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

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Abstract

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

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Introduction

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

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

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

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

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

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

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

Materials and Methods

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

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

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

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

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

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

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

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

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

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

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

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

Results

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

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

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

Table 1. Baseline characteristics of colorectal cancer cases and controls

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

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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