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)	

Table 2. Serum levels of oxLDL, oLAB, total cholesterol, and α-tocopherol and BMI for colorectal cancer cases and controls

	Cases		Controls		*P*
	n		*n*		
oxLDL (units/L), median (25th-75th percentiles)	119	39.2 (31.6-47.8)	316	36.2 (29.2-44.7)	0.045
oLAB (units/L), median (25th-75th percentiles)	153	201.0 (142.0-312.0)	376	192.0 (135.5-272.5)	0.120
Total cholesterol (mmol/L), mean ± SD	159	5.22 ± 0.96	382	5.17 ± 0.98	0.225
α-Tocopherol (μmol/L), median (25th-75th percentiles)	155	21.87 (15.67-27.35)	377	21.69 (17.30-26.75)	0.834
BMI (kg/m^2), mean ± SD	158	23.1 ± 3.4	380	23.2 ± 2.8	0.779

oLAB levels displayed no correlation with serum levels of oxLDL, total cholesterol, or α-tocopherol in either gender.

Table 4 shows ORs and 95% CIs for colorectal cancer by serum levels of oxLDL and oLAB after adjusting for confounding factors. ORs (95% CIs) across quartiles for serum oxLDL adjusted for gender, age, and study area (OR1) were 1.21 (0.57-2.55), 1.49 (0.71-3.14), and 2.34 (1.03-5.30; P_{trend} = 0.030). OR (95% CI) for serum oxLDL adjusted for gender, age, study area, smoking and drinking habits, intake frequency of green leafy vegetables, time spent in sports or physical exercise, family history of colorectal cancer, and BMI (OR2) was significantly higher in the highest quartile compared with the lowest quartile [3.65 (1.50-8.92); P_{trend} = 0.004]. OR1 and OR2 for oLAB tended to be higher in the highest quartile of serum oLAB but not significantly (OR1, 1.66; 95% CI, 0.91-3.01; P_{trend} = 0.148; OR2, 1.68; 95% CI, 0.90-3.13; P_{trend} = 0.140).

When the analysis was limited to incident cases and corresponding controls, the higher risk was still found in relation to higher serum levels of oxLDL. OR2s (95% CIs) for colorectal cancer across quartiles of serum oxLDL were 3.11 (1.09-8.87), 2.25 (0.79-6.39), and 4.77 (1.50-15.10; P_{trend} = 0.027). OR2s (95% CIs) for colorectal cancer across quartiles of serum oLAB were 0.67 (0.32-1.41), 0.89 (0.41-1.92), and 1.22 (0.51-2.62; P_{trend} = 0.412).

Associations of serum oxLDL and oLAB with risk of colorectal cancer were also evaluated after further adjustment for quintiles of total cholesterol and α-tocopherol (OR3). However, no substantial change in results was observed. When evaluated by gender, no apparent difference between males and females was noted.

The same analyses were attempted using only colon cancer cases (n = 80 for oxLDL and n = 106 for oLAB) and corresponding controls (n = 215 for oxLDL and n = 261 for oLAB). OR3s (95% CIs) for colon cancer across quartiles of serum oxLDL were 2.97 (0.97-9.06), 1.90 (0.55-6.59), and 4.68 (1.19-18.38; P_{trend} = 0.062). A similar trend was observed for serum oLAB levels: OR3s (95% CIs) across quartiles were 1.75 (0.73-4.20), 1.69 (0.68-4.15), and 2.20 (0.90-5.37; P_{trend} = 0.119).

Furthermore, modified data sets excluding cases diagnosed within 2 years from baseline were also analyzed. Results of these analyses were consistent with those of analyses without exclusion (data not shown).

Table 3. Spearman correlation coefficients (no. subjects) among serum levels of oxLDL, oLAB, total cholesterol, and α-tocopherol among control subjects

	oxLDL	oLAB
Males		
oLAB	0.066 (136)	
Total cholesterol	0.525* (138)	-0.023 (172)
α-Tocopherol	0.397* (140)	0.011 (169)
Females		
oLAB	0.021 (161)	
Total cholesterol	0.429* (166)	-0.093 (191)
α-Tocopherol	0.227* (168)	0.006 (192)

*P < 0.001.

Discussion

The present investigation represents the first prospective study to examine associations between serum oxLDL and risk of colorectal cancer. Significant positive associations were observed between serum oxLDL levels and risk of colorectal cancer. There was no association between serum oLAB levels and risk of colorectal cancer. Risk of colorectal cancer was higher in the presence of higher levels of serum oxLDL, independent of confounders. The mechanisms involved in this association between oxLDL and colorectal cancer remain unclear.

The adjustment for lifestyle factors, family history, and BMI somewhat strengthened the positive association between oxLDL and risk of colorectal cancer. This may not be in line with our initial hypothesis that serum oxLDL levels represent a marker reflecting lifestyles related to the cancer. Serum oxLDL may be a predictor of the risk independently of other risk factors.

There are some reports that studied the association between serum or plasma oxLDL levels and coronary heart disease (7, 28). It is well known that oxLDL is found in monocyte-derived macrophages in atherosclerosis lesions and that plasma oxLDL levels were significantly higher in patients with coronary artery disease (28). Several studies have been carried out on the modified forms of oxLDL, which are prepared by oxidizing LDL under various conditions *in vitro* (28). However, there is little information about oxLDL present *in vivo* (28).

We have also studied associations between serum carotenoids levels and risk of colorectal cancer in this prospective epidemiologic study. We found inverse associations of some carotenoids with colorectal cancer risk in men.[9] Crohn disease is a chronic inflammatory disorder and is associated with increased risk of colon cancer (29). Although the etiology of Crohn disease is unknown, patients with Crohn disease have increased

[9] Unpublished data.

Table 4. ORs and 95% CIs for colorectal cancer risk by serum levels of oxLDL and oLAB

	Range	Cases	Controls	OR1	95% CI	P_{trend}	OR2	95% CI	P_{trend}	OR3	95% CI	P_{trend}
oxLDL (units/L)												
Q1	≤29.1	22	79	1.00	—	0.030	1.00	—	0.004	1.00	—	0.038
Q2	29.2-36.1	26	79	1.21	0.57-2.55		1.55	0.70-3.46		1.15	0.49-2.72	
Q3	36.2-44.6	31	79	1.49	0.71-3.14		1.90	0.84-4.28		1.38	0.54-3.51	
Q4	≥44.7	40	79	2.34	1.03-5.30		3.65	1.50-8.92		3.10	1.04-9.23	
oLAB (units/L)												
Q1	≤135.4	34	94	1.00	—	0.148	1.00	—	0.140	1.00	—	0.212
Q2	135.5-191.9	41	96	1.14	0.64-2.01		0.98	0.54-1.80		1.11	0.58-2.11	
Q3	192.0-272.4	28	92	0.87	0.46-1.64		0.75	0.39-1.48		0.74	0.36-1.52	
Q4	≥272.5	50	94	1.66	0.91-3.01		1.68	0.90-3.13		1.69	0.85-3.35	

NOTE: OR1: OR adjusted for gender, age, and study area; OR2: OR adjusted for gender, age, study area, smoking and drinking habits, intake frequency of green leafy vegetables, time spent in sport or physical exercise, family history of colorectal cancer, and BMI; OR3: OR adjusted for gender, age, study area, smoking and drinking habits, intake frequency of green leafy vegetables, time spent in sport or physical exercise, family history of colorectal cancer, BMI, and serum levels of total cholesterol and α-tocopherol.

production of ROS (29). It was reported that lipid peroxidation and F_2 isoprostane was significantly higher in patients with Crohn disease than in healthy control subjects (30).

Various potentially toxic oxidized lipids are contained in oxLDL such as lipid peroxides, oxysterol, and aldehydes (31). These oxidized lipids elicit oxidative stress and lipid peroxidation (31). As oxLDL reduces antioxidant enzymes such as Cu/Zn superoxide dismutase (32) and glutathione peroxidase (33) and ROS degradation is decreased following increases in oxLDL (31), ROS levels are elevated. Lipid peroxidation is initiated by ROS attacks, generating large amounts of reactive products that have been implicated in tumor initiation and promotion (34). Increased levels of malondialdehyde, a major genotoxic carbonyl compound generated by lipid peroxidation (34), have been reported in tumor tissue from colorectal cancer patients compared with normal mucosa from the same individuals (35).

In another experimental study (8), oxLDL-induced oxidative stress enhanced p53 DNA binding activity and p53 protein synthesis. As a tumor suppressor, p53 is induced by various kinds of cell stress (36) to protect the cell. Genetic information is protected by the functions of p53, including induction of cell cycle arrest or apoptosis after DNA damage and maintenance of genomic stability (37). Given the above, high levels of oxLDL might induce excess stress against the cell. This stress may induce DNA damage and mutation, because oxidative stress is known to cause such damage (38). Mutation of *p53* gene is found in >50% of all human cancers and >75% of colorectal adenocarcinomas (39). Mutation of the *p53* gene is known to play crucial roles in tumor development and progression (37).

Cyclooxygenase-2 (COX-2) expression is reportedly induced by oxLDL in a murine macrophage-like cell line (40) and human monocytes (41). COX is an enzyme that initiates the conversion of arachidonic acid into all of the prostaglandins and thromboxanes (42). Lipid peroxidation is necessary for initiation of COX activity (43), and reactive oxygen intermediates (ROI) induce COX-2 (44). Levels of arachidonic acid (45) and prostaglandin E_2 (46) are higher in colon tumor than in normal colonic mucosa. Prostaglandin E_2, a major product of COX, stimulates proliferation and growth of human colorectal cancer cells (47).

Analysis of COX-2 expression (induced by cytokines, growth factors, and mitogens) has revealed elevated levels in up to 90% of sporadic colon carcinomas and 40% of colonic adenomas but no elevation in normal colonic epithelium (48). Recent clinical epidemiologic studies have shown that COX inhibitors such as aspirin and other nonsteroidal anti-inflammatory agents exert preventive effects on colorectal cancer (49, 50). Such inhibition of COX-2 is considered to lead to decreased incidence of colorectal cancer, although the mechanisms are not fully understood.

Functions of oxLDL such as increasing oxidative stress and inducing COX-2 expression might play an important role in colorectal carcinogenesis. At the very least, oxidative stress is increased in subjects with high levels of serum oxLDL, and oxidative stress should be related to colorectal carcinogenesis.

Epidemiologic studies showed the close association between insulin resistance and colon cancer risk (51). The consumption of excess dietary energy results in the development of insulin resistance with increased circulating levels of insulin, triglycerides, and nonesterified fatty acids. These circulating factors subject colonic epithelial cells to a proliferative stimulus and also expose them to reactive oxygen intermediates. Other study reported that LDL oxidizability is increased in insulin resistance subjects compared with healthy subjects (52). These long-term exposures are expected to result in the promotion of colon cancer.

Serum oLAB levels were not significantly associated with risk of colorectal cancer. Serum oLAB is generated from immunoresponses against oxLDL. Serum oLAB levels, in addition to serum oxLDL levels, may therefore also depend on various lifestyle factors such as dietary intake of antioxidants and smoking habits. Plasma oLAB levels are reported to show a negative correlation with plasma oxLDL levels in healthy subjects (53), and oLAB may play a role in maintaining low levels of blood oxLDL. Wide ranges of serum oLAB levels might reflect interindividual differences in immune responses rather than in oxLDL generation. The immune system is also affected by various lifestyle factors such as smoking habits. We considered that almost no relationship between serum oLAB and oxLDL in controls was derived from interindividual differences in immune responses. Interindividual difference in immune responses may

have also attenuated the association between serum oLAB and risk of colorectal cancer.

Although oxLDL is an oxidant and α-tocopherol is an antioxidant, our results show positive association between serum oxLDL and α-tocopherol levels. We suggest that this association was observed because serum LDL binds to α-tocopherol (54). Similarly, serum oxLDL is positively associated with serum cholesterol levels.

Cases included both colon and rectal cancers. Risk for colon cancer only was increased with high serum oxLDL levels after adjusting for gender, age, study area, and potential confounders. The sample population for rectum cancer cases was too small to analyze associations between serum levels of oxLDL and oLAB and risk of rectum cancer. These associations warrant further study.

In conclusion, the present study showed that increased levels of serum oxLDL represent a risk factor for colorectal cancer among Japanese. Although further investigations are needed to clarify the role of oxLDL in tumorigenesis for colorectal cancer, serum oxLDL levels may be one biomarker for predicting risk of colorectal cancer.

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A prospective study of reproductive and menstrual factors and colon cancer risk in Japanese women: Findings from the JACC study

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The effects of reproductive factors on the etiology of colon cancer in Asian populations remain unexplored. So we examined 38,420 Japanese women aged 40–79 years who responded to a questionnaire on reproductive and other lifestyle factors from 1988 to 1990 in the Japan Collaborative Cohort Study for Evaluation of Cancer Risk. During an average 7.6 years of follow-up, we documented 207 incident colon cancers. Multivariate analysis indicated that colon cancer risk was likely to be lower among parous women than among nulliparous. Women who had two abortions or more had a 72% higher risk of developing colon cancer [relative risk (RR) 1.72; 95% confidence interval (CI) 1.16–2.55; trend $P<0.01$] compared with women who never had an abortion. The RR of colon cancer among postmenopausal women significantly decreased with increasing age at menarche (trend $P=0.01$). No apparent association between colon cancer and gravida, age at first birth, age at menopause, or duration of menstruation was seen. These prospective data support the hypothesis that female reproductive events modify colon cancer risk, and suggest that reproductive factors, particularly age at menarche and having an abortion, may be of importance in the etiology of colon cancer among Japanese women. (Cancer Sci 2004; 95: 602–607)

In 1980, McMichael and Potter[1)] reviewed the results of two earlier case-control studies of colorectal cancer together with other epidemiologic, metabolic, and animal studies, and suggested that reproductive events and endogenous and exogenous sex hormones may affect carcinogenesis in the large bowel via their effects on hepatic function and bile acid formation. Briefly, endogenous estrogens increase bile acid production. Progestin, pregnancy, and high-dose oral contraceptives reduce bile acid production; therefore, they decrease the risk of colon cancer. Since then, the results of several further studies,[2–26)] most of which were conducted in high-risk Western countries using a case-control design,[2–19)] dealing with this issue have been published. These studies suggested that some aspects of reproductive history including parity, age at first birth, age at menarche, and estrogen use after menopause may affect the development of colon cancer. However, these studies are inconsistent as to whether such reproductive factors are surrogates for hormonal effects or for some other lifestyle characteristics, such as diet or physical activity. Furthermore, the effects of reproductive factors on the etiology of colon cancer in Asian populations remain unexplored. Here, we report the findings from a large prospective study conducted among Japanese. Our study offers further evidence in support of the hypothesis proposed by McMichael and Potter.[1)]

Materials and Methods

The JACC study. The Japan Collaborative Cohort Study for Evaluation of Cancer Risk, the JACC Study (sponsored by the Ministry of Education, Culture, Sports, Science and Technology of Japan) is a nationwide multicenter collaborative study to prospectively evaluate the various risks and/or protective factors influencing cancer mortality and incidence. Study methods and ethical issues have been described in detail elsewhere.[27)] Briefly, our study was initiated in 1988, and enrollment continued until the end of 1990. Forty-five areas were selected from 7 out of 8 districts in Japan, thus covering almost the entire country. We enrolled 127,477 apparently healthy inhabitants in these areas with completion of the questionnaire. Two strategies were applied to obtain informed consent for participation, i.e., requesting individuals to sign the cover page of the questionnaire, or at the group level, by explaining the aim of the study and the confidentiality of the data to community leaders. Of 127,477 enrolled, 110,792 (46,465 men and 64,327 women), aged 40–79 years, were followed. Of 64,327 women, 38,720 lived in 24 study areas covered by cancer registries. Among those, we excluded from analysis 14 with a history of colon cancers at baseline, and 287 subjects with less than one year of follow-up time, leaving 38,420 women were enrolled in the present study (one woman had both exclusion criteria).

The present study protocol was approved by the Ethics Committee of Fujita Health University, Toyoake, Japan.

Data collection. A self-administered questionnaire was used to assess the baseline characteristics of participants. It covered medical history and included lifestyle-related items such as diet, physical activity, drinking and smoking, and family history of several medical conditions including cancer. For women, information was obtained on menstrual factors (age at menarche and age at menopause), reproductive variables (number of pregnancies, number of parity, and age at first birth). The number of abortions was calculated as the number of pregnancies minus the parity number. Induced and spontaneous abortions as well as stillbirths were included in our criteria without regard for gestational week. Among menopausal women, the duration of menstruation was defined as age at menopause minus age at menarche.

Follow-up and identification of colon cancer cases. We used population registries in local municipalities to determine the vital and residential status of the subjects. Registration of death is re-

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quired by the Family Registration Law in Japan and is enforced throughout the country. For logistical reasons, we discontinued the follow-up of subjects who moved out of their study areas.

We ascertained the incidence of cancer by consulting the records of population-based cancer registries, supplemented by a systematic review of death certificates. In some areas, medical records were also reviewed in local major hospitals. The follow-up was conducted from the time of the baseline survey through the end of 1997 except for three areas, where it ended in 1994, 1995, and 1996. During the study period, only 3.0% (1164) of the participants were lost to follow-up due to moving.

The incidence to death ratio for female colon cancer was 2.33 in the cohort covered by cancer registries. This figure is comparable with those in acceptably accurate population-based cancer registries in Japan[28] (1.69 to 3.03) and indicates that a high proportion of colon cancer cases was identified. The proportion of Death Certificate Only (DCO) registrations was 7.7% (16 of 207 cases).

Finally, the 7.6-year follow-up analyses verified 207 incident cases of colon cancer among 37,420 women. Because of missing values for certain reproductive variables, the total number of cases and person-years of follow-up varied somewhat among analyses (gravida: 192 cases during 272,684 person-years of follow-up; parity: 190 cases during 268,750 person-years; age at menarche: 180 cases during 270,253 person-years of follow-up; age at menopause: 154 cases during 190,989 person-years of follow-up).

Statistical analysis. In the present study, variables of interest were gravida, parity, age at first birth, number of abortions, age at menarche, age at menopause, and duration of menstruation. For each participant, the person-years of follow-up were calculated from the date of filling out the baseline questionnaire to development of colon cancer, death from any cause, moving out of the study area, or the end of follow-up period, whichever occurred first. Sixteen of 207 colon cancer cases were discovered only by death certificate and their person-years of follow-up were calculated from the date of enrollment to death from colon cancer. We used Cox proportional hazards modeling to compute relative risks (RRs), adjusting for age at enrollment. In another multivariate analysis, study area (Hokkaido and Tohoku, Kanto, Chubu, Kinki, Chugoku, Kyushu), smoking status (never, past, current), alcohol consumption (none, past, present), exercise: "How long do you take exercise or sports in a week?" (≥5, 3–4, 1–2 h per week, seldom), green leafy vegetable intake (3–7, 1–2 days per week, seldom), meat intake (3–7, 1–2 days per week, seldom), family history of colon cancer, and body mass index (weight in kilograms/[height in meters]^2) were further adjusted. Other reproductive and menstrual factor were also adjusted. These variables were assessed by the baseline questionnaire and were selected as covariates because they were known or suspected to modify the risk of colon cancer. In the analysis, all variables were entered as dummy variables except for age at enrollment. Missing values for each covariate were treated as an additional category and were included in the model. A linear trend of association was assessed by the regression model assigning score (0, 1, 2,...) to the levels of the independent variable.

Estrogens appear to influence colon cancer risk. In premenopausal women, ovarian sources of estrogen are of prime important but in postmenopausal women, conversion of androgens to estrogen in adipose tissue is the major source of estrogen, and the serum level of endogenous estrogen in postmenopausal women is lower than that in premenopausal women. We hypothesized that menopausal status may modify the association between reproductive factors and colon cancer risk, and to test this, we performed the same analysis as above only among menopausal women at baseline.

All data were analyzed using SAS software. The 95% confidence intervals (CIs) were presented for all RRs. All P values were based on 2-sided tests, in which $P<0.05$ was considered statistically significant.

Results

Association of age at menarche, gravida, parity, age at first birth, and the number of abortions with the risk of colon cancer. Table 1 presents the age-adjusted and multivariate RRs for colon cancer by age at menarche, gravida, parity, age at first birth, and the number of abortions among all subjects. With reference to age at menarche, compared to women whose menarche occurred at age 12 or less, the point estimates tended to be below unity, but no consistent trend in risk emerged. There was no association of gravida with colon cancer risk, whereas the multivariate RR of colon cancer for parous women compared with nulliparous women was 0.65 (95% CI: 0.35–1.20). The multivariate RRs by the number of deliveries were 0.63 for one birth, 0.80 for two, 0.57 for three, 0.60 for four and more. The point estimates were below unity, but there was no consistent pattern of trends. Among parous women, no consistent trend in risk was observed. There was also no association between age at first birth and colon cancer risk among parous women. The subjects who had had 2 or more abortions had a significantly increased risk compared to those with no abortions (RR: 1.72, 95% CI: 1.16–2.55) among the women with any pregnancy. There was a significantly increasing trend for an association between the number of abortions and the risk of colon cancer (P value for trend <0.01)

Association of reproductive and menstrual factors with the risk of colon cancer among menopausal women at baseline. Table 2 shows the age-adjusted and multivariate RRs for colon cancer by age at menarche, parity, age at menopause, and duration of menstruation only among menopausal women. The RRs of colon cancer was 0.64 (95% CI: 0.32–1.28) for women who had experienced menarche at age 13–15 and 0.49 (95% CI: 0.24–1.01) for those who did so at age 16 or more compared with those who did so at age 12 and under. There was a significantly decreasing pattern for a relation between age at menarche and the risk of colon cancer. We observed no significant association between parity and risk of colon cancer. In relation to age at menopause, the point estimates of colon cancer risk were below unity for subsequent age groups above 45, but there was no consistent pattern of trends. There were no apparent association between duration of menstruation and colon cancer risk.

Discussion

Most of the previous studies conducted in Western populations at high risk for colon cancer suggested that reproductive factors might be important in the etiology.[2–14, 16–18, 20–26] If reproductive and hormonal factors are determinants of colon cancer risk, it would be extremely valuable to determine whether their effects are similar in different populations. Although one case-control study[19] analyzed this issue among Japanese women, we attempted to resolve this question by means of a prospective study in order to avoid some of the problems inherent in a case-control study, such as selection and recall bias, which may distort the results.

Our prospective study found that parity was likely to have a protective effect against colon cancer risk, whereas, to our knowledge, only two[20, 23] of the seven published cohort studies[20–26] have shown a weak and statistically insignificant inverse effect of parity on colon cancer, and less than half[4, 6, 7, 11, 12, 14, 16] of the 18 case-control studies[2–19] found evidence of parity's protective effect. This protective effect was consistent in our study up to high parity number, though one case-control study has reported a U-shaped association between

Table 1. Adjusted relative risk (RR) for colon cancer by age at menarche, gravida, parity, age at first birth, and the number of abortions, JACC study, 1988–1997

	Person-years[1]	No. of cases[1]	RR (95% CI)[2]	RR (95% CI)[3]
Age at menarche				
≤12	17,649	12	1.00	1.00 [4]
13–15	159,100	101	0.67 (0.37–1.22)	0.74 (0.39–1.38)
≥16	93,352	67	0.53 (0.28–0.99)	0.62 (0.32–1.20)
P value for trend			<0.05	0.13
Gravida				
No pregnancy	13,357	11	1.00	1.00 [5]
Any pregnancy	259,326	181	1.00 (0.54–1.83)	0.82 (0.42–1.62)
1	13,631	11	1.00	1.00
2	57,649	33	0.94 (0.47–1.87)	1.39 (0.61–3.16)
3	75,319	45	0.87 (0.45–1.68)	1.27 (0.57–2.83)
≥4	112,727	92	0.89 (0.48–1.67)	1.28 (0.59–2.79)
P value for trend			0.70	0.87
Parity				
Nulliparous	13,438	14	1.00	1.00 [5]
Parous	255,311	176	0.77 (0.45–1.33)	0.65 (0.35–1.20)
1	19,199	15	1.00	1.00
2	97,564	60	1.04 (0.59–1.84)	1.24 (0.66–2.32)
3	87,065	48	0.75 (0.42–1.35)	0.88 (0.46–1.68)
≥4	51,483	53	0.75 (0.42–1.35)	0.90 (0.47–1.74)
P value for trend			0.10	0.24
Age at first birth (only parous women)				
<25	106,081	74	1.00	1.00 [6]
25– <30	105,979	77	1.09 (0.79–1.05)	1.04 (0.73–1.49)
30– <35	15,620	10	0.84 (0.43–1.63)	0.65 (0.31–1.40)
35–	3279	3	1.21 (0.38–3.83)	1.16 (0.35–3.83)
P value for trend			0.92	0.68
Number of abortions (only women with any pregnancy)				
0	158,765	105	1.00	1.00 [7]
1	57,820	40	1.29 (0.89–1.87)	1.29 (0.87–1.92)
≥2	36,467	31	1.69 (1.17–2.43)	1.72 (1.16–2.55)
P value for trend			<0.01	<0.01

1) Number of cases and person-years do not always add up to the total due to missing information for the risk factors.
2) Adjusted for age at baseline.
3) Adjusted for age at baseline, study area (Hokkaido and Tohoku, Kanto, Chubu, Kinki, Chugoku, Kyushu), smoking status (never, past, current), alcohol drinking habit (none, past, regular), exercise (≥5, 3–4, 1–2 days/week, seldom), meat intake (3–7, 1–2 days/week, seldom), green leafy vegetable intake (3–7, 1–2 days/week, seldom), family history of colon cancer (Y/N), and BMI at baseline (<18.5, 18.5– <22, 22– <25, 25– kg/m^2).
4) Additionally adjusted for menopausal status and parity.
5) Additionally adjusted for menopausal status and age at menarche.
6) Additionally adjusted for menopausal status, age at menarche, and parity.
7) Additionally adjusted for menopausal status and age at menarche.

the parity number and colon cancer risk.[14] Furthermore, the protective effect of parity became clear after adjustment for some confounding factors, such as smoking, alcohol consumption, intake of vegetables, physical activity, and body mass index. Several mechanisms have been suggested to explain the protective effect of parity on colon cancer, including modifications of estrogen profiles secondary to pregnancies and their effects on bile acid metabolism,[1, 29] immunological influences of ABO-incompatible fetal antigens,[30] increased physical activity associated with large families,[20] and unidentified lifestyle factors associated with having children.

In our study, there was an inverse association between age at menarche and colon cancer risk and the association was significant among menopausal women. Of five cohort studies[20–22, 24, 25] which examined the effect of age at menarche, only one[27] found this inverse association. It is unclear whether the effect of age at menarche on colon cancer risk is affected by some hormonal mechanism. Age at menarche may be a surrogate for some unidentified risk factors around puberty, such as body size, nutrition, or physical activity. Abdominal obesity, which is associated with hyperinsulinemia resulting from insulin resistance,[31] has been noted in girls even before puberty[32] and has been shown to be associated with an earlier onset of menarche.[33] Since insulin is a growth factor for colon epithelial cells, it has been suggested that hyperinsulinemia plays an important role as a colon cancer promoter.[34] In our study, the association between age at menarche and colon cancer risk still remained after multivariate adjustment; this is consistent with the above-mentioned reasoning and may suggest a role of childhood nutrition in the subsequent development of colon cancer. However, the reason why this association between age at menarche and colon cancer risk was observed more clearly among menopausal women also remains unclear. The predominant premenopausal profile of endogenous female sex hormones derived from the ovaries modifies the risk of female colon cancer through increased excretion of bile acids. The effect of hyperinsulinemia on the risk of colon cancer may predominate in postmenopausal women with low levels of female sex hormone. Adult women who had early menarche may have hyperinsulinemia, since tracking of serum insulin is observed especially in females.[35]

There are only a few studies on the effect of abortion or in-

Table 2. Adjusted relative risk (RR) for colon cancer by age at menarche, parity, age at menopause, and duration of menstruation among menopausal women at baseline, JACC study, 1988–1997

	Person-years[1]	No. of cases[1]	RR (95% CI)[2]	RR (95% CI)[3]
Age at menarche				
≤12	7653	9	1.00	1.00 [4]
13–15	99,600	82	0.61 (0.31–1.22)	0.64 (0.32–1.28)
≥16	80,038	58	0.47 (0.23–0.95)	0.49 (0.24–1.01)
P value for trend			<0.05	<0.05
Parity				
Nulliparous	7374	9	1.00	1.00 [5]
Parous	172,638	137	0.67 (0.34–1.32)	0.70 (0.36–1.39)
1	12,944	14	1.00	1.00
2	59,154	45	0.85 (0.46–1.55)	0.99 (0.52–1.89)
3	57,811	35	0.57 (0.31–1.07)	0.70 (0.36–1.35)
≥4	42,729	43	0.64 (0.34–1.18)	0.79 (0.41–1.53)
P value for trend			0.07	0.24
Age at menopause				
≤45	37,430	35	1.00	1.00 [6]
46– <50	51,011	44	0.94 (0.60–1.46)	0.87 (0.54–1.38)
50– <55	92,453	66	0.76 (0.50–1.15)	0.74 (0.49–1.14)
≥55	9956	9	0.83 (0.40–1.74)	0.73 (0.34–1.58)
P value for trend			0.19	0.16
Duration of menstruation (years)				
<30	31,264	27	1.00	1.00 [7]
30– <35	70,183	59	0.97 (0.61–1.52)	0.93 (0.59–1.49)
35– <40	74,796	53	0.86 (0.54–1.37)	0.83 (0.51–1.33)
≥40	11,085	10	1.00 (0.48–2.07)	0.94 (0.45–1.95)
P value for trend			0.63	0.51

1) Number of cases and person-years do not always add up to the total due to missing information for the risk factors.
2) Adjusted for age at baseline.
3) Adjusted for age at baseline, study area (Hokkaido and Tohoku, Kanto, Chubu, Kinki, Chugoku, Kyushu), smoking status (never, past, current), alcohol drinking habit (none, past, regular), exercise (≥5, 3–4, 1–2 days/week, seldom), meat intake (3–7, 1–2 days/week, seldom), green leafy vegetable intake (3–7, 1–2 days/week, seldom), family history of breast cancer (Y/N), and BMI at baseline (<18.5, 18.5– <22, 22– <25, 25– kg/m^2).
4) Additionally adjusted for parity and age at menopause.
5) Additionally adjusted for age at menarche and at menopause.
6) Additionally adjusted for age at menarche and parity.
7) Additionally adjusted for parity.

complete pregnancy on the risk of colon cancer. Negri *et al.*[13] found no consistent relation with the number of abortions, whereas Howe *et al.*[10] found a high number of non-live births among colorectal cases, and Peters *et al.*[14] reported a U-shaped association. The definitions of a failed pregnancy differed among the various studies. We found a consistent and positive association between the number of abortions and colon cancer risk. The adverse effect of abortion is similar to what has been observed in some studies on breast cancer,[36] but the underlying mechanisms remain unclear.

The fact that a first delivery early in life is a protective factor against colon cancer is supported by four cohort studies,[21–23, 25] though none of their results proved statistically significant. Evidence of a long-term shift in hormone profiles that would affect bile acid production after the first complete pregnancy[37, 38] may explain the protective effect not only of having been parous, but also of having given birth at an early age. However, we observed no association between age at first birth and colon cancer risk.

We found no effect of age at menopause or duration of menstruation. Previous results on these variables have been inconsistent.[13–16, 19–21] However, our study has an advantage over previous studies with respect to age at menopause and duration of menstruation, because few Japanese women had used estrogens after menopause. Hormone use may induce artificial menstruation, thus affecting accurate recall of when their periods had stopped naturally.

The study by Yoo *et al.*,[19] which is the first study on the association between reproductive factors and colorectal cancer in Japan, reported that menstrual regularity, late age at menopause, late age at first pregnancy, and late age at first full-term pregnancy were significantly associated with the risk of colorectal cancer. Yoo *et al.* also found a positive association between age at menarche and risk of distal colon cancer. Our study yielded a negative association, especially among postmenopausal women. The study by Yoo *et al.* gave no consideration to menopausal status and our study had no information on subsite. The effect of menarche on colon cancer needs further investigation.

There are both strengths and limitations in our study. The strengths include its prospective design and large sample size. Data on exposure were collected before diagnosis and prior to any colon cancer deaths, which could preclude recall bias. Moreover, since data on many kinds of exposure known or suspected to modify the risk of colon cancer were collected in the present study, we could elucidate the independent effects of reproductive factors by multivariate adjustment. One limitation of this study lies in the absence of information on the specific subsites of origin in the large bowel, since it has been suggested that the influence of sex hormones should be either greater at, or restricted to, the right side of the large bowel.[6] Another limitation arises from the validity of self-reported reproductive histories. Some reproductive exposures occurred long before enrollment or any diagnosis of disease. However, previous

studies on the validity of self-reported reproductive histories have shown good agreement between the respondents recall of reproductive events and their medical records.[39,40] Finally, our results may be chance findings, because the participants were not drawn uniformly from throughout Japan. Also, the number of incident cancer cases of the colon was small compared to those in Western studies.

In summary, the present study provides additional support for earlier suggestions by McMichael and Potter as well as other researchers that there is a hormonal component in the risk profile for female colon cancer. In Japan, the westernization of lifestyles has progressed rapidly since the early 1960s, suggesting that it will be necessary to examine the change of reproductive factors and their effect on colon cancer among Japanese women who have experienced largely westernized lifestyles since childhood.

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Bowel movement frequency and risk of colorectal cancer in a large cohort study of Japanese men and women

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The relationship between bowel movement (BM) frequency and the risk of colorectal cancer was examined in a large cohort of 25 731 men and 37 198 women living in 24 communities in Japan. At enrolment, each participant completed a self-administrated questionnaire on BM frequency and laxative use. Incidence rate ratios (IRR) with 95% confidence intervals (CI) were estimated using Cox's proportional-hazard model. During the follow-up period (average length 7.6 years), 649 cases of colorectal cancer, including 429 cases of colon cancer, were identified. Among women, subjects who reported a BM every 2–3 days had the lowest risk of developing colorectal (IRR = 0.71, 95% CI = 0.52–0.97) and colon cancer (IRR = 0.70, 95% CI = 0.49–1.00), whereas those reporting a BM every 6 days or less had an increased risk of developing colorectal (IRR = 2.47, 95% CI = 1.01–6.01) and colon cancer (IRR = 2.52, 95% CI = 0.93–6.82) compared with those reporting ⩾ 1 BM per day. A similar, but nonsignificant, association between the frequency of BM and cancer risk was observed in men. There was no association between colorectal or colon cancer risk and laxative use. Regulating BM frequency might therefore have a role in the prevention of colorectal cancer.
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An association between constipation and the risk of colorectal cancer has long been noted. Prolonged intestinal transit time might not only increase the duration of contact between carcinogens in the stools and the gut wall, but could also concentrate carcinogens by increasing colonic water absorption. A meta-analysis of 14 case–control studies that examined the association between constipation or infrequent bowel movements (BMs) and colorectal cancer and found a statistically significant 48% increase in the pooled odds ratios for colorectal cancer in association with constipation (Sonnenberg and Müller, 1993). Recent case–control studies have also reported a relatively consistent positive relationship between constipation and colorectal cancer (Kotake *et al*, 1995; Le Marchand *et al*, 1997; Ghadirian *et al*, 1998; Jacobs and White, 1998; Roberts *et al*, 2003).

Since bowel habits might be influenced by the presence of colorectal cancer, retrospective studies cannot exclude the effects of the cancer itself, as well as recall bias, on their results. However, few prospective studies have addressed this issue. The only cohort study, which had a 12-year follow-up period involving 84 577 women, of colorectal cancer incidence and BM frequency or laxative use reported negative results (Dukas *et al*, 2000). The influence of BMs on male colorectal cancer has not been previously studied prospectively.

We conducted a large cohort study to investigate the association between bowel habits, laxative use, susceptibility to diarrhoea and the colorectal cancer risk in Japanese men and women.

MATERIALS AND METHODS

All data were taken from the Japan Collaborative Cohort (JACC) Study, the methods of which have been described in detail elsewhere (Ohno and Tamakoshi, 2001). Briefly, the original study population consisted of 110 792 Japanese adults aged 40–79 years. Enrolment began in 1988 and continued until the end of 1990 in 45 areas across Japan. Most subjects were recruited from the general population or when undergoing routine health checks in the municipalities. Written informed consent for participation was obtained individually from subjects, with the exception of a few

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study areas in which informed consent was provided at the group level after explaining the aims of the study and confidentiality of the data to community leaders. The study protocol was approved by the Ethics Committee of Medical Care and Research of the Fujita Health University School of Medicine, Japan.

Analyses were restricted to data from the 65 184 participants who lived in the 24 study areas in which cancer registries were available. A further 58 subjects with a previous history of colorectal cancer, and 2197 subjects for whom information about bowel habits was not available, were excluded. Therefore, a total of 62 929 individuals (25 731 men and 37 198 women) were involved in this analysis.

All participants completed a self-administered questionnaire on enrolment. This covered demographic characteristics and lifestyle factors such as diet, tobacco smoking, alcohol consumption, physical activity, BM frequency, susceptibility to diarrhoea and laxative use over the past year. The alternative answers provided on the questionnaire for the frequency of BM were: 'daily', 'every 2–3 days', 'every 4–5 days' and 'every 6 days or less'. With regard to laxative use, the questionnaire asked only whether the participants used laxatives in the past one year at the time of enrolment; additional data on the type of laxative, the reason for use and the duration of use were not collected. Participants also provided information about susceptibility to diarrhoea by answering 'yes', 'no' or 'neutral' in response to the question: do you often have diarrhoea?

Population registries in the municipalities were used to determine the vital and residential status of subjects. Registration of death is required under the Family Registration Law in Japan, which applies throughout the country. Incidences of cancer were confirmed using records from the population-based cancer registries, which were supplemented by a systematic review of death certificates (Ohno and Tamakoshi, 2001); in some areas, medical records were also reviewed in major local hospitals. The mortality-to-incidence ratio for colorectal cancer was 0.28 in the cohort covered by the cancer registries. This figure is comparable with those calculated in the most accurate population-based cancer registries in Japan (Parkin *et al*, 2003), which indicates that most cases of colorectal cancer were identified in the study population.

The follow-up period ran from the time of the baseline survey through to the end of 1997 in all but three areas (in which it ran until the end of 1994, 1995 and 1996, respectively). The end point of the study was defined as the incidence of colorectal cancer (10th Revision of the International Classification of Diseases, ICD-10: C18–C20) or colon cancer (ICD-10: C18). The risk of rectal cancer was not analysed separately because of the relatively small number of cases observed. Subjects who moved out of the study area or died from causes other than colorectal cancer were treated as censored cases. During the study period, only 3.3% (2071) of the participants were lost from the follow-up as a result of a change of residence.

All analyses were carried out by sex using the SAS statistical package release 8.2 (SAS Inc., Cary, NC, USA). Differences in baseline characteristics between categories of BM frequency were tested using the chi-squared (χ^2) test or one-way analysis of variance (ANOVA). The follow-up period for each participant was calculated as the time between completing the questionnaire and either the diagnosis of colon or rectal cancer, death, moving out of the study area or the end of the study – whichever occurred first.

The incidence rate ratios (IRR) and 95% confidence intervals (CI) for colorectal and colon cancer were estimated, by sex, using Cox's proportional-hazard model according to the levels of BM frequency, laxative use and susceptibility to diarrhoea. The categories of 'every day' for BM, 'nonuse' for laxative use and 'no' or 'neutral' for susceptibility to diarrhoea were used as reference groups.

Analyses were adjusted for the following potential confounding factors: age (continuous variable); body mass index (BMI) calculated as weight (kg) [height (m)]$^{-2}$ and categorised as '$\geqslant 25\,kg\,m^{-2}$' or '$<25\,kg\,m^{-2}$'; intake frequency of green leafy vegetables ('daily' or 'not daily'); intake frequency of alcohol ('$\geqslant 5$ days per week' or '<5 days per week'); current smoking status ('smoker' or 'nonsmoker'); time spent walking per day ('$\leqslant 30$ min or '>30 min'); history of colorectal cancer in parents or siblings ('yes' or 'no'); and age at leaving full-time education ('$\geqslant 20$ years' or '<20 years'). For each covariate, missing values were treated as an additional category and were included in the model. To determine the influence of symptoms of colorectal cancer on bowel habits, analyses were repeated excluding the first 3 years of follow-up. In all cases, two-sided P-values <0.05 were considered to be statistically significant.

RESULTS

Within the study group, 1.1% of men and 4.0% of women reported infrequent BMs (every 4 days or less). The use of laxatives was more common among women (14.7%) than men (6.9%), whereas men were more likely to report frequent diarrhoea (20.3%) than were women (9.7%).

Table 1 shows the baseline characteristics of the study population by BM frequency. Regardless of sex, individuals who reported infrequent BMs – compared with those who reported BMs daily or every 2–3 days – had a lower average BMI, were less likely to spend >30 min walking per day and were more likely to use laxatives.

A significant difference in the intake frequency of green leafy vegetables and in smoking status across the BM groups was observed only among women: those who reported BMs daily or every 2–3 days were more likely to consume green leafy vegetables daily and less likely to be smokers. In addition, women who reported BMs every 2–3 days were, on average, younger than those in the other BM groups. Alcohol consumption did not differ between BM groups in women.

Among men, the number that reported daily alcohol intake increased linearly with BM frequency. Male subjects who reported BMs every 2–3 days had the lowest rate of frequent diarrhoea, whereas the number of women who reported frequent diarrhoea decreased linearly with BM frequency.

During the follow-up period (average length 7.6 years, standard deviation 1.9), a total of 649 cases of colorectal cancer were identified (379 in men and 270 in women), which included 429 cases of colon cancer (225 in men and 204 in women).

Age-adjusted IRRs were calculated for colorectal and colon cancer according to BM frequency (not shown). Regardless of sex, the ratios were <1.00 for subjects who reported BMs every 2–3 days relative to those who reported daily BMs: the IRRs for colorectal cancer were 0.74 in men (95% CI = 0.51–1.09) and 0.71 in women (95% CI = 0.52–0.97), whereas the IRRs for colon cancer were lower in men (0.45; 95% CI = 0.25–0.82) and the same in women (0.71; 95% CI = 0.49–1.00). In contrast, the age-adjusted IRRs for subjects who reported highly infrequent BMs (every 6 days or less) relative to those with daily BMs were >1.00: the IRRs for colorectal cancer were 1.14 in men (95% CI = 0.16–8.10) and 2.53 in women (95% CI = 1.04–6.15), whereas the IRRs for colon cancer were 1.78 in men (95% CI = 0.25–12.7) and 2.59 in women (95% CI = 0.96–6.98).

Adjustment for potential confounding factors (as discussed above) had no significant effects on the IRRs (Table 2). Furthermore, even after excluding the first 3 years of follow-up, there was a lower risk of colorectal or colon cancer in women who reported BMs every 2–3 days relative to those who reported daily BMs: the multivariate-adjusted IRRs were 0.64 for colorectal cancer (95% CI = 0.43–0.96) and 0.68 for colon cancer (95% CI = 0.43–1.05). Increased risks of colorectal and colon cancers were also observed in association with highly infrequent BMs

Table 1 Background characteristics of the participants at baseline by BM frequency by sex

Variable	BM frequency									
	Men					Women				
	⩾1 per day, ($n=22\,930$)	Every 2–3 days, ($n=2526$)	Every 4–5 days, ($n=222$)	Every 6 days or less, ($n=53$)	*P*-value[a]	⩾1 per day, ($n=25\,884$)	Every 2–3 days, ($n=9813$)	Every 4–5 days, ($n=1238$)	Every 6 days or less, ($n=263$)	*P* value[a]
Age (years)										
Mean	57.6	59.7	62.5	65.9	<0.0001	58.4	57.3	57.4	58.8	<0.0001
s.d.	10.2	11.2	11.3	11.6		9.9	10.5	10.8	11.0	
BMI ($kg\,m^{-2}$)										
Mean	22.7	22.2	21.7	21.7	<0.0001	23.1	22.6	22.5	22.0	<0.0001
s.d.	3.0	2.9	3.1	3.6		3.6	3.0	3.1	3.0	
Having green leafy vegetables every day (%)	26.2	26.1	20.7	22.6	0.29	32.5	27.8	27.1	24.7	<0.0001
Daily alcohol drinking (%)	48.4	36.0	33.3	28.3	<0.0001	5.2	4.7	4.3	4.9	0.15
Current smokers (%)	50.3	48.9	51.8	47.2	0.55	4.5	4.7	8.1	11.4	<0.0001
Daily walking time <30 min (%)	25.9	32.3	38.3	50.9	<0.0001	22.4	26.6	31.9	37.3	<0.0001
Having family history of colorectal cancer (%)	2.2	2.1	1.8	0.0	0.71	2.5	2.5	3.1	3.4	0.53
Age of final education completed ⩾20 years (%)	11.8	11.4	8.1	15.1	0.30	5.2	5.6	4.9	4.2	0.29
Use of laxatives (%)	4.6	21.8	46.2	60.5	<0.0001	8.5	24.1	48.5	64.3	<0.0001
Having frequent diarrhoea (%)	20.7	16.5	20.1	18.8	<0.0001	10.7	7.6	6.4	3.8	<0.0001

BM = bowel movement; BMI = body mass index; ANOVA = analysis of variance. [a]Test for homogeneity of characteristics between categories of BM frequency, using ANOVA (age, BMI) and χ^2 (other variables).

Table 2 IRR for colorectal and colon cancer according to BM frequency by sex

BM	Observed person-years	Colorectal cancer			Colon cancer		
		No. of cases	Multivariate-adjusted[a] IRR	95% CI[b]	No. of cases	Multivariate-adjusted[a] IRR	95% CI[b]
Men							
⩾1 per day	175 485	346	1.00		211	1.00	
Every 2–3 days	18 335	30	0.77	0.53–1.12	11	0.46	0.25–0.85
Every 4–5 days	1515	2	0.56	0.14–2.26	2	0.93	0.23–3.75
Every 6 days or less	321	1	1.16	0.16–8.27	1	1.86	0.26–13.4
Women							
⩾1 per day	196 472	204	1.00		155	1.00	
Every 2–3 days	72 891	51	0.71	0.52–0.97	38	0.70	0.49–0.996
Every 4–5 days	8937	10	1.12	0.59–2.11	7	1.01	0.47–2.17
Every 6 days or less	1880	5	2.47	1.01–6.01	4	2.52	0.93–6.82

IRR = incidence rate ratios; BM = bowel movement; BMI = body mass index. [a]Adjusted for age, BMI, intake frequency of green leafy vegetables, daily alcohol drinking, current smoking status, time spent for walking per day, family history of colorectal cancer and education. [b]CI: confidence interval.

(every 6 days or less), although they were not statistically significant.

Table 3 shows the associations between laxative use, susceptibility to diarrhoea and colorectal or colon cancer risk. There were weak nonsignificant positive associations between laxative use and cancer risk in both men and women, but no association between cancer risk and frequent diarrhoea.

DISCUSSION

This is the first prospective study, to our knowledge, that has reported a significant association between BM frequency and colorectal cancer risk. Infrequent BMs were associated with a significantly increased risk of colorectal cancer and a marginally increased risk of colon cancer in women. A similar, but

Table 3 IRR for colorectal and colon cancer according to laxative use and susceptibility to diarrhoea

		Colorectal cancer			Colon cancer		
	Observed person-years	No. of cases	Multivariate-adjusted[a] IRR	95% CI[b]	No. of cases	Multivariate-adjusted[a] IRR	95% CI[b]
Men							
Laxative use							
No	155 068	292	1.00		170	1.00	
Yes	10 015	33	1.28	0.89–1.86	20	1.31	0.81–2.11
Susceptibility to diarrhoea							
Normal	143 808	285	1.00		168	1.00	
Having frequent diarrhoea	35 775	68	1.08	0.82–1.41	40	1.08	0.76–1.53
Women							
Laxative use							
No	206 189	183	1.00		137	1.00	
Yes	33 097	41	1.20	0.85–1.69	33	1.26	0.86–1.85
Susceptibility to diarrhoea							
Normal	230 880	224	1.00		173	1.00	
Having frequent diarrhoea	23 417	26	1.18	0.79–1.78	16	0.95	0.57–1.59

IRR = incidence rate ratios; BMI = body mass index. [a]Adjusted for age, BMI, intake frequency of green leafy vegetables, daily alcohol drinking, current smoking status, time spent for walking per day, family history of colorectal cancer and education. [b]CI: confidence interval.

nonsignificant, association was found in men. These results were not altered by adjusting for potential confounding factors or excluding the first 3 years of follow-up from the analysis, which indicated that the effects of the cancers themselves on bowel habits were not responsible for the associations.

These results support the findings of recent case–control studies and of the meta-analysis carried out by Sonnenberg and Müller (1993), which reported a significantly increased risk of colorectal cancer in association with constipation or infrequent BMs. However, the findings from the Nurses' Health Study in the United States – only one published prospective data on the association between BM frequency and female colorectal cancer risk (Dukas *et al*, 2000) – did not support an association between infrequent BMs and the risk of colorectal cancer. One possible reason for the discrepancy between these results and those of the present study is that different criteria were used to define 'infrequent BM'. The Nurses' Health Study defined this as an average frequency of 'every third day or less'. However, in the present study, a significantly increased risk of colorectal and colon cancer was found only in subjects who reported BMs every 6 days or less relative to those reporting daily BMs. Therefore, we suggest that only highly infrequent BMs elevate the risk of colorectal cancer.

Daily BMs were found to increase the risk of colorectal and colon cancer compared with BMs every 2–3 days, in both men and women. This observation is in line with the results of a previous case–control study carried out in Japan (Kato *et al*, 1993). However, the Nurses' Health Study (Dukas *et al*, 2000) found no difference in colorectal cancer incidence between subjects who reported $\geqslant 2$ BMs per day and those who reported BMs once per day (multivariate-adjusted IRR = 0.89, 95% CI = 0.65–1.20). Unfortunately, limitations of the questionnaire used in the present study precluded us from determining the risk associated with $\geqslant 2$ BMs per day. On the basis of the combined findings of these studies, we speculate that subgroups that have highly frequent BMs might be at an increased risk of colorectal cancer. Experimental studies have reported elevated levels of prostaglandin E_2 (PGE_2) in the gastrointestinal tract in many diarrhoeal states (Burakoff and Percy, 1992), and increased levels of PGE_2 might be associated with carcinogenesis in the large intestine (Reddy *et al*, 1993). We did not observe a significant association between self-reported susceptibility to diarrhoea and colorectal cancer risk, and the results of previous epidemiological studies (case–control studies only) were inconsistent (Dales *et al*, 1979; Kune *et al*, 1987). Similar to 'constipation', the definition of 'diarrhoea' is equivocal. Some case–control studies have suggested that 'soft' or 'loose' faeces might increase the risk of colorectal cancer (Kato *et al*, 1993; Inoue *et al*, 1995). To have a conclusion, additional data on factors such as faecal consistency should be collected and analysed together with data on susceptibility to diarrhoea and BM frequency.

A weak nonsignificant positive association was found between laxative use and the risk of colorectal cancer in both men and women. Previously, the meta-analysis of Sonnenberg and Müller (1993) revealed a significant 46% increase in the risk of colorectal cancer associated with the use of laxatives. On the other hand, recent case–control studies (Jacobs and White, 1998; Nascimbeni *et al*, 2002; Roberts *et al*, 2003) and a prospective study (Dukas *et al*, 2000) found no relationship between these factors – although Dukas *et al* suggested that some types of laxative might influence intestinal pH and the metabolism of intestinal flora, thereby modifying colorectal cancer risk. The effects of laxative type were not investigated in the present study because of limitations of the questionnaire. Further prospective studies investigating the types of laxative and duration of use will be necessary to resolve this question.

The risk of rectal cancer was not analysed independently because of the small number of cases in the study group. Larger-scale prospective studies will be necessary to reveal the effects of bowel habits on the development of cancers of the large intestine at specific sites.

There were some limitations to the scope of the present study. For example, although the main risk factors for colorectal cancer were adjusted for in the analysis, other factors such as aspirin use and hormone replacement therapy in women might have confounded the results. Also, bowel habits were evaluated only through a self-reported questionnaire that was administered once at the baseline; the reproducibility and validity of the responses of subjects were therefore not confirmed.

In conclusion, this study shows that highly infrequent BMs can increase the risk of colorectal cancer in both men and women. Highly frequent BMs may also enhance this risk. Further

prospective studies are needed to confirm our findings and to clarify the risk associated with BMs for colorectal cancer by subsite.

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PAPER

A prospective study of body size and colon cancer mortality in Japan: The JACC Study

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OBJECTIVE: To determine whether body size measurements are risk factors for colon cancer death among the Japanese.
DESIGN AND SUBJECTS: A nationwide prospective study, the Japan Collaborative Cohort (JACC) Study from 1988 to 1999. The present analysis included 43 171 men and 58 775 women aged 40–79 y who respond to a questionnaire on current weight and height, weight around 20 y of age, and other lifestyle factors. Body mass index (BMI) at baseline and 20 y of age (B-BMI and 20-BMI, respectively) were calculated.
RESULTS: We identified 127 deaths from colon cancer during the follow-up of 424 698 person-years among men and 122 deaths during the follow-up of 591 787 person-years among women. After adjustments for the lifestyle factors known to modify the risk of colon cancer, weight at baseline showed a significant positive association in women, while no such association was seen in men. There was also a significant trend of increasing risk with the increase in B-BMI among women. Women with B-BMI $\geq 28\,kg/m^2$ had a relative risk (RR) of 3.41 (95% confidence interval (CI): 1.44–8.06) compared with those with BMI of 20–$<22\,kg/m^2$. 20-BMI also presented the same trend of increasing risk as B-BMI. Women with 20-BMI of <22 and B-BMI of $>26\,kg/m^2$, that is, excessive BMI gain, had a high RR of 3.41 (95% CI 1.29–9.02) compared with those with 20-BMI of <22 and B-BMI of $<22\,kg/m^2$. There were no corresponding trends of colon cancer risk for B-BMI, 20-BMI, or BMI change among men.
CONCLUSIONS: These study data suggest that obesity and excessive weight gain are associated with the risk of colon cancer death in Japanese women but no such relationship was found in Japanese men.
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Keywords: body size; body mass index; weight change; colon cancer; cohort study

Introduction

Colon cancer is now the fourth leading cause of cancer death among men and the third among women in Japan. This malignancy has markedly increased since the end of World War II. The ratio of the age-adjusted rate (adjusted by the 1985 Japanese model population) in 1999 to that in 1960 was 4.1 (from 3.6 to 14.7 per 100 000 population) and 2.7 (from 3.6 to 9.8 per 100 000 population) among men and women, respectively.[1] International comparison studies[2] and observations[3] of increased rates in subjects who migrate from low- to high-risk regions indicate that westernization or industrialization may lead to an increase in the rates of colon cancer. Although the precise causes of colon cancer remain unclear, various dietary components such as high consumption of red meat or animal fat, physical

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inactivity, and obesity have been studied as possible risk factors.[4–27]

Despite the number of prospective[4–18] and case–control[19–27] studies that have examined the association between body size and colon cancer in greater or lesser detail, the evidence of obesity as a risk factor is inconclusive. Several studies[4–13,19,22–24] have found positive associations between body mass and risk of colon cancer in men, whereas most of the studies[4–7,9,14–16,20–26] in women suggested either no association or only weakly positive associations. A few studies[8,17] have shown that obesity is indeed related to colon cancer in women. Some studies[20,26] found no association in either men or women, and one study[18] reported that men who developed colon cancer weighed slightly less than those who did not. Height also appeared to be associated with an increased risk of colon cancer in some studies,[11] but not all.[25] Few studies, however, have been addressed the effect of body size on colon cancer risk among Asians, who are generally shorter and leaner than Occidentals among whom the incident and mortality rates of colon cancer are higher. Since the prevalence of obesity has gradually increased in Japan in recent years, it is important to characterize its role in colon cancer mortality.

To elucidate the effects of body size on the risk of colon cancer death among Japanese, we prospectively examined the associations of height, weight and body mass index (BMI) at baseline (B-BMI), BMI around age 20 (20-BMI), and BMI change with colon cancer among Japanese men and women, using nationally representative large-scale cohort data.

Subjects and methods

JACC study

The Japan Collaborative Cohort Study for Evaluation of Cancer Risk, the JACC Study (sponsored by the Ministry of Education, Culture, Sports, Science, and Technology of Japan), is a nationwide multicenter collaborative study to prospectively evaluate various risks or preventive factors as they relate to cancer mortality and incidence. Study methods and ethical issues have been described in detail elsewhere.[27] Briefly, our study was initiated in 1988, and enrollment was continued until the end of 1990. Subjects were followed until the end of 1999 unless they had moved out of the study areas. A total of 45 municipalities were involved in this prospective study, including six cities (35% of the cohort population) and 34 towns and five villages (65%). These municipalities were selected from seven out of eight districts in Japan, thus covering almost the entire country. Enrollment was based on the participants in general health checkups periodically provided by these municipalities. We enrolled 127 477 apparently healthy inhabitants of these areas who had completed the questionnaire. Two strategies were applied to obtain informed consent for participation: in the majority of study areas. In some areas consent was obtained by signing the cover page of the questionnaire. In others, it was obtained at the group level by explaining the aim and confidentiality of the data to leaders of the community. Of 127 477 participants enrolled, 110 792 (46 465 men and 64 327 women) aged 40–79 y were followed up for mortality to the end of 1999.

The Ethics Committee of Fujita Health University approved this investigation.

Present study subjects

Of 110 792 subjects enrolled, we excluded from analysis 1258 with a history of any cancers at baseline, 6070 of unknown height, and 4393 of unknown weight. We also excluded subjects with extreme height (<120 cm or ≥ 200 cm: 47 subjects), weight (<30 kg or ≥ 120 kg: 27 subjects), or calculated BMI (<15 kg/m^2 or ≥ 45 kg/m^2: 201 subjects). To minimize confounding the data by undiagnosed diseases, we further excluded 933 subjects who had less than 1 year of follow-up time. Therefore, 43 171 men and 58 775 women were finally enrolled in the present study. In another analysis of the effects of BMI around aged 20 y and BMI change on colon cancer risk, we further excluded 27 483 subjects of unknown weight around 20 y of age, 65 extremely under- or overweight subjects (<30 kg or ≥ 120 kg), and 143 subjects with extreme calculated 20-BMI (<15 kg/m^2 or ≥ 45 kg/m^2). This left 31 585 men and 42 735 women eligible for the second analysis.

Data collection

A self-administrated questionnaire was used to assess baseline characteristics of the participants. It covered medical history and included lifestyle-related items such as diet, physical activity, drinking and smoking, and family history of several medical conditions including cancer. In the questionnaire, weight in kilograms and height in centimeters were entered by participants after the words 'Current weight and height' and 'Weight around 20 y of age'. BMI at baseline was computed as current weight in kilograms divided by current height in square meters. 20-BMI was also computed as weight around 20 y of age in kilograms divided by current height in square meters.

Follow-up and identification of colon cancer cases

Our primary end points were death from any causes or 31 December 1999 (censored). Those who had moved away were also treated as censored. The mean follow-up period was 10.0 y (9.8 y for men and 10.1 y for women).

The vital status of subjects was checked annually in each study area by reviewing their population register sheets from the Ministry of Public Management, Home Affairs, Post and Telecommunications. For the deceased, causes of death were determined by death certificates available from the Ministry of Health, Labor and Welfare and coded according to the ninth revision of International Classification of Diseases (ICD-9) by the end of 1994 and according to ICD-10 from

1995. Colon cancer cases were defined by 153.0–153.9 (ICD-9) or C18.0–C18.9 (ICD-10). Certification of vital status was believed to be accurate because of the firmly established population registration system in Japan.

Statistical analysis

In the present study, variables of interest are current weight and height, B-BMI, 20-BMI, and BMI change. Tertiles of weight and height were defined separately for men and women from the distribution of total study subjects. BMI categories were defined as follows: <20.0, $20.0-<22.0$, $22.0-<24.0$, $24.0-<26.0$, $26.0-<28.0$, $\geq 28.0\,kg/m^2$ to enable a detailed examination of the association of BMI and colon cancer mortality. In the analysis of BMI change, these six categories were combined into three (<22.0, $22.0-<26.0$, ≥ 26.0), and the subjects were divided into nine groups of B-BMI/20-BMI combinations.

For each participant, the person-years of follow-up were calculated from the date of filling out the baseline questionnaire to death, moving away from the community, or the end of 1999, whichever occurred first. We used Cox proportional hazards modeling to compute relative risks (RRs), adjusting for age at enrollment. In another multivariate analysis, further adjustments were made to smoking status (never, past, current), alcohol drinking habit (none, past, present), exercise (≥ 5, 3–4, 1–2 hours per week, seldom), green leafy vegetable intake (3–7, 1–2 days per week, seldom), meat intake (3–7, 1–2 days per week, seldom), and family history of colon cancer. These variables were assessed by the baseline questionnaire and were selected as covariates because they were known or suspected to modify the risk of colon cancer. In the analysis, all variables were entered as dummy variables except for age at enrollment. Tests for trends were performed by modeling the categories of variable of interest as equally spaced ordinal variable.

All data were analyzed using SAS (Statistical Analysis System) software. The 95% confidence intervals (CIs) were presented for all RRs. All *P*-values were based on two-sided tests, and $P<0.05$ was considered statistically significant.

Results

We identified 127 deaths from colon cancer during the follow-up of 424 698 person-years among men and 122 deaths during the follow-up of 591 787 person-years among women.

The associations of weight and height at baseline with colon cancer death risk by gender are presented in Tables 1 and 2. In multivariate analysis, weight at baseline showed a significant positive association in women, while no corresponding association was seen in men. We compared RRs among the nine categories of weight/height combinations to assess the effects of weight and height. Among men, the tallest were likely to show elevated RR at each stratum of weight, but no significant association was seen. RRs in light (<49.0 kg) and tall (≥ 153.1 cm) women were significantly higher (RR 3.48, 95% CI 1.27–9.50) than in women who were light and short (<149.0 cm). Women who were heavy (≥ 55.1 kg) and short, and those who were heavy and

Table 1 Adjusted relative risk (RR) for colon cancer death by weight and height at baseline among men, JACC study, 1988–1999

Baseline weight and height		*No. of deaths*	*Person-years*	*RR*[a]	*95% CI*	*RR*[b]	*95% CI*
Weight (kg)							
Lowest tertile (<56.0)		52	136 639	1.00		1.00	
Tertile 2 (56.0–<63.1)		37	145 847	0.95	0.62–1.46	0.90	0.52–1.55
Highest tertile (63.1–)		38	142 212	1.29	0.83–1.99	1.13	0.64–1.99
P-value for trend					0.30		0.72
Height (cm)							
Lowest tertile (<160.1)		55	153 418	1.00		1.00	
Tertile 2 (160.1–<165.1)		37	134 638	1.04	0.68–1.59	0.97	0.55–1.71
Highest tertile (165.1–)		35	136 642	1.34	0.87–2.08	1.58	0.91–2.73
P-value for trend					0.21		0.12
Weight (kg) and height (cm)							
Weight	Height						
<56.0	<160.1	33	84 550	1.00		1.00	
<56.0	160.1–<165.1	13	36 814	1.12	0.59–2.13	1.11	0.48–2.54
<56.0	165.1–	6	15 275	1.43	0.60–3.41	1.51	0.51–4.45
<56.0–<63.1	<160.1	13	49 754	0.87	0.46–1.65	0.77	0.32–1.84
<56.0–<63.1	160.1–<165.1	14	54 032	1.07	0.57–2.01	0.79	0.33–1.90
<56.0–<63.1	165.1–	10	42 062	1.22	0.59–2.50	1.58	0.70–3.57
63.1	<160.1	9	19 114	1.73	0.83–3.63	1.26	0.42–3.72
63.1	160.1–<165.1	10	43 792	1.04	0.51–2.13	0.92	0.36–2.34
63.1	165.1–	19	79 306	1.50	0.83–2.71	1.45	0.69–3.07

[a]Adjusted for age at baseline. [b]Adjusted for age at baseline, smoking status (never, past, current), alcohol consumption (none, past, regular), exercise (≥ 5, 3–4, 1–2 days/week, seldom), meat intake (3–7, 1–2 days/week, seldom), green leafy vegetable intake (3–7, 1–2 days/week, seldom) and family history of colon cancer.

Table 2 Adjusted RR for colon cancer death by weight and height at baseline among women, JACC study, 1988–1999

Baseline weight and height		*No. of deaths*	*Person-years*	*RR*[a]	*95% CI*	*RR*[b]	*95% CI*
Weight (kg)							
Lowest tertile (<49.0)		39	189 958	1.00		1.00	
Tertile 2 (49.0–<55.1)		46	214 488	1.49	0.97–2.29	1.87	1.06–3.29[e]
Highest tertile (55.1–)		37	187 341	1.65	1.04–2.62[e]	2.17	1.21–3.92[d]
P-value for trend					<0.05		<0.01
Height (cm)							
Lowest tertile (<149.0)		45	185 721	1.00		1.00	
Tertile 2 (149.0–<153.1)		43	208 873	1.26	0.83–1.92	1.30	0.77–2.19
Highest tertile (153.1–)		34	197 193	1.54	0.97–2.44	1.38	0.77–2.48
P-value for trend					0.07		0.26
Weight (kg) and height (cm)							
Weight	Height						
<49.0	<149.0	22	98 645	1.00		1.00	
<49.0	149.0–<153.1	9	61 920	0.93	0.43–2.02	0.62	0.17–2.23
<49.0	153.1–	8	29 393	2.24	0.99–5.05	3.48	1.27–9.50[e]
49.0–<55.1	<149.0	15	60 270	1.39	0.72–2.69	1.77	0.75–4.18
49.0–<55.1	149.0–<153.1	17	85 371	1.56	0.82–2.96	2.15	0.94–4.92
49.0–<55.1	153.1–	14	68 847	2.29	1.15–4.55[e]	2.71	1.10–6.71[e]
55.1–	<149.0	8	26 806	1.83	0.81–4.11	3.24	1.30–8.08[e]
55.1–	149.0–<153.1	17	61 582	2.30	1.21–4.38[e]	3.45	1.54–7.71[d]
55.1–	153.1–	12	98 953	1.45	0.70–2.98	1.27	0.46–3.53

[a]Adjusted for age at baseline. [b]Adjusted for age at baseline, smoking status (never, past, current), alcohol consumption (none, past, regular), exercise (≥5, 3–4, 1–2 days/week, seldom), meat intake (3–7, 1–2 days/week, seldom), green leafy vegetable intake (3–7, 1–2 days/week, seldom) and family history of colon cancer. [d]$P<0.01$. [e]$P<0.05$.

medium height (149.0–<153.1 cm) had multivariate-adjusted RRs of 3.24 (95% CI 1.30–8.08) and 3.45 (95% CI 1.54–7.71), respectively, compared with light and short women. However, the RR for tall and heavy women was 1.27 (95% CI 0.46–3.53).

The relations between B-BMI and BMI in young adults (20-BMI), and colon cancer death risk by gender are shown in Table 3. Among men, those with B-BMI of <20.0 had a significantly lower RR (0.44, 95% CI 0.21–0.93) than those with BMI of 20–<22. 20-BMI in men also showed no association with risk. In contrast, there was a significant trend of increasing risk with the increase in B-BMI among women. The strongest association was for the highest category (B-BMI ≥28) (RR 3.41, 95% CI 1.44–8.06). 20-BMI of women also presented the same trend of increasing risk as B-BMI. 20-BMI was significantly correlated with B-BMI among both men and women (Pearson $r=0.52$, $P<0.0001$, and $r=0.45$, $P<0.0001$, respectively).

We compared RRs among the nine categories of 20-BMI/B-BMI combinations to assess the effects of 20-BMI and B-BMI, and the effect of BMI change (Table 4). When the subjects with low 20-BMI (<22.0) and low B-BMI (<22.0) were referenced, no association was seen in men by multivariate analysis, whereas the RR of women with medium 20-BMI (22–<26) and B-BMI (22–<26) was 2.01 (95% CI 1.02–3.97), and those with high 20-BMI (≥26) and B-BMI (≥26) was 3.33 (95% CI 1.46–7.63). We also found that women with low 20-BMI and high B-BMI, that is, excessive BMI gain, had a high RR of 3.41 (95% CI 1.29–9.02).

Discussion

In Japan, the incidence and mortality rate of colon cancer are much lower than that in Western countries. This difference may be attributed in part to the fact that both Japanese men and women are generally shorter and lighter than Occidentals. Therefore, we examined whether BMI exhibited a positive association with colon cancer in such a low-risk population, as had been observed in some Western countries. Interestingly, in the Japanese population, BMI at entry into the study was strongly predictive of colon cancer over the almost 10-year follow-up period only among women but not among men.

Among prospective studies,[4–18] at least six[4–9] included both men and women and presented separate estimates of RR of obesity for colon cancer. All six studies showed positive associations in men, but only two[6,8] reported positive associations in women. As for the role of obesity in the etiology of colon cancer, Giovanucci[28] has proposed that obesity results in insulin resistance, and that the resulting prolonged elevated insulin levels may increase colon cancer risk by acting as a tumor growth promoter or mitogen. Mckeown-Eyssen[29] also suggested that the serum levels of glucose and triglycerides, which tend to be higher in obese people, may affect the fecal bile acids that have been implicated in the pathogenesis of colon cancer.

Although the reasons for the gender difference in previous studies,[4,5,7,9] that is, that the association between increased BMI and colon cancer risk is stronger in men than in women, are not completely understood, the male tendency toward