Reduced Low-Density-Lipoprotein Cholesterol Causing Low Serum Cholesterol Levels in Gastrointestinal Cancer. A Case Control Study

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Several epidemiological studies suggested an inverse relation between serum cholesterol level and cancer mortality. We analyzed the relation between gastrointestinal cancers and serum cholesterol levels. A total of 631 patients were recruited as cancer-bearing cases, comprising 181 esophageal cancers, 251 gastric cancers and 199 colorectal cancers. A case-control analysis was conducted on the serum TC, HDL-C, LDL-C and TG levels. TC and LDL-C were significantly lower in cancer-bearers by approximately 15 mg/dl. Furthermore, analyses by cancer site also showed significantly lower TC and LDL-C levels in cancer-bearers than in controls for all three sites. In this analysis, early stage cancer-bearers showed a significant decrease in TC levels by approximately 11 mg/dl compared with controls, and also a similar decrease in LDL-C levels. These results suggest that low TC levels are not related to cancer stage. Furthermore, findings of no significant differences in HDL-C and TG between cancer-bearing cases and controls in addition to a specific decrease in LDL-C in cancer-bearers suggest that hypocholesterolemia observed in these cases stems from low LDL-C. However, cancer-bearers and controls showed a similar distribution of TC and LDL-C levels. We should be aware that latent cancer bearers may be present among subjects with hypocholesterolemia.

Key Words: Serum cholesterol, Low-density-lipoprotein cholesterol, Gastrointestinal cancer

The underlying cause and development of diseases are generally known to be associated with genetic factors and environmental factors. Recently, as one aspect of environmental factors, lifestyle-related diseases have been highlighted (1,2). Specifically, undesirable lifestyles such as overeating, excessive fat and salt intake, insufficient dietary fiber, drinking, smoking, lack of exercise, and excessive intake of hyperoxidized substances increase the risks not only of chronic diseases such as obesity, diabetes, hyperlipemia and arteriosclerosis, but also of malignant diseases (3). Furthermore, among gastrointestinal cancers in Japan, gastric cancer that had the higher incidence in the past has declined, with an accompanied concomitant increase in colorectal cancer (4). A factor that contributes to this tendency is the recent change in lifestyle, especially Westernization of eating habits that lead to an increased fat intake. Accompanying this increase trend, an elevation of serum cholesterol levels has also been observed (4). On the other hand, several epidemiological studies suggested an inverse relation between serum cholesterol levels and cancer mortality (5-10). However, previous studies examined cardiovascular diseases, and the relation between cancers of all sites and serum cholesterol levels.

In the present study, we focused on cancers of the gastrointestinal tract, a site that has important physiological functions of digestion, absorption, nutrition and metabolism, and is most susceptible to eating habits. Specifically, we conducted a case-control study comparing the serum lipids in cancer-bearers (esophageal cancer, gastric cancer and colorectal cancer) and non-cancer-bearers, and analyzed the relation between gastrointestinal cancers and serum cholesterol levels.

Materials and Methods

Among 942 patients who underwent resection of gastrointestinal cancers at our department between 1998 and 2000, 631 patients (518 males and 113 females) were recruited as cancer-bearing cases after excluding those with synchronous or metachronous cancers, a history of gastrointestinal surgery (exclud-

ing appendectomy), and those under treatment for hyperlipemia or diabetes that might secondarily affect the serum lipid levels. In addition, 2104 patients seen during the same period, who did not match the above exclusion criteria were recruited as noncancer-bearing controls. Subjects who received health examination within the past two years and were judged to have no abnormalities were recruited as controls.

The diagnoses of esophageal cancer, gastric cancer and colorectal cancer were confirmed by histopathological examinations of the surgically or endoscopically resected tissues, which showed findings of malignant tumors in all cases. From the histopatholgical findings, the cancers were defined as early stage cancers when the tumors infiltrated up to the submucosa, and as advanced stage cancers when the tumors infiltrated the muscularis propria and deeper layers.

For each case, a control matched for age (divided into 13 age groups of 5-year intervals), gender, and body mass index (BMI: weight/height2) (divided into 45 groups in units of 0.5) was selected randomly from the control group.

The gastrointestinal cancers comprised 181 esophageal cancers, 251 gastric cancers and 199 colorectal cancers. The cancer-bearers and controls had identical backgrounds (Table I). There were 259 early stage cancers (63 esophageal cancers, 136 gastric cancers, and 60 colorectal cancers) and 372 advanced stage cancers (118 esophageal cancers, 115 gastric cancers, and 139 colorectal cancers).

Serum samples were collected at two time points: during each participant's initial visit and at a subsequent visit. Total cholesterol (TC), high-density-lipoprotein cholesterol (HDL-C) and triglycerides (TG) measured at the examination were used as indices of serum lipids. Low-density-lipoprotein cholesterol (LDL-C) was estimated according to Friedewald (11) which is TC - TG/5 - HDL-C. All measurements were averaged. A case-control analysis was conducted on the serum TC, HDL-C, LDL-C and TG levels of the cancer-bearing cases and nontumor-bearing controls.

Paired t test was used to compare the cases and controls (only TG was analyzed after converting to a logarithmic scale). A p value less than 0.05 was considered significant. The values are presented as means ± SD.

Results

The results of case-control analyses of cholesterol levels for all gastrointestinal cancers are shown in Table II. The TC level for gastrointestinal cancer-bearers was 181±34 mg/dl compared with 196±36 mg/dl for controls, and was significantly lower ($p < 0.001$) by approximately 15 mg/dl. The LDL-C level for cancer-bearers was 104±31 mg/dl compared with 119±35 mg/dl for controls, and was significantly lower ($p < 0.001$) by approximately 15 mg/dl. The HDL-C level was 51±15 mg/dl for gastrointestinal cancers and 51±16 mg/dl for controls, with no significant difference. Likewise, the TG level was 129±76 mg/dl for gastrointestinal cancers and 132±73 mg/dl for controls, with no significant difference. Therefore, compared with controls, TC and LDL-C were significantly lower ($p<0.001$) in cancer-bearers by approximately 15 mg/dl. Furthermore, analyses by cancer site also showed significantly lower TC and LDL-C levels in cancer-bearers than in controls for all three sites.

The mean TC and LDL-C for cancer-bearers and controls combined were 189 mg/dl and 111 mg/dl,

Table I - Background of study population

	Total		Esophageal cancer		Gastric cancer		Colorectal cancer	
	Cancer bearer	Control	Cancer bearer	Control	Cancer bearer	Control	Cancer bearer	Control
N	631	631	181	181	251	251	199	199
Male gender (%)	82.1	82.1	87.3	87.3	80.9	80.9	78.9	78.9
Age (years)	62.7±11	62.5±11	63.0±9	62.9±9	61.9±11	61.7±11	63.6±12	63.2±12
Height (m)	1.63±0.06	1.63±0.08	1.63±0.08	1.64±0.08	1.62±0.08	1.63±0.08	1.63±0.08	1.62±0.08
Body weight (kg)	58.9±11	59.3±10	58.3±10	57.1±9	59.4±11	59.8±11	60.0±12	59.5±11
Body mass index (kg/m²)	22.2±3.2	22.3±3.0	21.5±2.8	21.6±2.7	22.4±3.1	22.5±3.0	22.6±3.4	22.6±3.3

Table II - Effect of all gastrointestinal cancers on cholesterol levels

	Total		Esophageal cancer		Gastric cancer		Colorectal cancer	
	Cancer bearer	Control	Cancer bearer	Control	Cancer bearer	Control	Cancer bearer	Control
Total cholesterol (mg/dl)	181±34	196±36†††	181±35	193±35††	180±32	197±39†††	182±35	198±33†††
LDL cholesterol (mg/dl)	104±31	119±35†††	104±33	116±35††	105±28	120±37†††	103±33	119±32†††
HDL cholesterol (mg/dl)	51±15	51±16	52±16	50±15	50±13	51±17	52±15	53±15
Triglycerides (mg/dl)	129±76	132±73	128±85	134±84	126±67	129±65	133±79	134±71

† p<0.05, †† p<0.01, ††† p<0.001

Table III - No. of cases (%) less than 25 percentile values

	No. of cases (%) less than 25 percentile values			
	Total cholesterol (<165mg/dl)		LDL cholesterol (<89mg/dl)	
Cancer-bearer	200 (31.7%)	]†††	201 (31.9%)	]†††
Control	107 (17.0%)		113 (17.9%)	

††† p<0.001

respectively, and the corresponding 25 percentile values were 165 mg/dl and 89 mg/dl. The number (proportion) of subjects with TC less than 165 mg/dl was 200 (31.7%) in cancer bearers and 107 (17.0%) in controls, and was 1.9-fold higher in cancer bearers. The number (proportion) of subjects with LDL-C less than 89 mg/dl was 201 (31.9%) in cancer bearers and 113 (17.9%) in controls, and was 1.8-fold higher in cancer bearers. The differences in proportion were significant (p<0.001) for TC and LDL-C by chi-square test (Table III). However, cancer-bearers and controls showed a similar distribution of TC and LDL-C levels (Fig.1).

The results of case-control analyses of cholesterol levels for early and advanced stage gastrointestinal cancers are shown in Table IV. The TC level for early stage cancer-bearers was 186±32 mg/dl compared with 197±30 mg/dl for controls, and was significantly lower (p<0.001) by approximately 11 mg/dl. The LDL-C level for early stage cancer-bearers was 104±30 mg/dl compared with 119±30 mg/dl for controls, and was significantly lower (p<0.001) by approximately 15 mg/dl. The HDL-C level was 54±15 mg/dl for early stage cancer-bearers and 52±16 mg/dl for controls, with no significant difference. Similarly, the TG level was 140±82 mg/dl for early stage cancers and 135±76 mg/dl for controls, with no significant difference. Therefore, the TC and LDL-C levels were significantly lower in early stage cancer-bearers than in controls (p<0.001). When analyzed by cancer site, TC and LDL-C levels were significantly lower in gastric cancer- and colorectal cancer-bearers than in controls. For esophageal cancers, the LDL-C level in cancer-bearers appeared to be lower than in controls but the difference was not significant (p=0.117), and HDL-C level was significantly higher compared with controls (p=0.003). As a result, there was no significant difference in TC for esophageal cancers.

The TC level for advanced stage cancer-bearers was

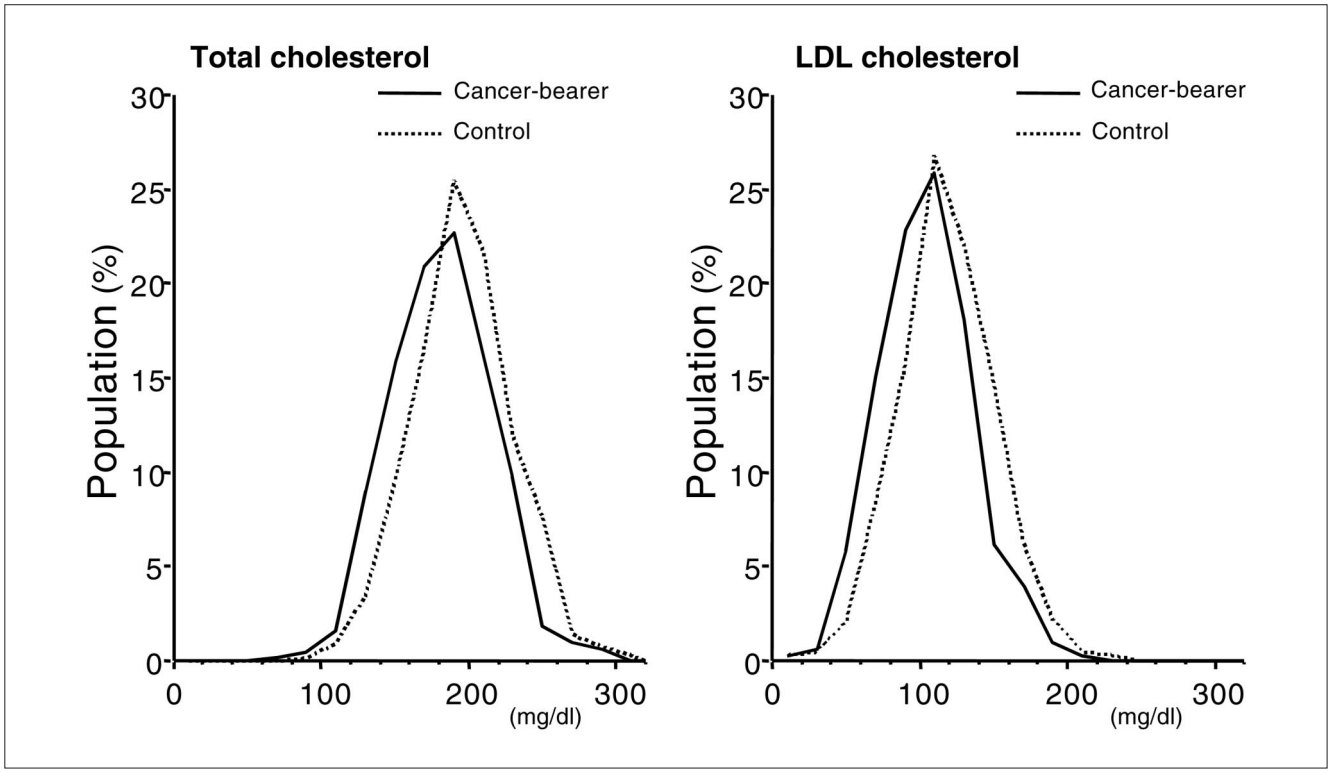

Fig. 1 - Distribution of serum TC and LDL-C concentration in patients with (cancer bearer: solid line) and without (control: broken line) gastrointestinal cancer.

178±34 mg/dl compared with 195±39 mg/dl for controls, showing a significantly lower ($p<0.001$) level by approximately 17 mg/dl. The LDL-C level for advanced stage cancer-bearers was 105±32 mg/dl compared with 118±38 mg/dl for controls, showing a significantly lower ($p<0.001$) level by approximately 13 mg/dl. The HDL-C level was 49±14 mg/dl for advanced stage cancer-bearers and 51±15 mg/dl for controls, with no significant difference. Similarly, the TG level was 121±71 mg/dl for advanced stage cancers and 129±70 mg/dl for controls, with no significant difference. Therefore, the TC and LDL-C levels were significantly lower in advanced stage cancer-bearers than in controls ($p<0.001$). When analyzed by cancer site, the TC and LDL-C levels were significantly lower in cancer-bearers for all three types of cancers.

We compared the preoperative and postoperative TC, LDL-C, HDL-C and TG levels in 441 cases showing a stable general condition and no recurrence 2 years after surgery (Table V). Increase in TC level was observed in 58.6% (259 cases) of the cases, while increases in LDL-C, HDL-C and TG levels were observed in 52.3% (231 cases), 68.3% (302 cases) and 28.1%(124 cases), respectively. A slightly larger proportion of cases showed increases in TC, LDL-C and HCL-C levels after surgery compared to those showing no change or decrease, but a considerably larger proportion of cases showed decrease in TG level after surgery.

Discussion

Excessive fat intake has become evident accompanying the Westernization of lifestyle in Japan, and fat intake has increased by over 2-fold compared with 1970s levels (4). For this reason, TC levels that were previously low increased to levels comparable with those in various other industrialized countries, and the mortality of ischemic heart disease has shown a steep rise. High TC levels are a risk factor for ischemic heart diseases, and it was suggested desirable to keep TC levels as low as possible. However, when examining all-causes mortalities, high mortality is observed not only in cases with high TC levels but also with low TC levels, and a J- or U-shaped relation between TC and total mortality has been demonstrated (5,6,12). A high prevalence of malignant diseases in the low TC popu-

Table IV - Effect of early and advanced stage gastrointestinal cancers on cholesterol levels

	Total		Esophageal cancer		Gastric cancer		Colorectal cancer	
	Cancer bearer	Control	Cancer bearer	Control	Cancer bearer	Control	Cancer bearer	Control
Total cholesterol (mg/dl)								
Early stage	186±32	197±30†††	192±34	193±30	185±33	199±30†††	182±29	198±32††
Advanced stage	178±34	195±39†††	176±35	194±38†††	176±30	194±47††	182±37	198±34†††
LDL cholesterol (mg/dl)								
Early stage	104±30	119±30†††	105±33	114±30	105±29	121±29†††	99±27	117±34††
Advanced stage	105±32	118±38†††	103±33	117±37††	106±27	119±45††	105±35	120±32†††
HDL cholesterol (mg/dl)								
Early stage	54±15	52±17	57±12	49±15††	53±14	52±15	56±19	54±15
Advanced stage	49±14	51±15	49±17	51±15	48±12	50±16	50±14	51±15
Triglycerides (mg/dl)								
Early stage	140±82	135±76	150±106	146±98	137±78	129±66	138±61	136±72
Advanced stage	121±71	129±70	116±69	127±76	114±50	129±63	132±86	132±71

† p<0.05, †† p<0.01, ††† p<0.001

Table V - Changes of preoperative and postoperative serum lipid levels: Number of cases (%) that showed increased levels after operation

	Total		Esophageal cancer		Gastric cancer		Colorectal cancer	
	Case	(%)	Case	(%)	Case	(%)	Case	(%)
Total cholesterol (mg/dl)	259	58.6	68	55.3	85	47.5	106	76.3
Early stage	118	56.5	33	58.9	49	46.7	36	75.0
Advanced stage	141	60.8	35	52.2	36	48.6	70	76.9
LDL cholesterol (mg/dl)	231	52.3	55	44.7	72	40.2	104	74.8
Early stage	115	55.0	31	55.4	45	42.9	39	81.3
Advanced stage	116	50.0	24	35.8	27	36.5	65	71.4
HDL cholesterol (mg/dl)	302	68.3	87	70.7	134	74.9	81	58.3
Early stage	146	69.9	42	75.0	80	76.2	24	50.0
Advanced stage	156	67.2	45	67.2	54	73.0	57	62.2
Triglycerides (mg/dl)	124	28.1	21	17.1	41	22.9	62	44.6
Early stage	43	20.6	8	14.3	20	19.0	15	31.3
Advanced stage	81	34.9	13	19.4	21	28.4	47	51.6

lation has attracted attention. Four explanations for this phenomenon may be proposed: 1. a coincidental result; 2. presence of other causal factors that simultaneously decrease TC levels and increase cancer risk; 3. hypocholesterolemia induces an increase in cancer, and 4. hypocholesterolemia is a result of the pathological effect of cancer (13).

In regards to the possibility of a coincidental result, it appears unlikely since this phenomenon has already been reported by many studies.

Other possible factors that simultaneously decrease TC levels and increase cancer risk may include smoking and alcohol consumption. In general, smoking increases TC, LDL-C and TG, and decreases HDL-C (5). In addition, alcohol consumption has almost no effect on TC but increases HDL-C and TG (14). Therefore, many confounding factors are involved in the changes of serum lipid levels, and their relation with cancer is complicated and remains undefined at present.

Even if hypocholesterolemia per se is a carcinogenetic factor or if it increases cancer risk, there is no evidence that explains the mechanisms of this association. In contrast, low TC levels detected at the beginning of some studies may reflect the presence of cancer in a latent or preclinical form, and this hypothesis is generally accepted (5,15). In prospective studies, although malignant diseases were excluded at entry, the duration from the beginning of observation to the onset of cancer, progression from early stage to advanced stage cancer and eventually death was too short. Therefore, it is reasonable to assume that latent cancer was already present at the beginning of the study.

In Japan, also, the large-scale Japan Lipid Intervention Trial (J-LIT) once again highlighted the issue of hypocholesterolemia and cancer (16). However, most previous studies examined cardiovascular diseases, and the relation between cancers of all sites and cholesterol levels. Therefore, we limited the present study to cancers occurring in the gastrointestinal tract (esophageal cancer, gastric cancer and colorectal cancer) and examined the relation of these cancers with serum lipids.

In the present study, the TC level of all gastrointestinal cancer-bearers was significantly lower than that of controls by approximately 15 mg/dl, which is in agreement with previous findings. By cancer site, the TC level was significantly lower in esophageal cancer, gastric caner and colorectal cancer. Furthermore, the LDL-C level of cancer-bearers was also significantly lower. In the case of gastrointestinal cancers, bearers of advanced stage cancers probably include patients with malnutrition caused by impaired food passage or anorexia, and the preclinical cancer effect should be considered in these patients. We, therefore, conducted the same analysis on early stage cancer-bearers who were most likely to have almost no subjective symptoms and were less affected nutritionally by reduced oral intake. In this analysis, early stage cancer-bearers showed a significantly lower TC level by approximately 11 mg/dl compared with controls, and also a significantly reduced LDL-C level. These results suggest that the low TC level in cancer-bearers is not caused by reduced food intake or a poor nutritional status. Studies of the time-trend in TC levels have reported that TC levels decline gradually from 10 years before the diagnosis of colorectal cancer (17), and that TC levels decrease by more than 10 mg/dl in the 6-year period before cancer death although there is no definite change before that (18). The results of the present study also showed that low TC levels were not related to the cancer stage, and suggest that some abnormalities in the lipid metabolic pathways may already be present from the very early stage. Furthermore, findings of no significant differences in HDL-C and TG between cases and controls in addition to a specific decrease in LDL-C in cancer-bearers suggest that hypocholesterolemia observed in cancer-bearers stems from low LDL-C.

As for the cause of low LDL-C in malignant tumors, the presence of substances that up-regulate the LDL receptors have been reported in acute myelogenous leukemia cells (19-21), gallbladder and lung cancer cell lines (22,23).

The mechanisms for the development of hypocholesterolemia have been hypothesized as increased LDL uptake by tumor cells as a result of up-regulation of LDL receptors and increased LDL consumption by cancer cells leading to lowered serum LDL-C. According to this hypothesis, LDL uptake by tumors should depend on tumor volume. Reports have shown that cholesterol is consumed during cancer growth leading to lowered serum cholesterol (14), and substances derived from cancer cells lower cholesterol (24,25). However, even though these may be observable in advanced cancers with large volumes, in general such effects are unlikely to be manifested at serum level in the case of small early cancers. In the present study, however, LDL-C was significantly lower compared with controls even in early staged cancers, suggesting the presence of abnormalities in the lipid metabolism at the early cancer stage, in addition to up-regulation of LDL receptors. Therefore, the present finding of a significant reduction of LDL-C levels in cancer-bearers

does not contradict these previous observations. However, the exact mechanism cannot be elucidated and further basic and clinical studies are required.

Although we found significantly higher HDL-C in early stage esophageal cancers than in controls, the reason remains unknown. We compared the preoperative and postoperative TC, LDL-C, HDL-C and TG levels in patients who were followed for 2 years, and found no fixed trend of changes. However, direct comparison of data among patients is considered difficult due to individual differences in the amount of food intake and nutrition absorption following gastrointestinal resection.

In a large-scale epidemiological study conducted in the United States MRFIT, although all-causes mortality was elevated in the group with TC less than 168 mg/dl and mortality from malignant neoplasms was increased 2.1-fold at TC of 168 mg/dl or greater, the significant relation between low TC and cancer mortality disappeared after a follow-up period of 5 years and above (5). In addition, subjects with LDL-C lower than 80 mg/dl and those showing a 50% decrease in LDL-C by treatment with cholesterol-lowering agents have been suggested to possess underlying diseases such as cancer (16,26). However, as shown in the present study, although there were approximately 2-fold more cancer bearers than controls within the 25 percentile of TC (165 mg/dl) and LDL-C (89 mg/dl), many cancer-bearers had similar TC and LDL-C levels as the controls (Fig.1). These findings show that it is difficult to discriminate cancer-bearers using TC and LDL-C levels as indices. However, we should be aware that latent cancer bearers may be present among subjects with hypocholesterolemia.

Cholesterol is a component of the cell membrane, and also serves as a precursor for the synthesis of steroid hormones and bile acids. Therefore, cholesterol is indispensable for the human body. When administering cholesterol-lowering agents, there is a concern that over-reduction of cholesterol levels may increase the risk of cancer. The mechanism of whether lowered cholesterol induces cancer or whether cholesterol is lowered as a result of cancer has long been debated but remains unsolved. In the present study, even in early cancers occupying small volumes, TC was lowered compared to controls. Again, this mechanism is unclear. Yet, hypercholesterolemia is associated with increased mortality from coronary events as a result of arteriosclerosis, and hypocholesterolemia is a causal factor of increased mortality from nonvascular diseases such as cancer. Fundamental knowledge needed to understand the abnormal cholesterol levels manifesting in a cancer state remains illusive, and further analyses are required.

Acknowledgements: We are grateful to Koji Shimamoto for thoughtful comments on the manuscript.

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Received: September 9, 2003

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