Materials and Methods

The JACC Study. The JACC Study for evaluation of cancer risk sponsored by the Monbusho started in 1988 to 1990, during which period, 110,792 male and female inhabitants aged 40 to 79 years completed a baseline questionnaire. The details of this study are described elsewhere (28, 29). In brief, participants were enrolled from 45 study areas throughout Japan, mostly from general populations or examinees of municipal health check-ups. Informed consent for participation was obtained individually from each participant, except in a few study areas where it was provided at the group level after the aim of the study and confidentiality of the data had been explained to community leaders. The Ethical Board of the Nagoya University School of Medicine approved the protocol of this investigation, including the procedures used to obtain informed consent.

Potential participants for the present analysis were restricted to 60,569 men and women who lived in 22 study areas where information on cancer incidence is available, and a food frequency questionnaire (FFQ) to estimate food and nutrient intake was included in the baseline questionnaire.

Diet and Other Exposure Data. The baseline questionnaire covered lifestyle factors, including dietary habits, smoking and drinking, and physical activity, as well as medical history, education, family history of cancer, and height and weight.

The dietary component of the questionnaire included 40 food items (33). For 33 foods or dishes, we asked about the average intake frequency without specifying portion size information. We used five response choices: almost never, 1 to 2 times a month, 1 to 2 times a week, 3 to 4 times a week, and almost everyday. For rice, miso soup (soup of fermented soybean paste with soybean curd, vegetables, and/or seaweeds, etc.), and four nonalcoholic beverages, the number of bowls or cups consumed per day was inquired. The frequency of alcohol consumption was asked with the usual amount on one occasion. Nutrient intakes were computed using the Japanese food composition table (34) assuming the standard portion sizes. Values for total, water-soluble, and insoluble fiber, obtained by enzymatic-gravimetric methods by Prosky et al. (35), were derived from the food composition table.

Energy-adjusted intakes of nutrients, including total, soluble, insoluble, fruit, vegetable, and bean fiber, were calculated by the residual method (36). Natural logarithms of energy and nutrient intakes were used to improve the normality of their distribution.

The FFQ was validated by referring to four 3-day weighed dietary records over a 1-year period as a standard (33). We reanalyzed data from the validation study to consider skewed distributions of nutrient intakes and within-person variation in intakes (37, 38). The de-attenuated correlation coefficients for energy-adjusted intakes between the FFQ and dietary records were 0.46 for total dietary fiber, 0.42 for soluble fiber, 0.47 for insoluble fiber, 0.33 for fruit fiber, 0.41 for vegetable fiber, and 0.37 for bean fiber. The ratios of mean intakes estimated by the FFQ to those calculated from the dietary records were 0.60, 0.51, 0.58, 0.84, 0.53, and 0.50 for total, soluble, insoluble, fruit, vegetable, and bean fiber, respectively (part of total dietary fiber was not classified as soluble or insoluble fiber in the food composition table). We did not estimate intake of cereal fiber by the FFQ because the correlation coefficient was <0.3.

Of the 60,569 potential participants, we excluded 159 men and women with a history of colorectal cancer, 17,221 without sufficient responses to the FFQ to estimate nutrient intake (judged by predefined criteria), and 74 with an implausibly high or low intake of total energy (<500 or >3,500 kcal/day), leaving 16,636 men and 26,479 women (71.2% of potential participants) eligible for the analysis. Participants included in the analysis were younger (mean age ± SD, 56.4 ± 10.1 years for men and 56.7 ± 9.9 years for women) and likely to have a family history of colorectal cancer in parents and/or siblings (2.4% in men and 2.8% in women) than those excluded (61.0 ± 10.2 years for men and 62.7 ± 9.4 years for women, 1.9% in men and 2.1% in women, respectively). In women, the analytic cohort tended to be more highly educated (beyond high school, 11.4%) and included fewer ever smokers (6.6%) compared with those left out (9.1% and 9.0%, correspondingly). Other baseline characteristics, including drinking habits, body mass index (BMI), walking time, time of exercise, and engagement in sedentary work were comparable between the two groups.

Follow-up. We used population registries in the municipalities to determine the vital and residential status of the participants. Registration of death is required by the Family Registration Law in Japan and is adhered to nationwide. For logistical reasons, we discontinued the follow-up of those who had moved out of their given study areas.

We ascertained the incidence of cancer by means of a linkage with the records of population-based cancer registries, supplemented by a systematic review of death certificates. In some study areas, medical records in local major hospitals were also reviewed. In 3 out of 22 areas, population-based cancer registries were not available. Therefore, hospital-based cancer registries or inpatient records of hospitals treating cancer patients were used to collect information on cancer incidence in such areas. The mortality and incidence data were coded following the rules of the 10th Revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10). We defined colorectal cancer as C18, C19, and C20 of the ICD-10 code, colon cancer as C18, and rectal cancer as C20.

The follow-up was conducted from the time of the baseline survey through the end of 1997 except for one area (to the end of 1994). During the study period, only 2.8% (n = 1,190) of the subjects were lost to follow-up due to moving away. In the analytic cohort, the proportion of death-certificate-only registrations was 3.8% (17 of 443 cases) for colorectal cancer. The mortality-to-incidence ratio was 0.24, which is comparable with those available from representative population-based cancer registries in Japan (0.20 to 0.53; ref. 31).

Statistical Analysis. BMI at baseline was calculated from reported height and weight: BMI = (weight in kilograms)/(height in meters)^2. The age- and sex-adjusted mean intake of dietary fiber by bowel movement frequency was computed using the analysis of covariance. We counted person-time of follow-up for each participant from the date of filling out the baseline questionnaire to the date of diagnosis of colorectal cancer, the date of death from any cause, the date of emigration outside the study area, or the end of the follow-up period, whichever came first. For cases identified only with a death certificate, the date of death was assumed to be that of diagnosis. Those who died from causes other than colorectal cancer or who moved out of their study areas were treated as censored cases.

The rate ratios (RR) with 95% confidence intervals (95% CI) for colorectal cancer over sex-specific quartiles of energy-adjusted intakes of total, soluble, insoluble, fruit, vegetable, or bean dietary fiber (the RRs for the second, third, and highest quartiles versus the lowest) were estimated using proportional hazards models (39) adjusted for age, sex, and other potential confounders selected based on prior knowledge (40-42). The RRs were adjusted for age (as a continuous variable), sex, area (Hokkaido and Tohoku, Kanto, Chubu, Kinki, Chugoku, or Kyushu), educational level (attended school until the age of ≤15, 16-18, or ≥19 years), family history of colorectal cancer in parents and/or siblings (yes or no), alcohol consumption [never drink, ex-drinkers, or current drinkers who consume <2 or ≥2 Japanese drinks (<46 g or ≥46 g of ethanol) per day for

Table 1. Baseline characteristics by quartile of energy-adjusted intake of total dietary fiber among 16,636 men and 26,479 women in the JACC Study, 1988 to 1997

	Quartiles of energy-adjusted intake of total dietary fiber			
	1	2	3	4
Men				
n	4,159	4,159	4,159	4,159
Intake of total dietary fiber (g/day)	6.7 ± 2.0	9.4 ± 2.1	11.3 ± 2.6	13.4 ± 3.0
Age (y)	53.6 ± 9.4	55.3 ± 9.7	56.8 ± 10.0	59.7 ± 10.3
Education beyond high school (%)	18.1	19.0	21.3	23.1
Family history of colorectal cancer in parents and/or siblings (%)	2.1	2.7	2.5	2.4
Alcohol consumption				
Current drinkers (%)	84.0	79.0	74.8	59.8
Former drinkers (%)	3.0	4.0	6.7	12.1
Smoking				
Current smokers (%)	59.3	53.8	51.2	44.6
Former smokers (%)	24.6	27.2	27.1	29.8
BMI (kg/m^2)	22.7 ± 2.7	22.8 ± 3.9	22.7 ± 2.7	22.6 ± 2.9
Walking time >30 min/day (%)	64.3	68.1	71.7	70.2
Exercise ≥1 h a week (%)	27.6	30.7	33.6	37.8
Sedentary work (%)	27.9	31.5	33.9	36.2
Consumption of beef ≥3 times a week (%)	8.8	6.8	6.6	6.0
Consumption of pork ≥3 times a week (%)	13.6	19.7	24.8	25.6
Energy intake (kcal/day)	1,658 ± 460	1,744 ± 452	1,745 ± 473	1,614 ± 443
Folate intake (μg/day)	302 ± 131	380 ± 138	439 ± 151	500 ± 158
Calcium intake (mg/day)	391 ± 144	480 ± 147	543 ± 156	598 ± 165
Vitamin D intake (μg/day)	6.0 ± 3.2	7.2 ± 3.4	8.2 ± 3.6	8.9 ± 3.8
Women				
n	6,619	6,620	6,620	6,620
Intake of total dietary fiber (g/day)	7.4 ± 2.1	9.8 ± 2.1	11.5 ± 2.2	13.4 ± 2.8
Age (y)	54.7 ± 9.6	55.9 ± 9.7	56.8 ± 9.9	59.3 ± 9.9
Education beyond high school (%)	9.9	11.3	12.1	12.4
Family history of colorectal cancer in parents and/or siblings (%)	2.5	2.8	3.0	2.9
Alcohol consumption				
Current drinkers (%)	29.6	26.2	22.1	19.1
Former drinkers (%)	1.7	1.6	1.7	1.7
Smoking				
Current smokers (%)	7.8	4.8	3.7	3.9
Former smokers (%)	1.7	1.4	1.4	1.6
BMI (kg/m^2)	22.9 ± 3.1	22.7 ± 3.0	22.9 ± 3.6	22.8 ± 3.1
Walking time >30 min/day (%)	68.7	71.6	73.7	73.7
Exercise ≥1 h a week (%)	19.5	22.8	25.1	27.7
Sedentary work (%)	31.1	34.7	36.7	38.1
Consumption of beef ≥3 times a week (%)	11.8	11.0	8.6	6.0
Consumption of pork ≥3 times a week (%)	17.1	21.8	24.0	21.6
Energy intake (kcal/day)	1,391 ± 373	1,432 ± 345	1,438 ± 320	1,381 ± 333
Folate intake (μg/day)	321 ± 137	390 ± 141	435 ± 145	487 ± 155
Calcium intake (mg/day)	423 ± 151	504 ± 154	555 ± 158	586 ± 166
Vitamin D intake (μg/day)	6.2 ± 3.2	7.4 ± 3.4	8.2 ± 3.5	8.9 ± 3.9

NOTE: Plus-minus values are means ± SD.

men, and never drink, ex-drinkers, or current drinkers for women], smoking (never smoke, ex-smokers, or current smokers), BMI (<20.0, 20.0-24.9, or ≥25.0 kg/m^2), daily walking habits (≤30 or >30 min/day), exercise (seldom or never, or 1-2, 3-4, or ≥5 h a week), sedentary work (yes or no), consumption of beef (almost never, 1-2 times a month, 1-2 times a week, ≥3 times a week) and pork (almost never, 1-2 times a month, 1-2 times a week, ≥3 times a week), energy intake (as a continuous variable), and energy-adjusted intakes of folate, calcium, and vitamin D (sex-specific quartile for each). We considered walking time because that was the major physical activity in the study population (43). The RRs and 95% CIs were also computed for colon, rectal, and colorectal cancer among men, women, and both sexes combined. Missing values for each covariate were treated as an additional category in the variable and were included in the proportional hazards model. As a basis for the trend tests, the dietary fiber intake was scored from 0 to 3 according to the sex-specific quartile of intake, and the score was included in the model (21).

We repeated all the analyses after excluding the first 2 years of follow-up in which 79 cases of colorectal cancer were diagnosed. All *P* values were two-sided, and all the analyses were done using the Statistical Analysis System (44).

Results

Mean intake of total dietary fiber was 100% and 80% higher in the highest quartile than in the lowest for men and women, respectively (Table 1). Men and women with higher dietary fiber intake were older, more likely to be highly educated, to walk more than 30 min/day, to exercise more than 1 h/week, and to engage in sedentary work, whereas the proportions of current drinkers and smokers decreased with an increasing total fiber intake. For dietary variables, individuals with higher intake of dietary fiber more frequently consumed pork but less frequently ate beef. We further found increasing trends in intakes of folate, calcium, and vitamin D with an increasing level of total fiber intake. The major sources of dietary fiber were miso soup (18.2%), rice (14.1%), fruits other than oranges (8.7%), and green leafy vegetables (7.2%).

During the 327,273 person-years of follow-up (mean ± SD, 7.6 ± 1.9 years), 443 cases of incident colorectal cancer were documented. In all participants, we found a decreasing trend in risk of colorectal cancer with increasing intake of total dietary fiber after adjustment for potential confounding factors (Table 2). The multivariate RRs across quartiles were 1.00, 0.96 (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 inverse associations were similarly found between intake of total dietary fiber and the risk of colorectal or colon cancer among men. In women, those with high intakes of total dietary fiber were at a decreased risk of colorectal or colon cancer, although the trend in RRs with increasing intakes did not reach statistical significance. The multivariate RRs for female rectal cancer were greater than unity for higher levels of fiber intakes. These figures, however, were unstable because of the small number of cases (n = 39). The major confounders that changed the age- and sex-adjusted RRs for the highest quartile of total dietary fiber for colorectal cancer by more than 5% were area and energy-adjusted intake of calcium for men and women combined, area, alcohol consumption, and energy-adjusted intakes of calcium and vitamin D for men, and area for women.

When dietary fiber was classified into water-soluble and insoluble fiber, the reduction in risk of colorectal or colon cancer associated with a higher intake was observed in the multivariate RRs for both kinds of fiber (Table 3). The risk of rectal cancer was not correlated with soluble or insoluble dietary fiber. It was difficult to estimate the RRs for soluble and insoluble fiber controlled for each other because the intakes of these two kinds of fiber were very highly correlated (Spearman's correlation coefficient = 0.95), and this adjustment resulted in inflated CIs; the multivariate RRs for colorectal cancer across quartiles of intakes were 1.00, 0.76 (95% CI, 0.51-1.13), 0.78 (0.46-1.32), and 0.69 (0.36-1.32; P_{trend} = 0.32) for soluble dietary fiber and 1.00, 1.27 (95% CI, 0.85-1.89), 0.94 (0.56-1.59), and 1.02 (0.54-1.94; P_{trend} = 0.85) for insoluble dietary fiber among men and women combined.

For food sources of fiber (Table 4), bean fiber intake was somewhat inversely correlated with the risk of colorectal cancer (P_{trend} for multivariate RRs = 0.055), particularly that of colon cancer (P_{trend} for multivariate RRs = 0.037). On the other hand, the intake of vegetable fiber tended to be associated with rectal cancer risk (P_{trend} for multivariate RRs = 0.060). The positive association

Table 2. RRs with 95% CIs for colorectal cancer by sex and quartile of energy-adjusted intake of total dietary fiber in the JACC Study, 1988 to 1997

	Quartiles of energy-adjusted intake of total dietary fiber				P_{trend}
	1	2	3	4	
Men and women combined (n = 43,115)					
Person-years	78,849	81,220	83,145	84,059	
Colorectal cancer					
Number of cancer cases	97	114	102	130	
Age- and sex-adjusted RR (95% CI)	1.00	1.03 (0.78-1.35)	0.83 (0.63-1.10)	0.90 (0.69-1.18)	0.23
Multivariate RR (95% CI)*	1.00	0.96 (0.72-1.27)	0.72 (0.53-0.99)	0.73 (0.51-1.03)	0.028
Colon cancer					
Number of cancer cases	71	79	60	81	
Age- and sex-adjusted RR (95% CI)	1.00	0.97 (0.70-1.33)	0.66 (0.47-0.93)	0.74 (0.53-1.03)	0.019
Multivariate RR (95% CI)*	1.00	0.90 (0.64-1.26)	0.56 (0.38-0.83)	0.58 (0.38-0.88)	0.002
Rectal cancer					
Number of cancer cases	25	30	40	47	
Age- and sex-adjusted RR (95% CI)	1.00	1.06 (0.62-1.80)	1.30 (0.78-2.14)	1.33 (0.81-2.18)	0.19
Multivariate RR (95% CI)*	1.00	0.98 (0.56-1.70)	1.13 (0.64-2.00)	1.10 (0.59-2.07)	0.67
Men (n = 16,636)					
Person-years	30,631	31,855	32,224	32,187	
Colorectal cancer					
Number of cancer cases	51	76	54	77	
Age-adjusted RR (95% CI)	1.00	1.27 (0.89-1.82)	0.82 (0.56-1.21)	1.00 (0.69-1.44)	0.41
Multivariate RR (95% CI)*	1.00	1.12 (0.77-1.62)	0.62 (0.40-0.96)	0.69 (0.43-1.11)	0.023
Colon cancer					
Number of cancer cases	33	48	26	42	
Age-adjusted RR (95% CI)	1.00	1.23 (0.79-1.91)	0.60 (0.35-1.00)	0.80 (0.50-1.28)	0.068
Multivariate RR (95% CI)*	1.00	1.06 (0.66-1.69)	0.43 (0.24-0.76)	0.52 (0.28-0.96)	0.004
Rectal cancer					
Number of cancer cases	18	23	27	35	
Age-adjusted RR (95% CI)	1.00	1.10 (0.59-2.05)	1.19 (0.65-2.17)	1.34 (0.74-2.40)	0.31
Multivariate RR (95% CI)*	1.00	0.96 (0.50-1.83)	0.91 (0.46-1.80)	0.95 (0.45-2.02)	0.89
Women (n = 26,479)					
Person-years	48,219	49,366	50,921	51,872	
Colorectal cancer					
Number of cancer cases	46	38	48	53	
Age-adjusted RR (95% CI)	1.00	0.75 (0.49-1.15)	0.86 (0.57-1.29)	0.80 (0.53-1.19)	0.42
Multivariate RR (95% CI)*	1.00	0.73 (0.47-1.14)	0.84 (0.54-1.33)	0.75 (0.46-1.25)	0.41
Colon cancer					
Number of cancer cases	38	31	34	39	
Age-adjusted RR (95% CI)	1.00	0.73 (0.46-1.18)	0.73 (0.46-1.16)	0.70 (0.44-1.10)	0.15
Multivariate RR (95% CI)*	1.00	0.72 (0.44-1.18)	0.71 (0.42-1.20)	0.64 (0.36-1.13)	0.15
Rectal cancer					
Number of cancer cases	7	7	13	12	
Age-adjusted RR (95% CI)	1.00	0.92 (0.32-2.62)	1.57 (0.62-3.95)	1.27 (0.49-3.29)	0.42
Multivariate RR (95% CI)*	1.00	1.15 (0.39-3.38)	2.14 (0.78-5.83)	1.82 (0.59-5.65)	0.19

*The RRs were adjusted for age (as a continuous variable), sex, area (Hokkaido and Tohoku, Kanto, Chubu, Kinki, Chugoku, or Kyushu), educational level (attended school until the age of ≤15, 16-18, or ≥19 y), family history of colorectal cancer in parents and/or siblings (yes or no), alcohol consumption [never drink, ex-drinkers, or current drinkers who consume <2 or ≥2 Japanese drinks (<46 or ≥46 g of ethanol) per day for men, and never drink, ex-drinkers, or current drinkers for women], smoking (never smoke, ex-smokers, or current smokers), BMI (<20.0, 20.0-24.9, or ≥25.0 kg/m^2), daily walking habits (≤30 or >30 min/day), exercise (seldom or never, or 1-2, 3-4, or ≥5 h a week), sedentary work (yes or no), consumption of beef (almost never, 1-2 times a month, 1-2 times a week, ≥3 times a week) and pork (almost never, 1-2 times a month, 1-2 times a week, ≥3 times a week), energy intake (as a continuous variable), and energy-adjusted intakes of folate, calcium, and vitamin D (sex-specific quartile for each).

of fruit fiber with age- and sex-adjusted RRs for colorectal cancer disappeared after adjustment for potential confounding factors.

All the findings in Tables 2–4 remained essentially the same when we excluded the first 2 years of follow-up from the analyses (data not shown). The multivariate RRs (95% CI) in men and women combined over quartiles of intake of total dietary fiber were 1.00, 0.95 (0.69-1.30), 0.74 (0.52-1.04), and 0.70 (0.48-1.02; P_{trend} = 0.029) for colorectal cancer; 1.00, 0.92 (0.64-1.34), 0.62 (0.40-0.94), and 0.56 (0.35-0.90; P_{trend} = 0.005) for colon cancer; and 1.00, 0.92 (0.49-1.71), 1.13 (0.61-2.12), and 1.08 (0.54-2.16; P_{trend} = 0.69) for rectal cancer.

Discussion

In this cohort of Japanese population, dietary fiber intake was inversely associated with colorectal cancer risk. The association was stronger for the risk of colon cancer, and no clear relationship was observed for rectal cancer risk. In addition, no material differences appeared in the strength of associations with the risk between soluble and insoluble dietary fiber.

Many possible mechanisms have been proposed to explain putative risk-reducing effect of increased dietary fiber intake (7-9). When entering the large bowel, fiber increases stool bulk and dilutes fecal carcinogens. It also shortens fecal transit time and, thus, reduces the contact of the colon epithelium to carcinogens in stool. Indeed, severe constipation (bowel movement every 6 days or less) was linked with the risk of female colorectal cancer in the JACC Study (45). In the present population, the intake of total dietary fiber decreased with decreasing frequency of bowel movement; the age- and sex-adjusted mean intakes ± SE were 10.49 ± 0.02, 9.84 ± 0.04, 9.39 ± 0.10, and 9.24 ± 0.23 g/day for bowel movement frequency of once or more than once a day, once every 2 to 3 days, once every 4 to 5 days, and once every 6 days or more, respectively (P_{trend} < 0.0001). The bowel movement frequency, therefore, may be considered as an intermediate factor in the causal pathway. Furthermore, dietary fiber can bind to bile acids that produce carcinogenic metabolites.

Moreover, fiber acts as a substrate for bacterial fermentation, and short-chain fatty acids are produced. These fatty acids prevent the conversion from primary to the more toxic secondary bile acids by lowering colonic pH. The butyrate, one of the major short-chain fatty acids, has specific anti-carcinogenic effects; it reduces cell proliferation and induces apoptosis. Fermentable fiber has the potential to selectively enhance the growth of the flora such as those of certain lactic acid bacteria and bifidobacteria. Recently, hyperinsulinemia has been related to colorectal carcinogenesis (46, 47). Dietary fiber can delay the absorption of starch, reducing the consequent postprandial hyperinsulinemia (41).

The majority of case-control studies reported inverse associations between dietary fiber intake and colorectal cancer risk. A combined analysis of 13 case-control studies yielded summary odds ratios for colorectal cancer of 1.00, 0.79, 0.69, 0.63, and 0.53 across the quintiles of intake compared with the lowest one (2). Large-scale case-control studies after this pooled analysis also supported the protective effects of fiber (3-6).

The findings of prospective studies, however, are rather inconsistent. Park et al. (48) pooled 13 cohort studies and

Table 3. RRs with 95% CIs for colorectal cancer by quartile of energy-adjusted intake of soluble and insoluble dietary fiber in the JACC Study, 1988 to 1997 (*n* = 43,115)

	Quartiles of energy-adjusted intake of soluble or insoluble dietary fiber				P_{trend}
	1	2	3	4	
Soluble dietary fiber (g/day)	1.2 ± 0.4	1.7 ± 0.4	2.1 ± 0.4	2.6 ± 0.5	
Person-years	79,325	80,944	82,891	84,113	
Colorectal cancer					
Number of cancer cases	98	106	113	126	
Age- and sex-adjusted RR (95% CI)	1.00	0.97 (0.74-1.28)	0.94 (0.71-1.23)	0.90 (0.68-1.17)	0.40
Multivariate RR (95% CI)*	1.00	0.85 (0.64-1.14)	0.76 (0.55-1.04)	0.67 (0.47-0.95)	0.022
Colon cancer					
Number of cancer cases	70	77	64	80	
Age- and sex-adjusted RR (95% CI)	1.00	0.98 (0.71-1.36)	0.73 (0.52-1.03)	0.77 (0.56-1.07)	0.049
Multivariate RR (95% CI)*	1.00	0.85 (0.61-1.20)	0.58 (0.39-0.85)	0.55 (0.36-0.84)	0.002
Rectal cancer					
Number of cancer cases	27	22	49	44	
Age- and sex-adjusted RR (95% CI)	1.00	0.73 (0.42-1.29)	1.50 (0.94-2.41)	1.19 (0.73-1.93)	0.13
Multivariate RR (95% CI)*	1.00	0.66 (0.37-1.19)	1.26 (0.73-2.19)	0.94 (0.49-1.78)	0.64
Insoluble dietary fiber (g/day)	5.3 ± 1.5	7.0 ± 1.5	8.2 ± 1.8	9.6 ± 2.1	
Person-years	78,632	81,093	83,283	84,266	
Colorectal cancer					
Number of cancer cases	93	120	102	128	
Age- and sex-adjusted RR (95% CI)	1.00	1.12 (0.85-1.47)	0.86 (0.65-1.14)	0.91 (0.70-1.20)	0.21
Multivariate RR (95% CI)*	1.00	1.06 (0.80-1.40)	0.77 (0.56-1.05)	0.77 (0.55-1.08)	0.041
Colon cancer					
Number of cancer cases	67	86	58	80	
Age- and sex-adjusted RR (95% CI)	1.00	1.11 (0.80-1.52)	0.67 (0.47-0.95)	0.77 (0.55-1.07)	0.016
Multivariate RR (95% CI)*	1.00	1.05 (0.75-1.46)	0.59 (0.40-0.88)	0.63 (0.42-0.96)	0.004
Rectal cancer					
Number of cancer cases	25	29	42	46	
Age- and sex-adjusted RR (95% CI)	1.00	1.02 (0.59-1.74)	1.35 (0.82-2.22)	1.29 (0.78-2.12)	0.20
Multivariate RR (95% CI)*	1.00	0.95 (0.55-1.66)	1.20 (0.68-2.09)	1.08 (0.58-2.02)	0.66

NOTE: Plus-minus values are means ± SD.

*The RRs were adjusted for age (as a continuous variable), sex, area (Hokkaido and Tohoku, Kanto, Chubu, Kinki, Chugoku, or Kyushu), educational level (attended school until the age of ≤15, 16-18, or ≥19 y), family history of colorectal cancer in parents and/or siblings (yes or no), alcohol consumption [never drink, ex-drinkers, or current drinkers who consume <2 or ≥2 Japanese drinks (<46 or ≥46 g of ethanol) per day for men, and never drink, ex-drinkers, or current drinkers for women], smoking (never smoke, ex-smokers, or current smokers), BMI (<20.0, 20.0-24.9, or ≥25.0 kg/m^2), daily walking habits (≤30 or >30 min/day), exercise (seldom or never, or 1-2, 3-4, or ≥5 h a week), sedentary work (yes or no), consumption of beef (almost never, 1-2 times a month, 1-2 times a week, ≥3 times a week) and pork (almost never, 1-2 times a month, 1-2 times a week, ≥3 times a week), energy intake (as a continuous variable), and energy-adjusted intakes of folate, calcium, and vitamin D (sex-specific quartile for each).

Table 4. RRs with 95% CIs for colorectal cancer by quartile of energy-adjusted intake of fruit, vegetable, and bean dietary fiber in the JACC Study, 1988 to 1997 (n = 43,115)

	Quartiles of energy-adjusted intake of fruit, vegetable, or bean dietary fiber				P_{trend}
	1	2	3	4	
Fruit fiber (g/day)	0.4 ± 0.3	1.0 ± 0.4	1.7 ± 0.5	2.2 ± 0.3	
Person-years	81,817	82,545	82,840	80,072	
Colorectal cancer					
Number of cancer cases	90	103	128	122	
Age- and sex-adjusted RR (95% CI)	1.00	1.11 (0.84-1.47)	1.36 (1.04-1.79)	1.29 (0.98-1.69)	0.029
Multivariate RR (95% CI)*	1.00	1.05 (0.78-1.40)	1.23 (0.92-1.64)	1.06 (0.78-1.43)	0.55
Colon cancer					
Number of cancer cases	57	74	82	78	
Age- and sex-adjusted RR (95% CI)	1.00	1.26 (0.89-1.77)	1.38 (0.98-1.93)	1.29 (0.92-1.81)	0.14
Multivariate RR (95% CI)*	1.00	1.20 (0.84-1.71)	1.26 (0.88-1.81)	1.06 (0.73-1.54)	0.83
Rectal cancer					
Number of cancer cases	32	26	43	41	
Age- and sex-adjusted RR (95% CI)	1.00	0.79 (0.47-1.32)	1.29 (0.82-2.04)	1.23 (0.77-1.96)	0.14
Multivariate RR (95% CI)*	1.00	0.70 (0.42-1.19)	1.06 (0.65-1.73)	0.92 (0.55-1.54)	0.84
Vegetable fiber (g/day)	2.0 ± 0.7	3.1 ± 0.7	4.0 ± 0.8	5.1 ± 1.1	
Person-years	79,628	82,186	82,659	82,800	
Colorectal cancer					
Number of cancer cases	104	95	112	132	
Age- and sex-adjusted RR (95% CI)	1.00	0.83 (0.63-1.09)	0.90 (0.69-1.18)	0.94 (0.72-1.22)	0.87
Multivariate RR (95% CI)*	1.00	0.81 (0.60-1.08)	0.86 (0.64-1.16)	0.89 (0.65-1.24)	0.65
Colon cancer					
Number of cancer cases	76	62	68	85	
Age- and sex-adjusted RR (95% CI)	1.00	0.74 (0.53-1.03)	0.74 (0.53-1.03)	0.81 (0.60-1.12)	0.26
Multivariate RR (95% CI)*	1.00	0.71 (0.50-1.01)	0.69 (0.48-0.99)	0.74 (0.50-1.11)	0.17
Rectal cancer					
Number of cancer cases	23	29	43	47	
Age- and sex-adjusted RR (95% CI)	1.00	1.15 (0.66-1.98)	1.59 (0.96-2.64)	1.56 (0.94-2.59)	0.043
Multivariate RR (95% CI)*	1.00	1.16 (0.66-2.04)	1.64 (0.94-2.88)	1.68 (0.91-3.11)	0.060
Bean fiber (g/day)	0.2 ± 0.1	0.4 ± 0.1	0.7 ± 0.2	1.4 ± 0.6	
Person-years	78,611	82,828	83,166	82,669	
Colorectal cancer					
Number of cancer cases	103	104	115	121	
Age- and sex-adjusted RR (95% CI)	1.00	0.87 (0.67-1.15)	0.88 (0.67-1.15)	0.83 (0.63-1.08)	0.19
Multivariate RR (95% CI)*	1.00	0.84 (0.64-1.11)	0.83 (0.63-1.10)	0.74 (0.55-0.99)	0.055
Colon cancer					
Number of cancer cases	72	67	75	77	
Age- and sex-adjusted RR (95% CI)	1.00	0.80 (0.58-1.12)	0.81 (0.59-1.12)	0.73 (0.53-1.01)	0.081
Multivariate RR (95% CI)*	1.00	0.79 (0.56-1.12)	0.79 (0.56-1.11)	0.67 (0.47-0.95)	0.037
Rectal cancer					
Number of cancer cases	30	35	37	40	
Age- and sex-adjusted RR (95% CI)	1.00	1.01 (0.62-1.65)	0.98 (0.60-1.60)	0.97 (0.60-1.57)	0.87
Multivariate RR (95% CI)*	1.00	0.92 (0.56-1.52)	0.87 (0.52-1.45)	0.81 (0.48-1.37)	0.42

NOTE: Plus-minus values are means ± SD.

*The RRs were adjusted for age (as a continuous variable), sex, area (Hokkaido and Tohoku, Kanto, Chubu, Kinki, Chugoku, or Kyushu), educational level (attended school until the age of ≤15, 16-18, or ≥19 years), family history of colorectal cancer in parents and/or siblings (yes or no), alcohol consumption [never drink, ex-drinkers, or current drinkers who consume <2 or ≥2 Japanese drinks (<46 or ≥46 g of ethanol) per day for men, and never drink, ex-drinkers, or current drinkers for women], smoking (never smoke, ex-smokers, or current smokers), BMI (<20.0, 20.0-24.9, or ≥25.0 kg/m^2), daily walking habits (≤30 or >30 min/day), exercise (seldom or never, or 1-2, 3-4, or ≥5 h a week), sedentary work (yes or no), consumption of beef (almost never, 1-2 times a month, 1-2 times a week, ≥3 times a week) and pork (almost never, 1-2 times a month, 1-2 times a week, ≥3 times a week), energy intake (as a continuous variable), and energy-adjusted intakes of folate, calcium, and vitamin D (sex-specific quartile for each).

concluded that high dietary fiber intake was not related to a reduced risk of colorectal cancer; the summary relative risk was 0.94 (95% CI, 0.86-1.03) for the highest versus lowest quintiles of intake. On the contrary, the European Prospective Investigation into Cancer and Nutrition (EPIC) reported a lower risk of colorectal cancer with higher intake of total fiber (21, 22).

The discrepancy between the studies may, in part, be attributable to the difference in the extent of diversity of diet among the study population. In the EPIC, the analytic cohort included participants from eight countries and showed a very large variety of diet (21).

In our cohort, the low-level intake of dietary fiber may be related to the emergence of risk-reducing effect of dietary fiber. In fact, the above-mentioned pooled analysis of prospective studies (48) suggested an increase in the risk associated with very low fiber intake. The pooled RR comparing <10 g/day versus ≥10 g/day of dietary fiber intake was 2.16 (95% CI, 1.12-4.16) after correction for measurement error. Although the 40-item FFQ in the JACC Study may underestimate the intake, the data from the National Nutrition Survey (30) shows the low median intake of dietary fiber in Japan (13.3 g/day in 2003). Because the 25-percentile value was lower than 10 g/day in the survey (9.7 g/day), one fourth of Japanese might benefit from increasing intake of dietary fiber to prevent colorectal cancer if the results of the pooled analysis of cohorts (48) are true. The Japan Public Health Center–Based Prospective Study, another nationwide cohort study in Japan, did not find a clear dose-response relationship between dietary fiber and the risk of colorectal cancer, but reported an elevated risk in the subgroup of women with a very low intake of fiber [the lowest subtertile of the lowest quintile (mean, 8.3 g/day for the lowest quintile); ref. 27]. The low dietary fiber content in refined rice, the staple among Japanese, may result in the low intake of fiber in this population (7).

Moreover, the major food contributors to fiber will vary between countries, and the combination of miso soup and rice may be specific to Japan (27). These foods might be rich in some kinds of dietary fiber that reduce the risk of colorectal cancer. Indeed, bean fiber intake was somewhat inversely correlated with the risk in the present study as reported by Lin et al. (19). We cannot, however, rule out the possible confounding by some biofactors concentrated in the major sources of dietary fiber.

In this study, the inverse association of dietary fiber with the risk was predominantly found for colon cancer rather than rectal cancer. This may be biologically plausible because the rectum is empty most of the time (49), reducing the above-mentioned potential risk-reducing effects of fiber. The colon predominance in risk reduction in the present study is in line with some case-control (50) and cohort studies (21, 22).

Our analyses did not find a material difference in the effects of colorectal cancer risk for soluble and insoluble fiber. Of the five case-control studies that addressed such a difference, four are consistent with our results (3-5, 51), whereas Slattery et al. (6) reported a stronger inverse association of insoluble fiber with rectal cancer risk than that of soluble fiber. Wakai et al. (50) also found a decrease in the risk of colon cancer specifically associated with insoluble fiber in a case-control study. Soluble fiber is most effective for delaying starch absorption, thus reducing the glycemic load (41). On the other hand, insoluble fiber is most efficient for reducing the transit time of stool, provides bulk, dilutes fecal contents, and is converted to short-chain fatty acids, including butyrate as well as soluble fiber (7). The relative importance of soluble and insoluble fiber may depend on the underlying mechanism of colorectal carcinogenesis in the populations studied. In addition, it would not be easy for observational studies to separate the effects of soluble and insoluble fiber because intakes of these two kinds of fiber may be highly correlated as in the present study.

The percentage of individuals with a positive family history of colorectal cancer in parents and/or siblings was 2.4% in men and 2.8% in women in the present study. Considering the higher incidence rates in Japan than in the United States (31), these figures seem to be very low compared with those in the United States, where the percentage often exceeds 10% (17, 19, 20). In Japan, however, the low proportion is not specific to the JACC Study. The percentage was 1.3% for both men and women in the Japan Public Health Center-Based Prospective (JPHC) Study I (52). The proportions of participants who reported a family history of colorectal cancer in parents were 1.3% in men and 1.2% in women in the JPHC Study II (52), against 1.7% and 1.9% in our population, respectively. The corresponding figures for history in siblings were 0.5% and 0.5% in the JPHC Study II (52) and 0.8% and 0.9% in the present study. One possible reason for the low percentages in Japan is the rapid increase in incidence rates in the country (32). Another one may be the underreporting of family history. The sensitivity of self-reporting of past cancer history was previously reported to be quite low in Japan (36%; ref. 53), so that underreporting of family history may have occurred.

The strengths of the present study include its prospective design and large sample size. We assessed dietary intake before the diagnosis of colorectal cancer; thus, any errors of recall should have been nondifferential between cases and noncases.

Some methodologic limitations of our study, however, need consideration. First, because dietary habits could have changed during the follow-up, one-time administration of the FFQ at baseline might not sufficiently reflect the long-term exposure. However, the Nurses' Health Study has found that findings from baseline diet questionnaire were consistent with those from data updated with follow-up FFQs (20).

Second, possible residual confounding cannot be ruled out. For example, we could not consider the use of nonsteroidal anti-inflammatory drugs, which may confound the association of diet with colorectal cancer risk (41). In this study, physical activity was rather roughly measured, although it seemed not to be a major confounder. Third, the intakes of dietary fiber are likely to be underestimated due to the limited number of food items in our FFQ, as shown by the relatively low ratios of mean intakes estimated by the FFQ to those derived from the dietary records in the validation study. Finally, the dietary data from the 40-item FFQ did not allow us to estimate intakes of fiber from some food sources such as cereals. Further studies with comprehensive dietary instruments are required to address these issues.

In conclusion, this prospective study supported potential protective effects of dietary fiber intake against colorectal cancer and mainly against colon cancer. The highest intake may be related to a 25% decrease in the risk of colorectal cancer, compared with the lowest intake. The role of dietary fiber in the prevention of colorectal cancer seems to remain inconsistent. Further investigations in various populations are warranted.

Acknowledgments

The present investigators involved, with the co-authorship of this paper, in the JACC Study and their affiliations are as follows: Dr. Akiko Tamakoshi (present chairman of the study group), Nagoya University Graduate School of Medicine, Nagoya, Japan; Dr. Mitsuru Mori, Sapporo Medical University School of Medicine, Sapporo, Japan; Dr. Yutaka Motohashi, Akita University School of Medicine, Akita, Japan; Dr. Ichiro Tsuji, Tohoku University Graduate School of Medicine, Sendai, Japan; Dr. Yosikazu Nakamura, Jichi Medical School, Shimotsuke, Japan; Dr. Hiroyasu Iso, Graduate School of Medicine, Osaka University, Suita, Japan; Dr. Haruo Mikami, Chiba Cancer Center, Chiba, Japan; Dr. Yutaka Inaba, Juntendo University School of Medicine, Tokyo; Dr. Yoshiharu Hoshiyama, University of Human Arts and Sciences, Iwatsuki, Japan; Dr. Hiroshi Suzuki, Niigata University School of Medicine, Niigata, Japan; Dr. Hiroyuki Shimizu, Gifu University School of Medicine, Gifu, Japan; Dr. Hideaki Toyoshima, Nagoya University Graduate School of Medicine, Nagoya, Japan; Dr. Kenji Wakai, Aichi Cancer Center Research Institute, Nagoya, Japan; Dr. Shinkan Tokudome, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan; Dr. Yoshinori Ito, Fujita Health University School of Health Sciences, Toyoake, Japan; Dr. Shuji Hashimoto, Fujita Health University School of Medicine, Toyoake, Japan; Dr. Shogo Kikuchi, Aichi Medical University School of Medicine, Nagakuto, Japan; Dr. Akio Koizumi, Graduate School of Medicine and Faculty of Medicine, Kyoto University, Kyoto, Japan; Dr. Takashi Kawamura, Kyoto University Center for Student Health, Kyoto, Japan; Dr. Yoshiyuki Watanabe, Kyoto Prefectural University of Medicine Graduate School of Medical Science, Kyoto, Japan; Dr. Tsuneharu Miki, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan; Dr. Chigusa Date, Faculty of Human Life and Environment, Nara Women's University, Nara, Japan; Dr. Kiyomi Sakata, Wakayama Medical University, Wakayama, Japan; Dr. Takayuki Nose, Tottori University Faculty of Medicine, Yonago, Japan; Dr. Norihiko Hayakawa, Research Institute for Radiation Biology and Medicine, Hiroshima University, Hiroshima, Japan; Dr. Takesumi Yoshimura, Fukuoka Institute of Health and Environmental Sciences, Dazaifu, Japan; Dr. Akira Shibata, Kurume University School of Medicine, Kurume, Japan; Dr. Naoyuki Okamoto, Kanagawa Cancer Center, Yokohama, Japan; Dr. Hideo Shio, Moriyama Municipal Hospital, Moriyama, Japan; Dr. Yoshiyuki Ohno, Asahi Rosai Hospital, Owari-Asahi, Japan; Dr. Tomoyuki Kitagawa, Cancer Institute of the Japanese Foundation for Cancer Research, Tokyo; Dr. Toshio Kuroki, Gifu University, Gifu, Japan; and Dr. Kazuo Tajima, Aichi Cancer Center Research Institute, Nagoya, Japan.

References

1. Burkitt DP. Epidemiology of cancer of the colon and rectum. Cancer 1971;28:3–13.
2. Howe GR, Benito E, Castelleto R, et al. Dietary intake of fiber and decreased risk of cancers of the colon and rectum: evidence from the combined analysis of 13 case-control studies. J Natl Cancer Inst 1992;84:1887–96.
3. Slattery ML, Potter JD, Coates A, et al. Plant foods and colon cancer: an assessment of specific foods and their related nutrients (United States). Cancer Causes Control 1997;8:575–90.

4. Le Marchand L, Hankin JH, Wilkens LR, Kolonel LN, Englyst HN, Lyu LC. Dietary fiber and colorectal cancer risk. Epidemiology 1997;8:658–65.
5. Negri E, Franceschi S, Parpinel M, La Vecchia C. Fiber intake and risk of colorectal cancer. Cancer Epidemiol Biomarkers Prev 1998;7:667–71.
6. Slattery ML, Curtin KP, Edwards SL, Schaffer DM. Plant foods, fiber, and rectal cancer. Am J Clin Nutr 2004;79:274–81.
7. Bingham SA. Mechanisms and experimental and epidemiological evidence relating dietary fibre (non-starch polysaccharides) and starch to protection against large bowel cancer. Proc Nutr Soc 1990;49:153–71.
8. Slavin JL, Martini MC, Jacobs DR, Jr., Marquart L. Plausible mechanisms for the protectiveness of whole grains. Am J Clin Nutr 1999;70:459–63S.
9. Schatzkin A. Going against the grain? Current status of the dietary fiber-colorectal cancer hypothesis. Biofactors 2000;12:305–11.
10. Willett WC, Stampfer MJ, Colditz GA, Rosner BA, Speizer FE. Relation of meat, fat, and fiber intake to the risk of colon cancer in a prospective study among women. N Engl J Med 1990;323:1664–72.
11. Giovannucci E, Rimm EB, Stampfer MJ, Colditz GA, Ascherio A, Willett WC. Intake of fat, meat, and fiber in relation to risk of colon cancer in men. Cancer Res 1994;54:2390–7.
12. Steinmetz KA, Kushi LH, Bostick RM, Folsom AR, Potter JD. Vegetables, fruit, and colon cancer in the Iowa Women's Health Study. Am J Epidemiol 1994;139:1–15.
13. Kato I, Akhmedkhanov A, Koenig K, Toniolo PG, Shore RE, Riboli E. Prospective study of diet and female colorectal cancer: the New York University Women's Health Study. Nutr Cancer 1997;28:276–81.
14. Fuchs CS, Giovannucci EL, Colditz GA, et al. Dietary fiber and the risk of colorectal cancer and adenoma in women. N Engl J Med 1999;340:169–76.
15. Pietinen P, Malila N, Virtanen M, et al. Diet and risk of colorectal cancer in a cohort of Finnish men. Cancer Causes Control 1999;10:387–96.
16. Terry P, Giovannucci E, Michels KB, et al. Fruit, vegetables, dietary fiber, and risk of colorectal cancer. J Natl Cancer Inst 2001;93:525–33.
17. McCullough ML, Robertson AS, Chao A, et al. A prospective study of whole grains, fruits, vegetables and colon cancer risk. Cancer Causes Control 2003;14:959–70.
18. Mai V, Flood A, Peters U, Lacey JV, Jr., Schairer C, Schatzkin A. Dietary fibre and risk of colorectal cancer in the Breast Cancer Detection Demonstration Project (BCDDP) follow-up cohort. Int J Epidemiol 2003;32:234–9.
19. Lin J, Zhang SM, Cook NR, et al. Dietary intakes of fruit, vegetables, and fiber, and risk of colorectal cancer in a prospective cohort of women (United States). Cancer Causes Control 2005;16:225–33.
20. Michels KB, Fuchs CS, Giovannucci E, et al. Fiber intake and incidence of colorectal cancer among 76,947 women and 47,279 men. Cancer Epidemiol Biomarkers Prev 2005;14:842–9.
21. Bingham SA, Day NE, Luben R, et al. Dietary fibre in food and protection against colorectal cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC): an observational study. Lancet 2003;361:1496–501.
22. Bingham SA, Norat T, Moskal A, et al. Is the association with fiber from foods in colorectal cancer confounded by folate intake? Cancer Epidemiol Biomarkers Prev 2005;14:1552–6.
23. Alberts DS, Martinez ME, Roe DJ, et al. Lack of effect of a high-fiber cereal supplement on the recurrence of colorectal adenomas. Phoenix Colon Cancer Prevention Physicians' Network. N Engl J Med 2000;342:1156–62.
24. Schatzkin A, Lanza E, Corle D, et al. Lack of effect of a low-fat, high-fiber diet on the recurrence of colorectal adenomas. Polyp Prevention Trial Study Group. N Engl J Med 2000;342:1149–55.
25. Bonithon-Kopp C, Kronborg O, Giacosa A, Rath U, Faivre J. Calcium and fibre supplementation in prevention of colorectal adenoma recurrence: a randomised intervention trial. European Cancer Prevention Organization Study Group. Lancet 2000;356:1300–6.
26. Byers T. Diet, colorectal adenomas, and colorectal cancer. N Engl J Med 2000;342:1206–7.
27. Otani T, Iwasaki M, Ishihara J, Sasazuki S, Inoue M, Tsugane S. Dietary fiber intake and subsequent risk of colorectal cancer: The Japan Public Health Center-Based Prospective Study. Int J Cancer 2006;119:1475–80.
28. Ohno Y, Tamakoshi A, the JACC Study Group. Japan Collaborative Cohort Study for Evaluation of Cancer Risk Sponsored by Monbusho (JACC Study). J Epidemiol 2001;11:144–50.
29. Tamakoshi A, Yoshimura T, Inaba Y, et al. Profile of the JACC study. J Epidemiol 2005;15(Suppl 1):S4–8.
30. Research Group on Health and Nutrition Information. The National Health and Nutrition Survey in Japan, 2003, by Ministry of Health, Labour and Welfare of Japan. Tokyo: Dai-ichi Publishing; 2006.
31. Parkin DM, Whelan SL, Ferlay J, Teppo L, Thomas DB. Cancer incidence in five continents, vol. 8. Lyon: IARC; 2002.
32. Ajiki W, Tsukuma H, Oshima A. Cancer incidence and incidence rates in Japan in 1999: estimates based on data from 11 population-based cancer registries. Jpn J Clin Oncol 2004;34:352–6.
33. Date C, Fukui M, Yamamoto A, et al. Reproducibility and validity of a self-administered food frequency questionnaire used in the JACC Study. J Epidemiol 2005;15(Suppl 1):S9–23.
34. Science and Technology Agency. Standard tables of food composition in Japan, 5th ed. Tokyo: Printing Bureau, Ministry of Finance; 2000.
35. Prosky L, Asp NG, Schweizer TF, DeVries JW, Furda I. Determination of insoluble, soluble, and total dietary fiber in foods and food products: interlaboratory study. J Assoc Off Anal Chem 1988;71:1017–23.
36. Willett W, Stampfer MJ. Total energy intake: implications for epidemiologic analyses. Am J Epidemiol 1986;124:17–27.
37. Willett W. Correction for the effects of measurement error. In: Willett W, editor. Nutritional epidemiology, 2nd ed. New York, Oxford: Oxford University Press; 1998. p. 302–20.
38. Wakai K, Tamakoshi K, Date C, et al. Dietary intakes of fat and fatty acids and risk of breast cancer: a prospective study in Japan. Cancer Sci 2005;96:590–9.
39. Cox DR. Regression models and life-tables (with discussions). J R Stat Soc B 1972;34:187–220.
40. Giovannucci E. Modifiable risk factors for colon cancer. Gastroenterol Clin North Am 2002;31:925–43.
41. Hawk ET, Limburg PJ, Viner JL. Epidemiology and prevention of colorectal cancer. Surg Clin North Am 2002;82:905–41.
42. Martinez ME. Primary prevention of colorectal cancer: lifestyle, nutrition, exercise. Recent Results Cancer Res 2005;166:177–211.
43. Iwai N, Hisamichi S, Hayakawa N, et al. Validity and reliability of single-item questions about physical activity. J Epidemiol 2001;11:211–8.
44. SAS Institute Inc. SAS/STAT user's guide, version 8. Cary (NC): SAS Institute Inc; 1999.
45. Kojima M, Wakai K, Tokudome S, et al. Bowel movement frequency and risk of colorectal cancer in a large cohort study of Japanese men and women. Br J Cancer 2004;90:1397–401.
46. Kaaks R, Toniolo P, Akhmedkhanov A, et al. Serum C-peptide, insulin-like growth factor (IGF)-I, IGF-binding proteins, and colorectal cancer risk in women. J Natl Cancer Inst 2000;92:1592–600.
47. Ma J, Giovannucci E, Pollak M, et al. A prospective study of plasma C-peptide and colorectal cancer risk in men. J Natl Cancer Inst 2004;96:546–53.
48. Park Y, Hunter DJ, Spiegelman D, et al. Dietary fiber intake and risk of colorectal cancer: a pooled analysis of prospective cohort studies. JAMA 2005;294:2849–57.
49. McNeil NI, Rampton DS. Is the rectum usually empty?—a quantitative study in subjects with and without diarrhea. Dis Colon Rectum 1981;24:596–9.
50. Wakai K, Hirose K, Matsuo K, et al. Dietary risk factors for colon and rectal cancers: a comparative case-control study. J Epidemiol 2006;16:125–35.
51. Levi F, Pasche C, Lucchini F, La Vecchia C. Dietary fibre and the risk of colorectal cancer. Eur J Cancer 2001;37:2091–6.
52. Watanabe S, Tsugane S, Sobue T, Konishi M, Baba S. Baseline data of the Japan Public Health Center-Based Prospective Study on Cancer and Cardiovascular Disease (JPHC Study). Tokyo: Japan Public Health Association; 1996.
53. Yoshinaga A, Sasaki S, Tsugane S. Sensitivity of self-reports of cancer in a population-based prospective study: JPHC Study Cohort I. J Clin Epidemiol 2001;54:741–6.

Host and environmental factors for gastric cancer in Babol, the Caspian Sea Coast, Iran

Reza Ghadimi[a,d], Hassan Taheri[b], Sadao Suzuki[a], Mehrdad Kashifard[b], Akihiro Hosono[a], Imaneh Esfandiary[a], Ali A. Moghadamnia[c], Rezvan Ghadimi[d] and Shinkan Tokudome[a]

To clarify host and environmental factors for gastric carcinogenesis, we obtained information about gastric cancer mortality in Babol, in the North of Iran, and recruited 130 participants aged 30–80 years from the general population of Babol in 2004. A urea breath test, assessment of IgG antibodies to *Helicobacter pylori*, a pepsinogen test, a marker of chronic atrophic gastritis, and determination of urinary excretions of sodium and potassium were performed. Diet and lifestyle information was also obtained using a questionnaire. The stomach cancer mortality rate for men in Babol (38.2/10^5) was found to be somewhat lower than that for Japanese men (45.1/10^5), while the mortality for women (26.9/10^5) was higher than for Japanese women (20.9/10^5). Positive rates for the urea breath test were 77.5 and 81.8% for Iranian men and women, respectively. *Helicobacter pylori* IgG antibodies were present in 68.7 and 73.7% of Iranian men and women, respectively, both values being marginally higher than for Japanese. We also found 51.0 and 52.8% to be positive for a pepsinogen test, significantly higher than the Japanese values. Urinary excretions of salt and potassium in this population appeared approximately the same as the consumption in Japanese. The elevated gastric cancer mortality in both men and women in Babol seems, by and large, to be related to higher *H. pylori* infection rates and prevalence of chronic atrophic gastritis. Certain factors, including *H. pylori* DNA diversity, host factors and their interactions, together with the level of medical practice, prevalence of and access to secondary prevention of stomach cancer, may also be associated with the relatively high mortality. *European Journal of Cancer Prevention* 16:192–195 © 2007 Lippincott Williams & Wilkins.

European Journal of Cancer Prevention 2007, 16:192–195

Keywords: antibodies to ***Helicobacter pylori***, pepsinogen test, chronic atrophic gastritis, salt consumption, stomach cancer

[a]Department of Health Promotion and Preventive Medicine, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan, Departments of [b]Internal Medicine and [c]Physiology and Pharmacology, [d]Babol University of Medical Sciences, Babol, Iran

Correspondence to Professor Shinkan Tokudome, Department of Health Promotion and Preventive Medicine, Nagoya City University Graduate School of Medical Sciences, Mizuho-ku, Nagoya 467-8601, Japan
Tel: +81 52 853 8174; fax: +81 52 842 3830;
e-mail: tokudome@med.nagoya-cu.ac.jp

Sponsorship: Ministry of Education, Culture, Sports, Science and Technology, Japan.

Introduction

Stomach cancer is the second most common cancer in terms of incidence and mortality in the world, but the distribution varies greatly across countries and areas (Correa and Haenszel, 1998; Parkin *et al.*, 2002). In Japan, Korea, China and other developing countries in Asia and South America, this malignancy is more frequent than in the West (Parkin *et al.*, 2002). It is the most prevalent gastrointestinal cancer in Iran (Nadim and Noorai, 2000; Naghavi, 2000) where Ardabil, a North-western province, has the highest incidence of gastric adenocarcinoma (Sadjadi *et al.*, 2003). Physicians in Babol, a city near the Caspian Sea, have reported that the number of patients with gastric neoplasm increased recently (Bijani and Babaei, 2002).

The variation in gastric cancer mortality rates suggests that they are influenced largely by environmental factors, rather than the genetic background (Hwang *et al.*, 1994). It is a paradigm that the risk of gastric cancer is largely due to *Helicobacter pylori* infection, intake of salt (Hill, 1998), nitrates (Sandor *et al.*, 2001), fresh fruit and vegetables (Serafini *et al.*, 2002) and smoking habits, along with host factors (Tokudome *et al.*, 2005). In particular, *H. pylori* is known to be involved in gastric cancer development, and the International Agency for Research on Cancer categorized the bacterium as a class I human carcinogen in 1994 (Asaka *et al.*, 1997; Helicobacter and Cancer Collaborative Group, 2001). Its colonization of the stomach mucosa triggers a series of inflammatory reactions and causes chronic atrophic gastritis (CAG), a primary step in mucosal changes in the stomach leading to cancer development: that is, normal mucosa → chronic active gastritis → CAG → intestinal metaplasia → dysplasia → carcinoma *in situ* (Fukao *et al.*, 1993; Correa and Miller, 1995). The early detection of gastric precancerous changes, mainly CAG, may be helpful for prevention of stomach cancer or diagnosis of the neoplasm at a curable stage. Previous studies have shown the pepsinogen level, which can easily be measured without discomfort for study participants, to be a reliable marker for the extent of CAG, while histopathological diagnosis needs multifocal endoscopic biopsy samples to accurately quantify its extent (Miki *et al.*, 2003).

In the present study, we first collected information on the mortality statistics of stomach cancer in Babol, Iran, and then conducted a collaborative epidemiologic study on host and local environmental factors, examining the prevalence of *H. pylori* infection and markers of CAG along with salt and potassium urinary excretions, for comparison with relevant data for Japan.

Study participants and methods

Babol is a town located in Mazandaran Province in the North of Iran near the Caspian Sea. According to the census of 1999, the population is about 450 000, of which approximately 46% were registered as urban dwellers and 54% as villagers. Approximately 90% of them are of Aryan Caucasian origin. We obtained information on population and number of deaths due to gastric cancer for both sexes during 1999–2003 from the Statistics Center of Babol University of Medical Sciences.

We randomly recruited 130 participants (50 men and 80 women), aged 30–80 years, from the general population of Babol in August 2004.

After providing informed consent, each participant was interviewed by a trained interviewer using a semi-quantitative food frequency questionnaire and lifestyle questionnaire; then, body weight and height were measured. Oral mucous membranes, breath, overnight-fasting blood, second morning voiding urine and feces samples were obtained from each participant.

Serum antibodies for *H. pylori* were examined by enzyme immunoassay (Kyowa Medics Co., Tokyo, Japan), and values ≥ 1.7 were defined as positive. Serum pepsinogen I and II levels were measured by chemical luminescence enzyme immunoassay (Eiken Chemicals Co., Tokyo, Japan), a pepsinogen I level ≤ 70 ng/ml and a pepsinogen I/II ratio ≤ 3.0 being defined as positive (Miki *et al.*, 2003). For the urea breath test, UBiT-IR300 kits (Otsuka Pharmaceutical Co., Tokyo, Japan) were used with 2.5‰ as the positive cutoff (Ohara *et al.*, 1998). For this purpose, a single UBiT tablet containing 100 mg of ^{13}C-urea was ingested with 100 ml of water under fasting conditions (Ohara *et al.*, 2004). As the values differed by sex and age, age adjustment was made for the rates, adopting the World Population (Parkin *et al.*, 2002) as standard, for comparison with the figures for Japan. Using second morning voiding urine, excretions of sodium and potassium were analyzed by electrode assay and excretions of creatinine by an enzymatic method with adjustment for creatinine (Kawasaki *et al.*, 1993), and were then compared with the consumption in the Japanese after adjustment for age.

The study protocol was approved by the Internal Review Board of Nagoya City University and the Research Committee of Babol University of Medical Sciences.

Results

The average population of Babol during 1999–2003 was 450 464 (individuals aged 15 years or older numbered around 317 700), and the mean annual number of deaths from gastric cancer during the same period was 69.5 (41.5 males and 28.0 females). The age-adjusted gastric cancer mortality rates in the population aged 15 years or older in Babol, Iran were $38.2/10^5$ 95% confidence interval: 26.5–49.9 for males and $26.9/10^5$ (95% confidence interval 16.9–36.9) for females. The corresponding Japanese values were $45.1/10^5$ (95% confidence interval 44.6–45.6) and $20.9/10^5$ (95% confidence interval 20.5–21.2), respectively.

The mean ages for the 50 male and 80 female participants were 50.5 ± 1.7 and 49.6 ± 1.1 years, respectively. Smoking rates in Babol (28.7% of male and 2.9% of female participants) were lower than those in Japan in both sexes (Table 1). The age-adjusted body mass indexes in this population were 26.1 for men and 29.1 for women, being higher than Japanese values (Ministry of Health, Labour and Welfare, Japan, 2004).

After adjusting for age, urea breath test results were positive for 77.5% male and 81.8% female participants, and *H. pylori* IgG antibodies were found in 68.7 and 73.7%, respectively, in Babol, both higher than the Japanese values (Kikuchi *et al.*, 2000) (Table 2).

Positive pepsinogen tests indicated that the prevalence of CAG in both sexes of the general population of Babol was significantly higher than the reported values in Japanese (Watase *et al.*, 2004) (Table 2).

Age-adjusted means for salt excretions were 12.1 and 10.2 g/day for male and female participants, respectively, being slightly lower than the consumption in Japan (Ministry of Health, Labour and Welfare, Japan, 2004). Potassium excretions were 2.7 g/day for male and 2.4 g/day for female participants, being quite similar to the Japanese levels (Table 2).

Discussion

This first international ecological study on stomach cancer in Babol, on the Caspian Sea Coast, Iran, demonstrates that an age-adjusted mortality rate for stomach cancer for males in Babol is somewhat lower than that in Japanese males, but higher in Iranian than

Table 1 Comparison of selected characteristics between Iranians in Babol and Japanese

	Babol, Iran		Japan[a]	
	Male participants (n=50)	Female participants (n=80)	Male participants	Female participants
Body mass index (kg/m^2)[b]	26.1	29.1	23.5	22.7
(95% CI)	(24.9–27.3)	(28.1–30.1)	(23.4–23.6)	(22.4–22.9)
Tobacco smoking (%)[b]	28.7	2.9	51.5	13.0
(95% CI)	(15.3–42.0)	(0.0–7.1)	(46.5–56.4)	(9.6–16.4)
Alcohol drinking (%)[b]	11.3	0	54.9	10.8
(95% CI)	(3.1–19.4)	(0.0–0.0)	(49.9–59.9)	(7.6–14)

CI, confidence interval.
[a]Data from The National Nutritional Survey in Japan 2002.
[b]Adjusted for age.

Table 2 Comparison of data for *Helicobacter pylori* infection, pepsinogen test, salt and potassium excretions between Babol, Iran and Japan

	Babol, Iran		Japan[a]	
	Male participants (n=50)	Female participants (n=80)	Male participants	Female participants
Positive UBT (%)[b]	77.5	81.8	NA	NA
(95% CI)	(64.9–90.1)	(71.4–92.1)		
Positive *H. pylori* IgG (%)[b]	68.7	73.7	61.5[a]	56.7[a]
(95% CI)	(56.0–81.5)	(63.5–83.8)	(58.0–65.1)	(53.1–60.3)
Positive chronic atrophic gastritis (%)[b,c]	51.0	52.8	23.5[a]	21.8[a]
(95% CI)	(37.1–64.9)	(39.5–61.7)	(21.5–25.4)	(20.3–23.4)
Salt excretions (g/day)[b]	12.1	10.2	12.9[a]	11.3[a]
(95% CI)	(11.2–13.0)	(9.5–11.0)	(12.7–13.1)	(11.1–11.4)
Potassium excretions (g/day)[b]	2.7	2.4	2.5[a]	2.4[a]
(95% CI)	(2.5–2.9)	(2.3–2.5)	(2.5–2.5)	(2.3–2.4)

UBT, urea breath test; CI, confidence interval; NA, not available.
[a]Cited from references Kikuchi *et al.* (2000), Watase *et al.* (2004), and Ministry of Health, Labour and Welfare, Japan (2004).
[b]Adjusted for age.
[c]Positive chronic atrophic gastritis was defined as a serum pepsinogen I level $\leq$ 70 ng/ml and a pepsinogen I/II ratio $\leq$ 3.0.

Japanese females. The *H. pylori* infection rates, determined by the urea breath test and IgG, were higher in Babol than in Japan and the prevalence of CAG, diagnosed by the pepsinogen test, in the present Iranians were also significantly higher than in the Japanese. Thus, it seems plausible that Northern Iranians might have a higher gastric cancer risk in the female sex, in particular, when compared with the Japanese.

Expression of Cag A, a highly immunologic protein encoded by the Cag A gene, is crucial for gastric carcinogenesis. Most *H. pylori* strains in the Japanese are of the East Asian type which is more virulent than the Western varieties (Azuma, 2004), and the grades of inflammation, gastritis and atrophy are significantly elevated in gastritis patients infected with the East Asian type Cag A positive strain as compared with their counterparts infected with the Cag A negative or Western type Cag A positive strain (Azuma, 2004). No data about Cag A subtypes in Babol, however, are available at present.

Excessive salt intake is another risk factor for gastric cancer, and the promoting effect may be due to destruction of the mucosal barrier that protects the surface membranes of the stomach (Tatematsu *et al.*, 1975; World Cancer Research Fund, 1997; Nozaki *et al.*, 2002). In the present study, although daily salt consumption was higher than 6 g/day as recommended by the World Health Organization (1990), there are no significant differences in sodium excretions and intakes between the Iranian people living in Babol and the population of Japan. Similarly, no significant discrepancies were found between potassium excretions, a marker of consumption of vegetables and fruit, a preventive factor for stomach cancer, in Iranian people and intakes in the Japanese.

Other important risk factors that might contribute to variation in gastric cancer mortality rates between the two populations include smoking (Sasazuki *et al.*, 2002; Montani *et al.*, 2004) and drinking habits (Kikuchi *et al.*, 2002). Tobacco smoke contains well-known potent carcinogens, including benzopyrene (Rubin, 2001), and other chemicals that can increase mRNA expression of certain chemokines in gastric mucosa, which may augment inflammatory reactions. Furthermore, gastric defense mechanisms may be reduced among smokers (Kato *et al.*, 2004). As shown in Table 1, however, tobacco smoking and alcohol drinking rates were higher in the Japanese than in the Iranians.

In Babol, a population-based cancer registration system is not in operation and no data were available for cancer incidence. The mortality is generally accepted to be a reliable source of statistical information on cancer risk as it is collected from death certificates, which are legally required documents. The mortality rate may be proxy of incidence, however, because it is a function of both incidence and treatment modalities. Mortality is largely influenced by severity of disease and the time of diagnosis, and there is no special screening program for gastric cancer in Babol. Most patients are diagnosed at late stages and patients may not pay close attention to the physician's recommendations for secondary prevention. These factors would clearly be expected to increase the gastric cancer mortality rate. In addition, the location and types of gastric cancer impact on outcome and survival.

In conclusion, despite the weaknesses mentioned above and low-rank evidence provided by ecological study, our data showed simple but compelling evidence that the high stomach cancer mortality rate in Babol may be due to the high prevalence of *H. pylori* infection and CAG, suggesting that *H. pylori* is an essential factor for the onset of stomach cancer. The present study may also suggest an influence of host factors, including genetic polymorphisms, impacting on cellular immunity and human lymphocyte antigens, and interactions between host and environmental factors. Further studies, however, including our on-going case–control study, are necessary to elucidate host and environmental factors for the high gastric cancer mortality rate in this region of Iran.

Acknowledgements

The authors gratefully acknowledge the generous assistance of the staff of Babol University of Medical Sciences, and particularly Dr A. Noorbaran, Dr A. Bijani, Ms M. Baleghi, Mr A. Esfandiary, Ms P. Sajadi and the staff of the Department of Health Promotion and Preventive Medicine in Nagoya City University Graduate School of Medical Sciences, Ms K. Higuchi, Ms M. Watanabe and Ms S. Koshiba for their help.

References

Asaka M, Takeda H, Sugiyama T, Kato M (1997). What role does *Helicobacter pylori* play in gastric cancer and lymphoma? *Gastroentrology* **113 (Suppl 6)**: s56–s60.

Azuma T (2004). *Helicobacter pylori* Cag A protein variation associated with gastric cancer in Asia. *J Gastroentrol* **39**:97–103.

Bijani A, Babaei M (2002). *Death report from Babol.* Iran: Babol University of Medical Sciences.

Correa P, Haenszel W (1998). Epidemiology of gastric cancer. In: Correa P, Haenszel W, editors. *Epidemiology of cancer of digestive tract.* Vol. 2. The Hague: Martinus-Niijhoff. pp. 58–84.

Correa P, Miller MJS (1995). *Helicobacter pylori* and gastric atrophy: cancer paradoxes. *J Natl Cancer Inst* **87**:1731–1732.

Fukao A, Komatsu S, Tsubono Y, Hisamichi S, Ohori H, Kizawa T, *et al.* (1993). *Helicobacter pylori* infection and chronic atrophic gastritis among Japanese blood donors: a cross-sectional study. *Cancer Causes Control* 4:307–312.

Helicobacter and Cancer Collaborative Group (2001). Gastric cancer and *Helicobacter pylori*: a combined analysis of 12 case–control studies nested within prospective cohorts. *Gut* **49**:347–353.

Hill MJ (1998). Salt and gastric cancer. *Eur J Cancer Prev* **7**:173–175.

Hwang H, Dwyer J, Russell RM (1994). Diet, *Helicobacter pylori* infection, food preservation and gastric cancer risk: are there new roles for preventative factors? *Nutr Rev* **52**:75–83.

Kato I, Vivas J, Plummer M, Lopez G, Peraza S, Castro D, *et al.* (2004). Environmental factors in *Helicobacter pylori*-related gastric precancerous lesions in Venezuela. *Cancer Epidemiol Biomarkers Prev* **13**:468–476.

Kawasaki T, Itoh K, Uezono K, Sasaki H (1993). Estimation of 24-h urinary sodium and potassium excretion from predicted values of 24-h urinary creatinine excretion and fractional urine sodium/creatinine and potassium/creatinine. In: *7th Symposium on Salt.* Vol. 2. Amsterdam: Elsevier Science Publishers BV. pp. 257–262.

Kikuchi S, Nakajima T, Kobayashi O, Yamazaki T, Kikuchi M, Mori K, *et al.* (2002). U-shaped effect of drinking and linear effect of smoking on risk for stomach cancer in Japan. *Jpn J Cancer Res* **93**:953–959.

Kikuchi S, Nakajima T, Kobayashi O, Yamazaki T, Kikuchi M, Mori K, *et al.* (2000). Effect of age on the relationship between gastric cancer and *Helicobacter pylori*. *Jpn J Cancer Res* **91**:774–779.

Miki K, Morita M, Sasajima R, Hoshina R, Kanda E, Urita Y (2003). Usefulness of gastric cancer screening using the serum pepsinogen test method. *Am J Gastroenterol* **98**:735–739.

Ministry of Health, Labour and Welfare, Japan (2004). *The national nutritional survey in Japan 2002 [in Japanese].* Tokyo: Daiichi Shuppan.

Montani AM, Sasazuki S, Inoue M, Natsukawa S, Shaur K, Koizumi Y, *et al.* (2004). Association of *Helicobacter pylori* infection and environmental factors in non-cardia gastric cancer in Japan. *Gastric Cancer* **7**:46–53.

Nadim A, Noorai M (2000). Cancers. In: Azizi F, Hatami H, Janghorbani M, editors. *Epidemiology and control of common disease in Iran.* 1st ed. Tehran: Eshtiagh. pp. 216–217.

Naghavi M (2000). *Death report from 10 provinces in Iran.* 1st ed. Tehran: Ministry of Health. p. 384.

Nozaki K, Shimizu N, Inada K, Tsukamoto T, Inoue M, Kumagai T, *et al.* (2002). Synergistic promoting effects of *Helicobacter pylori* infection and high salt diet on gastric carcinogenesis in Mongolian gerbils. *Jpn J Cancer Res* **93**:1083–1089.

Ohara S, Kato M, Asaka M, Toyota T (1998). Studies of ^{13}C-urea breath test for diagnosis of *Helicobacter pylori* infection in Japan. *J Gastroenterol* **33**: 6–13.

Ohara S, Kato M, Saito M, Fukuda S, Kato C, Hamada S, *et al.* (2004). Comparison between a new ^{13}C-urea breath test, using a film-coated tablet, and the conventional ^{13}C-urea breath test for the detection of *Helicobacter pylori* infection. *J Gastroenterol* **39**:621–628.

Parkin DM, Whelan SL, Ferlay J, Teppo L, Thomas DB (2002). *Cancer incidence in five continents.* Vol. VIII. Lyon: IARC Scientific Publications. No. 155.

Rubin H (2001). Synergistic mechanisms in carcinogenesis by polycyclic aromatic hydrocarbons and by tobacco smoke: a bio-historical perspective with updates. *Carcinogenesis* **22**:1903–1930.

Sadjadi AR, Malekzadeh R, Derakhshan MH, Sepehr AR, Nouraie M, Sotoudeh M, *et al.* (2003). Cancer occurrence in Ardabile: results of a population-based cancer registry from Iran. *Int J Cancer* **107**:113–118.

Sandor J, Kiss I, Farkas O, Ember I (2001). Association between gastric cancer mortality and nitrate content of drinking water: ecological study on small area inequalities. *Eur J Epidemiol* **17**:443–447.

Sasazuki S, Sasaki S, Tsugane S (2002). Cigarette smoking, alcohol consumption and subsequent gastric cancer risk by subsite and histologic type. *Int J Cancer* **101**:560–566.

Serafini M, Bellocco R, Wolk A, Ekstrom AM (2002). Total antioxidant potential of fruit and vegetables and risk of gastric cancer. *Gastroenterology* **123**: 985–991.

Tatematsu M, Takahashi M, Fukushima S, Hananouchi M, Shirai T (1975). Effects in rats of sodium chloride on experimental gastric cancer induced by *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine or 1-nitroquinoline-1-oxide. *J Natl Cancer Inst* **55**:101–106.

Tokudome S, Soeripto, Triningsih FXE, Ananta I, Suzuki S, Kuriki K, *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.

Watase H, Inagaki T, Yoshikawa I, Furihata S, Watanabe Y, Miki K (2004). Five years follow up study of gastric cancer screening using the serum pepsinogen test method in Adachi City. *Jpn Assoc Detect Diag* **11**:77–81.

World Cancer Research Fund/America Institute for Cancer Research (1997). *Food, nutrition and prevention of cancer: a global perspective.* Washington, DC: American Institute for Cancer Research.

World Health Organization (1990). *Diet, nutrition and the prevention of chronic diseases.* Technical Series Reports, No. 797. Geneva: WHO.

Cancer Causes Control (2007) 18:259–267
DOI 10.1007/s10552-006-0111-x

ORIGINAL PAPER

Psychological attitudes and risk of breast cancer in Japan: a prospective study

Kenji Wakai · Masayo Kojima · Kazuko Nishio · Sadao Suzuki · Yoshimitsu Niwa · Yingsong Lin · Takaaki Kondo · Hiroshi Yatsuya · Koji Tamakoshi · Akio Yamamoto · Shinkan Tokudome · Hideaki Toyoshima · Akiko Tamakoshi · for the JACC Study Group

Received: 26 June 2006 / Accepted: 26 December 2006 / Published online: 14 February 2007

Abstract
Objective To examine the association between psychological factors and the risk of breast cancer prospectively in a non-Western population.
Methods Data from the Japan Collaborative Cohort (JACC) study were analyzed. From 1988 to 1990, 34,497 women aged 40–79 years completed a questionnaire on medical, lifestyle and psychosocial factors. The rate ratios (RRs) of their responses were computed by fitting to proportional hazards models.
Results During the mean follow-up period of 7.5 years, 149 breast cancer cases were documented. Those individuals who possessed "ikigai" (Japanese term meaning something that made one's life worth living) showed a significantly lower risk of breast cancer (multivariate-adjusted RR = 0.66; 95% confidence interval [CI] = 0.47–0.94). Those who perceived themselves as able to make decisions quickly also had a lower risk of breast cancer (multivariate-adjusted RR = 0.56; 95% CI = 0.36–0.87). The other factors investigated, including ease of anger arousal and self-perceived stress of daily life were not associated with breast cancer risk.
Conclusions Although further studies will be necessary to verify these findings, our results suggest that having "ikigai" and being decisive decrease an individual's subsequent risk of breast cancer.

Keywords Breast cancer Psychological factors Ikigai Decisiveness Prospective studies

K. Wakai (✉)
Division of Epidemiology and Prevention, Aichi Cancer Center Research Institute, 1-1 Kanokoden, Chikusa-ku, Nagoya 464-8681, Japan
e-mail: wakai@med.nagoya-u.ac.jp

M. Kojima S. Suzuki S. Tokudome
Department of Health Promotion and Preventive Medicine, Nagoya City University Graduate School of Medical Sciences, 1 Kawasumi, Mizuho-cho, Mizuho-ku, Nagoya 467-8601, Japan

K. Nishio Y. Niwa A. Tamakoshi
Department of Preventive Medicine/Biostatistics and Medical Decision Making, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya 466-8550, Japan

Y. Lin
Department of Public Health, Aichi Medical University School of Medicine, 21 Karimata, Yazako, Nagakute-cho, Aichi-gun, Aichi 480-1195, Japan

T. Kondo
Department of Medical Technology, Nagoya University School of Health Sciences, 1-1-20 Daiko-minami, Higashi-ku, Nagoya 461-8673, Japan

H. Yatsuya K. Tamakoshi H. Toyoshima
Department of Public Health/Health Information Dynamics, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya 466-8550, Japan

A. Yamamoto
Infectious Diseases Division, Hyogo Prefectural Institute of Public Health and Environmental Sciences, 2-1-29 Arata-cho, Hyogo-ku, Kobe 652-0032, Japan

Introduction

It has long been suggested that psychological factors might play a role in the etiology of breast cancer. Both immune and hormonal factors have been discussed as potential biological mechanisms underlying the associations between psychological factors and the general risk of developing cancer. Psychological factors can indirectly influence the breast cancer risk by altering behaviors such as sleep, exercise, diet, smoking, alcohol consumption, drug use, and poor adherence to medical regimens [1, 2]. Previous case–control studies have investigated the effects of various psychological factors on breast cancer development, including negative emotions, personality, stressful life events, methods of coping and social support, but have yielded inconsistent results [3, 4].

Prospective studies are superior in design to case–control studies as they avoid biases and can provide better evidence, but their results have also been inconclusive. Recent meta-analyses [5] and reviews [3, 4] reported no evidence of, or only weak associations with emotional repression and severe life events and the risk of breast cancer. Most of these earlier studies were, however, insufficient in sample size and length of follow-up, and potential confounding variables were rarely adequately adjusted [3, 4]. These deficiencies might have led to equivocal findings.

Recently, two large prospective studies have published their results. Lillberg et al. analyzed the Finnish Twin Cohort, which examined the association between psychosocial factors and breast cancer risk in over 10,000 women with a 15-year follow-up period [6–9]. They found a positive association with breast cancer risk in the accumulation of stressful life events and single major life events [9], but no association was observed in life satisfaction, neuroticism [7], extroversion, Type A behavior, hostility [8], and stress of daily activities [6]. Aro et al. reported the results of another Finnish cohort study including 10,892 women and a six- to nine-year follow-up period, and found that none of the psychological factors such as depression, trait anxiety, cynical distrust, or coping were associated with breast cancer risk [10].

Although these large studies were of a prospective design and had adjusted for major confounding factors, they were conducted in the same country. Psychosocial factors are subject to cultural influences, so evidence from different cultures is important. To further prospectively examine the association between psychological factors and the risk of breast cancer in a non-Western setting, we analyzed data from a large follow-up study, the Japan Collaborative Cohort Study (JACC) for the Evaluation of Cancer Risk, sponsored by Monbukagakusho (the Ministry of Education, Culture, Sports, Science and Technology of Japan). By performing multivariate analysis, we were able to separate the independent effects of psychological factors on breast cancer from those of established risk factors, such as age, family history of cancer, use of exogenous female hormones, and reproductive factors.

We focused on "ikigai" as a possible psychological factor that might be associated with breast cancer risk. "Ikigai" is a Japanese word that is believed to be an essential factor for maintaining health [11]. Japanese dictionaries define "ikigai" as something to live for; the joy and goal of living; the happiness and benefit of being alive. The term "ikigai" is a peculiar to the Japanese language [12], being less philosophical and more intuitive in its nuance than comparable terms in Western languages [13]. It is a comprehensive concept that reflects emotions such as happiness and life-satisfaction as well as the cognitive evaluation towards one's life [14]. Recently, some researchers have used "ikigai" directly and reported its associations with various health conditions [11, 12, 14–19] including total mortality [17]. It has not been evaluated for its relationship with breast cancer risk, but we hypothesized that it would have a protective effect on breast cancer development.

We also examined some personality characteristics such as decisiveness and ease of anger arousal in relation to breast cancer risk. Following the concept of the type-C cancer prone personality (self-effacing and non-assertive) proposed by Temoshok [20], we expected that those who were decisive and easily angered would be less likely to develop breast cancer. In addition, we examined the association between self-perceived stress and breast cancer risk, and hypothesized that it would have an adverse effect on breast cancer development.

Materials and methods

Study population

All data were taken from the Japan Collaborative Cohort study for Evaluation of Cancer Risk (JACC Study), which was a nationwide multicenter collaborative study sponsored by the Ministry of Education, Culture, Sports, Science and Technology of Japan (Monbukagakusho). The details of this study are described elsewhere [21, 22]. In brief, the original study population consisted of 110,792 Japanese adults aged 40–79, who were enrolled between 1988 and 1990 in 45 locations throughout Japan. Most of the subjects were recruited from the general population or when undergoing routine health checks in the municipalities. On enrollment, participants completed a self-administered questionnaire that assessed demographic characteristics, lifestyle habits and medical history, as well as psychosocial factors.

Informed consent for participation was obtained individually from each participant, with the exception of those in a few study areas in which informed consent was provided at the group level, after the study aim and data confidentiality had been explained to community leaders. The study protocol was approved by the Ethical Board of the Nagoya University School of Medicine, Japan.

The subjects of the present study were restricted to women living in 22 study areas where information on cancer incidence was available, and where psychological questions had been included in the baseline questionnaire. From these potential participants (n = 36,035), we excluded 277 with a history of breast cancer and 1,261 who failed to answer any of the four psychological questions. Thus, a total of 34,497 women were included in the present analysis (mean age ± standard deviation [SD] = 58.0 ± 10.1 years). The average response rate was 83% in 17 of the 22 study areas, which recruited all eligible residents for the cohort [22].

Psychological factors and other exposure data

The baseline questionnaire included four questions on psychological factors: having "ikigai" (do you have "ikigai", something that makes your life worth living?), decisiveness (do you make decisions quickly?), ease of anger arousal (are you easily angered?), and self-perceived stress of daily life (do you experience stress during your daily life?). Three or four possible responses were provided for each question (see Table 2). The questionnaire also covered behavioral and lifestyle factors, including smoking, drinking and dietary habits, and physical activity levels, as well as medical history, educational level, family history of cancer, height, body weight, and female reproductive factors.

In one study area out of 22, the question about ease of anger arousal was not asked. The 2,505 women of this study area were therefore omitted for analysis of this question, leaving 31,992 subjects.

Follow-up

We used population registries in the relevant municipalities to determine the vital and residential status of the participants. Registration of death is required by the Family Registration Law in Japan, which is adhered to nationwide. For logistical reasons, we discontinued the follow-up of those individuals who moved out of their given study areas.

We ascertained the incidence of cancer from the records of population-based and/or hospital-based cancer registries, together with a systematic review of death certificates. In some study areas, the medical records of the hospitals treating cancer patients were also used to collate information on cancer incidence. The follow-up period ran from the time of the baseline survey to the end of 1997 in all areas except one (where it continued until the end of 1994). During the study period, only 2.7% (n = 947) of the subjects were lost to follow-up because they moved out of their given study areas.

Statistical analysis

We calculated the 'person-time of follow-up' for each participant as the period between the date of completing the baseline questionnaire and whichever of the following events occurred first: the date of diagnosis of breast cancer, death from any cause, emigration outside the study area and the end of the follow-up period. For cases identified only on a death certificate, the date of death was assumed to be the date of diagnosis. In the analytic cohort, the proportion of death-certificate only (DCO) registrations for breast cancer was 3.4% (five of the 149 cases). The mortality-to-incidence ratio was 0.18, which was lower than that determined using representative population-based cancer registries in Japan (0.20–0.30) [23]. Those who died from causes other than breast cancer (n = 1,559) or who moved out of their study areas were treated as censored cases.

The rate ratios (RRs) with 95% confidence intervals (CIs) for breast cancer, according to the dichotomized responses to the psychological questions, were estimated using proportional hazards models [24]. The RRs were adjusted for the following potential confounding variables [25, 26]: age (using 10-year age groups); area (Hokkaido and Tohoku, Kanto, Chubu, Kinki, Chugoku or Kyushu); educational level (attended school until the age of ≤15, 16–18 or ≥19 years); family history of breast cancer in mother or sisters (yes or no); age at time of first menstrual cycle or menarche (≤13, 14–15, 16–17 or ≥18 y ears); age at menopause (premenopausal at baseline, ≤44, 45–49 or ≥50 years); age at first time of giving birth (≤24, 25–29 or ≥30 years); number of times of giving birth or parity (0, 1, 2, 3 or ≥4); use of exogenous female hormone (yes or no); alcohol consumption (never a drinker, ex-drinker, or current drinker consuming <15 or ≥15 g of ethanol daily); consumption of green leafy vegetables (≤2 times/week, 3–4 times/week or almost every day); daily walking habits (seldom or never, or ~30, 30–59 or ≥60 min/day); exercise (seldom or never, 1–2, 3–4 or ≥5 h/week); sedentary work (yes or no); height (<150.0, 150.0–159.9 or ≥160.0 cm); and baseline body-mass index (BMI) (<20.0, 20.0–24.9, 25.0–29.9 or ≥30.0 kg/m^2). We used age as the underlying time axis in the proportional hazards model. The BMI for each individual was calculated according to their reported height and weight using the following formula: BMI = (weight in kg)/(height in m)^2.

Missing values for each covariate were treated as an additional category in the variable and were included in the proportional hazards model. The proportional hazards assumption of the models was statistically tested using the time-dependent covariate method [27], and the explanatory variables analyzed were proved to satisfy the assumption. We repeated the analyses after excluding the first two years of follow-up, during which 31 cases of breast cancer were diagnosed. When the five cases of breast cancer identified only by death certificates were omitted from the analysis, the multivariate RRs were altered at most by 0.03.

The baseline characteristics of the participants by response to the psychological questions were compared using the t-test for continuous variables and the Chi-square test for categorical variables. Spearman's correlation coefficients were calculated to investigate the inter-correlation between the four psychological factors.

All p-values were two-sided and all analyses were performed using the Statistical Analysis System (SAS) version 8.2 [28].

Results

The absolute value of Spearman's correlation coefficients among the four psychological factors ranged from 0.03 to 0.33 (Table 1). Most variables were independent from others, and only mild correlations were detected between having "ikigai" and decisiveness, ease of anger arousal and perceived stress.

Participant baseline characteristics by response to the psychological questions are presented in Table 2. Those who stated that they have "ikigai" tended to attain a higher level of education, to have a drinking habit, to consume green leafy vegetables every day, and to engage in physical exercise for at least three hours per week. Predisposition of quick decision-making (decisiveness) was also associated with higher levels of education, a drinking habit and physical exercise. Women who were easily angered were less likely to have menopause at the baseline and more likely to be current drinkers, compared to subjects whose anger is less easily aroused. A self-perceived stress of daily life was associated with high education levels, pre-menopause, and rare physical exercise.

During the 259,023 person-years of follow-up (mean ± SD = 7.5 ± 1.9 years), 149 cases of incident breast cancer were documented. The impacts of psychological attitudes on breast cancer risks estimated using the proportional hazard models are shown in Table 3. The findings obtained using age-adjusted RRs did not differ significantly from those obtained using multivariate RRs. Women who reported having "ikigai" showed a significantly lower risk of breast cancer (multivariate-adjusted RR = 0.66; 95% CI = 0.47–0.94). Those who perceived themselves as decisive were also at a lower risk of breast cancer (multivariate-adjusted RR = 0.56; 95% CI = 0.36–0.87). By contrast, ease of anger arousal and self-perceived stress of daily life were not significantly associated with breast cancer risk. These findings were not significantly altered when the first two years of follow-up were excluded from the analysis. The multivariate-adjusted RRs (and 95% CIs) were 0.66 (0.45–0.98), 0.51 (0.31–0.86), 0.87 (0.49–1.53), and 0.96 (0.61–1.52) for possession of "ikigai", decisiveness, ease of anger arousal and self-perceived stress, respectively.

Table 1 Spearman's correlation coefficients among the four items for psychological attitudes in the Japan Collaborative Cohort Study

Factors	Psychological questions	Decisiveness	Ease of anger arousal	Psychological stress
Having "ikigai" (something that makes one's life worth living)				
	(Do you have "ikigai"?)	0.28	−0.08	−0.15
Decisiveness	(Do you make decisions quickly?)	–	0.03	−0.03
Ease of anger arousal	(Are you easily angered?)	–	–	0.33
Psychological stress of daily life	(Do you experience stress during your daily life?)	–	–	–

p < 0.001 for all the coefficients

Table 2 Baseline characteristics of female participants by response to psychological questions in the Japan Collaborative Cohort Study

Psychological questions	Having "ikigai" (something that makes one's life worth living)		Decisiveness		Ease of anger arousal		Psychological stress	
	(Do you have "ikigai"?)		(Do you make decisions quickly?)		(Are you easily angered?)		(Do you experience stress during your daily life?)	
Response	No/not particular	Yes/definitely yes	No/same as others	Yes	No/same as others	Yes	No or little/same as others	Yes, very much/considerably
n	18,898	14,557	25,996	8,032	27,468	4,162	26,629	7,092
Age (years)	58.4 ± 10.2	57.3 ± 9.9	58.4 ± 10.1	56.6 ± 9.9	58.3 ± 10.1	55.7 ± 10.0	58.7 ± 10.0	54.9 ± 9.8
Education beyond high school	9.0%	13.9%	9.8%	15.2%	10.9%	12.3%	10.3%	14.3%
Family history of breast cancer in mother and/or sisters	1.4%	1.6%	1.5%	1.7%	1.5%	1.7%	1.4%	1.8%
Age at menarche (years)	14.9 ± 1.8	14.8 ± 1.8	14.9 ± 1.8	14.8 ± 1.8	14.9 ± 1.8	14.7 ± 1.9	14.9 ± 1.8	14.6 ± 1.8
Menopause	73.6%	71.3%	74.0%	68.9%	73.6%	64.9%	75.1%	63.5%
Age at menopause (years)	48.6 ± 4.6	48.8 ± 4.7	48.7 ± 4.6	48.6 ± 4.9	48.7 ± 4.6	48.4 ± 5.1	48.8 ± 4.6	48.5 ± 5.0
Age at first birth (years)	25.1 ± 3.3	25.0 ± 3.2	25.1 ± 3.3	25.0 ± 3.3	25.0 ± 3.2	25.1 ± 3.4	25.0 ± 3.2	25.2 ± 3.3
Parity	2.6 ± 1.3	2.6 ± 1.2	2.7 ± 1.3	2.5 ± 1.3	2.6 ± 1.3	2.5 ± 1.2	2.7 ± 1.3	2.5 ± 1.2
Ever used exogenous female hormone	5.0%	5.6%	4.9%	6.3%	5.1%	7.4%	4.6%	7.9%
Alcohol consumption								
Current drinkers	22.1%	27.4%	22.8%	29.5%	24.2%	30.4%	23.6%	27.6%
Former drinkers	2.0%	1.9%	1.8%	2.3%	1.7%	2.8%	1.8%	2.7%
Daily consumer of green leafy vegetables	31.2%	38.5%	33.3%	38.3%	34.6%	31.4%	34.8%	32.9%
Walking time >30 min/day	69.6%	74.3%	71.4%	72.5%	72.3%	67.7%	72.0%	70.1%
Exercise ≥3 h/week	7.6%	12.2%	8.9%	11.6%	9.9%	8.8%	10.1%	7.7%
Sedentary work	34.5%	35.5%	33.8%	38.5%	34.5%	37.2%	33.9%	38.8%
Height (cm)	151.0 ± 5.9	151.7 ± 5.8	151.0 ± 5.8	152.2 ± 5.9	151.3 ± 5.9	152.0 ± 5.7	151.1 ± 5.9	152.1 ± 5.7
Body mass index (kg/m^2)	22.8 ± 3.2	23.0 ± 3.6	22.8 ± 3.1	23.2 ± 4.1	22.8 ± 3.4	22.9 ± 3.2	22.9 ± 3.4	22.8 ± 3.2

Plus-minus values are means ± SD

Table 3 Rate ratios (RRs) with 95% confidence intervals (CIs) for breast cancer by response to psychological questions among women in the Japan Collaborative Cohort Study, 1988–1997 (n = 34,497)

Response to questions	No. of women	Observed person-years	No. of cases	Age-adjusted		Multivariate-adjusted[a]	
				RR	95% CI	RR	95% CI
Having "ikigai" (something that makes one's life living)							
Do you have "ikigai"?							
No/not particular	18,898	140,544	95	1.00		1.00	
Yes/definitely yes	14,557	110,671	51	0.67	0.48–0.95	0.66	0.47–0.94
Decisiveness							
Do you make decisions quickly?							
No/same as others	25,996	194,173	123	1.00		1.00	
Yes	8,032	61,259	25	0.63	0.41–0.96	0.56	0.36–0.87
Ease of anger arousal							
Are you easily angered?							
No/same as others	27,468	203,334	119	1.00		1.00	
Yes	4,162	30,608	18	0.97	0.59–1.59	0.85	0.51–1.40
Psychological stress							
Do you experience stress during your daily life?							
No or little/same as others	26,629	199,786	115	1.00		1.00	
Yes, very much/considerably	7,092	53,354	34	1.05	0.72–1.55	1.01	0.69–1.50

The number of women does not equal to 34,497 for each question due to missing values

[a] Adjusted for age, study area, educational level, family history of breast cancer, age at menarche, age at menopause, age at first birth, parity, use of exogenous female hormone, alcohol drinking, consumption of green leafy vegetables, daily walking, exercise, sedentary work, height, and body mass index

Discussion

In this prospective cohort study of Japanese women, possession of "ikigai" and decisiveness were associated with a lower risk of breast cancer development. By contrast, ease of anger arousal and self-perceived stress of daily life were not significantly correlated with the breast cancer risk.

"Ikigai" is a term considered peculiar to the Japanese language [12] that has attracted attention from some researchers [13]. It has been a keyword for health promotion and welfare services for the Japanese elderly [11], but its favorable effects on health outcomes have rarely been examined epidemiologically. Honma et al. followed 6,274 subjects aged 70 years or older for three years and found that the presence of "ikigai" was associated with prolonged active life expectancy and actual life expectancy [29]. Another prospective study of 1,405 elderly people aged 65 years with a nine-year follow-up demonstrated a significantly lower risk of total mortality in those who have "ikigai" compared to those who do not [17]. As a possible explanation for the favorable effect of "ikigai" on health, the authors suggested that it might reflect an active physiological and psychological profile that encourages participation in social activities [17].

We were unable to further address the specific mechanism of the association between "ikigai" and breast cancer risk. However, according to a report based on the responses of 4,736 elderly to the self-administered questionnaires by Shirai et al. [14], Breslow's healthy lifestyle score [30] was associated with having "ikigai". In the present study, women who stated that they had "ikigai" tended to have healthier lifestyles than those who did not, for example, they were more likely to consume green leafy vegetables every day, and to participate in physical exercise. Even though we adjusted the possible confounding factors including education, drinking habits, diet and physical exercise, their healthy lifestyles might have contributed to the risk reduction.

To our knowledge, there are no comparable studies that examine such an association. As relative constructs, the Finnish Twin Cohort study examined life satisfaction and neuroticism, two measures reflecting anxiety and depression, and revealed no association with breast cancer risk [7]. Compared to these, the term of "ikigai" is more comprehensive, reflecting emotions as well as the positive attitudes toward one's life. Further studies are needed to verify our findings including establishment of the definition of "ikigai" and validation of its construct with other psychological measures.

Decisiveness also showed a lower risk of breast cancer in the present study. Having a sense of time urgency is a characteristic of the Type A coronary-prone behavior pattern, which also includes ambitiousness, competitive drive, and aggressiveness [31]. According to the Type C cancer-prone personality proposed by Temoshock et al. [32], a low Type A personality should be associated with an increased risk of breast cancer. However, the results of previous studies examining the relationship between Type A personality and breast cancer risk are inconclusive [4, 5]. The most recent large prospective study reported no association between the Type A personality as assessed by the Bortner scale and breast cancer risk [8]. Decisiveness, or time urgency has never been investigated solely in relation to cancer risk. It is suggested that some personality factors are affected by genetic factors which could influence predisposition to breast cancer [33]. Further studies are required to explore the backgrounds behind any association between decisiveness and breast cancer risk, including genetic factors.

In the present study, we found no association between the ease of anger arousal and breast cancer risk. Having difficulty in expressing anger was regarded as an important component of the breast cancer-prone personality in earlier studies [34, 35]. However, a meta-analysis that reviewed the results of nine case–control studies and one prospective study found no association between anger expression and breast cancer [5]. The most recent large prospective study reported no association between hostility, which includes ease of anger arousal, and breast cancer risk [8]. Our results seem in line with these recent studies. According to the review by Butow et al. [3], there is some evidence to suggest a positive relationship between anger suppression and breast cancer development, especially in women under 50 years of age [34, 36]. Feeling anger or ease of anger arousal is not necessarily the opposite of anger suppression, and it is possible for them to be distinguished [3]. Carefully designed studies will be needed to confirm the association between anger and breast cancer risk.

In the current analysis, we failed to observe a significant association between perceived stress of daily life and breast cancer risk. Against the general belief that psychological stress may increase the risk of breast cancer, its epidemiological evidence is limited. Previous reports based on case–control studies are inconclusive (reviewed in Ref. 4] and there are only three prospective studies reporting the relationship between perceived stress and breast cancer risk [6, 37, 38]. Achat et al. examined work-related stress levels of 26,936 postmenopausal women aged 46–72 in the Nurses' Health Study and found no association with breast cancer incidence [37]. Lillberg et al. also reported no association between the stress of daily activities and the risk of breast cancer from the results of the Finnish Twin Cohort study examining 10,519 women aged 18–70 years with a 20-year follow-up period [6]. By contrast, Helgesson et al. [38] conducted a relatively small cohort study involving 1,462 Swedish women aged 38–60 years with a 24-year follow-up period and demonstrated that self-reported stress levels predicted the risk of breast cancer. Although the authors did not discuss the discrepancy, the Finnish Twin Cohort study found a significant positive relationship between accumulated and single major life events and breast cancer risk [9]. The recent meta-analysis [5] and the review [3] also suggested a weak positive influence of severe life events on breast cancer risk. These results suggest a substantial difference between experiencing stressful life events and perceiving stress in terms of their impact on breast cancer development. The sources of stress are unlimited, and responses can vary between individuals and/or situations [39, 40]. Further studies capturing broad aspects of stress, including its sources and the responses it invokes, will be necessary to verify the association with breast cancer risk.

The strengths of the present study derive mainly from its prospective design, which is less subjective to recall and selection bias compared to case–control studies. In particular, avoiding recall bias is critical for examining the associations of psychological and behavioral factors with the risk of cancer [41]. In the current analysis, we assessed the baseline characteristics of all subjects when they were free from breast cancer, and then followed them prospectively. In addition, it should be noted that we adjusted our analysis for most established risk factors, including behavioral factors (such as alcohol consumption, diet and daily exercise) and those related to female reproductive hormones (such as age at menarche, menopause and first time of giving birth, parity and use of exogenous female hormones). To exclude the possibility that undiagnosed cancers affected the responses to our questionnaire, we repeated the analysis after excluding the first two years of follow-up, and confirmed that similar results were obtained. The results were unchanged even after excluding the first four years of follow-up (data not shown).

Our cohort population has been confirmed to be similar to the Japanese general population in the light of demographic and lifestyle features [21]. The prevalence of women who perceived psychological stress and who were decisive in our study were comparable to those in other population-based cohort studies in Japan [42, 43]. Although the percentage of the subjects who reported to have "ikigai" was lower (44%) than that of the other cohort (56.8%) [42], this may partly be attributable to the differences in the questions and the provided responses between the two studies.

We excluded 1,261 subjects (3.5%) who neglected all psychological questions from the total participants for the present analysis. Although they were older and less educated than the rest of the subjects, other characteristics were comparable. The proportion of missing values in each question was 3.0% or less. Therefore, we believe that the effect of missing values is relatively small and our findings would reasonably be valid in Japanese populations. The applicability of the findings to other countries, however, requires further investigation because of the variation in psychological factors according to social and cultural backgrounds.

Some methodological issues do require further consideration. First, in previous research within the JACC Study, perceived stress assessed by the same questionnaire as the present study was significantly associated with stroke [44] and colorectal cancer mortality [45] in women. However, the association of other psychological factors such as "ikigai", decisiveness, and ease of anger arousal with illness risk have never been reported from the JACC Study group. We assessed psychological factors using single-item measures that were not systematically designed. Further studies using inventories that have been specifically devised to measure individual psychological concepts are therefore warranted to verify our findings. Second, we assessed the psychological factors at one specific time point in our present study; as chronic exposure might be relevant to the risk of breast cancer, repeated measurements could provide valuable additional information [46]. Finally, some residual confounding could not be ruled out because some potential confounding factors such as diet and physical activity were rather roughly measured. Moreover, a considerable number of missing values were found in the covariates, so that we treated the missing values for each covariate as a separate category [47]. However, as the multivariate-adjusted RRs were almost the same as the age-adjusted ones, the influence of the missing values on the results seems to be limited.

In conclusion, our analysis suggests that having "ikigai" and being decisive are associated with lower risks of breast cancer. If our findings are verified by further studies, the possession of positive psychological attitudes will be identified as an important factor in the prevention of breast cancer.

Acknowledgments The authors wish to express their sincere appreciation to K. Aoki (Professor Emeritus at Nagoya University School of Medicine, Japan, and former Chairman of the JACC Study Group) and H. Sugano (former Director of the Cancer Institute of the Japanese Foundation for Cancer Research), who greatly contributed to the initiation of this study. The investigators who co-authored this paper or were involved in the JACC Study (and their affiliations) are as follows: A. Tamakoshi (present Chairman of the study group, Nagoya University Graduate School of Medicine), M. Mori (Sapporo Medical University School of Medicine), Y. Motohashi (Akita University School of Medicine), I. Tsuji (Tohoku University Graduate School of Medicine), Y. Nakamura (Jichi Medical School), H. Iso (Graduate School of Medicine, Osaka University), H. Mikami (Chiba Cancer Center), Y. Inaba (Juntendo University School of Medicine), Y. Hoshiyama (University of Human Arts and Sciences), H. Suzuki (Niigata University School of Medicine), H. Shimizu (Gifu University School of Medicine), H. Toyoshima (Nagoya University Graduate School of Medicine), K. Wakai (Aichi Cancer Center Research Institute), S. Tokudome (Nagoya City University Graduate School of Medical Sciences), Y. Ito (Fujita Health University School of Health Sciences), S. Hashimoto (Fujita Health University School of Medicine), S. Kikuchi (Aichi Medical University School of Medicine), A. Koizumi (Graduate School of Medicine and Faculty of Medicine, Kyoto University), T. Kawamura (Kyoto University Center for Student Health), Y. Watanabe (Kyoto Prefectural University of Medicine Graduate School of Medical Science), T. Miki (Graduate School of Medical Science, Kyoto Prefectural University of Medicine), C. Date (Faculty of Human Life and Environment, Nara Women's University), K. Sakata (Wakayama Medical University), T. Nose (Tottori University Faculty of Medicine), N. Hayakawa (Research Institute for Radiation Biology and Medicine, Hiroshima University), T. Yoshimura (Fukuoka Institute of Health and Environmental Sciences), A. Shibata (Kurume University School of Medicine), N. Okamoto (Kanagawa Cancer Center), H. Shio (Moriyama Municipal Hospital), Y. Ohno (Asahi Rosai Hospital), T. Kitagawa (Cancer Institute of the Japanese Foundation for Cancer Research), T. Kuroki (Gifu University) and K. Tajima (Aichi Cancer Center Research Institute). The JACC Study has been financially supported by Grants-in-Aid for Scientific Research on Priority Areas from the Ministry of Education, Culture, Sports, Science and Technology of Japan (Nos. 61010076, 62010074, 63010074, 1010068, 2151065, 3151064, 4151063, 5151069, 6279102, 11181101, 17015022, and 18014011).

References

1. Cohen S, Rodriquez MS (1995) Pathways linking affective disturbances and physical disorders. Health Psychol 14:374–380
2. Spiegel D, Kato PM (1996) Psychosocial influences on cancer incidence and progression. Harv Rev Psychiatry 4:10–26
3. Butow PN, Hiller JE, Price MA, Thackway SV, Kricker A, Tennant CC (2000) Epidemiological evidence for a relationship between life events, coping style, and personality factors in the development of breast cancer. J Psychosom Res 49:169–181
4. Dalton SO, Boesen EH, Ross L, Schapiro IR, Johansen C (2002) Mind and cancer. Do psychological factors cause cancer? Eur J Cancer 38:1313–1323
5. McKenna MC, Zevon MA, Corn B, Rounds J (1999) Psychosocial factors and the development of breast cancer: a meta-analysis. Health Psychol 18:520–531
6. Lillberg K, Verkasalo PK, Kaprio J, Teppo L, Helenius H, Koskenvuo M (2001) Stress of daily activities and risk of

breast cancer: a prospective cohort study in Finland. Int J Cancer 91:888–893
7. Lillberg K, Verkasalo PK, Kapr J, Teppo L, Helenius H, Koskenvuo M (2002) A prospective study of life satisfaction, neuroticism and breast cancer risk (Finland). Cancer Causes Control 13:191–198
8. Lillberg K, Verkasalo PK, Kaprio J, Helenius H, Koskenvuo M (2002) Personality characteristics and the risk of breast cancer: a prospective cohort study. Int J Cancer 100:361–366
9. Lillberg K, Verkasalo PK, Kaprio J, Teppo L, Helenius H, Koskenvuo M (2003) Stressful life events and risk of breast cancer in 10,808 women: a cohort study. Am J Epidemiol 157:415–423
10. Aro AR, De Koning HJ, Schreck M, Henriksson M, Anttila A, Pukkala E (2005) Psychological risk factors of incidence of breast cancer: a prospective cohort study in Finland. Psycho Med 35:1515–1521
11. Nakanishi N (1999) 'Ikigai' in older Japanese people. Age Ageing 28:323–324
12. Demura S, Kobayashi H, Kitabayashi T (2005) QOL models constructed for the community-dwelling elderly with ikigai (purpose in life) as a composition factor, and the effect of habitual exercise. J Physiol Anthropol Appl Human Sci 24:525–533
13. Mathews G (1996) What makes life worth living? How Japanese and Americans make sense of their worlds. University of California Press, Berkeley, CA
14. Shirai K, Iso H, Fukuda H, Toyoda Y, Takatorige T, Tatara K (2006) Factors associated with "Ikigai" among members of a public temporary employment agency for seniors (Silver Human Resources Centre) in Japan; gender differences. Health Qual Life Outcomes 4:12
15. Bass SA (1996) An overview of work, retirement, and pensions in Japan. J Aging Soc Policy 8:57–78
16. Minami Y, Sasaki T, Arai Y, Hosokawa T, Hisamichi S (2002) Psychological profiles and health status in Japanese female patients with systemic lupus erythematosus: the Miyagi Lupus Collaborative Study. J Epidemiol 12:55–63
17. Nakanishi N, Fukuda H, Tatara K (2003) Changes in psychosocial conditions and eventual mortality in community-residing elderly people. J Epidemiol 13:72–79
18. Weiss RS, Bass SA, Heimovitz HK, Oka M (2005) Japan's silver human resource centers and participant well-being. J Cross Cult Gerontol 20:47–66
19. Yamamoto-Mitani N, Wallhagen MI (2002) Pursuit of psychological well-being (ikigai) and the evolution of self-understanding in the context of caregiving in Japan. Cult Med Psychiatry 26:399–417
20. Temoshok L (1985) Biopsychosocial studies on cutaneous malignant melanoma: psychosocial factors associated with prognostic indicators, progression, psychophysiology and tumor-host response. Soc Sci Med 20:833–840
21. Ohno Y, Tamakoshi A (2001) Japan collaborative cohort study for evaluation of cancer risk sponsored by monbusho (JACC study). J Epidemiol 11:144–150
22. Tamakoshi A, Ohno Y, Inaba Y et al (2005) Profile of the JACC study. J Epidemiol 15(Suppl 1):S4–S8
23. Parkin DM, Whelan SL, Ferlay J, Raymond L, Young J (1997) Cancer incidence in five Continents. IARC, Lyon
24. Cox DR (1972) Regression models and life tables. J R Stat Soc B34:187–220
25. WCRF/AICR (1997) Food nutrition and the prevention of cancer: a global perspective. World Cancer Research Fund/ American Institute of Cancer Research, Washington DC
26. Veronesi U, Boyle P, Goldhirsch A, Orecchia R, Viale G (2005) Breast cancer. Lancet 365:1727–1741
27. Ng'andu NH (1997) An empirical comparison of statistical tests for assessing the proportional hazards assumption of Cox's model. Stat Med 16:611–626
28. SAS Institute Inc. (1999) SAS/STAT user's guide. Version 8. Cary, NC
29. Honma Y, Naruse Y, Kagamimori S (1999) Physio-social activities and active life expectancy, life expectancy in Japanese elderly. Nippon Koshu Eisei Zasshi (in Japanese) 46:380–390
30. Breslow L, Breslow N (1993) Health practices and disability: some evidence from Alameda County. Prev Med 22:86–95
31. Friedman M, Rosenman RH (1971) Type A behavior pattern: its association with coronary heart disease. Ann Clin Res 3:300–312
32. Temoshok L (1987) Personality, coping style, emotion and cancer: towards an integrative model. Cancer Surv 6:545–567
33. Viken RJ, Rose RJ, Kaprio J, Koskenvuo M (1994) A developmental genetic analysis of adult personality: extraversion and neuroticism from 18 to 59 years of age. J Pers Soc Psychol 66:722–730
34. Greer S, Morris T (1975) Psychological attributes of women who develop breast cancer: a controlled study. J Psychosom Res 19:147–153
35. Jansen MA, Muenz LR (1984) A retrospective study of personality variables associated with fibrocystic disease and breast cancer. J Psychosom Res 28:35–42
36. Scherg H, Cramer I, Blohmke M (1981) Psychosocial factors and breast cancer: a critical reevaluation of established hypotheses. Cancer Detect Prev 4:165–171
37. Achat H, Kawachi I, Byrne C, Hankinson S, Colditz G (2000) A prospective study of job strain and risk of breast cancer. Int J Epidemiol 29:622–628
38. Helgesson O, Cabrera C, Lapidus L, Bengtsson C, Lissner L (2003) Self-reported stress levels predict subsequent breast cancer in a cohort of Swedish women. Eur J Cancer Prev 12:377–381
39. Steptoe A (1991) The links between stress and illness. J Psychosom Res 35:633–644
40. Selye H (1986) Stress, cancer, and the mind. In: Day SB (ed) Cancer, stress and death. Plenum Medical Book Company, New York, pp 11–20
41. Bleiker EM, van der Ploeg HM (1999) Psychosocial factors in the etiology of breast cancer: review of a popular link. Patient Educ Couns 37:201–214
42. Miyagi Cancer Society (2003) Report on the special survey for cancer prevention in Miyagi Prefecture. Sendai: Department of Public Health and Environment. Miyagi Prefecture
43. Watanabe S, Tsugane S, Sobue T, Konishi M, Baba S (1996) Baseline data of the Japan Public Health Center-based Prospective Study on Cancer and Cardiovascular Disease (JPHC study). Japan Public Health Association, Tokyo
44. Iso H, Date C, Yamamoto A et al (2002) Perceived mental stress and mortality from cardiovascular disease among Japanese men and women: the Japan Collaborative Cohort Study for Evaluation of Cancer Risk Sponsored by Monbusho (JACC study). Circulation 106:1229–1236
45. Kojima M, Wakai K, Tokudome S et al (2005) Perceived psychologic stress and colorectal cancer mortality: findings from the Japan Collaborative Cohort Study. Psychosom Med 67:72–77
46. Penninx BW, Guralnik JM, Pahor M et al (1998) Chronically depressed mood and cancer risk in older persons. J Natl Cancer Inst 90:1888–1893
47. Park Y, Hunter DJ, Spiegelman D et al (2005) Dietary fiber intake and risk of colorectal cancer: a pooled analysis of prospective cohort studies. JAMA 294:2849–2857