理解されつつある。しかしこれに加えて、臨床試験推進のためには、オペレーション機能が必須である。いろいろなプロジェクト・マネジメントも含め、試験の管理も必要であるし、ヘルプデスク的な機能、参加施設との対応も必要で、これなくしては臨床試験の円滑な推進はありえない。これらの機能をよく理解し、どれを自分たちで担うのか、どれを委託するのか、委託する場合には具体的に何を委託するのかを明確に特定しなければならない。また、これらの業務を委託する組織と友好な関係を保つとともに、自らそれらを育てていく努力も必要であろう。

8．謝　辞

この研究は本稿著者らが属する組織、研究班での活動を通して得たものであり、本稿著者らのオリジナルというより、それらの経験を代表してまとめたものと言える。これまでの研究に協力してくれたすべての方々と、我々にこれらの経験を与えて頂いた多くの研究参加者の方に心から感謝し、この研究結果が今後の臨床研究の発展のために少しでも役立つことを祈ります。本研究は厚生労働省研究費（がん研究助成金、厚生労働科学研究費）の補助を受けた。

Data management outsourcing for investigator-initiated clinical trials

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Key Words: clinical trial, data management, single institute, contract research organization

It has been well established that data management is an essential component in conducting clinical trials. To obtain data management of satisfactory quality, a certain amount of funding is needed, regardless of whether investigators have their own datacenter or a contract with a CRO (clinical research organization) for their data management. In addition to data management, an operations office is also necessary for smooth conduct of clinical trials. This office is responsible for the management of trials, institutions, investigators, budgets, and various projects. The principal investigators of a study should therefore familiarize themselves with all the functions necessary for clinical trials and decide who or what organization will be responsible for them.

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Case report

Familial adenomatous polyposis complicated by chronic myelogenous leukemia: response to imatinib mesylate

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Familial adenomatous polyposis (FAP) is an autosomal dominant disorder characterized by colonic polyposis and a predisposition for developing colorectal cancer. FAP is frequently complicated by extracolonic disease, but complications of leukemia are rare. We present the first case of FAP complicated by chronic myelogenous leukemia (CML) in a 38-year-old man. The patient had numerous adenomas in the colorectum and a family history compatible with FAP. He was diagnosed as having FAP in February 2000. Two years after the diagnosis, he developed leukocytosis with the Philadelphia chromosome abnormality, indicating complication with CML. Imatinib mesylate was administered for the treatment of CML, and hematologic and cytogenetic remission of CML was achieved in 6 months. Numerous polyps, 2 to 3 mm in diameter, observed in the rectum prior to the administration of imatinib, regressed in size, but not in number, after 1 year of treatment with imatinib. Eighteen months later, however, the polyps were enlarged. In this patient, imatinib administration led to the remission of CML and might also have been responsible for the temporary regression of adenomatous polyps of FAP.

Key words: familial adenomatous polyposis, chronic myelogenous leukemia, imatinib, regression

Introduction

Familial adenomatous polyposis (FAP) is an autosomal dominant disorder in which precancerous polyps grow in the colorectum. Left untreated, virtually all patients with FAP develop colon cancer in early adulthood.[1] Mutations of the adenomatous polyposis coli (*APC*) gene are thought to be responsible for the development of FAP.[2] Chronic myeloid leukemia (CML) manifests primarily as an increase in white blood cells (WBC) and is characterized by the Philadelphia chromosome translocation t(9;22)(q34;q11) resulting in the formation of the *BCR/ABL* fusion gene. Products of the *BCR/ABL* fusion gene are responsible for the development of CML.[3] Imatinib mesylate was designed to inhibit BCR/ABL tyrosine kinase of CML,[4] and the administration of imatinib effectively induces the remission of CML.[5] Imatinib mesylate is also effective against gastrointestinal stromal tumors (GIST).[6] Recently, imatinib was clinically tested for the treatment of advanced colorectal cancer (http://clinicaltrials.gov/ct/gui/show/NCT00041340?order=16) and adenomatous polyps of FAP (http://www.hereditarycc.org/cgi-bin/read.pl?i=199). We report a case with FAP complicated by CML. We administered imatinib mesylate to treat CML, and observed temporary regression of the adenomatous polyps of FAP during the administration of imatinib.

Case report

A 38-year-old man underwent screening for colon cancer after testing positive for occult blood in the stool in

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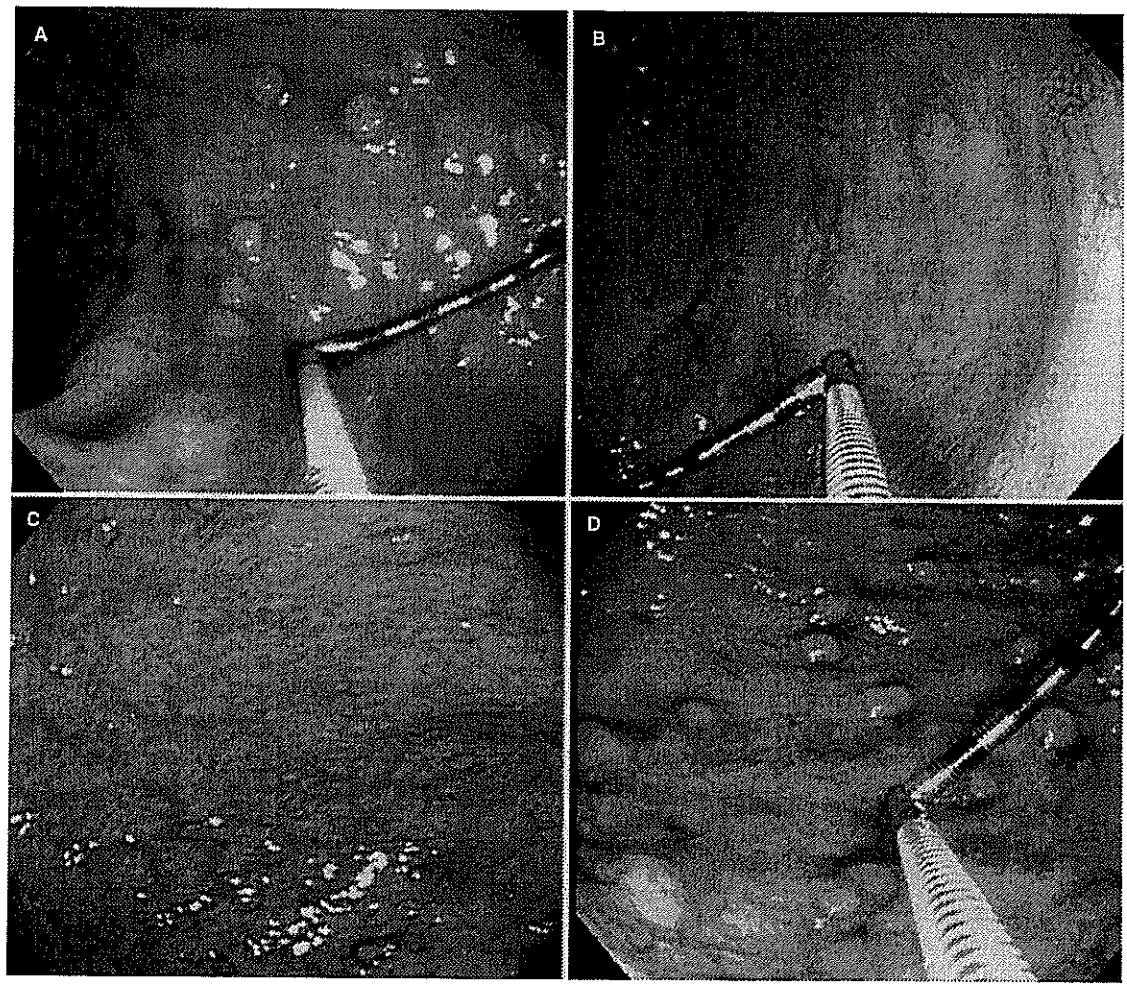

Fig. 1A–D. Endoscopic examination of the rectum. A polyp was marked to identify the same place in the rectum. *Hatched bar* on the wire indicates 2-mm intervals. **A** July 2002 (prior to the administration of imatinib); **B** and **C** after the administration of imatinib for 1 year (July 2003); **D** after administration of imatinib for 12 to 18 months (January 2004)

April 1999. Double-contrast barium enema and colonoscopy revealed numerous polyps in the colorectum. The patient was referred to the Osaka Medical Center for Cancer and Cardiovascular Disease in February 2000. His father had colorectal polyposis and had died of rectal cancer at the age of 36. Two of his father's brothers and his grandfather also had colorectal cancer. A germline mutation of the *APC* gene was not detected in this patient by a protein truncation test, which detects mutation in approximately 80% of FAP patients.[7] On the basis of the presence of colon polyposis and an autosomal dominant family history, the patient was diagnosed with FAP. He underwent prophylactic subtotal colectomy with ileorectal anastomosis in October 2000. He was under intensive colonoscopic surveillance semiannually, and polyps larger than 7 mm in diameter were removed. No colorectal cancer was detected in the removed tissues. In January 2002, his WBC count and serum lactic dehydrogenase levels increased. He was referred to the Division of Hematology-Oncology, Department of Internal Medicine, at the Hyogo College of Medicine in April 2002. Laboratory studies revealed a red blood cell count of 5×10^9/l, hemoglobin 15.7 g/dl, and a WBC count of 48.1×10^6/l, and platelet count of

222×10^6/l. Neutrophil alkaline phosphatase (NAP) activity was low (NAP rate 38%, score 82). A myelogram revealed hypercellular (nucleated cell count 987×10^6/l) and granulocyte-predominant marrow. Chromosomal analysis of bone marrow cells revealed 46XY, t(9;22)(q34;q11) in all 20 metaphases, which is known as the Philadelphia chromosome (Ph) and the critical genetic abnormality of CML. The BCR/ABL fusion transcript, which is generated as the molecular consequence of the Philadelphia chromosome, was present in 56% of bone marrow cells as detected by fluorescent in situ hybridization analysis. The patient was diagnosed with Ph(+) CML in the chronic phase. The patient was given imatinib mesylate 400 mg/day from July 2002. Owing to adverse reactions, including nausea and vomiting, the dose was reduced to 300 mg/day after 1 week. The patient achieved hematologic remission in 2 weeks based on blood count, and attained a complete cytogenetic response after 9 months of imatinib administration based on chromosome and fluorescent in situ hybridization analyses. A colonoscopy in July 2002, prior to the administration of imatinib (Fig. 1A), revealed a number of polyps 2 to 3 mm in diameter in the rectum. After 1 year of administration of imatinib (July 2003) (Fig. 1B and C), the adenomatous polyps showed significant regression in size, but not in number. Eighteen months after the beginning of imatinib administration (January 2004), the adenomatous polyps were again enlarged (Fig. 1D).

Discussion

We report a patient with FAP complicated by CML. Several cases of FAP complicated with leukemia have been reported, but the leukemia is usually the acute type.[5] To our knowledge, this is the first report of a FAP patient complicated by CML. Critical genetic changes of CML in the chronic phase are located on chromosomes 9 and 22,[3] and the *APC* gene of FAP is located on chromosome 5q;[2] thus, there seems no obvious genetic correlation between these diseases. It is possible that these two disorders occurred coincidentally at the same time in this patient.

The product of the *BCR/ABL* gene, which has tyrosine kinase activity, is constitutively produced in patients with Ph(+) CML.[3] Imatinib is a drug designed to interact with the ATP-binding site of the enzyme to inhibit intracellular signal transduction leading to apoptosis of tumor cells.[4] When administered to patients with Ph(+) CML, imatinib decreases the incidence of Ph(+) cells and *BCR/ABL* hybrid genes.[5] Furthermore, imatinib specifically inhibits the signal transduction of tyrosine kinases of c-Kit and platelet-derived growth factor receptors (PDGFR).[9] Recent reports revealed the efficacy of imatinib administration against GIST, which constitutively expresses c-Kit.[6] The present case of FAP was complicated by Ph(+) CML after prophylactic colectomy, while the patient was under careful follow-up. After administration of imatinib, the patient achieved a cytogenetically complete remission and a major molecular response of CML. Spontaneous regression of polyps of FAP is quite rare, and therefore prophylactic colectomy is recommended for the management of FAP.[1] Drugs that induce regression of polyps of FAP are limited to nonsteroidal anti-inflammatory drugs or, in a broad sense, cyclo-oxygenase-2 inhibitors.[10] As the patient did not take such drugs, imatinib mesylate was assumed to be responsible for the polyp regression. Thus, the temporary regression of colorectal adenomatous polyps might have been related to the administration of imatinib mesylate in our patient. Immunohistochemical analysis revealed no c-Kit expression in the adenomatous polyps (data not shown). Preliminary immunohistochemical analysis using currently available anti-PDGFRA antibody did not provide conclusive information on the expression of PDGFRA in adenomatous polyps. This issue and a mutation of the *PDGFR* gene in adenomatous polyps should be further analyzed to clarify the relationship between imatinib administration and polyps regression. Currently, this is the only case in which imatinib was administered to a FAP patient. Studies are currently under way in the United States to test imatinib for the treatment of colorectal cancer or FAP (http://clinicaltrials.gov/ct/gui/show/NCT00041340?order=16, http://www.hereditarycc.org/cgi-bin/read.pl?i=199). The present case might indicate the limited efficacy of imatinib for the regression of adenomatous polyps.

References

1. Lal G, Gallinger S. Familial adenomatous polyposis. Semin Surg Oncol 2000;18:314–23.
2. Bodmer W. Familial adenomatous polyposis (FAP) and its gene, *APC*. Cytogenet Cell Genet 1999;86:99–104.
3. Tauchi T, Broxmeyer HE. BCR/ABL signal transduction. Int J Hematol 1995;61:105–12.
4. Druker BJ, Tamura S, Buchdunger E, Ohno S, Segal GM, Fanning S, et al. Effects of a selective inhibitor of the Abl tyrosine kinase on the growth of Bcr-Abl positive cells. Nat Med 1996;2:561–6.
5. Kantarjian H, Sawyers C, Hochhaus A, Guilhot F, Schiffer C, Gambacorti-Passerini C, et al. International STI571 CML Study Group. Hematologic and cytogenetic responses to imatinib mesylate in chronic myelogenous leukemia. N Engl J Med 2002;346:645–52.
6. Nishida T, Hirota S, Taniguchi M, Hashimoto K, Isozaki K, Nakamura H, et al. Familial gastrointestinal stromal tumours with germline mutation of the KIT gene. Nat Genet 1998;19:323–4.
7. Powell SM, Petersen GM, Krush AJ, Booker S, Jen J, Giardiello FM, et al. Molecular diagnosis of familial adenomatous polyposis. N Engl J Med 1993;329:1982–7.

8. Greenberg MS, Anderson KC, Marchetto DJ, Li FP. Acute myelocytic leukemia in two brothers with polyposis coli and carcinoma of the colon. Ann Intern Med 1981;95:702–3.
9. Buchdunger E, Cioffi CL, Law N, Stover D, Ohno-Jones S, Druker BJ, et al. Abl protein-tyrosine kinase inhibitor STI571 inhibits in vitro signal transduction mediated by c-kit and platelet-derived growth factor receptors. J Pharmacol Exp Ther 2000; 295:139–45.
10. Koehne CH, Dubois RN. COX-2 inhibition and colorectal cancer. Semin Oncol 2004;31:12–21.

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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

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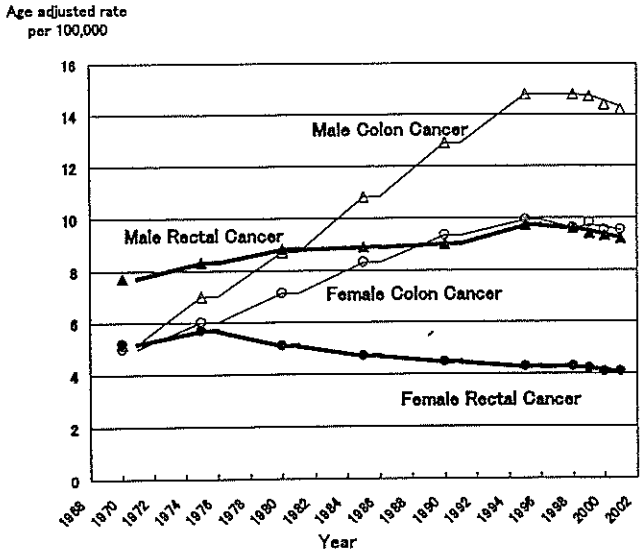

Figure 1. Trends in colon and rectal cancer mortality from 1970 to 2001 in Japan (age adjusted, per 100,000). Age-adjusted mortality rate was standardized on the age distribution of the Japanese standard population (1985 model). From Ref. 8.

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									0.80
Low[b]	264,277	80	1.00		0.95	22	1.00		
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									0.26
Low[b]	154,940	42	1.00		0.77	13	1.00		
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									0.50
Low[b]	253,150	63	1.00		0.68	19	1.00		
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									0.97
Low[b]	158,635	39	1.00		0.60	9	1.00		
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									0.11
Low[e]	110,504	22	1.00		0.88	7	1.00		
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									0.14
Low[e]	231,552	58	1.00		0.93	11	1.00		
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									0.07
Low[e]	244,453	67	1.00		0.98	14	1.00		
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									0.68
Low[e]	227,757	60	1.00		0.95	15	1.00		
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]

		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]	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.

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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: Méat 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

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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)

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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,

Hachioji, Japan). Values for oxLDL and oLAB could not be measured in all serum samples, because some initial samples yielded insufficient sera and other various substances were also measured from the same samples.

Serum samples of subjects had been stored for ~10 years until assay. Distribution of mean ± SD values for serum oxLDL levels in study controls [males: 36.1 ± 11.1 units/L (n = 144); females: 39.0 ± 11.4 units/L (n = 172)] was similar to that in our previous study (24) using fresh sera [males: 41.6 ± 12.2 units/L (n = 158); females: 42.7 ± 13.9 units/L (n = 158)]. Distributions of serum oLAB were also similar, with median values (25th-75th percentiles) at 191.0 (128.0-241.0) units/L in males (n = 179) and 192.0 (142.0-304.0) units/L in females (n = 197) for the present study compared with 170.7 (130.9-301.2) units/L in males (n = 158) and 209.0 (152.6-312.5) units/L in females (n = 158) for the previous study (25). Subjects in this and our previous study were Japanese ages 40 to 79 years, and the same ELISA kits were used. Serum levels of oxLDL and oLAB had thus not changed substantially during long-term storage.

Statistical Analyses. Body mass index (BMI) was calculated as body weight (kg) divided by height (m) squared. Baseline characteristics were compared between cases and controls using χ^2 tests. Mean differences for serum total cholesterol levels and BMI between cases and controls were examined using t tests. Because serum oxLDL, oLAB, and α-tocopherol levels are log normally distributed (25, 26), mean differences between cases and controls were examined using t tests after converting serum levels of oxLDL, oLAB, and α-tocopherol to logarithmic values. Relationships among serum levels of oxLDL, oLAB, total cholesterol, and α-tocopherol were examined using Spearman correlation coefficients. α-Tocopherol was included in this analysis because it binds to LDL and may be associated with decreased risk of colorectal cancer (21).

Conditional logistic regression models with gender, age, and study area strata were applied to calculate odds ratios (OR) and 95% confidence intervals (95% CI) for colorectal cancer. ORs were computed according to quartile levels of serum oxLDL and oLAB. Cases were categorized into four groups according to the quartile in controls for serum oxLDL and oLAB. To test for linear trends in ORs over quartiles, each quartile was coded as 0, 1, 2, or 3 and then incorporated into logistic models as a single variable.

Potential confounding was considered by smoking habits (never, former, or current smokers and unknown), drinking habits (never, former, or current drinkers and unknown), intake frequency of green leafy vegetables (1-2 times/mo or less, 1-2 times/wk or more, and unknown), time spent in sports or physical exercise (little, 1 h/wk or more, and unknown), family history of colorectal cancer (yes, no, and unknown), and BMI (<20.0, 20.0-24.9, or ≥25.0 kg/m^2 and unknown). Moreover, ORs for colorectal cancer by serum levels of oxLDL and oLAB were also computed after adjustment for the above confounding factors and quartiles of serum total cholesterol and α-tocopherol, because LDL binds to cholesterol and α-tocopherol. Elevated serum cholesterol levels are linked with increased colon cancer risk (27), and α-tocopherol is an antioxidant that inhibits mutagenesis and cell transformation (21). We therefore calculated these ORs to know the risk in relation to serum oxLDL and oLAB independent of α-tocopherol and total cholesterol.

Two-sided Ps < 0.05 were considered statistically significant. All statistical analyses were done using the Statistical Analysis System.

Results

Table 1 summarizes baseline characteristics of study subjects. No significant differences between cases and controls were observed for age distribution, smoking and drinking habits, family history of colorectal cancer, intake frequency of green leafy vegetables, or time spent in sports or physical exercise.

Table 2 compares serum levels of oxLDL, oLAB, total cholesterol, and α-tocopherol and BMI between cases and controls. Serum oxLDL levels were significantly higher in cases than in controls. BMI and serum levels of oLAB, α-tocopherol, and total cholesterol did not differ significantly between cases and controls.

Table 3 shows relationships among serum levels of oxLDL, oLAB, total cholesterol, and α-tocopherol in control subjects. Serum oxLDL levels were significantly and positively correlated with serum levels of total cholesterol and α-tocopherol in both genders. Serum

Table 1. Baseline characteristics of colorectal cancer cases and controls

	Cases (%)	Controls (%)	P (χ^2 test)
n	161 (100.0)	395 (100.0)	
Male	75 (46.6)	187 (47.3)	
Female	86 (53.4)	208 (52.7)	
Age (y)			
40-49	14 (8.7)	36 (9.1)	0.743
50-59	48 (29.8)	131 (33.2)	
60-69	65 (40.4)	159 (40.3)	
70-79	34 (21.1)	69 (17.5)	
Smoking habit			
Current smoker	37 (23.0)	96 (24.3)	0.674
Ex-smoker	23 (14.3)	51 (12.9)	
Nonsmoker	93 (57.8)	218 (55.2)	
Unknown	8 (5.0)	30 (7.6)	
Drinking habit			
Current drinker	75 (46.6)	168 (42.5)	0.503
Ex-drinker	2 (1.2)	12 (3.0)	
Nondrinker	78 (48.4)	195 (49.4)	
Unknown	6 (3.7)	20 (5.1)	
Family history of colorectal cancer			
Yes	10 (6.2)	14 (3.5)	0.161
No	151 (93.8)	381 (96.5)	
Intake frequency of green leafy vegetables			
1-2 times/mo or less	23 (14.3)	57 (14.4)	0.100
1-2 times/wk or more	126 (78.3)	325 (82.3)	
Unknown	12 (7.5)	13 (3.3)	
Time spent in sport or physical exercise			
Little	97 (60.2)	247 (62.5)	0.591
1 h/wk or more	57 (35.4)	125 (31.6)	
Unknown	7 (4.3)	23 (5.8)	