 times/week	20 (37.0)	1.00		1.00	
	3–4 times/week	6 (11.1)	0.45	0.18–1.11	0.54	0.20–1.52
	Almost every day	28 (51.9)	1.12	0.63–2.00	0.91	0.44–1.91
			Trend P = 0.60		Trend P = 0.83	
Fruits other than oranges	≤1–2 times/week	16 (32.0)	1.00		1.00	
	3–4 times/week	5 (10.O)	0.38	0.14–1.05	0.63	0.21–1.85
	Almost every day	29 (58.0)	1.29	0.70–2.38	1.32	0.61–2.90
			Trend P = 0.27		Trend P = 0.39	
Fruit juice	Seldom	13 (29.5)	1.00		1.00	
	≤1–2 times/week	15 (34.1)	0.69	0.33–1.46	0.69	0.28–1.71
	≥3–4 times/week	16 (36.4)	0.83	0.40–1.72	0.93	0.39–2.22
			Trend P = 0.67		Trend P = 0.95	

[a]: Number (%).
[b]: Hazard ratio adjusted for age.
[c]: Confidence interval.
[d]:Hazard ratio adjusted for age (category), menopausal status, number of pregnancies, history of sex hormone use, BMI, physical activity, and education (categories in Table 1).
*P value < 0.05.

confounding factors. The highest and intermediate intakes of Chinese cabbage and the highest intake of dried or salted fish were still positively associated with the risk of ovarian cancer death, which increased dose-dependently. However, HR for the highest intake of soybean curd (tofu) was attenuated, and did not remain significant. Regarding HRs for other kinds of foods, no significant change was found after being adjusted for age and selected confounding factors.

Discussion

It has been reported that ovarian cancer was associated with menstrual and reproductive, anthropometric, and lifestyle factors (2). Our result regarding the age at menarche was not associated with risk of ovarian cancer death, yet the number of pregnancies and one of childbirth showed significant inverse associations with the risk, as was reported in previous studies (2–4). The use of sex hormones is a crucial factor affecting the development of ovarian cancer. Intake of oral contraceptives has a substantial and well-documented protective effect against ovarian cancer (2–4). Conversely, the experience of hormone replacement therapy may be related to a slight increase in the risk (14). We could find no significant effect on the risk of ovarian cancer death regarding the use of sex hormones because we simply asked the history of sex hormone use, and could not differentiate the use of oral contraceptives from hormone replacement therapy.

Hereditary history of cancer is another important factor which affects the development of breast or ovarian cancer in first-degree relatives (2). However, the association of cancer in first-degree relatives did not show a significant association with the risk.

According to some studies, obesity represents an independent risk factor related to ovarian cancer (15–19), and analogously, increasing total physical activity was associated with a lower risk of ovarian cancer (20,21). Although, in the present study HRs for BMI and physical activity did not reach such a level of statistical significance, their associations with ovarian cancer were consistent with the recent reports.

There are data showing that cigarette smoking is associated with the risk of developing ovarian cancer (22,23). However, our result regarding smoking history showed no association with the risk of ovarian cancer death. In this study, we could make only two categories, "yes" and "no," to evaluate the effect of smoking on the risk because of the low number of ovarian cancer deaths. The relationship between smoking and various histological types of ovarian cancer was reported early (24), and thus it is necessary for our study to obtain more precise information regarding histological types, such as mucinous or not. The effect of alcohol consumption on ovarian cancer is conflicting. Recent studies have found that alcohol does not increase the risk of developing ovarian cancer (25,26), which is congruent with our result.

It has been suggested that high red meat intake slightly increases ovarian cancer risk, while white meat such as poultry intake seems to have protective effects (2). A decreased risk associated with milk intake was reported in Taiwan (27), though an increased risk has been shown in the Swedish Mammography Cohort (28). Additionally, it has been suggested that consumption of red meat, fish, or eggs does not have any considerable influence on the risk of ovarian cancer in middle-aged and older women (29). According to a meta-analysis, milk and dairy products were not found to be associated with ovarian cancer risk (30). Red meat, white meat, eggs, fresh fish, milk, and dairy products were not associated with the risk of ovarian cancer death in the present study. However, intake of dried or salted fish was significantly associated with the risk. Dried or salted fish is usually grilled and eaten. Thus, one possible explanation is that salted foods such as fish and meat are known to be a source of nitrosamines, which have carcinogenetic properties (31), and nitrosamines are produced by the grilling process.

There are several biologically plausible reasons why consumption of vegetables and fruits might prevent the appearance of cancer; they are rich in antioxidative micronutrients such as carotenoids, vitamin C, and vitamin E, as well as other anti-carcinogenic agents (32,33). It was also suggested that dietary vitamin A and β-carotene were modestly protective against ovarian cancer (34). Some epidemiological studies suggested that high consumption of vegetables could potentially reduce the risk of ovarian cancer; however, consumption of fruits did not show the same results (35–37). Moreover, in a recent cohort study, no significant relation was found between the intake of vegetables and fruits and incidence of ovarian cancer (38). Another cohort study with a large sample size also showed that a high intake of vegetables and fruits did not seem to provide protection against ovarian cancer (39). Our results were not able to elucidate the protective effect of vegetables and fruits against the risk of ovarian cancer death. Further study should be conducted in reference to the protective roles of vegetables and fruits.

Cabbage, broccoli, and other members of the genus *Brassica* have been widely regarded as potentially containing cancer-preventing agents (40). Although Chinese cabbage belongs to this same group, we found that high intake of Chinese cabbage was positively associated with the risk of ovarian cancer death in the present study. One possible explanation is that Japanese often eat pickled Chinese cabbage. Processing vegetables may decrease micronutrients such as antioxidants and vitamins (27). Supporting this theory, it was reported that pickled vegetable intake was associated with an increased risk of developing ovarian cancer (41). However, a further well-designed cohort study is needed to clarify the relationship between intake of Chinese cabbage and the risk of ovarian cancer death.

Recently, much focus has been placed on the protective qualities of soy-based foods against female malignancies such as breast cancer and endometrial cancer, in regard to their anti-estrogenic effects (6–8). In addition, it has been reported that intake of soy and isoflavone was inversely associated with the risk of ovarian cancer (9). In the present study, a significant preventive association was found between the intake of soybean curd (tofu) and the risk of ovarian cancer death after adjusting for age. However, after adjusting for age and other confounding factors, the statistical significance was negated. This may be the result of the low number of ovarian cancer deaths among participants. Intake of soy products is a very interesting issue at the forefront of preventing estrogen-related cancers.

Several limitations of the present study should be mentioned. First, the number of ovarian cancer deaths was very low in spite of a large scale cohort study, partly because of low mortality relating to ovarian cancer in Japan (18). Therefore, we could not present adequate HRs for ovarian cancer death. It is necessary to examine the HRs again using a sufficient number of cases in the future. Second, the participants in this cohort were not only people attending health screening programs, but also volunteers from the general population. This means that almost all of the participants may be more health-conscious and have better lifestyles than the general population itself. This selection bias could possibly make it difficult to detect the prospective effect of having a healthy lifestyle. Third, we could not adjust for total energy because a quantitative estimate of food consumption was not available. Regarding the reproducibility of FFQ examined by Spearman correlation coefficients, it should be assessed by more appropriate methods such as Kappa coefficient. Moreover, we could not disregard that people change their habits and lifestyles over time. Suzuki et al. reported that the dietary practices of subjects in the JACC Study had changed over 5 yr (42). Finally, co-morbidity of female malignancies such as breast cancer and endometrial cancer should be considered comprehensively, because these cancers are competitive and have been shown to share the same etiology (2).

In conclusion, the present study was conducted to prospectively assess the effect of dietary factors on the risk of ovarian cancer death in a large cohort of Japanese people. It was suggested that high intakes of dried or salted fish and Chinese cabbage could be potentially associated with the risk of ovarian cancer death. In contrast, a high intake of soy bean curd (tofu) may have preventive effects.

Acknowledgments and Notes

The authors wish to express their appreciation to Dr. Kunio Aoki, Professor Emeritus, Nagoya University School of Medicine and former chairman of the JACC Study Group, Dr. Yoshiyuki Ohno, former chairman of the study group, Asahi Rosai Hospital, and also Dr. Haruo Sugano, the former Director, Cancer Institute of the Japanese Foundation for Cancer Research, who greatly contributed to the initiation of the study. The present investigators in the JACC Study Group are as follows: Dr. A. Tamakoshi (present chairman of the study group), National Center for Geriatrics and Gerontology, Dr. M. Mori, Sapporo Medical University School of Medicine, Dr. Y. Motohashi, Akita University School of Medicine, Dr. K. Sakata, Iwate Medical University, Dr. I. Tsuji, Tohoku University Graduate School of Medicine, Dr. Y. Nakamura, Jichi Medical School, Dr. H. Mikami, Chiba Cancer Center, Dr. Y. Inaba, Juntendo University School of Medicine, Dr. Y. Hoshiyama, University of Human arts and Science, Dr. K. Wakai, Aichi cancer Center Research Institute, Dr. H. Suzuki, Niigata University Graduate School of Medical and Dental Science, Dr. H. Shimizu, Gifu University School of Medicine, Dr. H. Toyoshima, Nagoya University Graduate School of Medicine, Dr. S. Tokudome, Nagoya City University Graduate School of Medicine, Dr. S. Hashimoto and K. Suzuki, Fujita Health University School of Medical Science, Dr. S. Kikuchi, Aichi Medical University School of Medicine, Dr. A. Koizumi, Graduate School of Medicine and Faculty of Medicine, Kyoto University, Dr. T. Kawamura, Kyoto University Health Service, Dr. Y. Watanabe, K. Ozasa and Dr. T. Miki, Kyoto Prefectural

University of Medicine, Graduate School of Medical Science, Dr. H. Iso, Osaka University Graduate School of Medicine, Dr. C. Date, Faculty of Human Life and Environment, Nara Women's University, Dr. T. Nose and Y. Kurozawa, Tottori University Faculty of Medicine, Y. Fujino, University of Occupational and Environmental Health, Dr. T. Yoshimura, Fukuoka Institute of Occupational Health, Dr. A. Shibata, Kurume University School of Medicine Dr. N. Okamoto, Kanagawa Cancer Center, Dr. H. Shio, Moriyama Municipal Hospital, A. Yamamoto, Hyogo Prefectural Institute of Public Health and Environment Science, Dr. T. Kitagawa, Cancer Institute of the Japanese Foundation for Cancer Research, Dr. T. Kuroki, Gifu University, and Dr. K. Tajima, Aichi Cancer Center Research Institute. The former investigators in JACC Study Group are presented as the following (affiliations are those when they participated in the study): Dr. S. Hisamichi, Tohoku University Graduate School of Medicine, Dr. T. Shimamoto, University of Tsukuba, Dr. H. Tanaka, Tokyo Medical and Dental University, Dr. Y. Ito, Fujita Health University School of Health Sciences, Dr. M. Nakao, Kyoto Prefectural University of Medicine, Dr. T. Suzuki, Osaka Medical Center for Cancer and Cardiovascular Diseases, Dr. T. Hashimoto, Wakayama Medical University, Dr. N. Hayakawa, Research Institute for Radiation Biology and Medicine, Hiroshima University, Dr. K. Fukuda, Kurume University School of Medicine, and Dr. T. Ishibashi, Asama General Hospital. This work was supported by a Grant-in-Aid for Scientific Research on Priority Areas (2) (No. 14031221) from the Ministry of Education, Culture, Sports, Science, and Technology of Japan. The JACC Study was also supported by Grants-in-Aid for Scientific Research from the same ministry (Nos. 61010076, 62010074, 63010074, 1010068, 2151065, 3151064, 4151063, 5151069, 6279102, 1181101 and 17015022).

Address correspondence to Fumio Sakauchi, Department of Public Health, Sapporo Medical University School of Medicine, South 1, West 16, Chuo-ku, Sapporo 060-8556, Japan. Tel: +81-11-611-2111, ext. 2741. Fax: +81-11-641-8101. E-mail: sakauchi@sapmed.ac.jp

Submitted 27 February 2006; accepted in final form 13 October 2006.

References

1. Young RC: Gynecological malignancies. In *Harrison's Principles of Internal Medicine,* 15th ed, Braunwald E, Fauci AS, Kasper DL, Hauser SL, Longo DL, Jameson JL (eds). McGraw-Hill, 2001, pp 620–622.
2. Zografos GC, Panou M, and Panou N: Common risk factors of breast and ovarian cancer: recent view. *Int J Gynecol Cancer* **14**, 721–740, 2004.
3. Pike MC, Pearce CL, and Wu AH: Prevention of cancer of the breast, endomerium and ovary. *Oncogene* **23**, 6379–6391, 2004.
4. Riman T, Nisson S, and Persson IR: Review of epidemiological evidence for reproductive and hormonal factors in relation to the risk of epithelial ovarian malignancies. *Acta Obstet Gynecol Scand* **83**, 783–795, 2004.
5. Friedenrich CM and Orenstein MR: Physical activity and cancer prevention: Etiologic evidence and biological mechanism. *J Nutr* **132**, 3456S–3464S, 2002.
6. Dai Q, Franke AA, Jin F, Shu X-O, Hebert JR, et al.: Urinary excretion of phytoestrogens and risk of breast cancer among Chinese women in Shanghai. *Cancer Epidemiol Biomarkers Prev* **11**, 815–821, 2002.
7. Dai Q, Franke AA, Yu H, Shu X, Jin F, et al.: Urinary phytoestrogen excretion and breast cancer risk. *Cancer Epidemiol Biomarkers Prev* **12**, 497–502, 2003.
8. Xu WH, Zheng W, Xiang YB, Raun ZX, Cheng JR, et al.: Soya food intake and risk of endometrial cancer among Chinese women in Shanghai: population based case-control study. *BMJ* **328**, 1285–1288, 2004.
9. Zhang M, Xie X, Lee AH, and Binns CW: Soy and isoflavone are associated with reduced risk of ovarian cancer in south China. *Nutr Cancer* **49**, 125–130, 2004.
10. Ohno Y, Tamakoshi A, and the JACC Study Group: Japan collaborative cohort study for evaluation of cancer risk sponsored by Monbusho (JACC Study). *J Epidemiol* **11**, 144–150, 2001.
11. Date C, Fukui M, Yamamoto A, Wakai K, Ozeki A, et al.: Reproducibility and validity of a self-administered food frequency questionnaire used in the JACC Study. *J Epidemiol* **15**, 9s–23s, 2005.
12. SAS Institute: *SAS Technical Report P-217, SAS/STAT Software,* 1–52. SAS Institute, Inc., Cary, NC, 1991.
13. Iso H, Date C, Noda H, Yoshimura T, Tamakoshi A, for the JACC Study Group: Frequency of food intake and estimated nutrient intake among men and women: the JACC Study. *J Epidemiol* **15**, 24s–42s, 2005.
14. Glud E, Kjaer SK, Thomsen BL, Høgdall C, Christensen L, et al.: Hormone therapy and the impact of estrogen intake on the risk of ovarian cancer. *Arch Intern Med* **164**, 2253–2259, 2004.
15. Engeland A, Tretli S, and Bjorge T: Height, body mass index, and ovarian cancer: a follow-up of 1.1 million Norwegian women. *J Natl Cancer Inst* **95**, 1244–1248, 2003.
16. Anderson JP, Ross JA, and Folsom AR: Anthropometric variables, physical activity, and incidence of ovarian cancer: the Iowa Women's Health Study. *Cancer* **100**, 1515–1521, 2004.
17. Riman T, Dickman PW, Nilsson S, Nordlinder H, Magnusson CM, et al.: Some life-style factors and the risk of invasive epithelial ovarian cancer in Swedish women. *Eur J Epidemiol* **19**, 1011–1019, 2004.
18. Mori M, Nishida T, Sugiyama T, Komai K, Yakushiji M, et al: Anthropometric and other risk factors for ovarian cancer in case-control study. *Jpn J Cancer Res* **89**, 246–253, 1998.
19. Zhang M: Body weight and body mass index and ovarian cancer risk: case-control study in China. *Gynecol Oncol* **98**, 228–234, 2005.
20. Zhang M, Lee AH, and Binns CW: Physical activity and epithelial ovarian cancer risk: a case-control study in China. *Int J Cancer* **105**, 838–843, 2003.
21. Zhang M, Xie X, Lee AH, and Binns CW: Sedentary behaviors and epithelial ovarian cancer risk. *Cancer Causes Control* **15**, 83–89, 2004.
22. Zhang Y, Coogan PF, Palmer JR, Strom BL, and Rosenberg L: Cigarette smoking and increased risk of mucinous epithelial ovarian cancer. *Am J Epidemiol* **159**, 133–139, 2004.
23. Pan SY, Ugnat AM, Mao Y, Wen SW, and Johnson KC: Association of cigarette smoking with the risk of ovarian cancer. *Int J Cancer* **111**, 124–130, 2004.
24. Koch M: Risk factors in ovarian cancer of epithelial origin by pathological diagnosis. *Br J Cancer* **59**, 257–258, 1989.
25. Webb PM, Purdie DM, Bain CJ, and Green AC: Alcohol, wine, and risk of epithelial ovarian cancer. *Cancer Epidemiol Biomarkers Prev* **13**, 592–599, 2004.
26. Schouten LJ, Zeegers MP, Goldbohm RA, and van den Brandt PA: Alcohol and ovarian cancer risk: results from the Netherlands Cohort Study. *Cancer Causes Control* **15**, 201–209, 2004.
27. Yen ML, Yen BL, Bai CH, and Lin RS: Risk factors for ovarian cancer in Taiwan: a case-control study in a low-incidence population. *Gynecol Oncol* **89**, 318–324, 2003.
28. Larsson SC, Bergkvist L, and Wolk A: Milk and lactose intake and ovarian cancer risk in the Swedish Mammography Cohort. *Am J Clin Nutr* **80**, 1353–1357, 2004.
29. Larsson SC, and Wolk A: No association of meat, fish, and egg consumption with ovarian cancer risk. *Cancer Epidemiol Biomarkers Prev* **14**, 1024–1025, 2005.
30. Qin LQ, Xu JY, Wang PY, Hashi A, Hoshi K, et al.: Milk/dairy products consumption, galactose metabolism and ovarian cancer: meta-analysis of epidemiological studies. *Eur J Cancer Prev* **14**, 13–19, 2005.
31. Balbi JC, Larrinaga MT, Stefani ED, Mendilaharsu M, Ronco AL, et al.: Foods and risk of bladder cancer: a case-control study in Uruguay. *Eur J Cancer Prev* **10**, 453–458, 2001.
32. Steinmetz KA and Potter JD: Vegetables, fruits, and cancer. II Mechanisms. *Cancer Causes and Control* **2**, 427–442, 1991.
33. Stewart BW, McGregor D, and Kleihues P: *Principles of Chemoprevention* 61–90. IARC Sci Publ, Lyon, 1996.
34. Tung KH, Wilkens LR, Wu AH, McDuffie K, Hankin JH, et al.: Association of dietary vitamin A, carotenoids, and other antioxidants with the risk of ovarian cancer. *Cancer Epidemiol Biomarkers Prev* **14**, 669–676, 2005.

35. Schulz M, Lahmann PH, Riboli E, and Boeing H: Dietary determinants of epithelial ovarian cancer: a review of the epidemiologic literature. *Nutr Cancer* **50,** 120–140, 2004.
36. Pan SY, Ugnat AM, Mao Y, Wen SW, and Johnson KC: A case-control study of diet and the risk of ovarian cancer. *Cancer Epidemiol Biomarkers Prev* **13,** 1521–1527, 2004.
37. Larsson SC, Holmberg L, and Wolk A: Fruit and vegetable consumption in relation to ovarian cancer incidence: the Swedish Mammography Cohort. *Br J Cancer* **90,** 2167–2170, 2004.
38. Fairfield KM, Hankinson SE, Rosner BA, Hunter DJ, Colditz GA, et al.: Risk of ovarian carcinoma and consumption of vitamins A, C, and E and specific carotenoids. *Cancer* **92,** 2318–2326, 2001.
39. Schulz M, Lahmann PH, Boeing H, Hoffmann K, Allen N, et al.: Fruit and vegetable consumption and risk of epithelial ovarian cancer: The European prospective investigation into cancer and nutrition. *Cancer Epidemiol Biomarkers Prev* **14,** 2531–2535, 2005.
40. Beecher C WW: Cancer preventive properties of varieties of Brasscica oleracea: a review. *Am J Clin Nutr* **59,** 1166S–1170S, 1994.
41. Zang M, Yang ZY, Binns CW, and Lee AH: Diet and ovarian cancer risk: a case-control study in China. *Br J Cancer* **86,** 712–717, 2002.
42. Suzuki S, Kawado M, Hashimoto S, Tokudome S, Yoshimura T, et al.: Change in food intake frequency at five years after baseline in the JACC Study. *J Epidemiol* **15,** S48–S55, 2005.

Statistical Data

Reproducibility of a Short Food Frequency Questionnaire for Japanese General Population

Nahomi Imaeda,[1] Chiho Goto,[2] Yuko Tokudome,[2] Kaoru Hirose,[3] Kazuo Tajima,[4] and Shinkan Tokudome.[5]

BACKGROUND: In epidemiologic field studies, a food frequency questionnaire (FFQ) is one of the most feasible tools to assess usual dietary habits. The purpose of this study is to evaluate the reproducibility of consumption of foods and nutrients assessed with a self-administered short FFQ in a Japanese general population.

METHODS: We have investigated 1-year interval reproducibility of a self-administered short FFQ, comprising 47 food items, and 8 frequency categories, among 1,918 subjects (844 males and 1,074 females) who participated in health check-up programs in Central Japan.

RESULTS: Intakes of energy and 24 nutrients along with 15 food groups estimated using the first questionnaire (FFQ1) were approximately equal to those using the second (FFQ2). Spearman's rank correlation coefficients (CCs) between intakes of nutrients quantified with FFQ1 and FFQ2 in males were distributed as 0.74 - 0.66- 0.55 (maximum - median - minimum), and intraclass CCs (ICCs) as 0.85 - 0.78 - 0.67. Among females, Spearman's rank CCs were distributed as 0.73 - 0.62 - 0.54, and ICCs as 0.84 - 0.77 - 0.69. Percentages of exact agreement, exact agreement plus agreement within adjacent categories and disagreement according to quintile categorization were 43%, 80%, and 1%, for males, and 42%, 79%, and 1% for females. Reproducibility figures were higher for the elderly than for young people in both sexes.

CONCLUSIONS: Our FFQ yielded substantially high reproducibility and it may be applicable for assessing consumption of foods/food groups and energy and selected nutrients for the middle-aged and elderly population in Japan.

J Epidemiol 2007; 17:100-107.

Key words: food frequency questionnaire, diet assessment method, one-year interval reproducibility, middle-aged and elderly Japanese population.

There has been increasing interest in lifestyle, including dietary habits, as an etiological factor for chronic diseases. To establish strategies for lifestyle alterations, we need to adopt a comprehensive approach for evaluating dietary habits, alcohol consumption, smoking, physical exercise, and stress. However, Japanese dietary patterns differ from those of Western developed countries, due to its distinctive culture, climate, food supply system, cooking methods, and standard serving sizes.[1-3] Japanese cuisine is rich in variety; for example, the major contributors of protein are rice, soybeans, and fish rather than meat and eggs. Moreover, people often enjoy not only Japanese foods but also Chinese, American, Italian, and French foods.

Received October 19, 2006, and accepted March 5, 2007.
This study was partly supported by a Research Grant from the Ministry of Health, Labour and Welfare and a Grant-in-Aid for Scientific Research on Special Priority Areas of Cancer from the Japanese Ministry of Education, Culture, Sports, Science and Technology.
[1] Department of Food Science and Nutrition, Faculty of Human Life and Environmental Sciences, Nagoya Women's University;
[2] Department of Health and Nutrition, School of Health and Human Life, Nagoya-bunri University;
[3] Department of Planning and Information, Aichi Prefectural Institute of Public Health.
[4] Division of Epidemiology and Prevention, Aichi Cancer Center Research Institute;
[5] Department of Health Promotion and Preventive Medicine, Nagoya City University Graduate School of Medical Sciences.
Address for correspondence: Nahomi Imaeda, Nagoya Women's University, 3-40 Shioji-cho, Mizuho-ku, Nagoya 467-8610, Japan. (e-mail: nimaeda@nagoya-wu.ac.jp)

Food frequency questionnaires (FFQs) are generally accepted to be appropriate for ranking individuals according to consumption of foods and nutrients in large epidemiologic studies.[4,5] When dealing with dietary data assessed with FFQs, validity and reproducibility are of note. Many articles concerning reproducibility of intake of foods and nutrients have been reported using various types of questionnaires, study subjects and time frames. Because most epidemiologic studies are based on FFQs with more than 100 items, subjects are forced to concentrate their attention for almost 1 hour. Therefore, we have evolved a self-administered short FFQ with only 47 items for dietary studies of the middle-aged and elderly general Japanese population.[6]

The present study aimed to explore reproducibility of a short FFQ with 47 items to elucidate whether it provides accurate information about full range of foods and nutrients. For this purpose, consumption of 15 foods and energy and 24 macro- and micronutrients was measured with the FFQs administered at a one-year interval to middle-aged and elderly Japanese.

METHODS

Subjects were healthy members of the general population who participated in annual health check-ups at worksites or community centers in Aichi Prefecture, Central Japan, in 2002 and 2003. Of 3,828 subjects who had the health check-ups in the first year, 2,357 subjects were repeat participants of the next year. In our survey, registered nurses or public health nurses carried out interviews to fill-in missing information. After excluding 171 males and 86 females who had missing values in FFQs, or 3 males whose consumption was estimated less than 1000 kcal/day (4,184 J/day), or 17 females whose consumption was those 800 kcal/day (3,347 J/day), and 162 people who reported changing their diet before the second FFQ due to their health condition, finally we included 1,918 (844 males and 1,074 females, 23-86 years old) who gave informed consent to the present study.

Intake of 15 foods/food groups and energy, 24 macro- and micro-nutrients was assessed in 2002 (hereafter FFQ1) and in 2003 (hereafter FFQ2). The nutrients were protein, fat, carbohydrate, minerals (potassium, calcium, and iron), vitamins (carotene, vitamins A, D, E, B_1, B_2, folate, and C) and total dietary fiber (TDF) (soluble DF and insoluble DF). Fat was divided into saturated fatty acids, monounsaturated fatty acids, n-6 and n-3 polyunsaturated fatty acids (PUFAs), and n-3 highly-unsaturated fatty acids (n-3 HUFAs, including icosapentaenoic acid (IPA, 20:5), docosapentaenoic acid (DPA, 22:5) and docosahexaenoic acid (DHA, 22:6)) and cholesterol. Consumption of foods (grams/day) and nutrients was calculated using typical/standard values from the literature.[7,8]

First, we compared average daily intake for foods/food groups, energy, and macro- and micro-nutrients according to the FFQ1 and FFQ2. Differences were expressed as percentage values after each value was logarithmically transformed and adjusted for total energy, to allow calculation of intra-class correlation coefficients (hereafter ICCs), and Spearman's rank correlation coefficients (hereafter CCs) for intake of selected foods and nutrients between the two FFQs.[9-13] Furthermore, we compared the ICCs by 10-year age group.

Dividing intakes of foods and nutrients into quintiles based on the FFQ1 and FFQ2, we calculated the degree of misclassification across the quintiles as follows: the proportions categorized into the same quintiles, those categorized into the same quintiles plus adjacent quintiles, or those categorized into the opposite quintiles.

All statistical analyses were performed using SPSS® version 12.0.

Instructions about the purpose of the present study were noted at the top of the questionnaire. We obtained informed consent from participants. The protocol was approved by the Ethical Review Committee of the Nagoya City University Graduate School of Medical Sciences.

RESULTS

Characteristics of study subjects

Mean ± standard deviation (SD) values for age were 56.6±13.4 years for males and 57.0±10.1 for females. At baseline, the body mass index (BMI: kg/m^2) were 23.3±2.7 for males and 22.2±2.9 for females, and no changes were evident at the second survey. According to the distribution for BMI by age, the percentages of overweight individuals (BMI=25+) were distributed from 22% to 34% by age group in males. The percentage of underweight (BMI<18.5) individuals under 40 years of age was 17% and those overweight accounted for only 4% in females.

Intake of foods/food groups

Table 1 shows comparisons between the average daily intake of foods/food groups according to the FFQ1 and FFQ2. The values were approximately equal at both time points. Spearman's rank CCs with energy-adjustment (maximum-median-minimum) were distributed as 0.80 (alcohol) - 0.65 - 0.57 (green tea, coffee) for males, and 0.69 (rice) - 0.60 - 0.54 (oils) for females. ICCs with log-transformation and energy-adjustment were distributed as 0.87 (alcohol) - 0.78 - 0.68 (green tea) for males, and 0.85 (alcohol) - 0.76 - 0.69 (rice) for females.

For males, percentages of exact agreement with energy-adjustment were distributed as 59% (alcohol) - 44% - 41% (oil, other vegetables and seaweed), and exact agreement plus agreement within adjacent categories were 91% (alcohol) - 80% - 75% (meat), the median for disagreement was 1% (Table 2). For females, percentages of exact agreement with energy-adjustment were distributed as 46% (rice, green tea) - 41% - 38% (oil), exact agreement plus agreement within adjacent categories were distributed as 83% (rice, dairy products) - 78% - 74% (meat), and the median for disagreement was also 1%. We could not categorize alcohol intake into quintiles for females because 70% had no drinking habits.

Table 1. Comparison of mean daily intakes of foods/food groups and correlation coefficients (CCs) with food frequency questionnaire 1 (FFQ1) and FFQ2 .

	Males (n= 844)					Females (n=1,074)				
	FFQ1	FFQ2		FFQ1 vs. FFQ2		FFQ1	FFQ2		FFQ1 vs. FFQ2	
Food group	Consumption (g/day)	Consumption (g/day)	% difference*	Spearman's rank CC	ICC**	Consumption (g/day)	Consumption (g/day)	% difference*	Spearman's rank CC	ICC**
Rice (cooked)	524 ±216	508 ±215	-3	0.65	0.80	334 ±108	327 ±112	-2	0.69	0.69
Bread, noodles and potatoes	112 ± 77	118 ± 74	5	0.60	0.71	104 ± 59	106 ± 59	2	0.60	0.70
Soybean and soybean products	85 ± 51	83 ± 50	-2	0.71	0.81	90 ± 47	90 ± 49	0	0.65	0.79
Green-yellow vegetables	63 ± 51	64 ± 51	2	0.63	0.78	83 ± 54	85 ± 60	2	0.62	0.77
Other vegetables and seaweed	71 ± 50	72 ± 46	2	0.65	0.78	100 ± 56	100 ± 59	0	0.56	0.72
Fruit	56 ± 53	54 ± 54	-3	0.66	0.82	81 ± 63	80 ± 68	-1	0.66	0.76
Fish and other seafoods	57 ± 36	60 ± 37	4	0.66	0.80	58 ± 31	59 ± 33	2	0.65	0.79
Meat	34 ± 22	35 ± 23	4	0.59	0.78	34 ± 19	33 ± 22	-2	0.57	0.83
Eggs	22 ± 17	22 ± 16	1	0.66	0.76	23 ± 14	22 ± 14	-4	0.57	0.73
Dairy products	112 ±105	113 ±100	0	0.75	0.83	159 ±111	164 ±115	4	0.69	0.83
Oil	16 ± 10	16 ± 10	3	0.59	0.73	18 ± 9	17 ± 11	-4	0.54	0.71
Confectioneries	17 ± 22	17 ± 17	-1	0.60	0.73	25 ± 22	24 ± 22	-5	0.62	0.76
Green tea	343 ±254	339 ±254	-1	0.57	0.68	423 ±218	431 ±215	2	0.59	0.75
Coffee	156 ±115	154 ±116	-1	0.57	0.69	211 ±109	216 ±108	2	0.59	0.76
Alcohol beverage	118 ±140	128 ±158	8	0.80	0.87	16 ± 50	18 ± 56	11	0.56	0.85
Median				0.65	0.78				0.60	0.76

*: (FFQ2-FFQ1)/FFQ1 (%)

**: intraclass correlation coefficient

Consumption (grams per day) are shown as mean ± standard deviation.

ICCs for nutrients were calculated after values were log-transformed and energy-adjusted.

Intake of energy, macro- and micro-nutrients

Table 3 lists crude values for daily intake of energy, macro- and micro-nutrients based on the FFQ1 and FFQ2. The differences were distributed from -4% to 4% and the intakes of foods and nutrients assessed with both FFQs were very similar to these of previous semi-quantitative FFQs with more than 100 items.[14,15]

When the values of nutrients intakes were energy-adjusted, Spearman's rank CCs were distributed as 0.74 (soluble DF) - 0.66 - 0.55 (vitamin B1) for males, and 0.73 (insoluble DF) - 0.62 - 0.54 (energy) for females. ICCs were distributed as 0.85 (total DF, insoluble DF, soluble DF) - 0.78 - 0.67 (vitamin B_1) for males, and 0.84 (insoluble DF) - 0.77 - 0.69 (vitamin B_1) for females. For both sexes, the Spearman's rank CCs and ICCs for calcium, iron, and dietary fiber were high.

Percentages of exact agreement were distributed as 47% (vitamin D, soluble DF) - 43% - 37% (vitamin B_1, n-3PUFAs), exact agreement plus agreement with adjacent categories as 85% (insoluble DF) - 80% - 75% (vitamin B_1, PUFAs, n-3PUFAs), and disagreement were distributed as 1-2% in males (Table 4). For females, the respective percentages were 44% (calcium, total DF, insoluble DF, soluble DF) - 42% - 34% (PUFAs), 84% (total DF, soluble DF) - 79% - 74% (vitamin B_1, PUFAs, n-3PUFAs, n-3HUFAs), and 0% (total DF, insoluble DF) - 1% - 3% (energy).

Reproducibility by age

As a whole, no significant differences were observed in reproducibility indices for foods/food groups across age groups (data not shown). The median values of ICCs were more than 0.73 for foods/food groups by age group in both sexes. Figures for people aged 50 years or older were generally high for both sexes, and values for the group over 70 years were highest at 0.79 for males and 0.78 for females. With respect to macro- and micro-nutrients, the median indices were more than 0.70 for both sexes. Figures for the group aged over 70 years, in particular, exhibited the highest value of 0.82 for males and 0.78 for females. Those values for most nutrients, however, in males under 40 years of age, were rather lower than those for over 70 years ($p<0.01$). Figures for energy intake among females under 40 years of age were somewhat lower than for other age groups. Accordingly, this FFQ yielded equivalent or higher reproducibility values compared with the full version of semi-quantitative FFQ administered to Japanese female dietitians.[15]

Table 2. Level of agreement according to quintile classification of daily intake of foods/food groups based on food frequency questionnair 1 (FFQ1) and FFQ2 (%).

	Males			Females		
	Agreement		Disagreement	Agreement		Disagreement
Food group	Same quintiles	Same and +/- 1 quintiles	Opposite quintiles	Same quintiles	Same and +/- 1 quintiles	Opposite quintiles
Rice (cooked)	44	82	2	46	83	1
Bread, noodles and potatoes	43	77	2	41	80	2
Soybean and soybean products	44	83	1	41	80	1
Green-yellow vegetables	44	79	1	40	80	1
Other vegetables and seaweed	41	80	2	39	76	2
Fruit	44	80	1	39	80	1
Fish and other seafoods	45	80	1	42	79	1
Meat	41	75	1	39	74	1
Eggs	46	80	1	42	76	2
Dairy products	51	85	1	45	83	1
Oil	41	77	1	38	76	2
Confectioneries	43	78	2	42	78	1
Green tea	45	78	2	46	77	2
Coffee	45	78	2	45	77	2
Alcohol beverage	59	91	1	-	-	-
Median	44	80	1	41	78	1

Proportions for nutrients were calculated after intakes were energy-adjusted.

Table 3. Comparison of mean daily intakes of selected nutrients and correlation coefficients (CCs) with food frequency questionnaire 1 (FFQ1) and FFQ2.

Nutrient	Males					Females				
	FFQ1	FFQ2		FFQ1 vs. FFQ2		FFQ1	FFQ2		FFQ1 vs. FFQ2	
	Consumption (g/day)	Consumption (g/day)	% difference*	Spearman's rank CC	ICC**	Consumption (g/day)	Consumption (g/day)	% difference*	Spearman's rank CC	ICC**
Energy (MJ)	8.3 ± 1.8	8.2 ± 1.8	-1	0.71	0.84	6.8 ± 1.0	6.8 ± 1.0	-1	0.54	0.73
Protein (g)	61 ± 13	61 ± 13	1	0.63	0.77	55 ± 10	55 ± 11	0	0.60	0.75
Fat (g)	44 ± 12	44 ± 12	2	0.67	0.80	46 ± 11	45 ± 12	-2	0.64	0.78
Carbohydrate (g)	311 ± 85	306 ± 84	-1	0.67	0.79	235 ± 41	232 ± 45	-1	0.67	0.78
Potassium (mg)	2,290 ± 591	2,270 ± 580	-1	0.70	0.84	2,442 ± 559	2,449 ± 602	0	0.65	0.80
Calcium (mg)	532 ± 163	537 ± 157	1	0.71	0.84	602 ± 162	616 ± 174	2	0.66	0.81
Iron (mg)	7.5 ± 2.4	7.5 ± 2.4	0	0.71	0.84	8.2 ± 2.1	8.2 ± 2.2	0	0.68	0.81
Carotenes (mg)	2,951 ±1,465	3,006 ±1,481	2	0.63	0.78	3,525 ±1,539	3,594 ±1,743	2	0.62	0.77
Vitamin A (μg)	966 ± 506	1,008 ± 575	4	0.57	0.70	979 ± 421	1,021 ± 516	4	0.60	0.73
Vitamin D (μg)	8 ± 4	8 ± 4	4	0.66	0.80	8 ± 3	8 ± 4	2	0.63	0.77
Vitamin E (mg)	8.1 ± 2.4	8.3 ± 2.3	2	0.60	0.74	8.8 ± 2.2	8.8 ± 2.4	0	0.60	0.76
Vitamin B_1 (mg)	0.7 ± 0.1	0.7 ± 0.1	1	0.55	0.67	0.6 ± 0.1	0.6 ± 0.1	0	0.55	0.69
Vitamin B_2 (mg)	1.1 ± 0.3	1.1 ± 0.3	1	0.67	0.80	1.2 ± 0.3	1.2 ± 0.3	1	0.63	0.78
Folate (μg)	331 ± 114	334 ± 116	1	0.63	0.78	378 ± 117	383 ± 124	1	0.62	0.76
Vitamin C (mg)	93 ± 36	93 ± 36	0	0.67	0.80	118 ± 42	117 ± 42	-1	0.66	0.80
Total dietary fiber (g)	10.9 ± 3.6	11 ± 3.6	1	0.72	0.85	12.4 ± 3.7	12.5 ± 4.0	0	0.70	0.83
Insoluble dietary fiber (g)	7.7 ± 2.5	7.8 ± 2.5	1	0.73	0.85	9.0 ± 2.6	9.0 ± 2.8	0	0.73	0.84
Soluble dietary fiber (g)	2.0 ± 0.7	2.0 ± 0.7	1	0.74	0.85	2.2 ± 0.7	2.3 ± 0.8	1	0.71	0.83
Cholesterol (mg)	249 ± 76	250 ± 74	0	0.66	0.78	254 ± 66	250 ± 67	-2	0.60	0.75
Saturated fatty acids (g)	11.1 ± 2.6	11.1 ± 2.5	0	0.65	0.78	11.7 ± 2.7	11.6 ± 2.7	-1	0.66	0.80
Monounsaturated fatty acids (g)	16.2 ± 4.5	16.5 ± 4.4	2	0.60	0.73	16.7 ± 3.9	16.5 ± 4.4	-2	0.56	0.72
Polyunsaturated fatty acids (g)	13.6 ± 3.9	13.7 ± 3.8	1	0.57	0.72	14.2 ± 3.5	14.1 ± 3.9	-1	0.55	0.73
n-6 Polyunsaturated fatty acids (g)	2.3 ± 0.7	2.4 ± 0.7	2	0.59	0.74	2.4 ± 0.6	2.4 ± 0.6	-1	0.59	0.74
n-3 Polyunsaturated fatty acids (g)	11.3 ± 3.3	11.4 ± 3.3	1	0.56	0.70	11.8 ± 3.1	11.6 ± 3.3	-1	0.56	0.73
n-3 Highly-unsaturated fatty acids (g)	0.8 ± 0.4	0.8 ± 0.4	-4	0.60	0.77	0.8 ± 0.4	0.8 ± 0.3	-2	0.56	0.73
Median				0.66	0.79				0.62	0.77

*: (FFQ2-FFQ1)/FFQ1 (%)
**: intraclass correlation coefficient
Daily consumption is shown as mean ± standard deviation.
ICCs for nutrients were calculated after values were log-transformed and energy-adjusted.

Table 4. Level of agreement and disagreement according to quintile classification of daily intake of selected nutrients based on food frequency questionnaire 1 (FFQ1) and FFQ2 (%).

	Males			Females		
	Agreement		Disagreement	Agreement		Disagreement
Nutrient	Same quintiles	Same and +/- 1 quintiles	Opposite quintiles	Same quintiles	Same and +/- 1 quintiles	Opposite quintiles
Energy	45	83	1	39	76	3
Protein	41	80	1	38	79	1
Fat	43	80	1	41	78	1
Carbohydrate	44	82	1	43	81	1
Potassium	44	82	1	42	80	1
Calcium	43	83	1	44	81	1
Iron	40	83	1	42	81	1
Carotenes	42	79	2	39	79	1
Vitamin A	44	77	2	41	79	2
Vitamin D	47	81	1	42	78	1
Vitamin E	40	78	2	36	75	1
Vitamin B_1	37	75	2	37	74	2
Vitamin B_2	45	79	1	42	80	1
Folate	42	78	1	40	79	1
Vitamin C	43	81	1	43	79	1
Total dietary fiber	44	84	1	44	84	0
Insoluble dietary fiber	46	85	1	44	83	0
Soluble dietary fiber	47	84	1	44	84	1
Cholesterol	45	80	1	42	79	2
Saturated fatty acids	43	80	1	43	80	1
Monounsaturated fatty acids	42	77	1	35	76	1
Polyunsaturated fatty acids	40	75	1	34	74	2
n-6 polyunsaturated fatty acids	40	77	1	36	77	1
n-3 polyunsaturated fatty acids	37	75	1	36	74	2
n-3 highly-unsaturated fatty acids	44	78	2	43	74	1
Median	43	80	1	42	79	1

Proportions for nutrients were calculated after intakes were energy-adjusted.
The proportions categorized into the same quintiles, those categorized into the same quintiles plus adjacent quintiles, or those categorized into the opposite quintiles.

Table 5. Comparison of one-year interval reproducibility indices of Japanese short food frequency questionnaires.

Authors	Year	No. of food items	Sex	n	Median (range) of Spearman's rank CCs: Food groups	Median (range) of Spearman's rank CCs: Nutrients
Ogawa K et al[11]	2003	40	Male	55	0.50 (0.30-0.70)	0.49 (0.31-0.71)
			Female	58	0.57 (0.39-0.66)	0.50 (0.40-0.64)
Sasaki S et al[12]	2003	44	Male	101	0.50 (0.38-0.71)	0.49 (0.30-0.82)
			Female	108	0.49 (0.30-0.74)	0.50 (0.32-0.68)
Ishihara J et al[13]	2003	44	Male	143	0.51 (0.33-0.72)	0.57 (0.39-0.77)
			Female	146	0.50 (0.40-0.80)	0.54 (0.38-0.70)
Present study (2007)	2007	47	Male	844	0.65 (0.57-0.80)	0.66 (0.55-0.74)
			Female	1,074	0.60 (0.69-0.54)	0.62 (0.54-0.73)

CC: correlation coefficient

DISCUSSION

We formerly observed fairly high validity values for consumption of energy and macro- and micro-nutrients assessed with our questionnaire versus 3-day weighed diet records.[16] We also detected moderate validity between intake of fatty acids estimated with this questionnaire against plasma concentration.[17] In the present study, we observed substantially high one-year interval reproducibility value for the respective foods and nutrients assessed with the FFQ administered to middle-aged and elderly Japanese people. Median indices of Spearman's rank CCs for foods/food groups were greater than 0.60, the median ICC figures being greater than 0.76 for both sexes. The median Spearman's rank CCs for macro- and micro-nutrients were greater than 0.62, and the median ICC values were greater than 0.77 for both sexes.

Furthermore, we paid special attention to the differences in reproducibility indices by age group and observed slightly lower reproducibility values in young males under 40 years of age than in other age groups. This probably reflects their wide selection of foods/food groups and their active and free lifestyle. On the other hand, contrary to the report of Shimizu et al,[18] higher reproducibility values were noted in elderly people, which might be expected due to the fact that they lead rather traditional and ordinary lives, including dietary habits.[19]

Although women are generally more interested in the foods they eat and cook than men, there were no remarkable differences in reproducibility figures for foods and nutrients between sexes in the present study. Instead, as a whole, the reproducibility values for males were rather higher than those for females. The indices for the young generation under 39 years of age, in particular, were somewhat lower for consumption of staple foods, including rice, noodles and bread along with energy, presumably because women in the young generation are keen on diet to keep in shape.

We compared our one-year interval reproducibility values for foods/food groups and macro- and micro-nutrients with those indices of Japanese short FFQs, including approximately 50 items of foods/food groups (Table 5).[11-13] The median Spearman's rank CCs for foods and nutrients distributed between 0.49 and 0.57 in both sexes. Our reproducibility figures were 10% on average higher than those with smaller minimum-maximum ranges, which may be partly due to the fact that the number of subjects in this survey was greater than those in the recent literature.[11-13]

In conclusion, we previously observed fairly high relative validity values for consumption of foods and nutrients estimated with our short FFQ versus those assessed with 3-day weighed diet records.[14] Moderate validity was attained for intake of fatty acids measured with our FFQ against plasma concentration.[15] The present study detected substantially high one-year interval reproducibility values for consumption of foods and nutrients assessed with our FFQ. The abbreviated questionnaire requires less time to fill out and would thus be applicable to a middle-age and elderly general populace for assessing usual dietary habits.

ACKNOWLEDGMENTS

The authors wish to express their thanks to Ms. Y. Sano and Ms. K. Seno of the Toyokawa City Health Center; Ms. T. Yoshida and Ms. H. Tomura of Canon Sales Corporation, and to Dr. M.A. Moore for their technical and language assistance in preparing this manuscript. The authors wish to express our gratitude to all of the study participants.

REFERENCES

1. Nagata C, Ohwaki A, Kurisu Y, Shimizu H. Food diversity and validity of semiquantitative food frequency questionnaire. J Epidemiol 1998; 8:297-301.
2. Imaeda N, Tokudome Y, Ikeda M, Kitagawa I, Fujiwara N, Tokudome S. Foods contributing to absolute intake and variance in intake of selected vitamins, minerals and dietary fiber in middle-aged Japanese. J Nutr Sci Vitaminol 1999; 45: 519-32.
3. Tokudome Y, Imaeda N, Ikeda M, Kitagawa I, Fujiwara N, Tokudome S. Foods contributing to absolute intake and variance in intake of fat, fatty acids and cholesterol in middle-aged Japanese. J Epidemiol 1999; 9: 78-90.
4. Willett W. Nutritional Epidemiology. Oxford University Press, New York 1989.
5. Margetts BM, Nelson M. Design Concepts in Nutritional Epidemiology (2nd Ed.). Oxford University Press, Oxford 1991.
6. Tokudome S, Goto C, Imaeda N, Tokudome Y, Ikeda M, Maki S. Development of a data-based short food frequency questionnaire for assessing nutrient intake by middle-aged Japanese. Asian Pacific J Cancer Prev 2004; 5: 40-3.
7. Science and Technology Agency: Standard Tables of Food Composition in Japan, the fifth revised edition. Printing Bureau, Ministry of Finance; Tokyo, 2000.
8. Science and Technology Agency, Japan. Follow-up of Standard Tables of Food Composition in Japan. Ishiyaku Shuppan Tokyo, 1992. (in Japanese)
9. Beaton GH, Milner J, McGuire V, Feather TE, Little JA. Sources of variance in 24-hour dietary recall data: implications for nutrition study design and interpretation. Am J Clin Nutr 1979; 32: 2546-59.
10. Tsubono Y, Sasaki S, Kobayashi M, Akabane M, Tsugane S. Food composition and empirical weight methods in predicting nutrient intakes from food frequency questionnaire. Ann Epidemiol 2001; 11: 213-8.
11. Ogawa K, Tsubono Y, Nishino Y, Watanabe Y, Ohkubo T, Watanabe T, et al. Validation of a food-frequency questionnaire for cohort studies in rural Japan. Public Health Nutr 2003; 6: 147-57.
12. Sasaki S, Ishihara J, Tsugane S, JPHC. Reproducibility of a self-administered food frequency questionnaire used in the 5-year follow-up survey of the JPHC Study Cohort I to assess

food and nutrient intake. J Epidemiol 2003; 13: S115-24.
13. Ishihara J, Sobue T, Yamamoto S, Yoshimi I, Sasaki S, Kobayashi M, et al. Validity and reproducibility of a self-administered food frequency questionnaire in the JPHC Study Cohort II: study design, participant profile and results in comparison with Cohort I. J Epidemiol 2003; 13: S134-47.
14. Imaeda N, Fujiwara N, Tokudome Y, Ikeda M, Kuriki K, Nagaya T, et al. Reproducibility of a semi-quantitative food frequency questionnaire in Japanese female dietitians. J Epidemiol 2002; 12: 45-53.
15. Ishihara J, Inoue M, Kobayashi M, Tanaka S, Yamamoto S, Iso H, et al. Impact of the revision of a nutrient database on the validity of a self-administered food frequency questionnaire (FFQ). J Epidemiol 2006, 16: 107-16.
16. Tokudome Y, Goto C, Imaeda N, Hasegawa T, Kato R, Hirose K, et al. Relative validity of a short food frequency questionnaire for assessing nutrient intake versus three-day weighed diet records in middle-aged Japanese. J Epidemiol 2005; 15: 135-45.
17. Goto C, Tokudome Y, Imaeda N, Takekuma K, Kuriki K, Igarashi F, et al. Validation study of fatty acid consumption assessed with a short food frequency questionnaire against plasma concentration in middle-aged Japanese. Scand J Nutr 2006; 2: 77-82.
18. Shimizu H, Ohwaki A, Kurisu Y, Takatsuka N, Ido M, Kawakami N, et al. Validity and reproducibility of a quantitative food frequency questionnaire for a cohort study in Japan. Jpn J Clin Oncol 1999; 29: 38-44.
19. Morris MC, Tangney CC, Bienias JL, Evans DA, Wilson RS. Validity and reproducibility of a food frequency questionnaire by cognition in an older biracial sample. Am J Epidemiol 2003; 158: 1213-7.

Dietary Fiber and Risk of Colorectal Cancer in the Japan Collaborative Cohort Study

Kenji Wakai,[1] Chigusa Date,[5] Mitsuru Fukui,[6] Koji Tamakoshi,[2] Yoshiyuki Watanabe,[7] Norihiko Hayakawa,[8] Masayo Kojima,[4] Miyuki Kawado,[9] Koji Suzuki,[10] Shuji Hashimoto,[9] Shinkan Tokudome,[4] Kotaro Ozasa,[7] Sadao Suzuki,[4] Hideaki Toyoshima,[2] Yoshinori Ito,[3] and Akiko Tamakoshi[3] for the JACC Study Group

[1]Division of Epidemiology and Prevention, Aichi Cancer Center Research Institute; [2]Department of Public Health/Health Information Dynamics, and [3]Department of Preventive Medicine/Biostatistics and Medical Decision Making, Nagoya University Graduate School of Medicine; and [4]Department of Health Promotion and Preventive Medicine, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan; [5]Faculty of Human Life and Environment, Nara Women's University, Nara, Japan; [6]Department of Public Health, Osaka City University Graduate School of Medicine, Osaka, Japan; [7]Department of Epidemiology for Community Health and Medicine, Kyoto Prefectural University of Medicine Graduate School of Medical Science, Kyoto, Japan; [8]Department of Epidemiology, Research Institute for Radiation Biology and Medicine, Hiroshima University, Hiroshima, Japan; and [9]Department of Hygiene, Fujita Health University School of Medicine and [10]Department of Public Health, Fujita Health University School of Health Sciences, Toyoake, Japan

Abstract

To examine the association of dietary fiber with the risk of colorectal cancer in a population with a high incidence of cancer and a low fiber intake, we analyzed the data from the Japan Collaborative Cohort Study. From 1988 to 1990, 43,115 men and women aged 40 to 79 years completed a questionnaire on dietary and other factors. Intake of dietary fiber was estimated using a food frequency questionnaire. Rate ratios (RR) were computed by fitting proportional hazards models. During the mean follow-up of 7.6 years, 443 colorectal cancer cases were recorded. In all participants, we found a decreasing trend in risk of colorectal cancer with increasing intake of total dietary fiber; the multivariate-adjusted RRs across quartiles were 1.00, 0.96 [95% confidence interval (95% CI), 0.72-1.27], 0.72 (0.53-0.99), and 0.73 (0.51-1.03; P_{trend} = 0.028). This trend was exclusively detected for colon cancer: the corresponding RRs were 1.00, 0.90 (95% CI, 0.64-1.26), 0.56 (0.38-0.83), and 0.58 (0.38-0.88; P_{trend} = 0.002). The decrease in RRs with increasing intake of dietary fiber was larger in men than in women. No material differences appeared in the strength of associations with the risk between water-soluble and insoluble dietary fiber. For food sources of fiber, bean fiber intake was somewhat inversely correlated with colorectal cancer risk. This prospective study supported potential protective effects of dietary fiber against colorectal cancer, mainly against colon cancer. The role of dietary fiber in the prevention of colorectal cancer seems to remain inconsistent, and further investigations in various populations are warranted. (Cancer Epidemiol Biomarkers Prev 2007;16(4):668–75)

Introduction

In the early 1970s, Burkitt hypothesized that dietary fiber may protect against colorectal cancer, based on the observation that colorectal cancer was rare in rural Africans, and they ate a diet rich in fiber from unrefined grains and/or leafy vegetables (1). Since then, many case-control studies reported an inverse association between dietary fiber intake and the risk of colorectal cancer (2-6). Furthermore, many animal models show different inhibitory effects of various types of fiber on colon tumor development (7-9). On the contrary, many prospective studies showed no protective effects of fiber (10-20), although a recent international cohort study in Europe has reported an inverse association between fiber intake and colorectal cancer risk (21, 22). In addition, increasing fiber intake did not reduce adenoma recurrence in large intervention trials (23-25). Thus, Burkitt's hypothesis has not fully been supported.

The short-term study of recurrent adenomas in the clinical trials, however, may have little relevance to the progression of adenomas to colorectal cancer (26). As for cohort studies on this issue, all have been conducted in Western populations (10-20) except for one in Japan (27). Because food sources of dietary fiber greatly vary (21) and genetic susceptibility to colorectal cancer may differ between ethnic groups, prospective studies are warranted also in non-Western populations. Le Marchand et al. (4) suggested that the risk reduction associated with fiber from vegetables was larger in Japanese than in Caucasians.

We have been conducting a large cohort study named as the Japan Collaborative Cohort (JACC) Study for the evaluation of cancer risk sponsored by the Monbusho, the Ministry of Education, Culture, Sports, Science and Technology of Japan (JACC Study; refs. 28, 29). The study involves subjects throughout Japan with a relatively low level of dietary fiber intake; median, 13.3 g/day in 2003 (30). The potential protective effects of dietary fiber may have a threshold intake level, so it may be informative to conduct investigations in populations with a low intake.

Japan is one of the countries with the highest incidence rate of colorectal cancer (31); the rate per 100,000 population (standardized to the World Population) was 49.9 in men and 27.2 in women in 1999 (32). Furthermore, immigrant studies suggest the higher genetic susceptibility to colorectal cancer risk in Japanese; Japanese Americans showed a higher incidence rate than U.S. Caucasians (31). Our cohort, therefore, may be appropriate to address the issue. Thus, we examined the association of dietary fiber intake with colorectal cancer risk by analyzing the data from the JACC Study.

Received 8/7/06; revised 12/8/06; accepted 1/30/07.

Grant support: Grant-in-Aid for Scientific Research on Priority Areas (2) (14031222) from the Ministry of Education, Culture, Sports, Science and Technology of Japan, and by a traveling grant from the Princess Takamatsu Cancer Research Fund. The JACC Study has also been supported by Grants-in-Aid for Scientific Research from the Ministry of Education, Science, Sports and Culture of Japan (Monbusho) (61010076, 62010074, 63010074, 1010068, 2151065, 3151064, 4151063, 5151069, 6279102, 11181101, 17015022, and 18014011).

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Requests for reprints: Kenji Wakai, Division of Epidemiology and Prevention, Aichi Cancer Center Research Institute, 1-1 Kanokoden, Chikusa-ku, Nagoya 464-8681, Japan. Phone: 81-52-764-2988; Fax: 81-52-763-5233. E-mail: wakai@aichi-cc.jp

doi:10.1158/1055-9965.EPI-06-0664