MDCT

The diagnosis and location were established by barium enema and/or colonoscopy before CT scanning. The time interval between barium enema and/or colonoscopy and MDCT was ⩽1 week. No specific preparation, such as laxatives, enema, or oral contrast agents, was performed before MDCT examination.

We used an Aquiline 16 CT scanner (Toshiba Medical Systems, Tokyo, Japan). For imaging of the whole body, we used the 16 high resolution central detectors. From these detectors we selected a 2 mm slice thickness and reconstructed the data at 5 mm intervals. Other parameters were a 0.5 second helical rotation time, 135 kVp, and 300 mAs. Iopamidol 100 ml (Iopamiron; Nihon Schering, Tokyo, Japan) was administered through a peripheral venous line at 3 ml/s using a power injector (Autoenhance A-50; Nemoto Kyorindo, Tokyo, Japan). CT scanning began 120 seconds after the start of injection of the contrast medium and scan data were acquired from the neck to the upper femur within one breathhold in approximately 20 seconds. Multiplanar reformation was reconstructed by a freestanding workstation (ZAIO, Tokyo, Japan) if diagnostic radiologists considered it necessary.

FDG-PET

Patients fasted for at least four hours before the examination. Patients received an intravenous injection of 200–250 MBq of [18F] fluoro-2-deoxy-D-glucose and then rested for approximately 60 minutes before undergoing imaging. Image acquisition was performed with use of an Advance NXi (GE Medical Systems, Milwaukee, Wisconsin, USA). Two dimensional emission scanning from the groin to the base of the skull (6–7 bed positions) was performed, lasting five minutes per bed position, in combination with a transmission scan lasting 1.5 minutes per bed position (transmission scanning time was corrected to allow for decay of the transmission sources). Data acquired were reconstructed by iterative ordered subsets expectation maximisation (21 subsets, two iterations).

Image analysis

At first, MDCT images were prospectively evaluated by two radiology physicians in consensus. They were assessed for detectability of the tumour, depth of tumour infiltration (T factor), regional lymph node involvement (N factor), and distant metastasis (M factor).

T factor on MDCT was defined by a modified TNM stage: tumour confined to the bowel wall was classified as T1 or T2. T1 was defined as an intraluminal elevated mass without thickening of the bowel wall. T2 was defined as thickening of the bowel wall (>5 mm) without invasion into the surrounding tissue. Tumour exposed out of the bowel wall but with no extension to the surrounding organs was considered as T3. Tumour infiltration into adjacent organs was considered T4. Lymph nodes were considered positive when the short axis was greater than 1 cm in diameter or there were clusters of three or more smaller nodes (each <1 cm). Lesions in the liver not characteristic of a cyst or haemangioma were considered suspicious of metastases. Also in the lung, pulmonary nodules without calcification were regarded as suspicious of metastases.

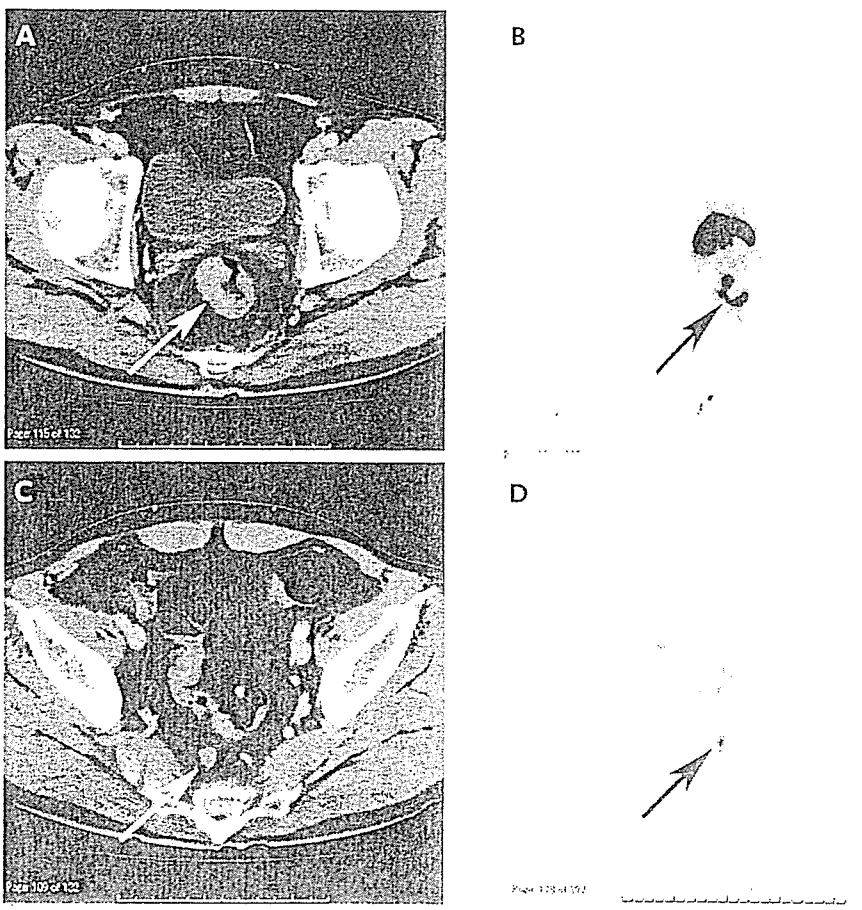

Figure 1 (A) Primary rectal tumour was exposed to the rectal wall but no extension to the pelvic side walls on computed tomography (CT) (arrow). (B) At the same level as (A), avid uptake was demonstrated on positron emission tomography (PET) (arrow). (C) A superior rectal lymph node was greater than 1 cm on CT (arrow). (D) At the same level as (C), PET showed uptake corresponded to the lymph node demonstrated on CT (arrow). This case was preoperatively diagnosed as TNM stage T3N1 and confirmed at surgery and on histopathological examination.

Table 1 Comparisons of MDCT and macroscopic diagnosis in staging depth of tumour invasion with colorectal carcinoma

Pathological staging	MDCT diagnosis					Macroscopic diagnosis			
	Tx	T1	T2	T3	T4	T1	T2	T3	T4
T1	2	0	2	1	0	1	4	0	0
T2	0	0	1	3	0	1	0	3	0
T3	0	0	5	17	2	0	3	18	3
T4	0	0	0	1	3	0	0	0	4

MDCT, multidetector row computed tomography.

All FDG-PET images were interpreted with knowledge of the patient's medical history and MDCT findings, and were evaluated with respect to detectability of the primary tumour, lymph node involvement, and distant metastases by two nuclear radiology physicians. T factor was not evaluated because the layers of intestinal wall and neighbouring structures cannot be differentiated on FDG-PET. Uptake higher than background was considered to be increased. Physicians interpreted the FDG-PET images by visually correlating the FDG-PET and MDCT images (fig 1). This approach was chosen because it represents the routine practice of combined reading of FDG-PET and MDCT images in our hospital. On the basis of their visual correlation, physicians assigned a TNM stage on FDG-PET. Regarding N factor, we chose to analyse the imaging studies on a nodal station bases and not on an individual lymph node basis. It seemed impossible for us to make a precise correlation between individually sampled and mapped lymph nodes on imaging studies.

Preoperative staging decision

Both MDCT and FDG-PET results were presented at the colorectal cancer conference, comprising surgeons, medical oncologists, endoscopists, nuclear radiology physicians, and radiation oncologists. All conference members confirmed the MDCT and FDG-PET findings. When a clear differentiation between different tumour stages on MDCT and FDG-PET was not possible, both stages were noted and confirmed after surgery. Based on the consensus of the conference, patients were divided into two groups. Patients considered as unresectable were referred to the Division of Gastrointestinal Medical Oncology, where chemotherapy, chemoradiotherapy, or best supportive care was performed. If unresectable factors were negative, the patient was admitted to a surgical ward and curative resection was attempted. In our hospital, neoadjuvant therapy was not routinely performed. These decisions on diagnosis and treatment plan were recorded and compared with surgical and pathological results.

Macroscopic diagnosis

For the 37 patients who proceeded to surgery, detection of the primary tumour, its depth of invasion, lymph node status, and liver metastases were macroscopically diagnosed either during surgery or through a node collection and classification procedure immediately after resection. These procedures were performed with knowledge of the preoperative imaging findings.

Data analysis

Resected specimens were examined by pathologists without knowing the preoperative MDCT and FDG-PET findings. The diagnostic accuracy of MDCT, FDG-PET, and macroscopic diagnosis of T and N factors were assessed using the histopathological findings as the gold standard. Comparison of diagnostic and pathological parameters was performed using the McNemar test. The level of statistical significance was determined at 5% in all cases.

RESULTS

All 44 patients tolerated both MDCT and FDG-PET examinations without any complications. Based on both MDCT and FDG-PET, 10 lesions of distant metastases were revealed in five patients and defined as unresectable: three bone metastases, three lung metastases, two liver metastases, and two distant lymph node metastases. MDCT showed eight of these 10 lesions; one each of bone and distant lymph node metastasis were missed. FDG-PET showed nine of the 10 lesions; one lung metastasis was missed. These five patients did not undergo surgical resection. Two patients were refused any anticancer treatment and left our hospital although their tumours were potentially resectable. Thus the remaining 37 patients were defined as resectable and underwent surgery. As expected, all lesions were resected with regional lymph node dissection.

The tumour detection rate was 95% for MDCT, 100% for FDG-PET, and 100% for intraoperative macroscopic diagnosis. The two cases which were not detected on MDCT were 0.7 cm and 1.8 cm adenocarcinomas, both limited to the submucosal layer. Regarding T factor, concordance rate with pathological findings was 57% for MDCT and 62% for macroscopic diagnosis (table 1). The difference was not significant ($p = 0.813$). In three of seven cases, tumours were diagnosed as T4 at surgery but histopathologically with no evidence of invasion to the adjacent organ. In contrast, in one case, MDCT showed no evidence of invasion to the adjacent organ but the tumour was found to have invaded the vagina

Table 2 Comparisons of MDCT, PET, and macroscopic diagnosis in staging lymph node metastasis with colorectal carcinoma

	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value(%)	Accuracy (%)
MDCT	58 (11/19)	67 (12/18)	65 (11/17)	60 (12/20)	62 (23/37)
PET	37 (7/19)	83 (15/18)	70 (7/10)	43 (15/27)	59 (22/37)
Macroscopic diagnosis	68 (13/19)	72 (13/18)	72 (13/18)	68 (13/19)	70 (26/37)

MDCT, multidetector row computed tomography; PET, positron emission tomography.

at surgery and combined resection was performed. Invasion was confirmed histopathologically.

Regarding N factor, overall accuracy was 62% for MDCT, 59% for FDG-PET, and 70% for macroscopic diagnosis (table 2). Sensitivity, specificity, positive predictive value, and negative predictive value were calculated as 58%, 67%, 65%, and 60%, respectively, for MDCT; 37%, 83%, 70%, and 43%, respectively, for FDG-PET; and 68%, 72%, 72%, and 68%, respectively, for macroscopic diagnosis. Macroscopic diagnosis showed a slightly higher accuracy but values were not significantly different between these modalities ($p = 0.624$ for MDCT *v* macroscopic diagnosis; $p = 0.466$ for FDG-PET *v* macroscopic diagnosis).

Of the 44 patients, FDG-PET findings resulted in treatment changes in only one (2%) patient who had bone and distant lymph node metastases detected only by FDG-PET. Although MDCT detected lung metastases that were not demonstrated on FDG-PET in one case, the patient had other distant metastases and the treatment plan was not influenced by the MDCT findings.

DISCUSSION

CT examination is an established method for staging colorectal carcinoma. However, recent studies have shown low accuracy rates due to considerably low sensitivity for detection of lymph node metastases and for local tumour extension.[20–23] MDCT is expected to improve diagnostic accuracy by scanning a wider region with better resolution. To evaluate the usefulness of FDG-PET, we compared the diagnostic accuracy of FDG-PET with this up to date technology.

The efficacy of imaging techniques is usually evaluated by retrospective reading by radiologists blinded to the clinical information. However, this is not practical and many physicians often feel that actual diagnostic results are different from the results reported. We wished to evaluate the usefulness of FDG-PET in the clinical setting. Recently, integrated PET-CT scanners have been introduced into the clinical situation.[24] Using this technique, PET, CT, and integrated PET-CT images are displayed together on the monitor. This type of PET scanner and reading style will become routine. Thus in this study, FDG-PET images were interpreted with knowledge of the patient's medical history and MDCT images.

For detection of a primary tumour, FDG-PET was positive in all 44 lesions but MDCT gave two false negative lesions. We did not use any preparation before the MDCT studies. If sufflation of air or water into the bowel cavity and administration of antiperistaltic drug had been performed, the detection rate might have been improved. In contrast, FDG-PET was positive in all lesions, including those that were negative with MDCT. Such high sensitivity confirms the results of previous reports.[15–17] The injected dose that we used was lower than the conventional dose reported. However, we had confirmed in our preliminary study that image quality with this dose did not deteriorate. This may have been due to differences in the physique of Japanese and Western patients. We should try to reduce radiation exposure while preserving diagnostic accuracy.

CT studies over the last decade showed accuracy rates of 41–82% in T staging.[20–23] Our result (57%) was comparable with these reports. Even with the improved imaging resolution of MDCT, it is still difficult to discriminate bowel wall layers as conventional single detector spiral CT. MDCT did not demonstrate satisfactory results for diagnosis of N factor, as reported in previous studies.[25–27] Microscopic metastasis or uninvolved swelling of lymph nodes results in misdiagnosis. As long as a diagnosis is made based on the size of lymph nodes, a certain percentage of false positive and negative lymph nodes is unavoidable. In this study, FDG-PET had low sensitivity (37%) and high specificity (83%), as reported in previous studies.[16–18] FDG-PET was no better than MDCT. The high false negative rate was attributed to limited spatial resolution, which was a disadvantage in detecting micrometastases, and the proximity of the dose to the primary tumour to lymph node metastases.

The accuracy of intraoperative macroscopic diagnosis was superior but not significantly different from that of MDCT and FDG-PET. By palpation and inspection, lymph nodes in the immediate vicinity of the primary tumour could be differentiated more easily than by MDCT or FDG-PET. Moreover, macroscopic diagnosis was made with knowledge of the MDCT and FDG-PET findings. Nevertheless, accurate diagnosis of lymph node metastasis is difficult, even at surgery.

FDG-PET has the advantage of studying the whole body at one examination and synchronous tumours have been identified on FDG-PET. However, MDCT can also scan the whole body in a shorter time than FDG-PET. In this study, distant metastases revealed only 10 lesions in five patients. While patient numbers were too small to compare the usefulness of the diagnostic modalities, MDCT and FDG-PET showed various corresponding metastatic lesions.

In assessing the influence of FDG-PET findings on clinical management, changes in therapeutic decision making were made in only 2% (1/44) of cases, which is less than in other investigations. The incidence of management alterations due to FDG-PET was reported as 16–50%.[8 13 18 28 29] The reason may be selection of patients in the other studies as many were already known to have advanced disease and FDG-PET was performed to detect recurrences or metastases.

The results of this study suggest that the diagnostic accuracy of FDG-PET for the initial staging of CRC was not superior to routine MDCT and was not influential in terms of patient management. We believe routine evaluation of patients with a suspicion of CRC by FDG-PET is not necessary; it should be performed on selected patients who have suggestive but inconclusive metastatic lesions with other modalities.

ACKNOWLEDGEMENTS

This work was supported by the Foundation for Promotion of Cancer Research in Japan.

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Conflict of interest: None declared.

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Original Article

Dietary Risk Factors for Colon and Rectal Cancers: A Comparative Case-Control Study

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BACKGROUND: In Japan, the incidence rate of colon cancer has more rapidly increased than that of rectal cancer. The differential secular trends may be due to different dietary factors in the development of colon and rectal cancers.
METHODS: To compare dietary risk factors between colon and rectal cancers, we undertook a case-control study at Aichi Cancer Center Hospital, Japan. Subjects were 507 patients with newly diagnosed colon (n = 265) and rectal (n = 242) cancers, and 2,535 cancer-free outpatients (controls). Intakes of nutrients and food groups were assessed with a food frequency questionnaire, and multivariate-adjusted odds ratios (ORs) were estimated using unconditional logistic models.
RESULTS: We found a decreasing risk of colon cancer with increasing intakes of calcium and insoluble dietary fiber; the multivariate ORs across quartiles of intake were 1.00, 0.90, 0.80, and 0.67 (trend p = 0.040), and 1.00, 0.69, 0.64, and 0.65 (trend p = 0.027), respectively. For rectal cancer, a higher consumption of carotene and meat was associated with a reduced risk; the corresponding ORs were 1.00, 1.10, 0.71, and 0.70 for carotene (trend p = 0.028), and 1.00, 0.99, 0.68, and 0.72 for meat (trend p = 0.036). Carbohydrate intake was positively correlated with the risk of rectal cancer (ORs over quartiles: 1.00, 1.14, 1.42, and 1.54; trend p = 0.048). This association was stronger in women, while fat consumption was inversely correlated with the risk of female colon and rectal cancers.
CONCLUSIONS: Dietary risk factors appear to considerably differ between colon and rectal cancers.
J Epidemiol 2006; 16:125-135.

Key words: Diet, Colonic Neoplasms, Rectal Neoplasms, Case-Control Studies, Japan.

In Japan, the age-standardized incidence rate of colorectal cancer increased until around 1990 and has leveled off thereafter.[1] It is now at among the highest levels in the world; the incidence rate standardized with the World Population was estimated to be 49.9 (per 100,000 population) in men and 27.2 in women in 1999.[1]

The incidence of colon cancer has increased more rapidly than that of rectal cancer. Between 1975 and 1999, the colon-to-rectal ratio of incidence (standardized with the World Population) rose from 0.85 to 1.67 in men and from 1.17 to 2.13 in women.[1,2] The ratio greatly varies among countries,[3] being much higher in cancer registries in the United States and Canada (median = 2.1 in men and 2.6 in women) than those in Asian countries excluding Japan (1.2 in men and 1.4 in women). Registries in European countries have intermediate values (1.5 in men and 2.0 in women).

If dietary risk factors of colon cancer differ from those of rectal cancer, the different secular trends in incidence between the two sites and international variation in the colon-to-rectal ratio of incidence may partly be explained by changes and international varia-

Received December 6, 2005, and accepted February 23, 2006.
This work was supported in part by Grants-in-Aid for Scientific Research on Priority Areas of Cancer from the Japanese Ministry of Education, Culture, Sports, Science and Technology (Nos. 12218242 and 17015052) and a Grant-in-Aid for the Third-Term Comprehensive Ten-Year Strategy for Cancer Control from the Ministry of Health, Labour and Welfare of Japan.
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tion in dietary habits. In Asian countries, however, only a small number of studies[4-7] have examined differences in dietary risk factors between cancers of the colon and rectum. It is therefore not clear whether the predominant increase in incidence of colon cancer in Japan is ascribable to changes in diet. We need further data to know why the proportion of rectal cancer in all colorectal cancer cases is relatively high in Asian countries.

To further address these issues, we conducted the present case-control study comparing dietary risk factors between colon and rectal cancers in the Hospital-based Epidemiologic Research Program at Aichi Cancer Center (HERPACC).

METHODS

The Hospital-based Epidemiologic Research Program at Aichi Cancer Center

HERPACC was initiated in Aichi Cancer Center Hospital (ACCH), Nagoya, in 1988, with information on lifestyle factors collected from all first-visit outpatients, using a self-administered questionnaire checked by a trained interviewer. Each patient is asked about his or her lifestyle including dietary habits when healthy or before the current symptoms developed. The questionnaire data are loaded into the HERPACC database and routinely linked with the hospital cancer registry system to update the data on cancer incidence. Written informed consent for participation is obtained from each patient. The ethical board of Aichi Cancer Center reviewed and approved the protocol of this investigation. Further details of HERPACC have been described elsewhere.[6,8]

Cases and Controls

The present study is based on data collected between January 2001 and September 2004 because the present version of the food frequency questionnaire was adopted in January 2001. Among all first-visit outpatients during this period (n = 25,941), the questionnaire was given to 21,417 (82.6%). Of the remaining 4,524 patients (17.4%), 2,041 (7.9%) were excluded because of the absence of an interviewer and so were 1,222 (4.7%) due to a consultation visit by someone other than patients themselves. Others were left out because they were too young (< 18 years) or too ill to fill out the form or for other miscellaneous reasons. Of the 21,417 outpatients who were asked to complete the questionnaire, 20,814 (97.2%) provided adequate responses to the questionnaire.

Patients aged 20 to 79 years with cancers of the colon (n = 323) or rectum (n = 276) (International Statistical Classification of Diseases and Related Health Problems, 10th Revision [ICD-10]: C18 and C20), newly and histopathologically diagnosed, were deemed to be potential cases. We excluded 85 patients with a prior history of cancer and seven with an implausibly high or low estimated intake of total energy (<500 or 3,500+ kcal/day), leaving 507 cases eligible for the analysis (colon cancer: n = 265; rectal cancer: n = 242).

We randomly selected five controls for each case from the 14,931 cancer-free individuals, with matching for age (5-year strata), sex, and calendar year of the first visit. Those with a history of cancer (n = 1,188) and an extreme value of energy intake (n = 125) were excluded as in the case patients. Finally, 2,535 controls were included in this study.

Diet and Other Exposure Data

The HERPACC questionnaire applied included items on demographic characteristics, family and individual medical history, height and weight, exercise, smoking and drinking habits, and vitamin use, as well as consumption of selected foods and beverages.

The dietary component of the questionnaire comprised 47 food items.[9] We asked the subjects about the average intake frequency without specifying portion size, during the period of one year before onset of the present disease or before the interview. For staple foods such as rice, bread, and noodles, the usual number of bowls or slices consumed at one time, as well as the intake frequency, was inquired for breakfast, lunch, and supper, separately. The frequency of alcohol consumption was asked with the usual amount on one occasion. Nutrient intakes and food group consumption were estimated assuming the standard portion sizes.

Energy-adjusted intakes of nutrients and food groups were calculated by the residual method,[10] with natural logarithms used to improve the normality of their distribution except for the ratio of n-6 fatty acid intake to that of n-3 fatty acids. The food frequency questionnaire was validated by referring to 3-day weighed dietary records as a standard.[9] The de-attenuated correlation coefficients for energy-adjusted intakes of nutrients for the present analysis ranged from 0.12 to 0.86 in men (median = 0.43) and from 0.17 to 0.64 in women (0.38). The coefficients (not de-attenuated) for energy-adjusted consumption of food groups varied from 0.19 to 0.57 in men (median = 0.42) and from 0.19 to 0.61 in women (0.42).

Statistical Analysis

Body mass index (BMI) at baseline was calculated from reported height and weight: BMI = (weight in kg)/(height in m)^2.

To assess the strength of the associations between intakes of nutrients or food groups and risk of colon or rectal cancer, odds ratios (ORs) were computed. To directly compare dietary risk factors between colon and rectal cancers based on a common control group, we pooled controls matched to colon cancer cases and those matched to rectal cancer cases in the analysis. Cases and controls were categorized into four groups according to sex-specific quartile levels of energy-adjusted intakes of nutrients or food groups among controls. The ORs with 95% confidence intervals (CIs) for the second, third, and highest quartiles versus the lowest were estimated using unconditional logistic models[11] adjusted for the matching variables and potential confounding factors.[12-14]

The ORs were adjusted for sex, age (as a continuous variable), calendar year of the first visit to the hospital (2001, 2002, or 2003-2004), season of first visit (spring, summer, autumn, or winter), reason for the visit (self recommendation, recommenda-

tion by family or friends, referral by physicians, secondary screening, or others), family history of colorectal cancer in parents and/or siblings (yes or no), BMI (<20.0, 20.0-24.9, 25.0-29.9, or 30.0+ kg/m^2), exercise (none, <0.50, 0.50-0.99, or 1.00+ hours/day), alcohol drinking (nondrinkers, ex-drinkers, or current drinkers who daily consumed <1.0, 1.0-1.9, or 2.0+ Japanese drinks [one Japanese drink is equivalent to 23g of ethanol]), smoking habit (nonsmokers, ex-smokers, or current smokers), multivitamin use (at least once per week for one year or longer; yes or no), and total energy intake (as a continuous variable). Missing values for each covariate were treated as an additional category in the variable and were included in the logistic model. As a basis for the trend tests, we assigned scores of 0, 1, 2, and 3 to the first (or lowest), second, third, and fourth quartiles of nutrient intakes or food group consumption, respectively, and included the score in the model. All p values were two-sided, and all the analyses were performed using the Statistical Analysis System®, release 8.2.[15]

RESULTS

Table 1 shows the distribution of cases and controls by background characteristics; sex, age, and calendar year of the first visit were exactly matched between cases and controls. Values for mean age ± standard deviation were 61.7 ± 9.2 and 61.6 ± 9.3 years in cases and controls for colon cancer, respectively. The corresponding figures were 58.6 ± 10.7 and 58.5 ± 10.6 years for the rectal cancer subjects. As expected, the case group included a higher proportion of patients referred by physicians than the control group.

Cases of both colon and rectal cancers were more likely to have a family history of colorectal cancer than the controls. Other characteristics, such as season of first visit to the hospital, BMI, exercise, drinking and smoking habits, multivitamin use, and energy intake, were similarly distributed in cases and controls.

The greater the intake of calcium and insoluble dietary fiber, the lower the multivariate OR (OR2) for colon cancer (Table 2; trend p = 0.040 for calcium and 0.027 for insoluble dietary fiber). The risks for the highest quartile of intake of calcium and insoluble dietary fiber were 33% and 35% lower than those for the lowest quartile, respectively (OR2: 0.67 [95% CI: 0.46-1.00] for calcium and 0.65 [95% CI: 0.45-0.96] for insoluble dietary fiber). Inverse associations were also suggested between colon cancer risk and intakes of protein, fat, vitamin C, and total dietary fiber (trend p for OR2 < 0.10).

We found a decreased risk of rectal cancer associated with higher intakes of carotene and meat (Table 3; trend p for OR2 = 0.028 for carotene and 0.036 for meat). A negative correlation was also suggested between the risk of rectal cancer and intake of vitamin E (trend p for OR2 = 0.072). On the other hand, an increasing risk was found with increasing intake of carbohydrate (trend p for OR2 = 0.048).

In women, intakes of protein, fat, calcium, vitamin E, cholesterol, and total dietary fiber were inversely correlated with the risk of colon cancer (trend p < 0.10, Table 4), while no significant associations were noted in men. A reduced risk of rectal cancer associated with a higher consumption of carotene and meat was observed particularly in women (Table 5). Inverse associations were also found for fat, vitamin E, folate, monounsaturated and n-6 polyunsaturated fatty acids, and green-yellow vegetables in women (trend p < 0.10). In contrast, women who took diet high in carbohydrate were at more than twice the risk of developing rectal cancer. The ORs for the third and the highest quartiles were 2.14 (95% CI: 1.05-4.36) and 2.53 (95% CI: 1.22-5.24; trend p = 0.003), respectively. An increasing risk with an increasing ratio of dietary n-6 polyunsaturated fatty acids (PUFA) to n-3 PUFA was detected for male rectal cancer (trend p = 0.042).

DISCUSSION

In this case-control study, we found a decreased risk of colon cancer with increasing intakes of calcium and insoluble dietary fiber, while a higher consumption of carotene and meat was associated with a reduced risk of rectal cancer. Carbohydrate intake was linked to the risk of rectal cancer, particularly in women, while fat consumption was inversely correlated with the risk of colon and rectal cancers in women.

People take much less meat and more cereals in Asian countries than in the United States and Canada (http://faostat.fao.org/faostat/), which may account for the lower colon-to-rectal ratios in Asia. Further investigations, however, are needed because the differences in risk for the consumption of meat and carbohydrate between colon and rectal cancers have not been fully supported by previous investigations.

Calcium intake has been related to a decreased risk of colorectal cancer in prospective studies.[16-18] In addition, randomized controlled trials showed that calcium supplementation prevents recurrence of colorectal adenomas, precursors of cancers.[19] The present study provides further support for role of calcium in the prevention of colorectal cancer. Some investigations demonstrated a greater risk reduction for cancer of the colon than that of the rectum as in our case.[16,18]

An inverse association of dietary fiber and colon cancer risk was here detected specifically for insoluble dietary fiber. Many epidemiologic studies have not substantiated a protective association between dietary fiber and colorectal cancer,[20-22] although a recent large prospective study in Europe showed a decreased risk of colorectal cancer associated with dietary fiber intake.[23]

An earlier investigation reporting protective effects of dietary fiber against colorectal cancer did not find a substantial difference in risk between soluble and insoluble fibers.[24] Whereas adsorption of carcinogens to insoluble dietary fiber in the intestinal tract is one of the mechanisms by which dietary fiber is believed to protect against colorectal cancer,[25] the roles of different types of fiber should be further elucidated. Our finding that the association of dietary fiber was mainly with colon rather than rectal cancer is

Table 1. Background characteristics of cases and controls for colon and rectal cancers.

	Colon cancer		Rectal cancer	
	Cases (n = 265)	Controls (n = 1,325)	Cases (n = 242)	Controls (n = 1,210)
Sex				
Men	149 (56.2)	745 (56.2)	146 (60.3)	730 (60.3)
Women	116 (43.8)	580 (43.8)	96 (39.7)	480 (39.7)
Age (years)				
20-29	1 (0.4)	5 (0.4)	1 (0.4)	5 (0.4)
30-39	4 (1.5)	20 (1.5)	17 (7.0)	85 (7.0)
40-49	19 (7.2)	95 (7.2)	22 (9.1)	110 (9.1)
50-59	83 (31.3)	415 (31.3)	83 (34.3)	415 (34.3)
60-69	106 (40.0)	530 (40.0)	81 (33.5)	405 (33.5)
70-79	52 (19.6)	260 (19.6)	38 (15.7)	190 (15.7)
Calendar year of first visit				
2001	73 (27.5)	365 (27.5)	67 (27.7)	335 (27.7)
2002	83 (31.3)	415 (31.3)	69 (28.5)	345 (28.5)
2003-2004	109 (41.1)	545 (41.1)	106 (43.8)	530 (43.8)
Season of first visit to the hospital				
Spring	66 (24.9)	332 (25.1)	67 (27.7)	310 (25.6)
Summer	92 (34.7)	415 (31.3)	62 (25.6)	348 (28.8)
Autumn	51 (19.2)	341 (25.7)	62 (25.6)	314 (26.0)
Winter	56 (21.1)	237 (17.9)	51 (21.1)	238 (19.7)
Reason to visit the hospital				
Self recommendation	37 (14.0)	407 (30.7)	32 (13.2)	361 (29.8)
Recommendation by family or friends	49 (18.5)	289 (21.8)	47 (19.4)	245 (20.2)
Referral by physicians	136 (51.3)	366 (27.6)	126 (52.1)	301 (24.9)
Secondary screening	38 (14.3)	243 (18.3)	36 (14.9)	284 (23.5)
Others	5 (1.9)	20 (1.5)	1 (0.4)	19 (1.6)
Family history of colorectal cancer in parents and/or siblings				
Yes	38 (14.3)	100 (7.5)	24 (9.9)	77 (6.4)
No	227 (85.7)	1,225 (92.5)	218 (90.1)	1,133 (93.6)
Body mass index (kg/m^2)				
< 20.0	40 (15.2)	226 (17.3)	38 (15.8)	206 (17.1)
20.0-24.9	166 (62.9)	791 (60.4)	146 (60.8)	748 (62.2)
25.0-29.9	54 (20.5)	276 (21.1)	50 (20.8)	229 (19.0)
≥ 30.0	4 (1.5)	16 (1.2)	6 (2.5)	20 (1.7)
Exercise (hours/day)				
None	75 (29.1)	337 (26.0)	67 (29.1)	330 (27.8)
< 0.50	103 (39.9)	564 (43.5)	93 (40.4)	513 (43.3)
0.50-0.99	49 (19.0)	229 (17.7)	47 (20.4)	184 (15.5)
≥ 1.00	31 (12.0)	167 (12.9)	23 (10.0)	158 (13.3)
Alcohol drinking				
Nondrinkers	130 (49.4)	627 (47.8)	99 (41.8)	508 (42.6)
Ex-drinkers	25 (9.5)	103 (7.9)	16 (6.8)	82 (6.9)
Current drinkers (Japanese drinks/day)				
< 1.0	65 (24.7)	309 (23.6)	60 (25.3)	338 (28.4)
1.0-1.9	22 (8.4)	134 (10.2)	32 (13.5)	130 (10.9)
≥ 2.0	21 (8.0)	139 (10.6)	30 (12.7)	134 (11.2)
Smoking				
Nonsmokers	132 (49.8)	667 (50.4)	104 (43.0)	560 (46.4)
Ex-smokers	78 (29.4)	379 (28.6)	65 (26.9)	342 (28.3)
Current smokers	55 (20.8)	277 (20.9)	73 (30.2)	306 (25.3)
Multivitamin use (at least once per week for one year or longer)				
Yes	24 (9.1)	113 (8.5)	15 (6.2)	99 (8.2)
No	241 (90.9)	1,212 (91.5)	227 (93.8)	1,111 (91.8)
Energy intake (kcal/day, mean ± SD)	1,580 ± 351	1,616 ± 342	1,609 ± 370	1,634 ± 352

Percentages in parentheses

Table 2. Odds ratios (ORs) for colon cancer by quartile (Q1-Q4) of energy-adjusted intake of nutrients or food groups in men and women (265 cases and 2,535 controls).

	OR1 (95% confidence interval)*					OR2 (95% confidence interval)†				
Nutrients/food groups	Q1	Q2	Q3	Q4	Trend p	Q1	Q2	Q3	Q4	Trend p
Protein	1.00	0.82 (0.58 - 1.17)	0.76 (0.53 - 1.08)	0.84 (0.60 - 1.19)	0.28	1.00	0.74 (0.52 -1.07)	0.65 (0.45 - 0.95)	0.74 (0.51 - 1.07)	0.084
Fat	1.00	1.06 (0.76 - 1.49)	0.72 (0.50 - 1.05)	0.89 (0.63 - 1.28)	0.22	1.00	1.00 (0.71 - 1.42)	0.67 (0.45 - 0.98)	0.78 (0.54 - 1.13)	0.064
Carbohydrate	1.00	1.14 (0.79 - 1.66)	1.09 (0.75 - 1.59)	1.33 (0.93 - 1.91)	0.16	1.00	1.15 (0.77 - 1.70)	1.02 (0.67 - 1.53)	1.16 (0.76 - 1.79)	0.65
Calcium	1.00	1.03 (0.73 - 1.46)	0.90 (0.63 - 1.29)	0.78 (0.54 - 1.13)	0.14	1.00	0.90 (0.62 - 1.28)	0.80 (0.55 - 1.17)	0.67 (0.46 - 1.00)	0.040
Carotene	1.00	0.78 (0.54 - 1.13)	1.00 (0.70 - 1.42)	0.96 (0.67 - 1.37)	0.85	1.00	0.75 (0.51 - 1.10)	0.89 (0.61 - 1.29)	0.87 (0.59 - 1.28)	0.69
Retinol	1.00	0.87 (0.60 - 1.26)	0.93 (0.65 - 1.34)	1.12 (0.79 - 1.59)	0.44	1.00	0.86 (0.58 - 1.25)	1.00 (0.69 - 1.46)	1.06 (0.73 - 1.54)	0.57
Vitamin D	1.00	1.03 (0.72 - 1.47)	0.88 (0.61 - 1.28)	1.02 (0.71 - 1.45)	0.88	1.00	1.03 (0.71 - 1.49)	0.85 (0.58 - 1.24)	1.04 (0.72 - 1.51)	0.92
Vitamin E	1.00	0.81 (0.56 - 1.16)	1.03 (0.73 - 1.45)	0.79 (0.55 - 1.14)	0.44	1.00	0.75 (0.52 - 1.09)	0.95 (0.67 - 1.36)	0.73 (0.50 - 1.08)	0.28
Folate	1.00	0.73 (0.51 - 1.05)	0.89 (0.62 - 1.26)	0.88 (0.62 - 1.25)	0.70	1.00	0.65 (0.44 - 0.95)	0.82 (0.57 - 1.19)	0.75 (0.51 - 1.11)	0.32
Vitamin C	1.00	0.78 (0.54 - 1.12)	0.94 (0.66 - 1.33)	0.79 (0.55 - 1.14)	0.38	1.00	0.72 (0.49 - 1.04)	0.84 (0.58 - 1.21)	0.65 (0.44 - 0.96)	0.072
SFA‡	1.00	0.89 (0.62 - 1.28)	0.87 (0.60 - 1.24)	1.01 (0.71 - 1.43)	1.00	1.00	0.77 (0.53 - 1.12)	0.77 (0.53 - 1.12)	0.83 (0.57 - 1.20)	0.35
MUFA§	1.00	1.02 (0.71 - 1.46)	1.09 (0.77 - 1.56)	1.04 (0.72 - 1.51)	0.73	1.00	0.94 (0.65 - 1.36)	1.04 (0.71 - 1.52)	0.92 (0.62 - 1.36)	0.80
PUFA‖	1.00	0.92 (0.64 - 1.32)	1.03 (0.72 - 1.46)	1.01 (0.71 - 1.45)	0.80	1.00	0.79 (0.54 - 1.15)	1.00 (0.69 - 1.45)	0.90 (0.61 - 1.31)	0.88
Cholesterol	1.00	0.86 (0.60 - 1.23)	0.95 (0.67 - 1.36)	0.92 (0.64 - 1.30)	0.76	1.00	0.81 (0.56 - 1.17)	0.88 (0.61 - 1.26)	0.77 (0.52 - 1.13)	0.25
Soluble dietary fiber	1.00	0.90 (0.64 - 1.28)	0.83 (0.58 - 1.18)	0.78 (0.55 - 1.13)	0.16	1.00	0.89 (0.62 - 1.28)	0.77 (0.53 - 1.12)	0.75 (0.52 - 1.10)	0.11
Insoluble dietary fiber	1.00	0.74 (0.52 - 1.05)	0.74 (0.52 - 1.05)	0.72 (0.51 - 1.03)	0.078	1.00	0.69 (0.48 - 1.00)	0.64 (0.44 - 0.93)	0.65 (0.45 - 0.96)	0.027
Total dietary fiber	1.00	0.84 (0.59 - 1.20)	0.79 (0.55 - 1.13)	0.76 (0.53 - 1.09)	0.13	1.00	0.78 (0.54 - 1.12)	0.71 (0.49 - 1.03)	0.72 (0.49 - 1.05)	0.074
n-3 PUFA	1.00	0.91 (0.63 - 1.30)	1.05 (0.74 - 1.49)	0.95 (0.66 - 1.36)	0.98	1.00	0.90 (0.62 - 1.30)	1.02 (0.71 - 1.47)	0.89 (0.61 - 1.30)	0.72
n-6 PUFA	1.00	0.88 (0.61 - 1.26)	1.10 (0.77 - 1.56)	1.02 (0.71 - 1.45)	0.65	1.00	0.75 (0.51 - 1.09)	1.01 (0.70 - 1.46)	0.84 (0.57 - 1.24)	0.77
n-6 PUFA/n-3 PUFA	1.00	0.93 (0.65 - 1.34)	1.22 (0.87 - 1.72)	0.90 (0.62 - 1.30)	0.97	1.00	0.95 (0.65 - 1.38)	1.24 (0.87 - 1.77)	0.84 (0.57 - 1.23)	0.71
Soy foods	1.00	1.37 (0.96 - 1.95)	0.97 (0.66 - 1.42)	1.07 (0.74 - 1.55)	0.76	1.00	1.41 (0.98 - 2.04)	0.99 (0.67 - 1.47)	1.02 (0.69 - 1.50)	0.59
Meat	1.00	1.06 (0.74 - 1.52)	1.17 (0.82 - 1.68)	1.06 (0.74 - 1.54)	0.62	1.00	1.11 (0.76 - 1.61)	1.19 (0.82 - 1.73)	0.95 (0.65 - 1.41)	0.93
Fish	1.00	1.20 (0.84 - 1.72)	1.03 (0.71 - 1.50)	1.11 (0.77 - 1.60)	0.78	1.00	1.18 (0.81 - 1.70)	1.00 (0.68 - 1.47)	1.10 (0.75 - 1.62)	0.83
Green-yellow vegetables	1.00	0.89 (0.63 - 1.27)	0.88 (0.62 - 1.25)	0.79 (0.55 - 1.14)	0.23	1.00	0.86 (0.59 - 1.23)	0.80 (0.55 - 1.16)	0.75 (0.51 - 1.10)	0.13
Other vegetables	1.00	1.17 (0.83 - 1.67)	0.83 (0.57 - 1.21)	1.09 (0.76 - 1.56)	0.90	1.00	1.11 (0.77 - 1.59)	0.78 (0.52 - 1.15)	0.96 (0.66 - 1.40)	0.45
Fruit	1.00	0.80 (0.56 - 1.15)	0.74 (0.51 - 1.06)	0.90 (0.64 - 1.28)	0.50	1.00	0.73 (0.50 - 1.06)	0.71 (0.48 - 1.04)	0.73 (0.50 - 1.06)	0.12

* : adjusted for sex, age, and year of first visit.

† : further adjusted for season of first visit to the hospital, reason for the visit, family history of colorectal cancer, body mass index, exercise, alcohol drinking, smoking, multivitamin use, and energy intake.

‡ : saturated fatty acids

§ : monounsaturated fatty acids

‖ : polyunsaturated fatty acids

Table 3. Odds ratios (ORs) for rectal cancer by quartile (Q1-Q4) of energy-adjusted intake of nutrients or food groups in men and women (242 cases and 2,535 controls).

Nutrients/food groups	OR1 (95% confidence interval)*					OR2 (95% confidence interval)†				
	Q1	Q2	Q3	Q4	Trend p	Q1	Q2	Q3	Q4	Trend p
Protein	1.00	0.81 (0.57 - 1.17)	0.92 (0.64 - 1.31)	0.70 (0.48 - 1.03)	0.13	1.00	0.83 (0.57 - 1.22)	0.91 (0.62 - 1.32)	0.71 (0.47 - 1.06)	0.16
Fat	1.00	0.86 (0.60 - 1.24)	0.85 (0.59 - 1.23)	0.73 (0.50 - 1.07)	0.12	1.00	0.86 (0.59 - 1.25)	0.90 (0.61 - 1.31)	0.73 (0.49 - 1.09)	0.17
Carbohydrate	1.00	1.03 (0.70 - 1.53)	1.27 (0.87 - 1.86)	1.37 (0.94 - 2.00)	0.060	1.00	1.14 (0.75 - 1.74)	1.42 (0.93 - 2.19)	1.54 (0.96 - 2.47)	0.048
Calcium	1.00	1.34 (0.92 - 1.94)	1.30 (0.89 - 1.89)	0.93 (0.62 - 1.40)	0.76	1.00	1.24 (0.85 - 1.82)	1.33 (0.89 - 1.97)	0.97 (0.63 - 1.50)	0.99
Carotene	1.00	1.07 (0.76 - 1.52)	0.75 (0.52 - 1.10)	0.74 (0.50 - 1.09)	0.044	1.00	1.10 (0.77 - 1.59)	0.71 (0.47 - 1.06)	0.70 (0.46 - 1.08)	0.028
Retinol	1.00	1.07 (0.74 - 1.55)	1.03 (0.71 - 1.50)	0.93 (0.63 - 1.37)	0.69	1.00	1.09 (0.74 - 1.60)	1.10 (0.75 - 1.62)	0.92 (0.61 - 1.39)	0.75
Vitamin D	1.00	0.81 (0.56 - 1.18)	0.88 (0.61 - 1.27)	0.95 (0.66 - 1.38)	0.88	1.00	0.77 (0.53 - 1.13)	0.81 (0.55 - 1.20)	0.97 (0.66 - 1.44)	0.91
Vitamin E	1.00	0.68 (0.47 - 0.99)	0.80 (0.56 - 1.13)	0.65 (0.45 - 0.94)	0.047	1.00	0.65 (0.44 - 0.95)	0.78 (0.54 - 1.13)	0.65 (0.43 - 0.97)	0.072
Folate	1.00	1.00 (0.70 - 1.42)	0.78 (0.53 - 1.14)	0.83 (0.57 - 1.21)	0.19	1.00	1.00 (0.69 - 1.45)	0.80 (0.53 - 1.19)	0.81 (0.53 - 1.23)	0.20
Vitamin C	1.00	0.91 (0.64 - 1.31)	0.78 (0.54 - 1.13)	0.84 (0.57 - 1.22)	0.24	1.00	0.94 (0.65 - 1.36)	0.82 (0.56 - 1.22)	0.84 (0.55 - 1.26)	0.31
SFA‡	1.00	1.25 (0.86 - 1.81)	1.21 (0.83 - 1.76)	0.89 (0.60 - 1.33)	0.58	1.00	1.19 (0.81 - 1.75)	1.25 (0.84 - 1.85)	0.86 (0.56 - 1.33)	0.57
MUFA§	1.00	0.76 (0.52 - 1.09)	0.66 (0.45 - 0.96)	0.82 (0.57 - 1.18)	0.22	1.00	0.73 (0.50 - 1.08)	0.64 (0.43 - 0.96)	0.76 (0.51 - 1.14)	0.15
PUFA‖	1.00	0.66 (0.45 - 0.96)	0.89 (0.62 - 1.27)	0.80 (0.56 - 1.16)	0.49	1.00	0.59 (0.40 - 0.88)	0.90 (0.62 - 1.30)	0.76 (0.51 - 1.12)	0.47
Cholesterol	1.00	1.04 (0.72 - 1.49)	0.79 (0.54 - 1.17)	0.97 (0.67 - 1.41)	0.57	1.00	1.06 (0.72 - 1.54)	0.79 (0.53 - 1.19)	0.89 (0.59 - 1.33)	0.33
Soluble dietary fiber	1.00	0.97 (0.68 - 1.39)	1.02 (0.71 - 1.46)	0.71 (0.48 - 1.06)	0.16	1.00	0.99 (0.68 - 1.43)	1.06 (0.73 - 1.54)	0.74 (0.49 - 1.12)	0.25
Insoluble dietary fiber	1.00	1.04 (0.73 - 1.49)	1.08 (0.75 - 1.55)	0.75 (0.50 - 1.12)	0.24	1.00	1.03 (0.70 - 1.49)	1.07 (0.73 - 1.56)	0.78 (0.51 - 1.20)	0.35
Total dietary fiber	1.00	0.91 (0.63 - 1.31)	1.01 (0.71 - 1.45)	0.72 (0.49 - 1.08)	0.21	1.00	0.88 (0.60 - 1.28)	1.01 (0.70 - 1.47)	0.76 (0.50 - 1.15)	0.35
n-3 PUFA	1.00	0.93 (0.65 - 1.34)	0.83 (0.57 - 1.20)	0.86 (0.59 - 1.24)	0.33	1.00	0.92 (0.63 - 1.34)	0.83 (0.56 - 1.23)	0.85 (0.57 - 1.27)	0.37
n-6 PUFA	1.00	0.99 (0.68 - 1.44)	0.87 (0.59 - 1.27)	1.01 (0.70 - 1.47)	0.90	1.00	0.93 (0.63 - 1.38)	0.85 (0.57 - 1.27)	0.97 (0.65 - 1.45)	0.78
n-6 PUFA/n-3 PUFA	1.00	0.87 (0.59 - 1.29)	1.03 (0.71 - 1.51)	1.23 (0.85 - 1.77)	0.18	1.00	0.88 (0.59 - 1.32)	1.03 (0.70 - 1.53)	1.23 (0.84 - 1.80)	0.21
Soy foods	1.00	1.11 (0.78 - 1.59)	0.81 (0.55 - 1.20)	1.03 (0.71 - 1.50)	0.73	1.00	1.19 (0.82 - 1.73)	0.85 (0.56 - 1.27)	1.03 (0.69 - 1.53)	0.70
Meat	1.00	0.93 (0.66 - 1.33)	0.65 (0.44 - 0.95)	0.76 (0.52 - 1.10)	0.050	1.00	0.99 (0.68 - 1.42)	0.68 (0.46 - 1.02)	0.72 (0.48 - 1.07)	0.036
Fish	1.00	0.77 (0.53 - 1.12)	0.81 (0.56 - 1.18)	1.00 (0.69 - 1.43)	0.99	1.00	0.75 (0.51 - 1.10)	0.75 (0.51 - 1.11)	1.03 (0.70 - 1.51)	0.98
Green-yellow vegetables	1.00	0.91 (0.64 - 1.30)	0.78 (0.54 - 1.14)	0.78 (0.54 - 1.14)	0.14	1.00	0.94 (0.65 - 1.35)	0.76 (0.52 - 1.13)	0.83 (0.55 - 1.24)	0.22
Other vegetables	1.00	1.19 (0.83 - 1.70)	0.90 (0.61 - 1.32)	0.84 (0.57 - 1.25)	0.21	1.00	1.13 (0.78 - 1.63)	0.92 (0.62 - 1.37)	0.78 (0.52 - 1.18)	0.16
Fruit	1.00	1.27 (0.88 - 1.84)	1.03 (0.69 - 1.52)	1.21 (0.82 - 1.78)	0.58	1.00	1.35 (0.92 - 1.97)	1.16 (0.77 - 1.76)	1.23 (0.81 - 1.87)	0.51

* : adjusted for sex, age, and year of first visit.

† : further adjusted for season of first visit to the hospital, reason for the visit, family history of colorectal cancer, body mass index, exercise, alcohol drinking, smoking, multivitamin use, and energy intake.

‡ : saturated fatty acids

§ : monounsaturated fatty acids

‖ : polyunsaturated fatty acids

Table 4. Odds ratios* (ORs) for colon cancer according to quartiles (Q1-Q4) of energy-adjusted intake of nutrients or food groups by sex.

	Men (149 cases and 1,475 controls)					Women (116 cases and 1,060 controls)				
Nutrients/food groups	Q1	Q2	Q3	Q4	Trend p	Q1	Q2	Q3	Q4	Trend p
Protein	1.00	0.79 (0.48 - 1.31)	0.79 (0.48 - 1.30)	0.78 (0.47 - 1.31)	0.38	1.00	0.71 (0.41 - 1.24)	0.48 (0.26 - 0.87)	0.67 (0.38 - 1.18)	0.077
Fat	1.00	1.05 (0.65 - 1.69)	0.70 (0.41 - 1.19)	0.94 (0.57 - 1.55)	0.49	1.00	0.96 (0.56 - 1.64)	0.60 (0.33 - 1.09)	0.59 (0.32 - 1.07)	0.035
Carbohydrate	1.00	1.21 (0.71 - 2.05)	0.89 (0.51 - 1.57)	0.81 (0.43 - 1.53)	0.33	1.00	0.93 (0.50 - 1.74)	1.04 (0.55 - 1.95)	1.51 (0.82 - 2.78)	0.15
Calcium	1.00	0.89 (0.54 - 1.47)	0.85 (0.51 - 1.41)	0.77 (0.46 - 1.30)	0.33	1.00	0.87 (0.51 - 1.51)	0.75 (0.42 - 1.33)	0.52 (0.28 - 0.97)	0.035
Carotene	1.00	0.71 (0.42 - 1.21)	0.95 (0.57 - 1.57)	0.86 (0.50 - 1.49)	0.88	1.00	0.81 (0.45 - 1.46)	0.81 (0.46 - 1.44)	0.92 (0.51 - 1.65)	0.78
Retinol	1.00	0.74 (0.44 - 1.24)	0.80 (0.48 - 1.33)	0.99 (0.60 - 1.63)	0.94	1.00	1.04 (0.57 - 1.88)	1.34 (0.74 - 2.40)	1.20 (0.67 - 2.17)	0.40
Vitamin D	1.00	0.98 (0.59 - 1.61)	1.02 (0.63 - 1.67)	0.97 (0.59 - 1.61)	0.96	1.00	1.09 (0.62 - 1.91)	0.63 (0.34 - 1.18)	1.19 (0.67 - 2.11)	0.96
Vitamin E	1.00	0.82 (0.49 - 1.37)	1.03 (0.63 - 1.68)	1.02 (0.61 - 1.71)	0.71	1.00	0.72 (0.41 - 1.24)	0.93 (0.55 - 1.59)	0.48 (0.25 - 0.90)	0.069
Folate	1.00	0.88 (0.53 - 1.45)	0.75 (0.45 - 1.27)	0.87 (0.51 - 1.48)	0.52	1.00	0.48 (0.26 - 0.89)	0.95 (0.55 - 1.63)	0.68 (0.38 - 1.23)	0.56
Vitamin C	1.00	0.74 (0.45 - 1.23)	0.74 (0.45 - 1.24)	0.72 (0.42 - 1.22)	0.26	1.00	0.74 (0.41 - 1.32)	1.03 (0.59 - 1.78)	0.61 (0.33 - 1.12)	0.25
SFA†	1.00	0.88 (0.53 - 1.46)	0.87 (0.52 - 1.46)	0.95 (0.57 - 1.60)	0.89	1.00	0.64 (0.36 - 1.14)	0.62 (0.35 - 1.10)	0.66 (0.38 - 1.17)	0.16
MUFA‡	1.00	0.87 (0.51 - 1.47)	1.27 (0.76 - 2.11)	1.21 (0.70 - 2.09)	0.27	1.00	1.07 (0.62 - 1.83)	0.87 (0.48 - 1.56)	0.67 (0.36 - 1.24)	0.16
PUFA§	1.00	1.14 (0.68 - 1.92)	1.22 (0.72 - 2.06)	1.32 (0.78 - 2.26)	0.29	1.00	0.55 (0.31 - 0.99)	0.88 (0.51 - 1.52)	0.58 (0.32 - 1.03)	0.18
Cholesterol	1.00	1.19 (0.71 - 2.01)	1.24 (0.74 - 2.09)	1.02 (0.58 - 1.80)	0.93	1.00	0.49 (0.28 - 0.87)	0.55 (0.31 - 0.95)	0.54 (0.31 - 0.95)	0.037
Soluble dietary fiber	1.00	0.95 (0.58 - 1.57)	0.91 (0.55 - 1.49)	0.77 (0.46 - 1.30)	0.32	1.00	0.85 (0.49 - 1.46)	0.61 (0.34 - 1.10)	0.77 (0.43 - 1.37)	0.22
Insoluble dietary fiber	1.00	0.62 (0.37 - 1.04)	0.72 (0.44 - 1.18)	0.67 (0.40 - 1.12)	0.20	1.00	0.84 (0.48 - 1.44)	0.58 (0.33 - 1.04)	0.69 (0.39 - 1.24)	0.11
Total dietary fiber	1.00	0.94 (0.57 - 1.56)	0.89 (0.53 - 1.47)	0.84 (0.50 - 1.43)	0.50	1.00	0.67 (0.38 - 1.17)	0.55 (0.31 - 0.97)	0.63 (0.35 - 1.13)	0.073
n-3 PUFA	1.00	1.03 (0.62 - 1.71)	1.14 (0.69 - 1.89)	0.97 (0.57 - 1.66)	0.98	1.00	0.72 (0.40 - 1.28)	0.88 (0.50 - 1.54)	0.81 (0.45 - 1.44)	0.60
n-6 PUFA	1.00	0.83 (0.48 - 1.43)	1.29 (0.78 - 2.13)	1.09 (0.63 - 1.87)	0.40	1.00	0.71 (0.41 - 1.24)	0.82 (0.46 - 1.46)	0.63 (0.35 - 1.12)	0.17
n-6 PUFA/n-3 PUFA	1.00	0.96 (0.58 - 1.59)	1.29 (0.80 - 2.07)	0.79 (0.48 - 1.31)	0.63	1.00	0.91 (0.51 - 1.64)	1.19 (0.68 - 2.07)	0.86 (0.47 - 1.57)	0.89
Soy foods	1.00	1.37 (0.83 - 2.26)	1.11 (0.66 - 1.88)	1.17 (0.69 - 1.96)	0.79	1.00	1.54 (0.88 - 2.69)	0.77 (0.42 - 1.43)	0.83 (0.44 - 1.54)	0.18
Meat	1.00	1.25 (0.75 - 2.09)	1.32 (0.79 - 2.20)	1.15 (0.68 - 1.95)	0.59	1.00	0.96 (0.54 - 1.69)	1.03 (0.58 - 1.83)	0.73 (0.40 - 1.34)	0.39
Fish	1.00	1.36 (0.82 - 2.26)	1.33 (0.79 - 2.21)	1.13 (0.66 - 1.92)	0.72	1.00	0.97 (0.55 - 1.70)	0.70 (0.38 - 1.29)	1.11 (0.63 - 1.95)	0.98
Green-yellow vegetables	1.00	0.97 (0.59 - 1.60)	0.96 (0.58 - 1.58)	0.88 (0.52 - 1.48)	0.62	1.00	0.90 (0.51 - 1.58)	0.71 (0.40 - 1.26)	0.69 (0.38 - 1.23)	0.15
Other vegetables	1.00	1.10 (0.68 - 1.80)	0.75 (0.44 - 1.28)	0.95 (0.58 - 1.58)	0.54	1.00	1.29 (0.74 - 2.27)	0.89 (0.48 - 1.62)	1.08 (0.60 - 1.94)	0.89
Fruit	1.00	0.57 (0.34 - 0.95)	0.67 (0.41 - 1.10)	0.67 (0.41 - 1.11)	0.19	1.00	1.00 (0.57 - 1.77)	0.75 (0.41 - 1.38)	0.90 (0.50 - 1.62)	0.54

* : adjusted for age, year of first visit to the hospital, season of first visit, reason for the visit, family history of colorectal cancer, body mass index, exercise, alcohol drinking, smoking, multivitamin use, and energy intake.

† : saturated fatty acids

‡ : monounsaturated fatty acids

§ : polyunsaturated fatty acids

95% confidence intervals in parentheses

Table 5. Odds ratios* (ORs) for rectal cancer according to quartiles (Q1-Q4) of energy-adjusted intake of nutrients or food groups by sex.

	Men (146 cases and 1,475 controls)					Women (96 cases and 1,060 controls)				
Nutrients/food groups	Q1	Q2	Q3	Q4	Trend p	Q1	Q2	Q3	Q4	Trend p
Protein	1.00	1.02 (0.61 - 1.69)	1.23 (0.75 - 2.01)	0.77 (0.43 - 1.37)	0.62	1.00	0.65 (0.35 - 1.21)	0.64 (0.35 - 1.20)	0.66 (0.36 - 1.24)	0.19
Fat	1.00	1.12 (0.67 - 1.88)	1.24 (0.74 - 2.09)	1.15 (0.67 - 1.96)	0.56	1.00	0.57 (0.31 - 1.02)	0.61 (0.33 - 1.12)	0.38 (0.19 - 0.75)	0.008
Carbohydrate	1.00	1.13 (0.67 - 1.92)	1.12 (0.63 - 2.00)	1.07 (0.54 - 2.10)	0.86	1.00	1.17 (0.55 - 2.52)	2.14 (1.05 - 4.36)	2.53 (1.22 - 5.24)	0.003
Calcium	1.00	1.44 (0.87 - 2.41)	1.40 (0.82 - 2.41)	1.26 (0.71 - 2.25)	0.51	1.00	1.11 (0.60 - 2.05)	1.27 (0.68 - 2.36)	0.73 (0.36 - 1.47)	0.53
Carotene	1.00	1.44 (0.87 - 2.36)	0.83 (0.47 - 1.45)	1.05 (0.58 - 1.91)	0.58	1.00	0.83 (0.46 - 1.48)	0.66 (0.36 - 1.23)	0.48 (0.24 - 0.95)	0.028
Retinol	1.00	1.12 (0.66 - 1.89)	1.39 (0.83 - 2.33)	1.18 (0.67 - 2.08)	0.40	1.00	1.09 (0.61 - 1.95)	0.82 (0.44 - 1.53)	0.76 (0.40 - 1.48)	0.31
Vitamin D	1.00	0.92 (0.56 - 1.51)	0.93 (0.56 - 1.53)	0.91 (0.54 - 1.54)	0.74	1.00	0.61 (0.32 - 1.16)	0.72 (0.38 - 1.37)	1.11 (0.60 - 2.03)	0.71
Vitamin E	1.00	0.87 (0.51 - 1.47)	1.18 (0.72 - 1.94)	1.00 (0.58 - 1.73)	0.69	1.00	0.48 (0.26 - 0.85)	0.47 (0.25 - 0.87)	0.42 (0.22 - 0.80)	0.006
Folate	1.00	1.17 (0.71 - 1.95)	1.06 (0.62 - 1.81)	1.14 (0.64 - 2.02)	0.77	1.00	0.87 (0.49 - 1.53)	0.60 (0.31 - 1.14)	0.59 (0.31 - 1.14)	0.063
Vitamin C	1.00	0.87 (0.53 - 1.41)	0.91 (0.55 - 1.52)	0.73 (0.42 - 1.27)	0.33	1.00	1.06 (0.58 - 1.94)	0.72 (0.37 - 1.41)	1.04 (0.55 - 1.97)	0.83
SFA†	1.00	1.14 (0.68 - 1.91)	1.32 (0.78 - 2.22)	1.02 (0.58 - 1.80)	0.83	1.00	1.39 (0.76 - 2.57)	1.21 (0.64 - 2.30)	0.72 (0.36 - 1.45)	0.32
MUFA‡	1.00	0.93 (0.55 - 1.57)	0.86 (0.50 - 1.48)	1.23 (0.71 - 2.14)	0.51	1.00	0.57 (0.31 - 1.04)	0.46 (0.24 - 0.88)	0.47 (0.24 - 0.89)	0.014
PUFA§	1.00	0.69 (0.40 - 1.19)	1.08 (0.65 - 1.79)	1.06 (0.63 - 1.78)	0.46	1.00	0.54 (0.29 - 1.01)	0.76 (0.43 - 1.36)	0.53 (0.27 - 1.01)	0.11
Cholesterol	1.00	1.15 (0.69 - 1.92)	1.05 (0.62 - 1.78)	1.11 (0.63 - 1.96)	0.82	1.00	0.98 (0.55 - 1.76)	0.54 (0.27 - 1.06)	0.73 (0.39 - 1.37)	0.15
Soluble dietary fiber	1.00	1.45 (0.88 - 2.38)	1.33 (0.80 - 2.23)	0.93 (0.53 - 1.65)	0.77	1.00	0.59 (0.32 - 1.09)	0.91 (0.51 - 1.63)	0.66 (0.34 - 1.26)	0.37
Insoluble dietary fiber	1.00	1.19 (0.72 - 1.98)	1.40 (0.85 - 2.33)	0.83 (0.46 - 1.50)	0.78	1.00	0.88 (0.49 - 1.58)	0.77 (0.41 - 1.42)	0.84 (0.44 - 1.60)	0.49
Total dietary fiber	1.00	1.04 (0.63 - 1.70)	1.17 (0.71 - 1.94)	0.83 (0.47 - 1.45)	0.68	1.00	0.69 (0.37 - 1.29)	0.92 (0.51 - 1.67)	0.78 (0.40 - 1.51)	0.64
n-3 PUFA	1.00	0.94 (0.56 - 1.57)	1.02 (0.61 - 1.69)	0.96 (0.56 - 1.65)	0.97	1.00	1.02 (0.57 - 1.82)	0.65 (0.34 - 1.25)	0.80 (0.42 - 1.53)	0.29
n-6 PUFA	1.00	1.07 (0.63 - 1.85)	1.10 (0.64 - 1.90)	1.57 (0.91 - 2.74)	0.11	1.00	0.86 (0.47 - 1.55)	0.73 (0.39 - 1.38)	0.58 (0.30 - 1.14)	0.098
n-6 PUFA/n-3 PUFA	1.00	0.73 (0.42 - 1.30)	1.28 (0.78 - 2.10)	1.45 (0.88 - 2.38)	0.042	1.00	1.16 (0.63 - 2.14)	0.70 (0.36 - 1.37)	1.03 (0.55 - 1.93)	0.71
Soy foods	1.00	1.32 (0.81 - 2.16)	0.88 (0.51 - 1.50)	1.12 (0.66 - 1.90)	0.93	1.00	1.00 (0.55 - 1.84)	0.77 (0.40 - 1.48)	0.96 (0.51 - 1.81)	0.71
Meat	1.00	0.97 (0.60 - 1.57)	0.56 (0.33 - 0.97)	0.85 (0.51 - 1.40)	0.24	1.00	1.05 (0.58 - 1.89)	1.01 (0.54 - 1.88)	0.52 (0.26 - 1.05)	0.093
Fish	1.00	0.92 (0.56 - 1.49)	0.79 (0.48 - 1.30)	0.89 (0.53 - 1.51)	0.53	1.00	0.55 (0.28 - 1.07)	0.77 (0.41 - 1.45)	1.29 (0.71 - 2.36)	0.33
Green-yellow vegetables	1.00	1.14 (0.70 - 1.86)	0.88 (0.52 - 1.49)	1.11 (0.65 - 1.90)	0.95	1.00	0.76 (0.42 - 1.38)	0.70 (0.38 - 1.28)	0.58 (0.30 - 1.12)	0.095
Other vegetables	1.00	1.47 (0.91 - 2.40)	0.96 (0.56 - 1.65)	0.92 (0.54 - 1.59)	0.41	1.00	0.81 (0.45 - 1.48)	0.92 (0.50 - 1.68)	0.72 (0.37 - 1.37)	0.40
Fruit	1.00	1.66 (1.01 - 2.72)	1.46 (0.86 - 2.49)	1.04 (0.58 - 1.86)	0.99	1.00	1.00 (0.53 - 1.88)	0.74 (0.37 - 1.49)	1.47 (0.79 - 2.73)	0.33

* : adjusted for age, year of first visit to the hospital, season of first visit, reason for the visit, family history of colorectal cancer, body mass index, exercise, alcohol drinking, smoking, multivitamin use, and energy intake.

† : saturated fatty acids

‡ : monounsaturated fatty acids

§ : polyunsaturated fatty acids

95% confidence intervals in parentheses

consistent with the finding of the European study mentioned above[23] and might be expected because the rectum is empty most of the time, reducing the putative protective effects of dietary fiber.[23]

The intake of carotene was negatively associated with the risk of rectal cancer, particularly in female subjects. Women who consumed much green-yellow vegetables tended to show a lower risk of rectal cancer. A risk-reducing effect of dietary carotene was suggested for rectal cancer in some earlier case-control studies.[4,26,27] The association, however, should be further examined in cohort studies because several large prospective studies have recently pointed to no preventive effects of fruit and vegetables, which are rich in carotene.[28-30]

Although red meat consumption has been linked to the risk of colorectal cancer,[31-33] we have failed to find any positive association of meat and in fact observed a relation to a somewhat decreased risk for rectal cancer. In Japan, red meat accounts for a smaller proportion of all meat consumption than in Western countries (http://faostat.fao.org/faostat/) and colorectal cancer risk may be reduced or unaltered by non-red meat,[32,34] so this might explain the lack of any deleterious effect of meat in our study. Our finding is consistent with the results of a case-control study in China, which reported an increased risk of rectal cancer associated with reduced consumption of meat.[5] Another case-control study conducted in Japan also reported that meat consumption was inversely correlated with the risk of rectal cancer.[6]

A high correlation between national per capita intake of fat and national rates of colon cancer has led to the hypothesis that consumption of fat increases risk of colon cancer. In general, however, neither case-control nor cohort studies have provided unequivocal support for this hypothesis.[35] In our study, intakes of fat, cholesterol, and monounsaturated fatty acids were inversely correlated with the risk of female colon and/or rectal cancer whereas a higher intake of carbohydrate was associated with rectal cancer risk, especially in women.

Some[36,37] but not all[38,39] case-control and cohort studies have suggested that higher intake of carbohydrate may increase colorectal cancer risk and this has been discussed in relation to insulin resistance. If this is the case, higher intake of fat and protein relative to carbohydrate may seemingly be linked to a decreased risk. As we suggested for colon cancer, Franceschi et al[40] found a decreased risk associated with a higher intake of protein.

Several significant associations between dietary variables and colon or rectal cancer risk appeared in women but not in men. This may partly be attributable to the difference in intake levels of nutrients or food groups between the sexes. For example, men took more carbohydrate (median of the estimated intake in controls: 242.6 g/day in men versus 207.2 g/day in women) but less green-yellow vegetables (median in controls: 49.5 g/day versus 69.2 g/day) from our present data (values are adjusted to the mean energy intake of 1,710 and 1,493 kcal/day for men and women, respectively). On the other hand, variation by sex may be due to random fluctuation because the numbers of cases by site of cancer and sex were relatively small.

Dietary risk factors could be directly compared between colon and rectal cancers in the present study because the procedures for identification of cases and data collection were exactly the same and the control group was common for the two sites of cancer.

Some methodological limitations, however, need consideration. First, because this was a hospital-based case-control study, the source population from which cases arise may differ from that for controls. To take this into consideration, we adjusted for the reason for the first visit to ACCH and the season. Second, as with other case-control studies, this study may suffer from recall bias. Although the questionnaires were completed before the diagnosis in ACCH, some case patients referred to the hospital might have known the diagnosis. It is unlikely, however, that the recall bias affected the findings differentially between colon and rectal cancers. Third, because we examined many nutrients and food groups in relation to the risk of colon and rectal cancers, multiple comparisons may be another issue. Some findings might have appeared by chance. The difference in dietary risk factors between colon and rectal cancers found in the present study, therefore, warrant confirmation in further investigations. The increase in incidence of colorectal cancer over time[1] may mean that most Japanese have changed their lifestyles, including their dietary consumption, so that detection of dietary risk or protective factors in case-control or cohort studies within the Japanese population faces particular problems. Finally, the limitations of the questionnaire may have prevented us from considering some potential confounding factors. For example, no information was available on non-steroidal anti-inflammatory drugs (NSAIDs), which may exert protective effects against colorectal cancer[41] and may confound associations between diet and the risk of cancer.

In conclusion, dietary preventive factors appear to considerably differ between colon and rectal cancers: calcium and insoluble dietary fiber may protect against colon cancer while carotene and meat may be more effective for rectal cancer. Carbohydrate intake was positively correlated with the risk of rectal cancer, especially in women.

ACKNOWLEDGMENTS

We are grateful to Hiroko Fujikura, Yukiko Yamauchi, Kazumi Hasegawa, Misato Sato, Kayoko Fukaya, Keiko Asai, Yoko Kamori, Masami Hattori, Kayoko Tomita, and Miwako Shimada for their data collection and preparation.

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Original article

Survival benefit of high ligation of the inferior mesenteric artery in sigmoid colon or rectal cancer surgery

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Background: The aim of this study was to assess the impact of inferior mesenteric artery (IMA) root nodal dissection before high ligation of the artery on survival in patients with sigmoid colon or rectal cancer.

Methods: Data on 1188 consecutive patients who underwent resection for sigmoid colon or rectal cancer, with high ligation of the IMA, were identified from a prospective database (April 1965 to December 1999). Survival of patients with involvement of nodes along the IMA proximal to the origin of the left colic artery (root nodes, station 253) through the bifurcation of the superior rectal artery (trunk nodes, station 252) was determined.

Results: Twenty patients (1·7 per cent) had metastatic involvement of station 253 lymph nodes and 99 (8·3 per cent) had metastases to station 252. The 5- and 10-year survival rates of patients with metastases to station 253 were 40 and 21 per cent, and those for patients with metastases to station 252 were 50 and 35 per cent, respectively.

Conclusion: High ligation of the IMA allows curative resection and long-term survival in patients with cancer of the sigmoid colon or rectum and nodal metastases at the origin of the IMA.

Presented to a meeting of the Japanese Society of Gastroenterological Surgery, Tokyo, Japan, July 2005

Paper accepted 21 March 2006

Published online in Wiley InterScience (www.bjs.co.uk). **DOI:** 10.1002/bjs.5327

Introduction

During surgery for sigmoid colon or rectal cancer, the inferior mesenteric artery (IMA) may be ligated at a point just below the origin of the left colic artery (low ligation) or at the origin of the IMA directly from the aorta (high ligation). The high-ligation technique enables *en bloc* removal of additional lymphatic drainage from cancers at and around the origin of the IMA, but it is unclear whether this confers a survival advantage.

There have been no prospective controlled or randomized studies of high *versus* low ligation. Guidelines published by Nelson *et al.*[1] recommend low ligation for rectal cancer surgery, except when metastases to lymph nodes beyond the origin of the left colic artery are suspected. However, this recommendation is based on the data from one French randomized trial in patients with left colonic cancer[2].

No study has investigated the detailed anatomical distribution of lymph node metastases along the IMA in a large series in which high ligation was performed routinely. The few studies on this issue included limited numbers of patients with colorectal cancer, ranging from 129 to 198[3–5]. Other studies have reported details of such lymph node distributions, but only in patients who underwent colorectal cancer resection and whose operative findings indicated the need for high ligation of the IMA[4,6,7]. This type of intraoperative determination is known to be unreliable[8]. At present, the true distribution of lymph node metastasis along the IMA in patients with sigmoid colon or rectal cancer who undergo potentially curative resection is unknown.

Some favourable outcomes after high ligation may be attributable to the stage migration phenomenon, which may arise as a result of more accurate staging owing to more extensive lymphadenectomy[6,9,10]. A proportion of patients will therefore be assigned to a more advanced stage than would otherwise be the case, although their prognosis is the same. If this occurs, the overall results in

each stage improve and the proportion of patients in more advanced stages increases[11].

The present study was a prospective analysis of the largest known series of curative resections for sigmoid colon or rectal cancer in which high ligation was performed routinely. The study was designed to circumvent the stage migration effect in order to provide direct information on the significance of lymph node metastases along the IMA. The aim was to evaluate whether patients with sigmoid colon or rectal cancer and metastasis in certain nodes that are left behind after low ligation would benefit from high ligation in terms of curability of resection and survival.

Patients and methods

Since the foundation of the Aichi Cancer Centre Hospital, high ligation of the IMA for proximally extended lymph node dissection in patients with sigmoid colon or rectal cancer has been adopted as a standard procedure, except when adequate exposure to allow ligation of the IMA on the aorta is considered too hazardous. Data on 1361 consecutive patients who had histologically proven adenocarcinoma of the sigmoid colon or rectum and who underwent high ligation of the IMA between April 1965 and December 1999 were documented prospectively. Dissection of all lymph nodes surrounding the root of the IMA was performed before IMA ligation and excision flush with the aorta, irrespective of the operative findings with regard to the presence or absence of lymph node metastasis (*Fig. 1*).

Eighteen patients with cancers confined to the mucosa were excluded. To examine the curative value of apparently complete resection of lymph nodes along the IMA, 155 patients in whom there was clear evidence of surgical incurability were also excluded. These patients had either macroscopic or microscopic residual tumour tissue left at operation, or underwent macroscopically complete resection of hepatic or peritoneal metastases. A total of 1188 patients remained eligible, and these formed the study population.

Rectal tumours were sited as follows: lower rectum (below the peritoneal reflection), upper rectum (above the peritoneal reflection) and rectosigmoid. Lateral pelvic lymphadenectomy was used for lower rectal cancer with T2 or deeper invasion. Twenty-nine of the patients with Dukes' C lower rectal cancer received adjuvant radiotherapy. Adjuvant chemotherapy, mainly using oral 5-fluorouracil prodrugs (uracil and tegafur, UFT), was administered to patients with Dukes' A (15 sigmoid colon, 56 rectal), Dukes' B (57 sigmoid colon, 88 rectal) or Dukes' C (57 sigmoid colon, 179 rectal) tumours deemed to be at high risk for metastasis.

Fig. 1 High ligation of the inferior mesenteric artery at its origin from the aorta. Ao, aorta; D, duodenum, HP, hypogastric plexus; IMA, inferior mesenteric artery; LSN, lumbar splanchnic nerve

Level of ligation of inferior mesenteric artery and pathological examination of lymph nodes

The inferior mesenteric lymph nodes conglomerate around the origin of the IMA, and their location has been defined ambiguously as both the root and the periphery[12]. The Japanese criteria (Japanese Society for Cancer of the Colon and Rectum, JSCCR)[13] define the nodes at the origin of the IMA (station 253) as those nodes that lie along the IMA proximal to the origin of the left colic artery (*Fig. 2*). They define the inferior mesenteric trunk nodes (station 252) as those nodes that lie along the IMA from distal to the origin of the left colic artery to the bifurcation of the superior rectal artery. A high ligation was defined as ligation of the IMA at its root and including dissection of station 253 nodes. A low ligation was defined as ligation of the IMA at or below the level of the origin of the left colic artery and removal of the pericolic and intermediate groups of lymph nodes only, including station 252 nodes, with the primary cancer.

All regional lymph nodes were dissected individually from the adipose connective tissue of the specimen immediately after resection by the surgeons who performed the operation. Node numbers and locations were recorded on

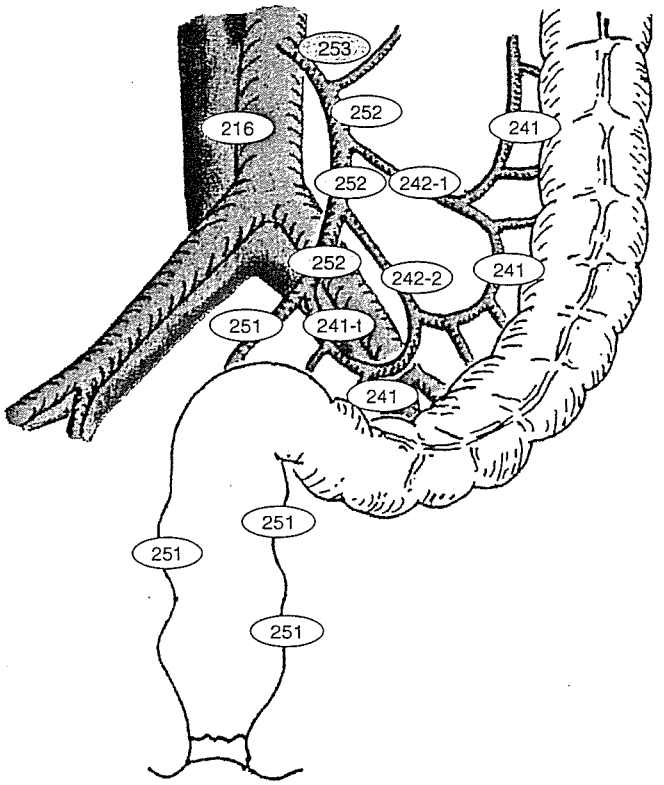


Fig. 2 Japanese Society for Cancer of the Colon and Rectum classification of lymph nodes[13] (shaded ovals denote inferior mesenteric lymph nodes)

a lymph node map (*Fig. 2*). Nodes were assigned to the appropriate station according to the classification of the JSCCR. Nodes found at each station were labelled and sent for pathological assessment. This system, which is standard practice in Japan, yields an exact topographical representation of the nodes combined with their number. Fat clearing methods were not used to collect lymph nodes from the specimen. All specimens were formalin fixed and paraffin embedded. A single section for each lymph node was routinely examined. Sections of 4 μm were cut and stained with haematoxylin and eosin for histological analysis. Special attention was paid to evaluation of the incidence of metastasis to lymph node stations 252 to 253 in relation to the tumour site, depth of invasion and survival data.

Statistical analysis

Overall and cancer-specific survival of patients with lymph node metastases along the IMA was calculated for each nodal station by the Kaplan–Meier method, irrespective of metastasis to other lymph node stations. Operative deaths were not excluded from the survival analysis. Follow-up data were documented prospectively.

Results

The characteristics of the 1188 patients who underwent potentially curative resection with high ligation are shown in *Table 1*. The overall hospital mortality rate was 0·2 per cent (three of 1188). The overall morbidity rate was 31·5 per cent (374 of 1188). Three hundred and forty-seven patients (29·2 per cent) had one or more surgical complications.

The mean number of nodes examined per patient was 28·6. A total of 107 patients had nodal involvement at stations 252 and/or 253. The incidence of metastasis to station 252 nodes was 8·3 per cent (99 of 1188). Station 252 nodal metastases occurred more frequently in patients with pT3 and pT4 lower rectal cancer (*Table 2*). The incidence of metastasis to station 253 nodes was 1·7 per cent (20 of 1188); this represented the frequency of residual metastatic nodes that would normally have been left behind in a low ligation. Of the 20 patients with station 253 nodal metastases, eight did not have cancer deposits in the station 252 nodes studied, that is they demonstrated skip metastases. There was a steady increase in the rate of

Table 1 Characteristic of 1188 patients who underwent a high ligation with curative intent

	No. of patients
Age (years)*	58·6 (59) (23–86)
Sex ratio (F : M)	482 : 706
Site of primary tumour	
Sigmoid colon	421 (35·4)
Rectosigmoid	202 (17·0)
Upper rectum	216 (18·2)
Lower rectum	349 (29·4)
Type of resection	
Sigmoidectomy	393 (33·1)
High anterior resection	141 (11·9)
Low anterior resection	329 (27·7)
Abdominoperineal resection	286 (24·1)
Hartmann's operation	15 (1·3)
Total pelvic exenteration	10 (0·8)
Other	14 (1·2)
Other surgery	
Lateral pelvic node dissection	301 (25·3)
Postoperative death	3 (0·2)
Postoperative morbidity	374 (31·5)
Urinary or sexual dysfunction	103 (8·7)
Ileus	77 (6·5)
Urinary tract infection	47 (3·9)
Wound infection	42 (3·5)
Anastomotic leakage	39 (3·3)
Intraabdominal or pelvic infection	39 (3·3)
Non-surgical (cardiac, respiratory, renal, cerebral)	27 (2·3)
No. of lymph nodes examined per patient*	28·6 (22·6) (7–115)

Values in parentheses are percentages unless otherwise indicated; *values are mean (median) (range).

Table 2 Nodal metastases to station 252

	Incidence of metastasis				
	pT1	pT2	pT3	pT4	Total
Sigmoid colon	2 of 100 (2)	0 of 67 (0)	7 of 169 (4·1)	5 of 85 (6)	14 of 421 (3·3)
Rectosigmoid	0 of 21 (0)	4 of 37 (11)	12 of 110 (10·9)	5 of 34 (15)	21 of 202 (10·4)
Upper rectum	1 of 30 (3)	0 of 51 (0)	13 of 105 (12·4)	3 of 30 (10)	17 of 216 (7·9)
Lower rectum	1 of 42 (2)	6 of 119 (5)	36 of 164 (22·0)	4 of 24 (17)	47 of 349 (13·5)
Total	4 of 193 (2·1)	10 of 274 (3·6)	68 of 548 (12·4)	17 of 173 (9·8)	99 of 1188 (8·3)

Values in parentheses are percentages. pT, pathological tumour stage.

positivity in station 253 nodes with increasing depth of invasion, irrespective of the tumour location; however, no station 253 nodal metastases occurred in patients with pT1 cancer (*Table 3*). Mean positive node yields of 2·0 from station 252 and 1·9 from station 253 were obtained from patients with nodal involvement along the IMA (*Table 4*).

Follow-up continued until January 2005 for all eligible patients. The median follow-up period for survivors was 79·3 months. Follow-up was completed in all patients with nodal metastases along the IMA. Actuarial overall survival rates were 50 (95 per cent confidence interval (c.i.) 41 to 60) per cent at 5 years and 35 (95 per cent c.i. 24 to 46) per cent at 10 years in patients with metastases to station 252, and 40 (95 per cent c.i. 19 to 62) per cent at 5 years and 21 (95 per cent c.i. 2 to 41) per cent at 10 years in patients with metastases to station 253 (*Fig. 3*). The cancer-specific survival rates were 53 (95 per cent c.i. 43 to 64) per cent at 5 years and 41 (95 per cent c.i. 30 to 53) per cent at 10 years in patients with metastases to station 252, and 42 (95 per cent c.i. 20 to 64) per cent at 5 years and 23 (95 per cent c.i. 2 to 43) per cent at 10 years in patients with metastases to station 253 (*Fig. 4*).

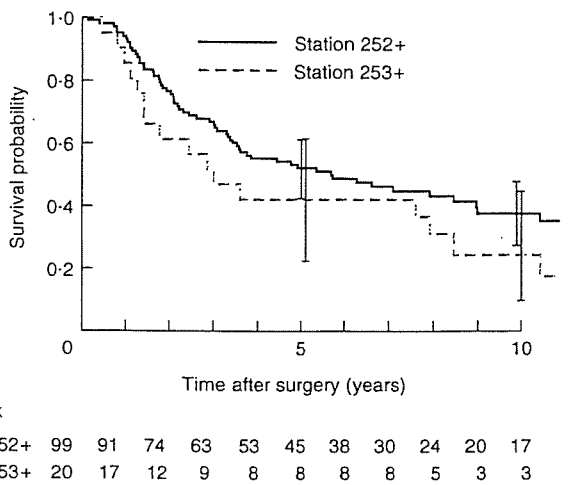


Fig. 3 Overall survival curves for patients with sigmoid colon or rectal cancer who underwent high ligation, according to inferior mesenteric lymph node status. +, Metastatic nodal disease present. Vertical bars represent 95 per cent confidence intervals

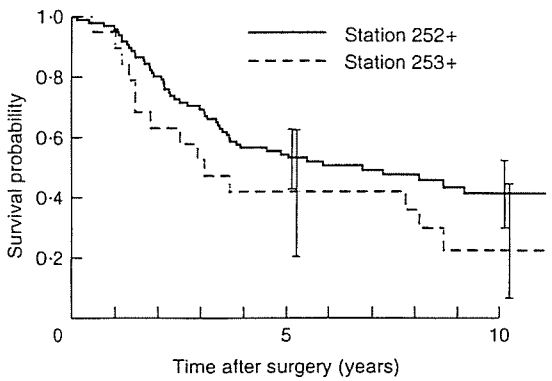
Discussion

In 1908, Moynihan[14] advised high ligation of the IMA in resections for cancer of the sigmoid colon or upper rectum. However, because the oncological effectiveness of high ligation of the IMA is not generally accepted, the level at which the IMA is ligated in operations for sigmoid colon or rectal cancer has varied greatly[3,4,7,15–20], depending largely on the surgeon[6,20]. Recent reports have shown a stage-specific survival benefit of high ligation[6,9,10]. However, these studies did not eliminate the stage migration phenomenon and failed to show a survival

Table 3 Nodal metastases to station 253

	Incidence of metastasis					
	pT1	pT2	pT3	pT4	Total	Skip Metastasis*
Sigmoid colon	0 of 100 (0)	1 of 67 (1)	2 of 169 (1·2)	3 of 85 (4)	6 of 421 (1·4)	4 of 421 (1·0)
Rectosigmoid	0 of 21 (0)	0 of 37 (0)	3 of 110 (2·7)	1 of 34 (3)	4 of 202 (2·0)	2 of 202 (1·0)
Upper rectum	0 of 30 (0)	0 of 51 (0)	2 of 105 (1·9)	0 of 30 (0)	2 of 216 (0·9)	0 of 216 (0)
Lower rectum	0 of 42 (0)	0 of 119 (0)	7 of 164 (4·3)	1 of 24 (4)	8 of 349 (2·3)	2 of 349 (0·6)
Total	0 of 193 (0)	1 of 274 (0·4)	14 of 548 (2·6)	5 of 173 (2·9)	20 of 1188 (1·7)	8 of 1188 (0·7)

Values in parentheses are percentages. *Node positive at station 253 without nodal involvement at station 252. pT, pathological tumour stage.



No. at risk

Station 252+	99	91	74	63	53	45	38	30	24	20	17
Station 253+	20	17	12	9	8	8	8	8	5	3	3

Fig. 4 Cancer-specific survival curves for patients with sigmoid colon or rectal cancer who underwent high ligation, according to inferior mesenteric lymph node status. +, Metastatic nodal disease present. Vertical bars represent 95 per cent confidence intervals

Table 4 Frequency of positive nodes in patients with nodal involvement along the inferior mesenteric artery

	Frequency of positive nodes	
	No. of positive nodes*	No. of nodes harvested*
Station 252	2·0 (1·0) (1–16)	5·8 (5·0) (1–23)
Station 253	1·9 (1·0) (1–6)	3·2 (3·0) (1–10)

*Values are mean (median) (range).

advantage for patients with advanced node metastases. Furthermore, other recent series did not find any survival benefit after high ligation[4,7,19,20]. There has been no randomized or prospective study of high *versus* low ligation in patients with sigmoid colon or rectal cancer.

This prospective (but uncontrolled) study introduced a novel concept[21] for evaluation of the effectiveness of high ligation in sigmoid colon or rectal cancer surgery. The methodological approach was based on the assumption that patients who survived in the long term after resection of lymph node metastases would not have done so if the involved lymph nodes had been left *in situ*. The frequency of metastasis in nodal stations that would be left behind after low ligation of the IMA was evaluated, and the therapeutic effect of node dissection was determined by examining the incidence of metastases and the survival rates of patients with nodal deposits in those particular stations, irrespective of nodal metastases to any other lymph node station.

Potentially curative resection was achieved in 20 patients with involvement of nodal station 253, and 5-year overall and cancer-specific survival rates were 40 and 42 per cent respectively. These results demonstrate the therapeutic benefit of high ligation, because there would probably have been no long-term survivors if low ligation had been performed. However, the benefit of routine use of high ligation in patients undergoing curative resection was low (1·7 per cent, 20 of 1188) and only 0·7 per cent of patients with sigmoid colon or rectal cancer are likely be cured by high ligation of the IMA (incidence rate of metastasis 1·7 per cent, times survival rate 42 per cent). This low incidence of metastasis in the lymph nodes at the base of the IMA does not undermine the rationale behind high ligation of this artery. Surgery must always be performed for the greater good of the patient, especially if it can be carried out without adding appreciably to the risk. The negligible operative mortality and morbidity rates in this study confirm that high ligation of the IMA can be performed safely. Urinary or sexual dysfunction was the most frequent postoperative complication. Three hundred and one of the patients with lower rectal cancer also underwent lateral pelvic lymph node dissection. The autonomic nerves are intentionally sacrificed or preserved depending on whether the cancer has spread to them. This additional step is considered to be the major cause of such complications.

Five-year survival rates after low ligation in patients with involvement of middle-level lymph nodes (station 252) along the IMA of 20·5 per cent[6] and 32 per cent[22] have been reported. In the present study, patients with involvement of nodal station 252 had appreciably higher survival rates (more than 50 per cent) after high ligation, suggesting a positive effect of high ligation of the IMA on survival. Resection with curative intent could be achieved by high ligation in 107 patients with nodal involvement at stations 252 and/or 253. Because some of these nodes are left behind in a low ligation, high ligation increased the curative resection rate by 9·0 per cent (107 of 1188) at worst (assuming that low ligation would have involved ligation of the superior rectal artery at a low level). The proportion of patients with node-positive disease (Dukes' C) was 40·3 per cent (479 of 1188) in this study, which suggests that low ligation would have led to residual metastases being left in the nodes of a maximum of one-quarter of these patients. Thus, high ligation might save the occasional patient and prove helpful in those who have nodal metastases limited to below the level of the left colic artery by providing a greater margin of safety when the artery, including all the surrounding glands and lymphatics, is excised by a single block dissection; however, these data are inconclusive. The survival benefit of high ligation still remains to be investigated. Likewise, to say that high ligation of the IMA is essential to remove nodes at