of Health Sciences; Dr. Shuji Hashimoto, Fujita Health University School of Medicine; Dr. Shogo Kikuchi, Aichi Medical University School of Medicine; Dr. Akio Koizumi, Graduate School of Medicine and Faculty of Medicine, Kyoto University; Dr. Takashi Kawamura, Kyoto University Center for Student Health; Dr. Yoshiyuki Watanabe and Dr. Tsuneharu Miki, Kyoto Prefectural University of Medicine Graduate School of Medical Science; Dr. Chigusa Date, Faculty of Human Environmental Sciences, Mukogawa Women's University; Dr. Kiyomi Sakata, Wakayama Medical University; Dr. Takayuki Nose, Tottori University Faculty of Medicine; Dr. Norihiko Hayakawa, Research Institute for Radiation Biology and Medicine, Hiroshima University; Dr. Takesumi Yoshimura, Institute of Industrial Ecological Sciences, University of Occupational and Environmental Health, Japan; Dr. Naoyuki Okamoto, Kanagawa Cancer Center; Dr. Hideo Shio, Moriyama Municipal Hospital; Dr. Yoshiyuki Ohno (former chairman of the study group), Asahi Rosai Hospital; Dr. Tomoyuki Kitagawa, Cancer Institute of the Japanese Foundation for Cancer Research; Dr. Toshio Kuroki, Gifu University; and Dr. Kazuo Tajima, Aichi Cancer Center Research Institute.

The past members of the JACC Study, other than the following eight, are listed in reference 9 (affiliations are those at the time of participation in the JACC Study): Dr. Takashi Shimamoto, Institute of Community Medicine, University of Tsukuba; Dr. Heizo Tanaka, Medical Research Institute, Tokyo Medical and Dental University; Dr. Shigeru Hisamichi, Tohoku University Graduate School of Medicine; Dr. Masahiro Nakao, Kyoto Prefectural University of Medicine; Dr. Takaichiro Suzuki, Research Institute, Osaka Medical Center for Cancer and Cardiovascular Diseases; Dr. Tsutomu Hashimoto, Wakayama Medical University; Dr. Teruo Ishibashi, Asama General Hospital; and Dr. Katsuhiro Fukuda, Kurume University School of Medicine.

REFERENCES

1. Rose DP, Connolly JM. Omega-3 fatty acids as cancer chemopreventive agents. Pharmacol Ther 1999;83:217–44.
2. Bartsch H, Nair J, Owen RW. Dietary polyunsaturated fatty acids and cancers of the breast and colorectum: emerging evidence for their role as risk modifiers. Carcinogenesis 1999;20:2209–18.
3. Anti M, Marra G, Armelao F, et al. Effect of omega-3 fatty acids on rectal mucosal cell proliferation in subjects at risk for colon cancer. Gastroenterology 1992;103:883–91.
4. Anti M, Armelao F, Percesepe A, et al. Modulating effect of omega-3 fatty acids on the proliferative pattern of human colorectal mucosa. Adv Exp Med Biol 1997;400B:605–10.
5. Calviello G, Palozza P, Maggiano N, et al. Cell proliferation, differentiation, and apoptosis are modified by n-3 polyunsaturated fatty acids in normal colonic mucosa. Lipids 1999;34:599–604.
6. Broitman SA, Vitale JJ, Vavrousek-Jakuba E, et al. Polyunsaturated fat, cholesterol and large bowel tumorigenesis. Cancer 1977;40:2455–63.
7. Sakaguchi M, Hiramatsu Y, Takada H, et al. Effect of dietary unsaturated and saturated fats on azoxymethane-induced colon carcinogenesis in rats. Cancer Res 1984;44:1472–7.
8. Reddy BS, Maeura Y. Tumor promotion by dietary fat in azoxymethane-induced colon carcinogenesis in female F344 rats: influence of amount and source of dietary fat. J Natl Cancer Inst 1984;72:745–50.
9. Nkondjock A, Shatenstein B, Maisonneuve P, et al. Specific fatty acids and human colorectal cancer: an overview. Cancer Detect Prev 2003;27:55–66.
10. Arab L, Akbar J. Biomarkers and the measurement of fatty acids. Public Health Nutr 2002;5:865–71.
11. Zeleniuch-Jacquotte A, Chajes V, Van Kappel AL, et al. Reliability of fatty acid composition in human serum phospholipids. Eur J Clin Nutr 2000;54:367–72.
12. Ohno Y, Tamakoshi A. Japan Collaborative Cohort Study for evaluation of cancer risk sponsored by Monbusho (JACC study). J Epidemiol 2001;11:144–50.
13. 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.
14. Wakai K, Hayakawa N, Kojima M, et al. Smoking and colorectal cancer in a non-Western population: a prospective cohort study in Japan. J Epidemiol 2003;13:323–32.
15. Folch J, Lees M, Sloane Stanley GH. A simple method for the isolation and purification of total lipids from animal tissues. J Biol Chem 1957;226:497–509.
16. Mantel N. Chi-square tests with one degree of freedom: extensions of the Mantel-Haenszel procedure. J Am Stat Assoc 1963;58:690–700.
17. Landis RJ, Heyman ER, Koch GG. Average partial association in three-way contingency tables: a review and discussion of alternative tests. Int Stat Rev 1978;46:237–54.
18. Breslow NE, Day NE. Conditional logistic regression for matched sets. In: Davis W, ed. Statistical methods in cancer research. Vol 1. Lyon, France: International Agency for Research on Cancer, 1980:248–79.
19. Holford TR, White C, Kelsey JL. Multivariate analysis for matched case-control studies. Am J Epidemiol 1978;107:245–56.
20. World Health Organization, International Agency for Research on Cancer. Human cancers by organ site; colorectal cancer. In: Stewart BW, Kleihues P, eds. World cancer report. Lyon, France: IARC Press, 2003:198–202.
21. Simon JA, Fong J, Bernert JT Jr, et al. Serum fatty acids and the risk of fatal cancer. Am J Epidemiol 1998;148:854–8.
22. Kuriki K, Nagaya T, Imaeda N, et al. Discrepancies in dietary intakes and plasma concentrations of fatty acids according to age among Japanese female dietitians. Eur J Clin Nutr 2002;56:524–31.
23. Kuriki K, Nagaya T, Imaeda N, et al. Plasma concentrations of (n-3) highly unsaturated fatty acids are good biomarkers of relative dietary fatty acid intakes: a cross-sectional study. J Nutr 2003;133:3643–50.
24. Bartoli GM, Palozza P, Marra G, et al. n-3 PUFA and alpha-tocopherol control of tumor cell proliferation. Mol Aspects Med 1993;14:247–52.
25. de Deckere EA. Possible beneficial effect of fish and fish n-3 polyunsaturated fatty acids in breast and colorectal cancer. Eur J Cancer Prev 1999;8:213–21.
26. Csordas A. Butyrate, aspirin and colorectal cancer. Eur J Cancer Prev 1996;5:221–31.
27. Giardiello FM, Offerhaus GJ, DuBois RN. The role of nonsteroidal anti-inflammatory drugs in colorectal cancer prevention. Eur J Cancer 1995;31A:1071–6.
28. Thun MJ, Namboodiri MM, Heath CW Jr. Aspirin use and reduced risk of fatal colon cancer. N Engl J Med 1991;325:1593–6.
29. IARC Working Group on the Evaluation of Cancer Preventive

Agents. Non-steroidal anti-inflammatory drugs. IARC handbook of cancer prevention. Vol 1. Lyon, France: International Agency for Research on Cancer, 1997.
30. Cheng J, Ogawa K, Kuriki K, et al. Increased intake of n-3 polyunsaturated fatty acids elevates the level of apoptosis in the normal sigmoid colon of patients polypectomized for adenomas/tumors. Cancer Lett 2003;193:17–24.
31. Arab L. Biomarkers of fat and fatty acid intake. J Nutr 2003; 133(suppl 3):925S–32S.
32. McMichael AJ, Potter JD. Reproduction, endogenous and exogenous sex hormones, and colon cancer: a review and hypothesis. J Natl Cancer Inst 1980;65:1201–7.
33. Tamakoshi K, Wakai K, Kojima M, et al. A prospective study on the possible association between having children and colon cancer risk: findings from the JACC Study. Cancer Sci 2004; 95:243–7.
34. Inoue M, Tajima K, Hirose K, et al. Subsite-specific risk factors for colorectal cancer: a hospital-based case-control study in Japan. Cancer Causes Control 1995;6:14–22.
35. Potter JD. Nutrition and colorectal cancer. Cancer Causes Control 1996;7:127–46.
36. Kato I, Akhmedkhanov A, Koenig K, et al. Prospective study of diet and female colorectal cancer: the New York University Women's Health Study. Nutr Cancer 1997;28:276–81.
37. Iso H, Sato S, Umemura U, et al. Linoleic acid, other fatty acids, and the risk of stroke. Stroke 2002;33:2086–93.

Perceived Psychologic Stress and Colorectal Cancer Mortality: Findings From the Japan Collaborative Cohort Study

MASAYO KOJIMA, MD, PHD, KENJI WAKAI, MD, PHD, SHINKAN TOKUDOME, MD, PHD, KOJI TAMAKOSHI, MD, PHD, HIDEAKI TOYOSHIMA, MD, PHD, YOSHIYUKI WATANABE, MD, PHD, NORIHIKO HAYAKAWA, MD, PHD, KOJI SUZUKI, PHD, SHUJI HASHIMOTO, PHD, MIYUKI KAWADO, MSC, SADAO SUZUKI, MD, PHD, YOSHINORI ITO, PHD, AND AKIKO TAMAKOSHI, MD, PHD, FOR THE JACC STUDY GROUP

Objective: The purpose of this research was to examine the relationship between perceived psychologic stress and colorectal cancer mortality in a prospective large-scale study. **Methods:** Between the years 1988 and 1990, 32,153 men and 45,854 women aged 40 to 79 years were enrolled. Participants completed a self-administered questionnaire that addressed demographic, lifestyle, and psychosocial characteristics. Subjects were subsequently followed for mortality until the end of 1999. Perceived psychologic stress was assessed using the question "Do you feel stress during your daily life?" The 4 possible responses, ranging from "little or none" (1) to "extreme" (4), were dichotomized as low (1 or 2) or high (3 or 4) stress. Relative risks (RRs) with 95% confidence intervals (CIs) for colon and rectal cancer according to the perceived level of stress were estimated using Cox's proportional hazard model. **Results:** During the follow-up period (average, 9.6 years), 193 colon cancer deaths (96 men and 97 women) and 127 rectal cancer deaths (88 men and 39 women) were confirmed within the study group. Women who reported high stress had a 1.64-fold higher risk of colon cancer mortality (multivariate-adjusted RR, 1.64; 95% CI, 1.01–2.66) compared with those reporting low stress. There was no significant association between perceived stress and female rectal cancer or male colon and rectal cancer mortality. **Conclusions:** Perceived psychologic stress was weakly associated with increased mortality from colon cancer in women. No positive or inverse association was found in men. Further studies are needed to confirm our results. **Key words:** colorectal carcinoma, psychosocial factors, perceived stress, cohort study.

BMI = body mass index; **CI** = confidence interval; **HPA axis** = hypothalamic–pituitary–adrenocortical axis; **ICD-10** = 10th Revision of the International Classification of Diseases; **OR** = odds ratio; **RR** = relative risk; **SAM system** = sympathetic–adrenal–medullary system.

INTRODUCTION

The human body responds to stress through the autonomic nervous system, the hypothalamic–pituitary–adrenocortical (HPA) axis and the cardiovascular, metabolic, and immune systems. However, the physiological systems that are activated by stress can themselves cause damage (1). According to Rosch (2), the idea that cancer might be related to stress or emotional factors is as old as the history of medicine. Many clinical and laboratory studies, as well as anecdotal reports, support the hypothesis that stress can significantly influence susceptibility and resistance to cancer, and can affect the course of the disease (2–4). However, epidemiologic studies have produced inconsistent results, largely owing to inappropriate study design and the difficulties measuring psychologic variables (5). Dalton et al. (6) reviewed the data from previous epidemiologic studies and found no association between major life events and cancer risk, and inconsistent conclusions were obtained with respect to depression and personality factors. The authors attributed these inconclusive results to methodologic weaknesses in the studies such as inadequacies in sample size, length of follow up, the detection of cancer cases, and control for confounding factors. This highlights the need for well-designed large prospective studies of the association between cancer risk and psychologic variables.

Colorectal cancer is the second leading cause of cancer-related death in most developed countries (7). Epidemiologic studies have revealed that several lifestyle factors such as a diet rich in fat but poor in vegetables and fiber combined with low physical activity increase the risk of colorectal cancer (8). Alcohol intake (9) and constipation (10,11) have also been suggested to increase the risk. The colon and rectum are known to be particularly sensitive to psychologic stress (12–15), and lifestyle factors and behaviors that are associated with colorectal cancer risk are also influenced by psychologic stress (1,16). Some case–control studies have reported a positive association between colorectal cancer risk and psychosocial stress factors such as job-related stress (17,18) and stressful life events (19,20). However, because having cancer itself is a stressful event, it is difficult for patients to accurately evaluate previous stressful events and their psychologic status without recall bias. Such biases could be avoided by examining the relationship between these factors in a prospective study.

Stress can be defined as a nonspecific response of the body to a demand from the environment or as a process of adapta-

From the Department of Health Promotion and Preventive Medicine, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan (M.K., S.T., S.S.); the Division of Epidemiology and Prevention, Aichi Cancer Center Research Institute, Nagoya, Japan (K.W.); the Department of Preventive Medicine/Biostatistics and Medical Decision Making, Nagoya University Graduate School of Medicine, Nagoya, Japan (K.W., A.T.); the Department of Public Health/Health Information Dynamics, Nagoya University Graduate School of Medicine, Nagoya, Japan (K.T., H.T.); the Department of Epidemiology for Community Health and Medicine, Kyoto Prefectural University of Medicine Graduate School of Medical Science, Kyoto, Japan (Y.W.); the Department of Epidemiology, Research Institute for Radiation Biology and Medicine, Hiroshima University, Hiroshima, Japan (N.H.); the Department of Public Health, Fujita Health University School of Health Sciences, Aichi, Japan (K.S., Y.I.); and the Department of Hygiene, Fujita Health University School of Medicine, Aichi, Japan (S.H., M.K.).

Address correspondence and reprint requests to Masayo Kojima, MD, PhD, 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. E-mail: masayok@med.nagoya-cu.ac.jp

This work was supported by a Grant-in-Aid for Scientific Research on Priority Areas (2; No. 14031222) from the Ministry of Education, Culture, Sports, Science and Technology of Japan. The JACC Study has also been supported by Grants-in-Aid for Scientific Research from the same ministry (Nos. 61010076, 62010074, 63010074, 1010068, 2151065, 3151064, 4151063, 5151069, 6279102, and 11181101).

Received for publication February 8, 2004; revision received July 21, 2004.
DOI: 10.1097/01.psy.0000151742.43774.6d

0033-3174/05/6701-0072

tion in reaction to psychologic, physical, or chemical stimuli. There are unlimited sources of stress, and responses vary greatly between individuals and in different situations (16,21). The way in which an individual perceives a situation determines their specific response to stressful stimuli (1). Common physiological responses to stress are alterations of the sympathetic–adrenal–medullary (SAM) system and the HPA axis. Both the autonomic nervous system and the HPA axis can, in turn, influence the immune system, and persistent suppression of the immune system increases the risk of cancer. More specifically, dysfunction of the autonomic nervous system might cause irregular bowel movements, which have recently been identified as a possible risk factor for colon cancer (22).

We therefore propose that individuals who experience high levels of perceived stress during their daily life are at a greater risk of mortality from colorectal cancer. To test this hypothesis, we evaluated the perceived levels of psychologic stress in healthy Japanese adults. The subjects were then followed prospectively to examine the association between psychologic stress and colorectal cancer death. Adjustments were made during analysis of the data for possible confounding factors.

MATERIALS AND METHODS

The Japan Collaborative Cohort Study for Evaluation of Cancer Risk

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 methods of the JACC Study have been described in detail elsewhere (23). Briefly, the original study population consisted of 110,792 Japanese adults aged 40 to 79, who were enrolled between the years 1988 and 1990 in 45 areas 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 psychologic attitudes toward life. Written informed consent for participation was obtained individually from subjects, with the exception of those in a few study areas in which informed consent was provided at the group level after the aim of the study and confidentiality of the data had been explained to community leaders. The study protocol was approved by the Ethics Committee of Medical Care and Research of Fujita Health University School of Medicine, Japan.

The focus of this study was the association between psychologic stress and colorectal cancer. We therefore excluded 73 individuals who reported a history of colorectal cancer, along with all of the respondents from the six areas in which the questionnaire did not include the psychologic evaluation section (n = 23,330). In addition, those who neglected to address this section (n = 7511) and those who did not answer the specific question about psychologic stress (n = 1867) were excluded; 10.7% of the eligible participants refused to answer this question. A total of 78,007 subjects (32,153 men and 45,854 women) were therefore included in the final analysis.

Evaluation of Perceived Psychologic Stress

Perceived psychologic stress was assessed in this study through responses to the question "Do you feel stress during your daily life?" Four possible answers were provided: little or none (1), moderate (2), high (3), and extreme (4). For the purposes of the analysis, these responses were dichotomized and subjects who chose response 1 or 2 were categorized as having high stress levels, whereas those that chose response 3 or 4 were categorized as having low stress levels.

Identification of Colorectal Cancer Cases and Follow Up of the Cohort

Subjects were followed for mortality until the end of 1999. The Family Registration Law in Japan requires registration of death. Therefore, mortality was determined using municipal resident registration records, and causes of death were confirmed using death certificates, with permission from the Ministry of Public Management, Home Affairs, Post and Telecommunications. The end point of the study was defined as death from colon cancer (International Classification of Diseases, 10th Revision [ICD-10]: C18) or rectal cancer (ICD-10: C20). Subjects who moved out of the study area or died from causes other than colorectal cancer were treated as censored cases. During the study period, only 3.3% (n = 2600) of the participants were lost from the follow up as a result of change of residence. We calculated the risk period for each subject as the interval between the date of questionnaire administration and whichever of the following occurred first: the date of death or the date of moving from the study area or December 31, 1999.

Statistical Analysis

Although colon and rectal cancers are often considered together, several differences have been identified in their etiologies (24). We therefore separately evaluated the risk of colon cancer and rectal cancer by sex. All analyses were performed using the SAS statistical package, release 8.2 (SAS Inc., Cary, NC).

First, to explore the background characteristics of psychologic stress, we calculated the means and proportions of the baseline variables for each level of perceived psychologic stress by gender. Mean values were compared using analysis of covariance with adjustment for age. The relationships between the baseline categorical variables and psychologic stress were examined using logistic regression, with adjustment for age, by gender; significant interactions between gender and baseline variables in relation to psychologic stress were further examined through logistic regression models. Then, to determine the impact of perceived psychologic stress on colorectal cancer mortality, age-adjusted relative risks (RR) with 95% confidence intervals (CIs) for colon and rectal cancers according to the perceived level of stress were estimated using Cox's proportional hazard model. We calculated the RRs for "high" versus "low" stress levels and tested for linear trends in the associations by including the responses as continuous variables. To adjust for the influence of possible confounding factors, multivariate adjusted models were computed. The first model included the following age and lifestyle factors, which are known to influence colorectal cancer risk: body mass index (BMI) calculated as weight (kg)/height (m^2) and categorized as "$\geq$25 kg/m^2" or "<25 kg/m^2;" history of colorectal cancer in parents or siblings ("yes" or "no"); current smoking status ("smoker" or "nonsmoker"); intake frequency of alcohol ("$\geq$5 days per week" or "<5 days per week"); sleep duration per night ("<7 hours" or "$\geq$7 hours"); intake frequency of green leafy vegetables ("daily" or "not daily"); time spent walking per day ("$\leq$30 minutes" or ">30 minutes"); and severe constipation (bowel movement frequency "once every 4 days or less" or "once every 3 days or more"). All of the variables of the baseline characteristics were then added to the second model, which included the following sociologic factors: age at leaving full-time education ("$\geq$20 years" or "<20 years"); marital status ("married" or "unmarried"); having children ("yes" or "no"); and being in full-time employment ("yes" or "no").

For each covariate, missing values were treated as an additional category in the variables and were included in the models. In all cases, two-sided probability (p) values <.05 were considered to be statistically significant.

RESULTS

During the follow-up period (average, 9.6 years; standard deviation, 2.0 years; total of 749,354 person-years), a total of 7685 deaths (4563 men and 3122 women) were recorded, which included 193 deaths from colon cancer (96 men and 97 women) and 127 deaths from rectal cancer (88 men and 39 women).

Table 1 presents the baseline characteristics of the study population for each level of perceived psychologic stress.

TABLE 1. Background Characteristics at Baseline of the Participants by Perceived Stress by Gender

		Men			Women			
		Perceived stress		Age-adjusted OR for having high stress (95% CI)	Perceived stress		Age adjusted OR for having high stress (95% CI)	*p* value for gender interaction
		Low (n = 24,816)	High (n = 7337)		Low (n = 36,634)	High (n = 9220)		
Sociodemographic characteristics								
Age	Mean	58.7	53.3		58.4	54.8		
	SD	10.1	9.5		10.0	9.7		
≥65 years	%	29.3	13.6	0.38 (0.35–0.41)	29.0	17.6	0.52 (0.49–0.56)	<.0001
Age of final education completed >20 years	%	9.8	16.8	1.89 (1.75–2.03)	4.6	7.7	1.60 (1.46–1.75)	.005
Married	%	93.5	93.9	1.14 (1.05–1.24)	82.3	85.3	1.12 (1.06–1.19)	NS
Having children	%	72.6	72.7	1.02 (0.96–1.08)	72.2	70.0	0.90 (0.86–0.95)	.002
Being in full-time employment	%	30.7	51.7	1.66 (1.55–1.78)	11.7	20.4	1.45 (1.38–1.52)	<.0001
Medical and life-style characteristics								
BMI (kg/m^2)	Mean	22.6	22.8		23.0	22.9		
	SD	2.9	5.2		3.8	3.2		
>25	%	18.1	19.9	1.05 (0.98–1.12)	23.3	22.0	0.92 (0.87–0.97)	.0009
Having family history of colorectal cancer	%	2.2	2.2	0.98 (0.82–1.17)	2.5	2.9	1.15 (0.998–1.32)	NS
Current smoker	%	50.0	53.0	1.04 (0.99–1.10)	4.3	6.1	1.43 (1.30–1.58)	<.0001
Daily alcohol drinker	%	50.8	51.0	0.95 (0.90–1.00)	5.0	5.8	1.19 (1.08–1.31)	.0002
Hours of sleep (hours/day)	Mean	7.6	7.2		7.2	6.9		
	SD	1.1	1.1		1.1	1.1		
<7 hours	%	14.2	23.4	1.85 (1.73–1.97)	24.9	35.8	1.65 (1.57–1.73)	.0006
Daily consuming green leafy vegetables	%	29.3	26.1	0.90 (0.85–0.95)	33.9	32.6	0.96 (0.92–1.01)	.04
Daily walking time <30 min	%	25.7	33.4	1.43 (1.35–1.51)	23.8	25.7	1.10 (1.05–1.16)	<.0001
Severe constipation; bowel movements less than once per 4 days	%	1.1	1.1	1.22 (0.94–1.58)	3.8	5.7	1.56 (1.41–1.74)	.04

OR = odds ratio estimated using logistic regression analysis; CI = confidence interval; SD = standard deviation; NS = not significant; BMI = body mass index.

Significant gender interactions were observed for all variables, with the exceptions of marital status and family history. Regardless of sex, subjects who reported high stress were more likely to be married than those who reported low stress, although this trend was only weakly significant. Stress was more strongly associated with younger age, higher education levels, having a full-time job, and having fewer hours of sleep per day in men compared with women. Daily consumption of green leafy vegetables was negatively associated with stress in men, but not in women. Having children and having a BMI ≥ 25 kg/m^2 were both inversely associated with stress in women, but not men. In addition, smoking, daily alcohol consumption, and severe constipation were all positively associated with stress in women alone.

Next, the impacts of perceived psychologic stress on colon and rectal cancer mortalities were estimated by gender, using Cox's proportional hazard model (Table 2). In men, there was no significant association between perceived psychologic stress and colon or rectal cancer mortality; the age-adjusted RRs were 1.01 (95% CI, 0.58–1.75) for colon cancer and 0.93 (95% CI, 0.52–1.66) for rectal cancer. These results were almost unchanged by adjustment for possible confounding factors. In women, a marginally significant association was found between the dichotomized levels of perceived psychologic stress and colon cancer mortality. Women who reported high psychologic stress had a 1.61-fold higher mortality risk (95% CI, 1.00–2.61) compared with those who reported low stress. This risk increased slightly after adjustment for lifestyle factors (multivariate adjusted RR_1, 1.64; 95% CI, 1.01–2.66). Even after adjusting for all of the baseline characteristics, including sociologic factors, the association between stress and female colon cancer remained significant (RR_2, 1.63; 95% CI, 1.002–2.640). The RR for rectal cancer mortality associated with perceived high psychologic stress in women was also greater than unity, although this relationship was not statistically significant (age-adjusted RR, 1.28; 95% CI, 0.59–2.81; multivariate adjusted RR_1, 1.27; 95% CI, 0.58–2.80; RR_2, 1.27; 95% CI, 0.58–2.81). No linear trend was observed between response to the stress question and colon or rectal cancer mortality in either men or women.

DISCUSSION

We found a weak but significant positive association between perceived psychologic stress and the risk of female colon cancer mortality. An increased risk of rectal cancer mortality was also observed in women, although the association was not statistically significant. No positive or inverse association was found between perceived psychologic stress and colon and rectal cancer mortality in men.

The strength of our study lies in the fact that we evaluated the baseline characteristics of all subjects when they were free from cancer and then followed them prospectively. In addition, our subjects were members of the general population recruited from a total of 45 different communities from across Japan. This study design significantly limited the influence of both recall and selection biases, which are unavoidable in case–control studies.

Iso et al. examined the relationship between perceived stress and mortality from cardiovascular diseases in the same initial population as the present study using a similar ques-

TABLE 2. Relative Risk (RR) for Colorectal Cancer Mortality According to the Level of Perceived Stress, Derived From Cox's Proportional Hazard Models by Gender

	Men			Women		
	Perceived stress			Perceived stress		
	Low (n = 24,816)	High (n = 7337)		Low (n = 36,634)	High (n = 9220)	
Person-years	233,849	70,320		355,038	90,147	
Colon cancer death	n = 80	n = 16	*p* value for trend‡	n = 75	n = 22	*p* value for trend‡
RR (95% CI)						
Age-adjusted RR	1.00 (reference)	1.01 (0.58–1.75)	.74	1.00 (reference)	1.61 (1.00–2.61)	.15
Multivariate RR_1*	1.00 (reference)	0.96 (0.55–1.67)	.59	1.00 (reference)	1.64 (1.01–2.65)	.15
Multivariate RR_2†	1.00 (reference)	0.95 (0.55–1.66)	.58	1.00 (reference)	1.63 (1.00–2.64)	.15
Rectal cancer death	n = 74	n = 14	*p* value for trend‡	n = 31	n = 8	*p* value for trend‡
RR (95% CI)						
Age-adjusted RR	1.00 (reference)	0.93 (0.52–1.66)	.69	1.00 (reference)	1.28 (0.59–2.81)	.76
Multivariate RR_1*	1.00 (reference)	0.95 (0.53–1.70)	.67	1.00 (reference)	1.27 (0.58–2.80)	.75
Multivariate RR_2†	1.00 (reference)	0.96 (0.53–1.73)	.61	1.00 (reference)	1.27 (0.58–2.81)	.75

* Multivariate RR_1 adjusted for following lifestyle factors: age, obesity, family history of colorectal cancer, smoking, drinking, daily consuming of green vegetables, walking, and constipation.

† Multivariate RR_2 adjusted for the lifestyle factors and following social factors: education, marital status, having children and being in a fulltime employment.

‡ *p* value for trend: the linear trends in the associations of stress levels and cancer risk were tested by entering the stress levels ranged from 1 to 4 as continuous variables in the models.

CI = confidence interval.

tionnaire (25). Their analysis revealed positive associations between perceived stress and increased stroke mortality in women, and between perceived stress and chronic heart disease in both sexes. Lifestyle factors that are associated with colorectal cancer risk—such as obesity, low physical activity, excessive alcohol consumption, and low vegetable intake—are also known risk factors for cardiovascular diseases. However, even when we adjusted for these factors in our analysis, the independent association between colon cancer mortality and perceived psychologic stress persisted in women. These observations indicate that for both female colon cancer and cardiovascular diseases, psychologic stress is possibly an independent risk factor separate from other lifestyle factors.

Colorectal cancer and psychologic stress were not positively associated among the male subjects in our study. Numerous epidemiologic studies have reported an increased prevalence of stress-related disorders—including acute stress disorder, posttraumatic stress disorder, and major depressive disorder—among women compared with men. However, we cannot conclude from our data alone that men are less susceptible than women to the effects of stress in relation to colorectal cancer risk. We observed significant gender interactions between most of the background characteristics examined and perceived stress levels. High stress was more strongly associated in men than in women with having a full-time job, and spending less time sleeping and walking. Having children and obesity were both inversely associated; by contrast, smoking and daily alcohol consumption were positively associated with stress in women alone. Although we adjusted for all of these variables in our multivariate analysis, it remains possible that a combination of perceived psychologic stress and differences in background characteristics might increase the risk of female colon cancer. We should also note that limitations of the questionnaire might provide an alternative explanation for the gender differences observed in the present study. The single question that was used to assess perceived stress levels might not have accurately reflected the psychologic burden of male subjects. Further studies will be necessary to clarify gender differences in the relationship between perceived psychologic stress and colorectal cancer risk.

Female sex hormones might have a role in the association between stress and colon cancer risk. It has been suggested that colon cancer might share etiologic factors with breast cancer in women (26,27). A number of studies have shown protective effects of parity on cancers of the colon, breast, and reproductive organs (28); modifications of hormone profiles caused by pregnancy and their effects on bile acid metabolism might be the main mechanisms of these associations (29,30). Recently, Helgesson et al. examined a cohort of 1462 Swedish women aged 38 to 60 years and followed these subjects for 24 years (31). The authors reported that stress associated with daily activities, which was measured using a four-item self-administered questionnaire, was associated with a twofold increase in the risk of subsequent breast cancer compared with individuals that reported no stress. Although the possible mechanisms of this association have not been addressed, the interaction between psychologic stress and female sex hormones in relation to cancer risk is worthy of further investigation.

Some limitations to the interpretation of our data should be noted. First, the end point of the study was death from colon or rectal cancer, so the risks reported here relate to fatal colon and rectal cancers only, not cancers that respond to curative treatments. Moreover, these data do not allow a discussion of whether perceived psychologic stress influences the development or progression of colorectal cancers. Second, perceived stress was assessed only on the basis of the response to a single question: "Do you feel stress during your daily life?" Stress is clearly a complex phenomenon, the measurement of which is controversial, and it is not possible to capture full data on this subject using any available tools at present. However, it is generally agreed that the reliability of a test increases with the number of questions (32). Our findings should therefore be confirmed using more sophisticated methods to assess psychologic stress from a range of perspectives, including general and specific types of stress that are related to different environments such as the home and workplace.

Third, although we observed a significant association between the dichotomized levels of stress and the risk of female colon cancer, there was no linear trend between the four separate responses to the stress question and colon cancer mortality. These data do not allow us to determine whether there is an acceptable level of perceived stress or whether the results are the result of limitations of the questionnaire.

In conclusion, perceived psychologic stress was weakly associated with increased mortality from colon cancer in women but not in men. Future studies should attempt to clarify these results in terms of gender differences and their relevance to other types of cancer. In addition, it will be important to explore the most appropriate methods of measuring stress in the context of its role as a possible risk factor for cancer.

The authors express their sincere appreciation to Dr. K Aoki, Professor Emeritus, Nagoya University School of Medicine, and the former chairman of the JACC Study Group, and Dr. H Sugano, the former Director of the Cancer Institute of the Japanese Foundation for Cancer Research, who greatly contributed to the initiation of the study.

The present members of the JACC Study and their affiliations are as follows: Dr. A. Tamakoshi (present chairman of the study group), Nagoya University Graduate School of Medicine; Dr. M. Mori, Sapporo Medical University School of Medicine; Dr. Y. Motohashi, Akita University School of Medicine; Dr. I. Tsuji, Tohoku University Graduate School of Medicine; Dr. Y. Nakamura, Jichi Medical School; Dr. H. Iso, Institute of Community Medicine, University of Tsukuba; Dr. H. Mikami, Chiba Cancer Center; Dr. Y. Inaba, Juntendo University School of Medicine; Dr. Y. Hoshiyama, Showa University School of Medicine; Dr. H. Suzuki, Niigata University Graduate School of Medical and Dental Sciences; Dr. H. Shimizu, Gifu University School of Medicine; Dr. H. Toyoshima, Nagoya University Graduate School of Medicine; Dr. S. Tokudome, Nagoya City University Graduate School of Medical Science; Dr. Y. Ito, Fujita Health University School of Health Sciences; Dr. S. Hashi-

moto, Fujita Health University School of Medicine; Dr. Shogo Kikuchi, Aichi Medical University School of Medicine; Dr. A. Koizumi, Graduate School of Medicine and Faculty of Medicine, Kyoto University; Dr. T. Kawamura, Kyoto University Center for Student Health; Dr. Y. Watanabe and Dr. Tsuneharu Miki, Kyoto Prefectural University of Medicine Graduate School of Medical Science; Dr. C. Date, Faculty of Human Environmental Sciences, Mukogawa Women's University; Dr. K. Sakata, Wakayama Medical University; Dr. T. Nose, Tottori University Faculty of Medicine; Dr. Norihiko Hayakawa, Research Institute for Radiation Biology and Medicine, Hiroshima University; Dr. T. Yoshimura, Institute of Industrial Ecological Sciences, University of Occupational and Environmental Health, Japan; Dr. K. Fukuda, Kurume University School of Medicine; Dr. N. Okamoto, Kanagawa Cancer Center; Dr. H. Shio, Moriyama Municipal Hospital; Dr. Y. Ohno (former chairman of the study group), Asahi Rosai Hospital; Dr. T. Kitagawa, Cancer Institute of the Japanese Foundation for Cancer Research; Dr. T. Kuroki, Gifu University; and Dr. Kazuo Tajima, Aichi Cancer Center Research Institute.

The past members of the study, other than the following seven members, were listed in reference 23 (affiliations are those at the time of study participation): Dr. T. Shimamoto, Institute of Community Medicine, University of Tsukuba; Dr. H. Tanaka, Medical Research Institute, Tokyo Medical and Dental University; Dr. S. Hisamichi, Tohoku University Graduate School of Medicine; Dr. M. Nakao, Kyoto Prefectural University of Medicine; Dr. T. Suzuki, Research Institute, Osaka Medical Center for Cancer and Cardiovascular Diseases; Dr. T. Hashimoto, Wakayama Medical University; and Dr. T. Ishibashi, Asama General Hospital.

REFERENCES

1. McEwen BS. Protective and damaging effects of stress mediators. N Engl J Med 1998;338:171–9.
2. Rosch PJ. Stress and cancer. In: Cooper CL, ed. Psychosocial Stress and Cancer. New York: John Wiley & Sons; 1984:3–19.
3. Peteet JR. Psychological factors in the causation and course of cancer. In: Day SB, ed. Cancer, Stress and Death, 2nd ed. New York: Plenum Medical Book Co; 1986:11–20.
4. Fox BH. A psychological measure as a predictor in cancer. In: Cohen J, ed. Psychological Aspects of Cancer. New York: Raven Press; 1982: 275–95.
5. Temoshock L, Heller BW. On comparing apples, oranges and fruit salad: a methodological overview of medical outcome studies in psychosocial oncology. In: Cooper CL, ed. Psychosocial Stress and Cancer. Chichester: John Wiley & Sons; 1984:231–60.
6. Dalton SO, Boesen EH, Ross L, Schapiro IR, Johansen C. Mind and cancer. Do psychological factors cause cancer? Eur J Cancer 2002;38: 1313–23.
7. Boyle P, Leon ME. Epidemiology of colorectal cancer. Br Med Bull 2002;64:1–25.
8. Colorectal cancer, human cancers by organ site. In: Stewart BW, Kleihues P, eds. World Cancer Report. Lyon: IARC, WHO; 2003: 198–202.
9. Longnecker MP, Orza M J, Adams ME, Vioque J, Chalmers TC. A meta-analysis of alcoholic beverage consumption in relation to risk of colorectal cancer. Cancer Causes Control 1990;1:59–68.
10. Sonnenberg A, Muller AD. Constipation and cathartics as risk factors of colorectal cancer: a meta-analysis. Pharmacology 1993;47(suppl 1): 224–33.
11. Jacobs EJ, White E. Constipation, laxative use, and colon cancer among middle-aged adults. Epidemiology 1998;9:385–91.
12. Camilleri M, Neri M. Motility disorders and stress. Dig Dis Sci 1989; 34:1777–86.
13. Wittmann T, Crenner F, Angel F, Hanusz L, Ringwald C, Grenier JF. Long-duration stress. Immediate and late effects on small and large bowel motility in rat. Dig Dis Sci 1990;35:495–500.
14. Bueno L, Gue M, Delrio C. CNS vasopressin mediates emotional stress and CRH-induced colonic motor alterations in rats. Am J Physiol 1992; 262:G427–31.
15. Empey LR, Fedorak RN. Effect of misoprostol in preventing stress-induced intestinal fluid secretion in rats. Prostaglandins Leukot Essent Fatty Acids 1989;38:43–8.
16. Steptoe A. Invited review. The links between stress and illness. J Psychosom Res 1991;35:633–44.
17. Spiegelman D, Wegman DH. Occupation-related risks for colorectal cancer. J Natl Cancer Inst 1985;75:813–21.
18. Courtney JG, Longnecker MP, Peters RK. Psychosocial aspects of work and the risk of colon cancer. Epidemiology 1996;7:175–81.
19. Kune S, Kune GA, Watson LF, Rahe RH. Recent life change and large bowel cancer. Data from the Melbourne Colorectal Cancer Study. J Clin Epidemiol 1991;44:57–68.
20. Courtney JG, Longnecker MP, Theorell T, Gerhardsson de V. Stressful life events and the risk of colorectal cancer. Epidemiology 1993;4: 407–14.
21. Selye, H. Stress, cancer, and the mind. In: Day SB, ed. Cancer, Stress and Death. New York: Plenum Medical Book Co; 1986:11–20.
22. Kojima M, Wakai K, Tokudome S, Tamakoshi K, Toyoshima H, Watanabe Y, Hayakawa N, Suzuki K, Hashimoto S, Ito Y, Tamakoshi A. 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.
23. Ohno Y, Tamakoshi A. Japan collaborative cohort study for evaluation of cancer risk sponsored by Monbusho (JACC study). J Epidemiol 2001; 11:144–50.
24. Potter JD. Nutrition and colorectal cancer. Cancer Causes Control 1996; 7:127–46.
25. Iso H, Date C, Yamamoto A, Toyoshima H, Tanabe N, Kikuchi S, Kondo T, Watanabe Y, Wada Y, Ishibashi T, Suzuki H, Koizumi A, Inaba Y, Tamakoshi A, Ohno Y. 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 2002;106:1229–36.
26. Howell MA. The association between colorectal cancer and breast cancer. J Chronic Dis 1976;29:243–61.
27. Fraumeni, JF Jr, Lloyd JW, Smith EM, Wagoner JK. Cancer mortality among nuns: role of marital status in etiology of neoplastic disease in women. J Natl Cancer Inst 1969;42:455–68.
28. Tamakoshi K, Wakai K, Kojima M, Watanabe Y, Hayakawa N, Toyoshima H, Yatsuya H, Kondo T, Tokudome S, Hashimoto S, Suzuki K, Ito Y, Tamakoshi A. A prospective study on the possible association between having children and colon cancer risk: findings from the JACC Study. Cancer Sci 2004;95:243–7.
29. McMichael AJ, Potter JD. Do intrinsic sex differences in lower alimentary tract physiology influence the sex-specific risks of bowel cancer and other biliary and intestinal diseases? Am J Epidemiol 1983;118:620–7.
30. McMichael AJ, Potter JD. Reproduction, endogenous and exogenous sex hormones, and colon cancer: a review and hypothesis. J Natl Cancer Inst 1980;65:1201–7.
31. Helgesson Ö, Vebrera C, Lapidus L, Bengtsson C, Lissner L. Self-reported stress levels predict subsequent breast cancer in a cohort of Swedish women. Eur J Cancer Prev 2003; 12:377–81.
32. Streiner DL, Norman GR. Reliability. In: Health Measurement Scales. A Practical Guide to their Development and Use. Oxford: Oxford University Press; 1995:104–27.

NUTRITION AND CANCER, 50(1), 23–32

Diet and Colorectal Cancer Mortality: Results From the Japan Collaborative Cohort Study

Masayo Kojima, Kenji Wakai, Koji Tamakoshi, Shinkan Tokudome, Hideaki Toyoshima, Yoshiyuki Watanabe, Norihiko Hayakawa, Koji Suzuki, Shuji Hashimoto, Yoshinori Ito, and Akiko Tamakoshi for the JACC Study Group

Abstract: *The relationship between diet and colorectal cancer mortality was analyzed in a prospective study of 45,181 men and 62,643 women aged 40–79 yr enrolled in the Japan Collaborative Cohort Study. Between 1988 and 1990, subjects completed a self-administered questionnaire on their sociodemographic characteristics, diet, and other lifestyle habits. During the follow-up period (average 9.9 yr), 284 colon cancer deaths (138 men and 146 women) and 173 rectal cancer deaths (116 men and 57 women) were confirmed. The only significant association of colorectal cancer mortality with vegetable intake was observed between male rectal cancer mortality and green leafy vegetable consumption [hazard ratio (HR) using Cox proportional hazard models = 0.6; 95% confidence interval (CI) = 0.3–0.9; P for trend = 0.02]. Yogurt intake was also inversely associated with male rectal cancer mortality (HR = 0.5; 95% CI = 0.2–1.0; P for trend = 0.04). Egg consumption was positively associated with male colon cancer mortality (P for trend = 0.04). Women with high fruit consumption had increased colon cancer mortality (HR = 1.6; 95% CI = 1.0–2.6; P for trend = 0.04). It should be noted that this study lacked statistical power due to small sample size and measurement error in the food-frequency questionnaire. Further investigation is therefore necessary to confirm the association between diet and colorectal cancer, especially by subsites and gender.*

Introduction

A large number of epidemiological and experimental studies have examined the relationship between colorectal cancer and dietary habits. In 1997, a review of major published studies by the World Cancer Research Fund and the American Institute for Cancer Research (WCRF/AICR) concluded that a high intake of vegetables reduces the risk of colorectal cancer, whereas a high intake of red meat probably increases the risk (1). The review also listed starch, fiber, and carotenoids as possible dietary protective factors and sugar, fat, egg, and processed meat as possible dietary risk factors. The British Working Group on Diet and Cancer of the Committee on Medical Aspects of Food and Nutrition Policy also reviewed the existing research on diet and colorectal cancer and recommended increased vegetable consumption and reduced consumption of red meat, particularly for high-meat consumers (2).

However, the published epidemiological reports on diet are not consistent. Most previous large cohort studies of the association between diet and colorectal cancer were conducted in the United States and western Europe. In Japan, only a few cohort studies of diet and cancer risk have been performed. Hirayama evaluated the associations between lifestyle factors and cancer risk in a cohort of 265,118 Japanese adults who were followed for 17 yr, starting in 1965 (3). In contrast to the results of studies of Western populations, they found only small associations of limited dietary factors (for example, green and yellow vegetables) with colorectal cancer (4). Since this study was performed, the dietary habits of the Japanese population have changed dramatically. Between 1971 and 2000, consumption of green and yellow vegetables increased by 100%, meat by 50%, and dairy products by 25%, whereas consumption of rice decreased by 50% (5,6). During the same period, the incidence (7) and mortality

M. Kojima and S. Tokudome are affiliated with the Department of Health Promotion and Preventive Medicine, Nagoya City University Graduate School of Medical Sciences, Mizuho, Nagoya, Japan, 467–8601. K. Wakai and A. Tamakoshi are affiliated with the Department of Preventive Medicine/Biostatistics and Medical Decision Making, Nagoya University Graduate School of Medicine, Showa-ku, Nagoya, Japan, 466–8550. K. Wakai is also affiliated with the Division of Epidemiology and Prevention, Aichi Cancer Center Research Institute, Chikusa-ku, Nagoya, Japan,464–8681. K. Tamakoshi and H. Toyoshima are affiliated with the Department of Public Health/Health Information Dynamics, Nagoya University Graduate School of Medicine, Showa-ku, Nagoya, Japan, 466–8550. Y. Watanabe is affiliated with the Department of Epidemiology for Community Health and Medicine, Kyoto Prefectural University of Medicine Graduate School of Medical Science, Kamigyo-ku, Kyoto, Japan, 602–8566. N. Hayakawa is affiliated with the Department of Epidemiology, Research Institute for Radiation Biology and Medicine, Hiroshima University, Hiroshima, Japan, 734–8553. K. Suzuki and Y. Ito are affiliated with the Department of Public Health, Fujita Health University School of Health Sciences, Toyoake, Aichi, Japan, 470–1192. S. Hashimoto is affiliated with the Department of Hygiene, Fujita Health University School of Medicine, Toyoake, Aichi, Japan, 470–1192.

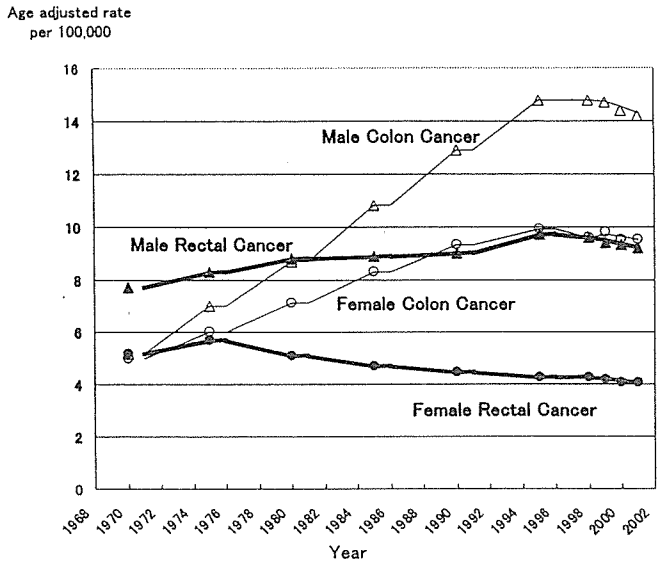

Figure 1. Trends in colon and rectal cancer mortality from 1970 to 2001 in Japan (age adjusted, per 100,000). Age-adjusted mortality rate was standardized on the age distribution of the Japanese standard population (1985 model). From Ref. 8.

rates (8) for colon cancer increased linearly until the mid-1990s in both sexes, whereas the rates for rectal cancer slightly increased in men and decreased in women (Fig. 1). These findings strongly suggest that the recent changes in the Japanese diet and other lifestyle factors contributed to the change in the incidence and mortality rate of colorectal cancer.

We therefore examined the association between diet and colorectal cancer risk in Japanese adults. Here we report results from the Japan Collaborative Cohort Study for Evaluation of Cancer Risk (JACC Study, sponsored by the Ministry of Education, Culture, Sports, Science and Technology of Japan), a nationwide multicenter collaborative study launched in 1988.

Materials and Methods

JACC Study

All data in the present analysis were drawn from the JACC Study. The methods of the study have been described in detail elsewhere (9). Briefly, the original study population consisted of 110,792 Japanese adults aged 40–79 enrolled between 1988 and 1990 in 45 areas throughout Japan. Most subjects were recruited at the general health check-ups provided periodically by municipalities. On enrollment, participants completed a self-administered questionnaire that included items on demographic characteristics, lifestyle habits, and medical history and provided informed consent for participation. The study protocol was approved by the Ethics Committee of Medical Care and Research of the Fujita Health University School of Medicine, Japan.

In the present analysis, we excluded 77 subjects who had a history of colorectal cancer. In addition, participants in the study area whose baseline questionnaire did not include the section on diet (n = 1,470) and participants who skipped all questions about diet (n = 1,421) were excluded from the analysis. Therefore, the final analysis included 107,824 subjects (45,181 men and 62,643 women).

Assessment of Dietary and Other Lifestyle Factors

The baseline questionnaire included questions about height and weight, medical history, family history of cancer, demographic characteristics, and lifestyle habits, including diet, tobacco smoking, alcohol consumption, and physical activity. In the food-frequency questionnaire (FFQ), participants were asked to categorize how often, on average, they consumed each of 33 foods typical in the Japanese diet; the five possible responses were "seldom," "0–2 times per month," "1–2 times per week," "3–4 times per week," and "almost every day." JACC Study nutrition experts validated the FFQ in 85 subjects selected from the 14 study areas (10). Briefly, after completing the FFQ, participants recorded their 3-day diets approximately every 3 mo for a year (four times total). From these data, the year-average food intake was estimated. Participants then filled out the FFQ again. Spearman's correlation coefficients between the first and the second FFQs for the 33 items ranged from 0.4 to 0.8; thus, reproducibility was deemed acceptable. When the second FFQ was validated against the 3-day diet records (four records for a total of 12 days), the correlation coefficients between the FFQ and the diet record estimates ranged from 0.07 (wild edible plants) to 0.62 (milk). In the present study, we analyzed 18 food items that had correlation coefficients of >0.3 for the association between the FFQ and the diet record estimates.

Identification of Colorectal Cancer Cases and Follow-Up of the Cohort

The subjects were followed for mortality until the end of 1999. Mortality was determined using the resident registration records of municipalities with permission from the Ministry of Public Management, Home Affairs, Post and Telecommunications. Registration of death is required by the Family Registration Law in Japan. Causes of death were confirmed with death certificates. The endpoint of this study was defined as death from colon cancer (*International Classification of Diseases*, 10th revision, ICD-10 C18) or rectal cancer (ICD-10 C20). Subjects who moved out of the study area or died from causes other than colorectal cancer were treated as censored cases. During the study period, only 3.5% (n = 3,769) of the participants were lost from the follow-up due to residence change. We computed each subject's period at risk as the time from the date of questionnaire administration to the date of death, the date of moving out of the study area, or December 31, 1999, whichever occurred first.

Statistical Analysis

Although colon and rectal cancers are often considered together, several differences in their etiologies have been identified (11). Additionally, as discussed previously, the secular trends in mortality over the last 30 yr for colon and rectal cancer in Japan are distinct (Fig. 1). Therefore, we evaluated the risk of colon cancer and rectal cancer separately by sex. All analyses were performed using the SAS statistical package, version 8.2 (SAS, Inc., Cary, NC). The hazard ratios (HRs) and 95% confidence intervals (CIs) for colon and rectal cancers, according to the intake frequencies for specific food items, were estimated using Cox's proportional hazard models through the "PHREG" procedure in SAS. We recategorized the intake frequency for each food item into three dummy variables and calculated the HR for "high" vs. "low" and "middle" vs. "low" levels of consumption of each food in the FFQ. To test for linear trends in the associations of food-intake frequency and cancer risk, the values 1–5 were assigned to the five responses (seldom, 0–2 times per month, 1–2 times per week, 3–4 times per week, and almost every day) respectively and entered as a continuous variable in the proportional hazard model. As diet is strongly influenced by residential area, we grouped subjects into six regions (Hokkaido and Tohoku, Kanto, Tokai, Kinki, Chugoku, and Kyushu) and used the "STRATA" statement of the PHREG procedure to consider area differences. We adjusted for the following potential confounding factors in the models: age, time spent walking daily (≤30 min or >30 min), age at leaving full-time education (>18 yr or ≤18 yr), history of colorectal cancer in parents or siblings (yes or no), body mass index {calculated as weight (kg)/[height (m)]^2; ≥25 or <25}, frequency of alcohol intake (≥5 days/wk or <5 days/wk), and current smoking status (smoker or nonsmoker). For each covariate, missing values were treated as an additional category in the variable and were included in the model. Two-tailed P values of ≤0.05 were considered statistically significant.

Power Calculations

During the follow-up period of 9.9 ± 2.2 yr (average ± SD), or 1,064,448 person-years at risk, 11,884 total deaths (7,074 men and 4,810 women) were observed. There were 284 cases of death from colon cancer (138 men and 146 women) and 173 from rectal cancer (116 men and 57 women). The power ranges for detection of the relative risk of 2.0 for high versus low levels of consumption, which were computed using the equation given by Breslow and Day (12), were as follows: 21.2–92.9% for male colon cancer, 42.1–94.9% for female colon cancer, 19.8–90.8% for male rectal cancer, and 0.08–55.6% for female rectal cancer. The following items had power values of <50% for detection of the relative risk of 2.0: beef, yogurt, carrot, and tomato for male colon cancer; beef, carrot, and tomato for male rectal cancer; and beef for female colon cancer. Because of the small number of cases of female rectal cancer, most items (except for milk, egg, and tofu) had power values of <50%.

Results

Tables 1 and 2 show HRs and 95% CI estimates of colon and rectal cancer mortality by sex and by frequency of meat and dairy product consumption. The HRs for the colon cancer mortality of men with a high intake of one of several types of meat (beef, pork, or chicken) compared with men with a low intake of that meat exceeded 1.0. However, only the comparison with medium and low intakes of chicken was statistically significant (adjusted HR = 1.7; 95% CI = 1.1–2.6). There was no significant positive or negative association of meat consumption with rectal cancer in men or with colon or rectal cancer in women. Yogurt intake was negatively associated with the risk of rectal cancer in men (trend $P = 0.04$); the risk for the high-intake group was less than one-half of the risk for the low-intake group. In women, there was a significant positive association of cheese intake and rectal cancer mortality (HR for high- vs. low-intake groups = 2.5; 95% CI = 1.1–5.7).

Tables 3 and 4 present adjusted HRs of colon and rectal cancer by sex and frequency of consumption of vegetables and other food items. Green leafy vegetables such as spinach were the only vegetables to show a significant negative association with male rectal cancer mortality. The HR for male rectal cancer mortality decreased linearly with increasing frequency of green leafy vegetable intake (trend $P = 0.02$), and the HR for the highest vs. lowest groups was 0.57 (95% CI = 0.3–0.9). However, a significantly increased HR for colon cancer mortality was observed for the groups of men with middle vs. low intakes of green leafy vegetables. In women, there was no significant association between vegetable consumption and colorectal cancer mortality. Fruit intake in women was positively associated with risk of colon cancer (trend $P = 0.04$) and negatively (although not significantly) associated with risk of rectal cancer.

Egg consumption was significantly associated with colon cancer mortality only in men (HR for men with high vs. low intake = 1.5; 95% CI = 1.0–2.4; trend $P = 0.04$, Table 3). Fish, tofu, boiled rice, and mushroom consumption were not related to colorectal cancer risk in men or women (Table 4).

Discussion

The JACC Study is the first nationwide cohort study of the association between diet and colorectal cancer to be conducted in Japan since that of Hirayama was completed over 20 yr ago (3). Despite the limited statistical power of the present study, we detected small but significant associations between the consumption of some foods and colorectal cancer mortality. Both chicken and egg consumption were positively associated with colon cancer, whereas intakes of yogurt and green leafy vegetables were inversely associated

Table 1. Hazard Ratio and 95% Confidence Interval for Colon and Rectal Cancer Mortality According to Intake Frequency of Meats and Dairy Products in Men[a]

		Colon Cancer				Rectal Cancer			
Food Frequency	Person-Years	No. of Cases	Adjusted HR	(95% CI)	*P* for Trend	No. of Cases	Adjusted HR	(95% CI)	*P* for Trend
Meat									
Beef									
Low[b]	188,305	46	1.00		0.96	44	1.00		0.17
Middle[c]	90,391	29	1.19	(0.73–1.94)		27	1.25	(0.76–2.08)	
High[d]	27,897	11	1.46	(0.74–2.86)		10	1.38	(0.68–2.78)	
Pork									
Low[b]	108,826	27	1.00		0.31	28	1.00		0.66
Middle[c]	149,495	51	1.55	(0.96–2.52)		40	1.08	(0.65–1.77)	
High[d]	71,016	17	1.14	(0.61–2.14)		20	1.11	(0.61–2.03)	
Ham and sausage									
Low[b]	175,115	55	1.00		0.31	48	1.00		0.64
Middle[c]	128,706	33	0.89	(0.58–1.38)		29	0.91	(0.57–1.45)	
High[d]	65,101	28	1.44	(0.90–2.31)		16	1.00	(0.56–1.78)	
Chicken									
Low[b]	133,538	31	1.00		0.07	36	1.00		0.24
Middle[c]	155,963	58	1.67	(1.08–2.59)		37	0.84	(0.53–1.33)	
High[d]	64,930	24	1.55	(0.90–2.66)		16	0.80	(0.44–1.45)	
Dairy products									
Milk									
Low[e]	88,178	22	1.00		0.28	25	1.00		0.68
Middle[f]	154,991	48	1.34	(0.80–2.22)		30	0.75	(0.44–1.29)	
High[g]	165,488	58	1.22	(0.74–2.02)		52	1.05	(0.64–1.71)	
Yogurt									
Low[e]	208,876	52	1.00		0.37	56	1.00		0.04
Middle[h]	45,889	15	1.32	(0.74–2.35)		9	0.80	(0.39–1.62)	
High[i]	50,482	12	0.80	(0.42–1.51)		7	0.46	(0.21–1.02)	
Cheese									
Low[e]	161,667	43	1.00		0.53	45	1.00		0.38
Middle[h]	89,289	31	1.53	(0.96–2.45)		15	0.72	(0.40–1.30)	
High[i]	64,442	20	1.17	(0.68–2.01)		21	1.19	(0.70–2.02)	
Butter									
Low[e]	161,374	54	1.00		0.98	36	1.00		0.32
Middle[h]	78,682	21	0.91	(0.55–1.52)		24	1.59	(0.95–2.68)	
High[i]	72,701	22	0.88	(0.53–1.46)		18	1.18	(0.66–2.09	

a: Hazard ratio (HR) adjusted for age, family history of colorectal cancer, body mass index, frequency of alcohol intake, current smoking status, walking time per day, and educational level and stratified by regions of enrollment by Cox proportional hazard model. Confidence interval (CI) estimates.
b: 0–2 per month.
c: 1–2 per week.
d: 3–7 per week.
e: Seldom.
f: 0.5–4 per week.
g: Every day.
h: 1–2 per month.
i: 1–7 per week.

with rectal cancer in men. Any investigated food items did not show significant associations with female colon cancer. A positive association was observed between both cheese and fruit intakes and female rectal cancer.

In the late 1990s, two expert committees concluded that increased vegetable consumption was recommended for the prevention of colorectal cancer (1,2). However, most recent cohort studies do not support the protective effect of vegetable consumption against colorectal cancer. The Nurses' Health Study and the Health Professionals Follow-up Study (13), The Netherlands Cohort Study on Diet and Cancer (14), and the Breast Cancer Detection Demonstration Project Follow-up Cohort (15) all found no association between fruit and vegetable consumption and colorectal cancer. Only the Swedish Mammography Screening Cohort (16) reported a significant negative association of total fruit and vegetable consumption with colorectal cancer risk. However, this association was driven mainly by fruit consumption and was stronger for the risk of rectal cancer than of colon cancer. The individual associations of vegetable and fruit consumption with colon and rectal cancer risk were not statistically significant. Sauvaget et al. recently reported the results of the Life

Table 2. HR and 95% CI for Colon and Rectal Cancer Mortality According to Intake Frequency of Meats and Dairy Products in Women[a]

		Colon Cancer				Rectal Cancer			
Food Frequency	Person-Years	No. of Cases	Adjusted HR	(95% CI)	*P* for Trend	No. of Cases	Adjusted HR	(95% CI)	*P* for Trend
Meat									
Beef									
Low[b]	264,277	80	1.00		0.95	22	1.00		0.80
Middle[c]	129,766	19	0.65	(0.38–1.11)		7	0.86	(0.34–2.15)	
High[d]	44,629	11	1.11	(0.57–2.14)		1	0.37	(0.05–2.84)	
Pork									
Low[b]	154,940	42	1.00		0.77	13	1.00		0.26
Middle[c]	214,478	48	0.98	(0.64–1.50)		15	0.78	(0.37–1.68)	
High[d]	102,841	20	0.93	(0.54–1.60)		3	0.32	(0.09–1.15)	
Ham and sausage									
Low[b]	253,150	63	1.00		0.68	19	1.00		0.50
Middle[c]	178,396	33	0.94	(0.61–1.44)		9	0.74	(0.33–1.65)	
High[d]	89,266	15	0.94	(0.53–1.66)		9	1.56	(0.69–3.53)	
Chicken									
Low[b]	158,635	39	1.00		0.60	9	1.00		0.97
Middle[c]	237,926	68	1.28	(0.86–1.90)		20	1.58	(0.71–3.48)	
High[d]	111,650	17	0.68	(0.38–1.21)		4	0.71	(0.22–2.32)	
Dairy Products									
Milk									
Low[e]	110,504	22	1.00		0.88	7	1.00		0.11
Middle[f]	204,875	49	1.40	(0.85–2.33)		15	1.34	(0.54–3.31)	
High[g]	268,252	61	1.16	(0.71–1.90)		26	1.64	(0.70–3.82)	
Yogurt									
Low[e]	231,552	58	1.00		0.93	11	1.00		0.14
Middle[h]	86,241	13	0.78	(0.43–1.44)		7	1.95	(0.74–5.09)	
High[i]	120,195	26	0.97	(0.61–1.56)		8	1.51	(0.60–3.8)	
Cheese									
Low[e]	244,453	67	1.00		0.98	14	1.00		0.07
Middle[h]	112,095	21	1.00	(0.61–1.65)		4	0.78	(0.25–2.41)	
High[i]	93,411	20	1.01	(0.61–1.69)		11	2.52	(1.11–5.72)	
Butter									
Low[e]	227,757	60	1.00		0.95	15	1.00		0.68
Middle[h]	100,819	17	0.88	(0.51–1.52)		6	1.11	(0.43–2.90)	
High[i]	116,954	25	1.07	(0.67–1.72)		8	1.29	(0.54–3.08)	

a: HR adjusted for age, family history of colorectal cancer, body mass index, frequency of alcohol intake, current smoking status, walking time per day, and educational level and stratified by regions of enrollment by Cox proportional hazard model. CI estimates.
b: 0–2 per month.
c: 1–2 per week.
d: 3–7 per week.
e: Seldom.
f: 0.5–4 per week.
g: Every day.
h: 1–2 per month.
i: 1–7 per week.

Span Study, a prospective study of 38,540 atomic bomb survivors from Hiroshima and Nagasaki in Japan (17). During a median follow-up period of 16 yr, they found that the consumption of fruit and green and yellow vegetables was associated with a reduction in stomach and lung cancer mortality but not with colorectal cancer mortality. We found no significant relationships between vegetables and colorectal cancer, with the exception of an association between green leafy vegetable intake and male rectal cancer. These findings are consistent with those of the recent prospective studies on vegetables and colorectal cancer risk. The discrepancies between the expert reports of the 1990s and recent prospective studies may partly be due to the recent improvements in agricultural and food technology, transportation, and storage systems in developed countries, including Japan. Globalization of food supplies has meant that all types of vegetables are available all year round. These recent changes have probably increased the variation in individual diets and decreased the differences between the diets of different populations, making it more difficult to assess long-term dietary exposures and detect relationships between diet and cancer risk, especially for vegetables.

Table 3. HR and 95% CI for Colon and Rectal Cancer Mortality According to Intake Frequency of Vegetables and Other Foods in Men[a]

		Colon Cancer				Rectal Cancer			
Food Frequency	Person-Years	No. of Cases	Adjusted HR	(95% CI)	*P* for Trend	No. of Cases	Adjusted HR	(95% CI)	*P* for Trend
Vegetables and fruits									
Green leafy vegetable									
Low[b]	146,277	34	1.00		0.40	46	1.00		0.02
Middle[c]	102,066	43	1.63	(1.03–2.55)		26	0.74	(0.46–1.20)	
High[d]	104,077	36	1.19	(0.74–1.91)		23	0.57	(0.34–0.94)	
Carrot									
Low[b]	202,058	57	1.00		0.33	55	1.00		0.62
Middle[c]	80,572	27	1.10	(0.69–1.75)		15	0.60	(0.34–1.07)	
High[d]	45,864	15	0.99	(0.55–1.76)		16	1.01	(0.57–1.79)	
Tomato									
Low[b]	249,738	62	1.00		0.66	63	1.00		0.16
Middle[c]	63,682	23	1.30	(0.80–2.11)		15	0.77	(0.44–1.36)	
High[d]	38,147	13	1.12	(0.61–2.07)		11	0.83	(0.43–1.58)	
Cabbage and lettuce									
Low[b]	154,471	43	1.00		0.33	39	1.00		0.55
Middle[c]	100,295	29	1.05	(0.65–1.68)		26	1.05	(0.64–1.73)	
High[d]	74,660	27	1.19	(0.73–1.94)		24	1.22	(0.73–2.05)	
Fruit									
Low[b]	150,932	40	1.00		0.63	40	1.00		0.78
Middle[c]	78,896	26	1.19	(0.72–1.96)		25	1.14	(0.69–1.89)	
High[d]	87,817	28	1.06	(0.64–1.75)		20	0.80	(0.46–1.41)	
Others									
Egg									
Low[b]	118,645	27	1.00		0.04	37	1.00		0.50
Middle[c]	117,116	37	1.40	(0.84–2.31)		21	0.56	(0.33–0.96)	
High[d]	188,707	70	1.54	(0.99–2.42)		52	0.82	(0.54–1.26)	
Fish									
Low[b]	159,005	43	1.00		0.80	45	1.00		0.87
Middle[c]	130,682	48	1.34	(0.88–2.04)		26	0.68	(0.42–1.11)	
High[d]	101,884	32	1.04	(0.65–1.66)		32	0.95	(0.60–1.51)	
Tofu									
Low[b]	148,384	41	1.00		0.46	40	1.00		0.53
Middle[c]	136,256	42	1.01	(0.65–1.58)		33	0.81	(0.51–1.31)	
High[d]	104,953	40	1.13	(0.72–1.76)		33	0.97	(0.60–1.55)	
Rice									
Low[e]	103,752	41	1.00		0.46	34	1.00		0.42
Middle[f]	198,834	67	0.92	(0.62–1.36)		58	0.86	(0.56–1.32)	
High[g]	128,319	28	0.81	(0.49–1.33)		23	0.59	(0.34–1.03)	
Mushroom									
Low[h]	125,272	33	1.00		0.97	27	1.00		0.89
Middle[i]	113,112	45	1.48	(0.94–2.32)		36	1.47	(0.89–2.43)	
High[j]	71,029	20	0.92	(0.52–1.61)		19	1.08	(0.60–1.96)	

a: HR adjusted for age, family history of colorectal cancer, body mass index, frequency of alcohol intake, current smoking status, walking time per day, and educational level and stratified by regions of enrollment by Cox proportional hazard model. CI estimates.
b: 0–2 per week.
c: 3–4 per week.
d: Every day.
e: 0–2 per day.
f: 3–4 per day.
g: 5 or more per day.
h: 0–2 per month.
i: 1–2 per week.
j: 3–7 per week.

Table 4. HR and 95% CI for Colon and Rectal Cancer Mortality According to Intake Frequency of Vegetables and Other Foods in Women[a]

Food Frequency	Person-Years	Colon Cancer				Rectal Cancer			
		No. of Cases	Adjusted HR	(95% CI)	*P* for Trend	No. of Cases	Adjusted HR	(95% CI)	*P* for Trend
Vegetables and fruits									
Green leafy vegetable									
Low[b]	174,726	42	1.00		0.64	14	1.00		0.23
Middle[c]	153,922	31	0.83	(0.52–1.32)		11	0.88	(0.40–1.94)	
High[d]	175,858	49	1.00	(0.66–1.52)		13	0.75	(0.35–1.60)	
Carrot									
Low[b]	222,180	51	1.00		0.51	13	1.00		0.13
Middle[c]	154,310	36	0.99	(0.64–1.51)		11	1.16	(0.51–2.61)	
High[d]	109,039	32	1.12	(0.71–1.75)		11	1.49	(0.66–3.37)	
Tomato									
Low[b]	311,777	74	1.00		0.23	16	1.00		0.50
Middle[c]	106,307	21	0.75	(0.46–1.22)		11	1.97	(0.90–4.29)	
High[d]	83,522	18	0.73	(0.43–1.24)		8	1.54	(0.64–3.68)	
Cabbage and lettuce									
Low[b]	183,139	42	1.00		0.44	15	1.00		0.48
Middle[c]	153,802	35	1.06	(0.67–1.66)		6	0.49	(0.19–1.27)	
High[d]	148,010	41	1.21	(0.78–1.87)		14	1.08	(0.51–2.25)	
Fruit									
Low[b]	142,584	28	1.00		0.04	12	1.00		0.35
Middle[c]	117,048	27	1.25	(0.73–2.13)		9	0.91	(0.38–2.19)	
High[d]	201,190	60	1.62	(1.02–2.57)		10	0.53	(0.22–1.26)	
Others									
Egg									
Low[b]	172,158	41	1.00		0.29	17	1.00		0.44
Middle[c]	174,238	34	1.01	(0.64–1.59)		14	0.79	(0.38–1.62)	
High[d]	254,445	63	1.17	(0.79–1.75)		19	0.75	(0.39–1.46)	
Fish									
Low[b]	216,873	53	1.00		0.98	20	1.00		0.46
Middle[c]	195,071	42	1.04	(0.69–1.56)		15	0.76	(0.38–1.51)	
High[d]	147,027	34	0.97	(0.62–1.50)		13	0.90	(0.44–1.84)	
Tofu									
Low[b]	180,160	44	1.00		0.35	19	1.00		0.55
Middle[c]	197,632	50	1.17	(0.78–1.77)		12	0.49	(0.23–1.03)	
High[d]	182,924	36	0.75	(0.48–1.18)		19	0.87	(0.45–1.67)	
Rice									
Low[e]	192,359	46	1.00		0.88	16	1.00		0.15
Middle[f]	351,332	82	0.91	(0.63–1.32)		31	1.04	(0.56–1.92)	
High[g]	68,607	12	0.91	(0.47–1.78)		9	2.06	(0.88–4.84)	
Mushroom									
Low[h]	135,144	33	1.00		0.54	6	1.00		0.12
Middle[i]	175,680	47	1.13	(0.72–1.77)		16	2.08	(0.81–5.34)	
High[j]	143,263	34	0.95	(0.59–1.54)		15	2.29	(0.88–5.93)	

a: Adjusted HR: hazard ratio adjusted for age, family history of colorectal cancer, body mass index, frequency of alcohol intake, current smoking status, walking time per day and educational level, and stratified by regions of enrollment by Cox proportional hazard model. CI: confidence interval estimates.
b: 0–2 per week.
c: 3–4 per week.
d: Every day.
e: 0–2 per day.
f: 3–4 per day.
g: 5 or more per day.
h: 0–2 per month.
i: 1–2 per week.
j: 3–7 per week.

Red meat consumption was considered a probable risk factor for colorectal cancer in the 1997 WCRF report (1). Since then, several other expert groups have reassessed the epidemiological data, including those published after the WCRF report (18–25). Similar to our data, the results of many of these studies did not reach statistically significant levels. However, the pooled results from recent meta-analyses are consistent and indicate an association between high intake of red meat and increased risk of colorectal cancer (24,25). Nevertheless, the nutritive value of red meat, which has an abundance of protein, minerals, and B vitamins, should not be undervalued (26). Further data are needed to clarify the optimal intake levels of red meat, taking into account both the adverse and beneficial effects on health.

We found a significant dose-response relationship between fruit intake and increased colon cancer risk in women. A protective effect of fruit against upper gastrointestinal tract cancers has been established, although the mechanisms for this effect are still unclear (1,27,28). However, the existing data on fruit consumption and colorectal cancer risk are limited and inconsistent. In their case-control study based in Japanese hospitals, Inoue et al. (29) found a nonsignificant increased risk of proximal colon cancer [age-adjusted odds ratio (OR) = 1.3; 95% CI = 0.7–2.4] but a decreased risk of distal colon cancer (OR = 0.4; 95% CI = 0.3–0.8) in patients who consumed fruit frequently. Future analyses of colon cancer risk by cancer subsite may clarify the association between fruit intake and colon cancer.

We found that yogurt consumption was inversely associated with rectal cancer mortality in men but not in women. In contrast, we found that the risk of female rectal cancer was positively associated with cheese intake. No association was observed between the consumption of any dairy product and colon cancer risk in men or women. A number of experimental and animal studies have suggested that fermented milk, lactic acid bacteria (LAB), and *Bifidobacterium* have beneficial effects on the colon (30,31). Norat and Riboli reviewed papers on dairy product consumption and colorectal cancer (32) and reported that cohort studies, but not case-control studies, have consistently found that high total dairy product intake and milk product intake protect against colorectal cancer. Dairy products are currently available with a wide variety of manufacturing processes in developed countries. Future epidemiological studies of the association between diet and colorectal cancer risk should specify the type and quantity of dairy products consumed so that any such association can be clarified.

We observed a marginally significant positive association between egg consumption and colon cancer mortality in males. In their review, Steinmetz and Potter (33) found that 9 of 11 available studies had reported a positive association between egg consumption and colon cancer risk. However, the most recent population-based cohort study on this subject reported no such association (34). Further investigation is necessary to reach a conclusion.

Against our expectation, we did not observe an association between fish intake and colorectal cancer in either gender in this study. Several clinical trials have suggested that fish oil supplements containing high levels of n-3 polyunsaturated fatty acids (n-3 PUFAs) may protect against colorectal cancer (35). The most recent case-control study conducted in Japan, which included 928 patients with colon cancer, 622 patients with rectal cancer, and 46,886 cancer-free outpatients, found that frequent fish consumption significantly decreased the OR for colon cancer in men and marginally decreased the OR in women (34). However, other epidemiological studies examining the association of fish intake and colorectal cancer risk have produced inconsistent results (36–38). As n-3 PUFA content varies by fish species, the frequency of fish intake does not necessarily correlate with the amount of n-3 PUFAs consumed. The Japanese population is among the highest consumers of fresh fish in the world (39). Future studies should specify in greater detail the types and quantities of fish consumed by subjects.

This large cohort study has a significant advantage over case-control studies, which cannot exclude the effect of recall bias. However, our study does have some limitations.

First, even though this is a large cohort study involving 110,792 Japanese adults with an average 10-yr follow-up period, the number of identified cases, especially for rectal cancer, is relatively low. This may induce error when examining the association between diet and colorectal cancer. Moreover, we measured the level of food intake using the original FFQ. All measurements are associated with a degree of error, which might influence the results of analyses. According to Willet (40), if only random within-person error is considered, the observed relative risk (RR_o) is computed as the estimated true relative risk (RR_t) to the power of the correlation coefficient (γ) between the true measure and the surrogate measure: $RR_o = (RR_t)^{\gamma}$. The correlation coefficient between our FFQ and the diet records of 3 days (× four times) ranged from 0.32 to 0.65 (average 0.44). According to Willet's equation, even if the true relative value were 1.5, the observed relative risk would be 1.18 for food items with correlation coefficients of <0.4. Therefore, our results might underestimate the true values. Additionally, as Kato et al. discussed (37), subjects in cohort studies tend to be homogeneous and health conscious. This may reduce the between-person variation in food consumption and make the detection of associations between diet and disease risk more difficult. Our results should therefore be further investigated and re-examined in prospective studies with large heterogeneous subject populations.

Second, because our endpoint was death from colon or rectal cancer, the risks reported are for fatal colon and rectal cancers and not for cancers amenable to curative treatment. We chose death rather than incidence as our endpoint as the study involved 110,792 Japanese adults from 45 areas throughout Japan, but incidence records were only available for the 65,184 participants who lived in the 24 study areas where cancer registries were available. As diet varies greatly between different residential areas, we gave priority to collecting samples from a broad range of areas to investigate the relationship between diet and colorectal cancer.

As a result of the small sample size and the measurement error in the present study, we are unable to draw firm conclusions about the relationship between colorectal cancer and diet in Japan. Further investigations, including the analysis of diet-influenced biomarkers with sufficient sample size, are needed to clarify the association between these factors and to establish effective strategies for the prevention of colorectal cancer.

Acknowledgments and Notes

The authors express their sincere appreciation to Dr. Kunio Aoki, Professor Emeritus, Nagoya University School of Medicine and the former chairman of the JACC Study Group, and Dr. Haruo Sugano, the former Director of the Cancer Institute of the Japanese Foundation for Cancer Research, who greatly contributed to the initiation of the study.

The present members of the JACC Study and their affiliations are as follows: Dr. Akiko Tamakoshi (present chairman of the study group), Nagoya University Graduate School of Medicine; Dr. Mitsuru Mori, Sapporo Medical University School of Medicine; Dr. Yutaka Motohashi, Akita University School of Medicine; Dr. Ichiro Tsuji, Tohoku University Graduate School of Medicine; Dr. Yosikazu Nakamura, Jichi Medical School; Dr. Hiroyasu Iso, Institute of Community Medicine, University of Tsukuba; Dr. Haruo Mikami, Chiba Cancer Center; Dr. Yutaka Inaba, Juntendo University School of Medicine; Dr. Yoshiharu Hoshiyama, University of Human Arts and Sciences Graduate School; Dr. Hiroshi Suzuki, Niigata University Graduate School of Medical and Dental Sciences; Dr. Hiroyuki Shimizu, Gifu University School of Medicine; Dr. Hideaki Toyoshima, Nagoya University Graduate School of Medicine; Dr. Shinkan Tokudome, Nagoya City University Graduate School of Medical Science; Dr. Yoshinori Ito, Fujita Health University School of Health Sciences; Dr. Shuji Hashimoto, Fujita Health University School of Medicine; Dr. Shogo Kikuchi, Aichi Medical University School of Medicine; Dr. Akio Koizumi, Graduate School of Medicine and Faculty of Medicine, Kyoto University; Dr. Takashi Kawamura, Kyoto University Center for Student Health; Dr. Yoshiyuki Watanabe and Dr. Tsuneharu Miki, Kyoto Prefectural University of Medicine Graduate School of Medical Science; Dr. Chigusa Date, Faculty of Human Environmental Sciences, Mukogawa Women's University; Dr. Kiyomi Sakata, Wakayama Medical University; Dr. Takayuki Nose, Tottori University Faculty of Medicine; Dr. Norihiko Hayakawa, Research Institute for Radiation Biology and Medicine, Hiroshima University; Dr. Takesumi Yoshimura, Institute of Industrial Ecological Sciences, University of Occupational and Environmental Health, Japan; Dr. Naoyuki Okamoto, Kanagawa Cancer Center; Dr. Hideo Shio, Moriyama Municipal Hospital; Dr. Yoshiyuki Ohno (former chairman of the study group), Asahi Rosai Hospital; Dr. Tomoyuki Kitagawa, Cancer Institute of the Japanese Foundation for Cancer Research; Dr. Toshio Kuroki, Gifu University; and Dr. Kazuo Tajima, Aichi Cancer Center Research Institute.

The past members of the Study, other than the following eight members, were listed in Ref. 9 (affiliations are those at the time of Study participation): Dr. Takashi Shimamoto, Institute of Community Medicine, University of Tsukuba; Dr. Heizo Tanaka, Medical Research Institute, Tokyo Medical and Dental University; Dr. Shigeru Hisamichi, Tohoku University Graduate School of Medicine; Dr. Masahiro Nakao, Kyoto Prefectural University of Medicine; Dr. Takaichiro Suzuki, Research Institute, Osaka Medical Center for Cancer and Cardiovascular Diseases; Dr. Tsutomu Hashimoto, Wakayama Medical University; Dr. Teruo Ishibashi, Asama General Hospital; and Dr. Katsuhiro Fukuda, Kurume University School of Medicine.

This work was supported by a Grant-in-Aid for Scientific Research on Priority Areas (2; No. 14031222) from the Ministry of Education, Culture, Sports, Science and Technology of Japan. The JACC Study has also been supported by Grants-in-Aid for Scientific Research from the same ministry (Nos. 61010076, 62010074, 63010074, 1010068, 2151065, 3151064, 4151063, 5151069, 6279102, and 11181101). Finally, we thank the anonymous reviewers whose helpful suggestions greatly improved the quality of the final manuscript. Address correspondence to M. Kojima, Department of Health Promotion and Preventive Medicine, Nagoya City University Graduate School of Medical Sciences, 1 Kawasumi, Mizuho, Nagoya, Japan, 467–8601. Phone: +81–52–853–8176. FAX:+81–52–842–3830. E-mail: masayok@med.nagoya-cu.ac.jp.

Submitted 4 February 2004; accepted in final form 14 July 2004.

References

1. WCRF/AICR: *Food Nutrition and the Prevention of Cancer: A Global Perspective*, Washington DC: World Cancer Research Fund/American Institute of Cancer Research, 1997.
2. COMA Working Group on Diet and Cancer: Nutritional Aspects of the Development of Cancer. Norwich, HMSO. UK Department of Health Report on Health and Social Subjects, 1998.
3. Hirayama T: *Life-Style and Mortality: A Large-Scale Census-Based Cohort Study in Japan*, Basel: Karger, 1990.
4. Hirayama T: Japanese studies on diet and cancer. In *Epidemiology of Diet and Cancer*, Hill MJ, Giacosa A, and Caygill CPJ (eds). London: Ellis Horwood, 1994, pp 17–64.
5. Ministry of Health, Labour and Welfare, Japan: *The National Nutrition Survey in Japan, 2001*, Tokyo: Daiichi Syuppan, 2003.
6. Yoshiike N, Matsumura Y, Iwaya M, Sugiyama M, and Yamaguchi M: National Nutrition Survey in Japan. *J Epidemiol* **6** Suppl, 189S–200S, 1996.
7. The Research Group for Population-Based Cancer Registration in Japan: Cancer incidence and incidence rates in Japan in 1998: estimates based on data from 12 population-based cancer registries. *Jpn J Clin Oncol* **33,** 241–245, 2003.
8. Statistics and Information Department, Minister's Secretariat, Ministry of Health, Labour and Welfare: *Vital Statistics of Japan 2000*, Tokyo: Health and Welfare Statistics Association, 2002.
9. Ohno Y and Tamakoshi A: Japan Collaborative Cohort Study for evaluation of cancer risk sponsored by Monbusho (JACC Study). *J Epidemiol* **11,** 144–150, 2001.
10. Ozasa K, Watanabe Y, Ito Y, Suzuki K, Tamakoshi A, et al.: Dietary habits and risk of lung cancer death in a large-scale cohort study (JACC Study) in Japan by sex and smoking habit. *Jpn J Cancer Res* **92,** 1259–1269, 2001.
11. Potter JD: Nutrition and colorectal cancer. *Cancer Causes Control* **7,** 127–146, 1996.
12. Breslow NE and Day NE: Design considerations. In *The Design and Analysis of Cohort Studies*, Lyon, France: International Agency for Research on Cancer, 1987, pp 272–315.
13. Michels KB, Giovannucci E, Joshipura KJ, Rosner BA, Stampfer MJ, et al.: Prospective study of fruit and vegetable consumption and incidence of colon and rectal cancers. *JNCI* **92,** 1740–1752, 2000.
14. Voorrips LE, Goldbohm RA, van Poppel G, Sturmans F, Hermus RJ, et al.: Vegetable and fruit consumption and risks of colon and rectal cancer in a prospective cohort study: The Netherlands Cohort Study on Diet and Cancer. *Am J Epidemiol* **152,** 1081–1092, 2000.
15. Flood A, Velie EM, Chaterjee N, Subar AF, Thompson.FE, et al.: Fruit and vegetable intakes and the risk of colorectal cancer in the Breast Cancer Detection Demonstration Project follow-up cohort. *Am J Clin Nutr* **75,** 936–943, 2002.
16. Terry P, Giovannucci E, Michels KB, Bergkvist L, Hansen H, et al.: Fruit, vegetables, dietary fiber, and risk of colorectal cancer. *JNCI* **93,** 525–533, 2001.
17. Sauvaget C, Nagano J, Hayashi M, Spencer E, Shimizu Y, et al.: Vegetables and fruit intake and cancer mortality in the Hiroshima/Nagasaki Life Span Study. *Br J Cancer* **88,** 689–694, 2003.
18. Truswell AS: Report of an expert workshop on meat intake and colorectal cancer risk convened in December 1998 in Adelaide, South Australia. *Eur J Cancer Prev* **8,** 175–178, 1999.
19. Truswell AS: Meat consumption and cancer of the large bowel. *Eur J Cancer Prev* **56** Suppl 1, 19S–24S, 2002.

20. Hill MJ: Meat and colo-rectal cancer. *Proc Nutr Soc* **58,** 261–264, 1999.
21. Hill M: Meat, cancer and dietary advice to the public. *Eur J Clin Nutr* **56** Suppl 1, 36S–41S, 2002.
22. Tasman-Jones C: Report on the workshop—red meat and colorectal cancer. *NZ Med J* **113,** 195–196, 1999.
23. Pearson M and Bruce A: *Does Meat Consumption Increase the Risk of Colon Cancer?*, Stockholm: Swedish Food Administration, 1998.
24. Sandhu MS, White IR, and McPherson K: Systematic review of the prospective cohort studies on meat consumption and colorectal cancer risk: a meta-analytical approach. *Cancer Epidemiol Biomarkers Prev* **10,** 439–446, 2001.
25. Norat T, Lukanova A, Ferrari P, and Riboli E: Meat consumption and colorectal cancer risk: dose-response meta-analysis of epidemiological studies. *Int J Cancer* **98,** 241–256, 2002.
26. Biesalski HK: Meat and cancer: meat as a component of a healthy diet. *Eur J Clin Nutr* **56** Suppl 1, 2S–11S, 2002.
27. Norat T and Riboli E: Fruit and vegetable consumption and risk of cancer of the digestive tract: meta-analysis of published case-control and cohort studies. *IARC Sci Publ* **156,** 123–125, 2002.
28. WHO, International Agency for Research on Cancer, International Association of Cancer Registries: *Patterns of Cancer in Five Continents*, Lyon, France: International Agency for Research on Cancer, 1990, p 17.
29. Inoue M, Tajima K, Hirose K, Hamajima N, Takezaki T, et al.: Subsite-specific risk factors for colorectal cancer: a hospital-based case-control study in Japan. *Cancer Causes Control* **6,** 14–22, 1995.
30. Fuller R: Probiotics in man and animals. *J Appl Bacteriol* **66,** 365–378, 1989.
31. Wollowski I, Rechkemmer G, and Pool-Zobel BL: Protective role of probiotics and prebiotics in colon cancer. *Am J Clin Nutr* **73** Suppl, 451S–455S, 2001.
32. Norat T and Riboli E: Dairy products and colorectal cancer. A review of possible mechanisms and epidemiological evidence. *Eur J Clin Nutr* **57,** 1–17, 2003.
33. Steinmetz KA and Potter JD: Egg consumption and cancer of the colon and rectum. *Eur J Cancer Prev* **3,** 237–245, 1994.
34. Jarvinen R, Knekt P, Hakulinen T, Rissanen H, and Heliovaara M: Dietary fat, cholesterol and colorectal cancer in a prospective study. *Br J Cancer* **85,** 357–361, 2001.
35. Hardman WE, Moyer MP, and Cameron IL: Fish oil supplementation enhanced CPT-11 (irinotecan) efficacy against MCF7 breast carcinoma xenografts and ameliorated intestinal side-effects. *Br J Cancer* **81,** 440–448, 1999.
36. de Deckere EA: Possible beneficial effect of fish and fish n-3 polyunsaturated fatty acids in breast and colorectal cancer. *Eur J Cancer Prev* **8,** 213–221, 1999.
37. Kato I, Akhmedkhanov A, Koenig K, Toniolo PG, Shore RE, et al.: Prospective study of diet and female colorectal cancer: the New York University Women's Health Study. *Nutr Cancer* **28,** 276–281, 1997.
38. Yang CX, Takezaki T, Hirose K, Inoue M, Huang XE, et al.: Fish consumption and colorectal cancer: a case-reference study in Japan. *Eur J Cancer Prev* **12,** 109–115, 2003.
39. Sasaki S, Horacsek M, and Kesteloot H: An ecological study of the relationship between dietary fat intake and breast cancer mortality. *Prev Med* **22,** 187–202, 1993.
40. Willett W: Correction for the effects of measurement error. In *Nutritional Epidemiology*, Oxford: Oxford University Press, 1990, pp 245–291.

Serum Oxidized Low-Density Lipoprotein Levels and Risk of Colorectal Cancer: A Case-Control Study Nested in the Japan Collaborative Cohort Study

Koji Suzuki,[1] Yoshinori Ito,[1] Kenji Wakai,[3,4] Miyuki Kawado,[2] Shuji Hashimoto,[2] Hideaki Toyoshima,[5] Masayo Kojima,[6] Shinkan Tokudome,[6] Norihiko Hayakawa,[7] Yoshiyuki Watanabe,[8] Koji Tamakoshi,[5] Sadao Suzuki,[6] Kotaro Ozasa,[8] Akiko Tamakoshi,[4] and Japan Collaborative Cohort Study Group

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

Abstract

Oxidative stress plays an important role in carcinogenesis, but few epidemiologic studies have examined associations with risk of colorectal cancer. Relationships between serum levels of oxidized low-density lipoprotein (oxLDL) and oxLDL antibody (oLAB) and colorectal cancer risk were investigated in a case-control study nested in the Japan Collaborative Cohort Study for Evaluation of Cancer Risk. Serum samples and lifestyle information were collected at baseline from 39,242 men and women between 1988 and 1990. Of these, 161 incidents and deaths from colorectal cancer were identified through 1999, and 395 controls were matched for gender, age, and study area. Measurements were taken of serum oxLDL levels in 119 cases and 316 controls and serum oLAB levels in 153 cases and 376 controls. Odds ratios (95% confidence intervals) across quartiles, adjusted for confounding factors, were 1.55 (0.70-3.46), 1.90 (0.84-4.28), and 3.65 (1.50-8.92) for oxLDL (P_{trend} = 0.004) and 0.98 (0.54-1.80), 0.75 (0.39-1.48), and 1.68 (0.90-3.13) for oLAB (P_{trend} = 0.140). Further adjustment for serum total cholesterol and α-tocopherol did not materially change these associations. Odds ratio (95% confidence interval) of the highest quartile of serum oxLDL compared with the lowest quartile was 3.40 (1.09-10.58; P_{trend} = 0.045). Analyses restricted to colon cancer cases and corresponding controls yielded similar relationships between serum oxLDL and oLAB levels and risk. In conclusion, higher levels of serum oxLDL may increase risk of colorectal cancer. (Cancer Epidemiol Biomarkers Prev 2004;13(11):1781–7)

Received 2/23/04; revised 5/24/04; accepted 5/28/04.

Grant support: Ministry of Education, Culture, Sports, Science, and Technology of Japan Scientific Research on Priority Areas grant-in-aid 14031222 and Scientific Research grants-in-aid 61010076, 62010074, 63010074, 1010068, 2151065, 3151064, 4151063, 5151069, 6279102, and 11181101.

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

Note: The present members of the JACC Study and their affiliations are as follows: A. Tamakoshi (Nagoya University Graduate School of Medicine; present Chairman of the JACC Study Group), 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 (Institute of Community Medicine, University of Tsukuba), H. Mikami (Chiba Cancer Center), Y. Inaba (Juntendo University School of Medicine), Y. Hoshiyama (Showa University School of Medicine), H. Suzuki (Niigata University Graduate School of Medical and Dental Sciences), H. Shimizu (Gifu University School of Medicine), H. Toyoshima (Nagoya University Graduate School of Medicine), 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 and T. Miki (Kyoto Prefectural University of Medicine Graduate School of Medical Science), C. Date (Faculty of Human Environmental Sciences, Mukogawa 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 (Institute of Industrial Ecological Sciences, University of Occupational and Environmental Health, Japan), K. Fukuda (Kurume University School of Medicine), N. Okamoto (Kanagawa Cancer Center), H. Shio (Moriyama Municipal Hospital), Y. Ohno (Asahi Rosai Hospital; former Chairman of the JACC Study Group), T. Kitagawa (Cancer Institute of the Japanese Foundation for Cancer Research), T. Kuroki (Gifu University), and K. Tajima (Aichi Cancer Center Research Institute). Past members of the JACC Study are listed in ref. 7 along with their affiliations at the time of participation, with the exception of the following: T. Shimamoto (Institute of Community Medicine, University of Tsukuba), H. Tanaka (Medical Research Institute, Tokyo Medical and Dental University), S. Hisamichi (Tohoku University Graduate School of Medicine), M. Nakao (Kyoto Prefectural University of Medicine), T. Suzuki (Research Institute, Osaka Medical Center for Cancer and Cardiovascular Diseases), T. Hashimoto (Wakayama Medical University), and T. Ishibashi (Asama General Hospital).

Requests for reprints: Koji Suzuki, Department of Public Health, Fujita Health University School of Health Sciences, 1-98 Dengakugakubo, Kutsukake-cho, Toyoake, Aichi 470-1192, Japan. Phone: 81-562-93-9424; Fax: 81-562-93-4595. E-mail: ksuzuki@fujita-hu.ac.jp

Introduction

Reactive oxygen species (ROS) cause oxidation of lipids, proteins, and DNA *in vivo* (1, 2), and free radical and lipid peroxides have been considered very important in carcinogenesis (3). Some studies have reported high lipid peroxidation in human colorectal cancer tissue (4, 5). However, few epidemiologic studies have investigated relationships between lipid peroxidation and colorectal cancer.

Oxidized low-density lipoprotein (oxLDL) is generated by the actions of ROS *in vivo*. The oxLDL is taken up by macrophages, which develop into foam cells, and oxLDL antibody (oLAB) is present in both atherosclerotic lesions and plasma (6). Thus, oxLDL is believed to play a critical role in the development and progression of

atherosclerosis (7). Serum oxLDL levels may be considered as a biomarker reflecting the state of oxidative stress and lipid metabolism *in vivo*. Experimental studies have indicated that oxLDL increases intracellular levels of ROS and lipid peroxidation products (thiobarbituric acid reactive substances; ref. 8). The oLAB plays a positive role in maintaining low levels of serum oxLDL.

Various lifestyle factors such as physical activity and diets reportedly affect oxLDL (9-14). Regular physical activity has been found to increase LDL resistance to oxidation and decrease plasma oxLDL concentration (9). Another study identified correlations between weight reduction and decreased oxLDL (10). Some epidemiologic studies have reported that physical activity (15-17) displays significant inverse associations with colorectal cancer and that obesity (18, 19) is associated with increased risk of colorectal cancer.

Vitamin E and lycopene have been shown to display powerful antioxidant properties, reducing LDL oxidation and oxidative damage to plasma proteins (11). Supplementation with antioxidant nutrients (vitamin E, vitamin C, and carotenoids) has been shown to protect LDL from oxidation (12-14). High dietary carotenoid intake possibly decreases the risk of colorectal cancer (20) and a meta-analysis (21) of five prospective nested case-control studies indicated that high plasma levels of α-tocopherol were associated with a modest decrease in the subsequent incidence of colorectal cancer.

Given the results of these previous studies, we hypothesize that serum oxLDL levels represent a biomarker reflecting oxidative stress and lifestyle factors such as physical activity and diet as related to colorectal cancer.

To the best of our knowledge, no studies have identified relationship between oxLDL and risk of colorectal cancer. We therefore examined correlations between serum levels of oxLDL and oLAB and risk of colorectal cancer in a case-control study nested in a large-scale Japanese cohort.

Materials and Methods

Study Subjects and Serum Samples. Study subjects were recruited in the Japan Collaborative Cohort (JACC) Study for Evaluation of Cancer Risk sponsored by Monbukagakusyo (Ministry of Education, Culture, Sports, Science, and Technology of Japan; ref. 22). This study involves 110,792 residents who were ages 40 to 79 years at baseline from 45 areas all over Japan. An epidemiologic survey of lifestyle factors was conducted using a self-administered questionnaire about heath conditions and lifestyles such as medical history, smoking habits, and alcohol consumption. Details of this study have been published elsewhere (22).

In addition to the questionnaire survey, participants in the JACC Study provided peripheral blood samples at health screening checkups sponsored by municipalities between 1988 and 1990. A total of 39,242 subjects (35.4% of respondents to the questionnaire survey) provided blood samples. Sera were separated from samples at laboratories in or near the surveyed municipalities as soon as possible after sampling. Serum derived from each subject was divided into three to five tubes (100-500 μL/tube) and stored at −80°C until analyzed.

Written informed consent for participation was obtained individually from subjects, with the exception of those in a few study areas in which informed consent was provided at the group level after the aim of the study and confidentiality of the data had been explained to community leaders. This study was approved by the Ethical Committee of Medical Care and Research at Fujita Health University.

Case Ascertainment and Control Selection. Subjects who died or moved away from study areas were identified using population registries, and causes of death were confirmed from death certificates. Incident cases of cancer could be identified by linkage with cancer registries in 24 of the 45 study areas. Follow-up for death was conducted from baseline to the end of 1999, and follow-up for incidence was conducted from baseline to the end of 1997, excluding three study areas (from baseline to the end of 1994, 1995, and 1996, respectively). Only 4% of subjects were lost to follow-up due to moving during the study period.

Death and incidence of colorectal cancer were defined by the codes "C18," "C19," and "C20" in the *International Statistical Classification of Diseases and Related Health Problem, 10th Revision* (23). During follow-up, 76 deaths from colorectal cancer [colon (C18), $n = 50$; rectum (C19 and 20), $n = 26$] and 185 incident cases of colorectal cancer (colon, $n = 123$; rectum, $n = 62$) were identified from subjects who had provided serum samples at baseline. Of these, 23 subjects with a history of colorectal and other cancers at baseline were excluded. For each case of colorectal cancer, two or three controls were selected from the remaining population without incident cancer or previous history of cancer, matching for gender, age (±3 years), and study area. A total of 49 cases and 56 controls without sufficient samples for measurement of serum levels of both oxLDL and oLAB were excluded from analysis. Following these exclusions, subjects without corresponding cases or controls were also excluded. Finally, serum levels of either oxLDL or oLAB could be measured in 161 cases (111 colon cancer cases and 50 rectum cancer cases) and 395 controls in this study. Of these, sufficient serum samples for determination of oxLDL and oLAB were available for 103 cases and 279 controls and 135 cases and 330 controls, respectively. For analyses using only incident cases and corresponding controls, the subjects were 82 cases and 216 controls for oxLDL and 111 cases and 266 controls for oLAB, respectively. Incident and dead cases were analyzed together to maximize sample size for main analysis.

Biochemical Analyses of Sera. All samples were analyzed by trained staff blinded to case-control status in 2001. Serum oxLDL and oLAB were determined by enzyme-linked immunoassay using commercially available kits (oxLDL: Oxidized LDL ELISA kit, Mercodia, Uppsala, Sweden; oLAB: oLAB ELISA kit, Biomedica, Vienna, Austria) in our laboratory. With regard to intraassay and interassay reproducibility, coefficients of variation for oxLDL (24) and oLAB (25) were <10%. Serum α-tocopherol levels were measured separately using high-performance liquid chromatography (26) in our laboratory. Serum total cholesterol was measured using an autoanalyzer at a single laboratory (SRL,