ORIGINAL CONTRIBUTION

Serum Cholesterol and Cancer Mortality in Japanese Civil Service Workers : Findings from a Nested Case-control Study

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To examine an association between serum cholesterol level and cancer mortality, a nested case-control study was conducted among 5,796 civil service workers in Japan who underwent periodic health examination. One-hundred and thirty-one deaths (cases), including 73 cancer deaths, were identified in the study period from 1980/1981 to September 1, 1991. Two controls were randomly selected for each case, matched for age, sex, year of examination and job status.

As a major result, an increase in serum cholesterol of 10 mg/dl significantly reduced cancer risk by 0.91 times in men, but not in women. This reduction of cancer risk in men was found not to be confounded by body mass index (BMI), smoking habits, and drinking habits. No significant association could be found between serum cholesterol level and specific sites of cancer. Separate analysis by follow-up period significantly revealed an inverse association between serum cholesterol and cancer deaths in men in 6 years or later after serum measurement. This inverse association was believed not to be ascribable to an effect of a preclinical cancer. *J Epidemiol*, 1993 ; 3 : 99-107.

serum cholesterol, nested case-control study, cancer, mortality

Many prospective epidemiological studies have examined the relationship between serum cholesterol level and ischemic heart disease, and indicated that its high mortality rate was largely ascribable to high serum cholesterol level particularly in the developed countries. An association of total mortality with serum cholesterol is, however, unique. Higher mortality was apparent in lower serum cholesterol populations as well as in higher serum cholesterol populations¹⁻⁹. This relation essentially implies higher mortality from diseases other than ischemic heart disease in lower serum cholesterol populations. Therefore, many studies have also examined the relationship between low serum cholesterol and total mortality, non-cardiovascular mortality or cancer mortality. In these studies, an inverse association of serum cholesterol level with cancer was confirmed^{1-5,10-33}.

In 1974, Rose and his colleagues reported an association of low cholesterol level with colon cancer³⁴. Since then, numerous prospective studies have been

undertaken to examine this particular association. Some studies have found no association between cholesterol level and cancer^{6,35-44}. An inverse association has been demonstrated in many studies, in which the association was mainly observed in men^{1-5,10-14,17-19,21-25}, smoking-related cancers^{6,18-20}, and patients diagnosed or dead within a few years after cholesterol measurement^{3,5,20-22,25-30}, though nowadays was reported that the association was found not only within a few years but also after many years of follow-up^{4,10-18}. In 1991, Law and Thompson⁴⁵ reviewed 33 published prospective studies, and reported a long-term inverse association of low serum cholesterol with cancer. Thus, low serum cholesterol is advancingly likely as a risk of cancer, but still remains controversial in several respects.

To our knowledge, in Japan where mean serum cholesterol is rather low, there were few published reports⁴⁶ which examined an association between cancers and serum cholesterol level, when excluded some

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studies done in collaboration with other countries^{25,27,47}. In the present study, therefore, we attempted to clarify an association between serum cholesterol level and cancer mortality among civil service workers in Japan, and to add a further evidence of a long-term inverse association between them.

MATERIALS AND METHODS

We conducted a nested case-control study among civil service workers who underwent periodic health examination in 1980 and 1981. Study population, identification of cases and control selection are as follows.

Study population

In 1980 and 1981, baseline and periodic health examinations were carried on a total of 5,796 (4,153 men and 1,643 women) civil service workers aged 25, 30, 35, 40, 45, 50, and 55 years old each year (response rate: 92%). The examination included self-administered questionnaire, anthropometric measurement and physical examination, electrocardiogram (ECG), urinalysis, and biochemical blood test. Blood specimens were drawn under fasting condition. Information collected by self-administered questionnaire included past history of major diseases, current health status, family history, smoking and drinking habits, and preference for foodstuffs and taste. Smoking (drinking) habits were inquired to classify daily-

smoker (drinker), occasional smoker (drinker), and ex- or non-smoker (drinker). For daily drinkers, alcohol consumption per day was estimated by assuming alcoholic volume of 27 g in 180ml of "sake", 633 ml of beer, or 1 double glass of whisky. Serum cholesterol was measured enzymatically⁴⁸.

Identification of cases

Study population was followed up to September 1, 1991 after examination. All dead subjects were identified among those who are continuously on active service and also among those retired, but subsequently supported by retirement pension. Causes of death, classified according to International Classification of Diseases (ICD-9), were routinely checked by reviewing documents sent to the pension office to notify the death of pensioners. Those who retired before September 1, 1991 and were not subsequently supported by pension, accounting for 11.8% (683 in number) of a total study population, were excluded from the present analysis, since their vital status could not be traced.

One-hundred and thirty-one deaths (94 deaths during active service and 37 deaths after retirement) were identified between the examination and September 1, 1991. Table 1 summarizes causes of death by sex and subsequent follow-up year. Seventy three deaths were due to cancers (60 men and 13 women), being accounted for 55.7% of 131 total deaths.

Table 1. Numbers of death by cause and follow-up year.

Follow-up year	Cause of death								Total
	Cancer ¹⁾	CHD ²⁾	CVD ³⁾	Liver ⁴⁾	Suicide ⁵⁾	Accident ⁶⁾	Others	Unknown	
Men									
0~ 1	6	0	1	0	0	0	1	1	9
2~ 5	17	2	1	4	2	1	6	1	34
6~ 8	15	3	2	2	3	1	4	0	30
9~11	22	1	2	3	0	0	4	2	34
total	60	6	6	9	5	2	15	4	107
Women									
0~ 1	1	0	1	0	0	0	0	0	2
2~ 5	7	0	1	0	0	0	3	0	11
6~ 8	5	1	0	0	0	0	1	0	7
9~11	0	0	0	1	0	2	1	0	4
total	13	1	2	1	0	2	5	0	24
Total	73	7	8	10	5	4	20	4	131

¹⁾ Cancer; ICD-9 codes included 140-208

²⁾ CHD; Coronary Heart Disease, ICD-9 codes included 410-414

³⁾ CVD; Cerebrovascular Disease, ICD-9 codes included 430-438

⁴⁾ Liver; not including liver cancer, ICD-9 codes included 570-573

⁵⁾ Suicide; ICD-9 codes included E950-959

⁶⁾ Accident; ICD-9 codes included E800-949 and E960-999

Control selection

Controls were selected from the same population matching to cases for age (within 1 year), sex, year of examination, and job status (blue or white color worker). First, we constructed potential sources of controls for each case, and then two controls were randomly selected from each source by identifying those whose year of employment was the nearest and who are confirmed as alive on September 1, 1991. There was one case who succumbed to liver cancer, and for whom we could not set up two eligible controls. This pair was also included in the present analysis.

Statistical methods

Analyses were performed separately by sex to explore the relationship between serum cholesterol level and total mortality, cancer mortality from all sites, and mortality from major primary sites of cancer (stomach, lung, digestive organ cancers, smoking-related cancers), when death occurred in 2 years or later after examination, i.e. excluding those who died in less than 2 years after examination, probably due to diseases already suffered. We included cancers of the esophagus, stomach, colon and rectum in cancer of the digestive organ. For men, smoking-related cancer was defined as cancers of the lung, mouth, larynx, esophagus, pancreas, bladder, and leukemia. For women, cancer of the cervix was also included¹⁹⁾ in smoking-related cancer. The entire follow-up period was divided into three periods: (1) 2 to 5 years, (2) 6 to 8 years, and (3) 9 to 11 years. All statistical analyses were conducted using the SAS programs at Nagoya University Computation Center. For multivariate analysis, we used a conditional logistic regression model for matched data⁴⁹⁾. In multivariate analyses, body mass index (BMI: weight(kg)/height(m)²), smoking habits, and drinking habits at baseline (1980 or 1981) were used as covariates.

RESULTS

Some selected characteristics of the study subjects are shown in Table 2. The cases were more likely to be non-drinkers and current smokers, but heavy drinkers defined as consumers of 81g or more alcohol per day, appeared to be more prevalent among the cases. They also more frequently suffered from hypertension or hepatitis; more often complaining of dizziness, weight loss or thirst at entry.

As shown in Table 3, there was no significant difference in mean serum cholesterol for "all causes" and "all causes except accident and suicide", though the mean values were consistently lower in the cases. For

Table 2. Characteristics of study subjects at entry.

	Case (n = 120)	Control (n = 239)
Alcohol drinking		
Non- drinker	35.9%	30.9%
Heavy drinker ¹⁾	9.4%#	4.3%
Smoking habits		
Smoker (daily)	66.1%	57.7%
Salty foods		
Preferred	21.2%	22.8%
Sweet foods		
Preferred	21.0%	19.7%
Oily foods		
Preferred	21.0%	15.0%
Amount of meal		
Large	8.3%	6.8%
Past history		
Hypertension	14.2%#	7.9%
Hepatitis	10.8%#	5.4%
Subjective complaints		
Dizziness	10.0%#	5.0%
Weight loss	8.3%*	3.3%
Thirst	17.5%**	6.7%

: $p < 0.1$

* : $p < 0.05$

** : $p < 0.01$: tested by χ^2

¹⁾ Heavy drinker : alcohol ≥ 81 g/day

"male cancer death", mean serum level was 177.3 mg/dl in the cases and 190.5 mg/dl in the controls; being significantly lower in the cases. In women, however, mean serum cholesterol was not significantly different. Crude and two kinds of adjusted relative risks were also summarized in Table 3. An increase in serum cholesterol of 10 mg/dl significantly reduced cancer risk by 0.91 times in men, but no reduction was noted in women. This reduction of cancer risk in men was found not to be confounded by BMI, smoking habits and drinking habits, since two adjusted relative risks were 0.89 (95% confidence interval 0.81-0.98) and 0.87 (0.78-0.97).

Table 4 gives the relative risks of death from some sites of cancer in men. In women, numbers of death from specific sites of cancer are too small to calculate the relative risks. Lung cancer death tended to show a positive, and stomach cancer death a negative association with serum cholesterol. Risk of dying from cancers of the digestive organ and from smoking-related cancers appeared to be lower, when serum cholesterol is higher.

Table 3. Means and standard deviations of serum cholesterol with its odds ratios for different causes of death.

Causes of death	N	Mean (mg/dl)	S.D.	Crude		Adjust A ¹⁾		Adjust B ²⁾	
				OR ³⁾	(95% CI)	OR ³⁾	(95% CI)	OR ³⁾	(95% CI)
Men									
All									
	case	182.6	34.6	0.96	(0.90-1.03)	0.94	(0.88-1.01)	0.94	(0.87-1.01)
	control	188.0	35.8						
All except suicide and accident									
	case	183.1	35.0	0.97	(0.90-1.04)	0.95	(0.88-1.02)	0.94	(0.87-1.02)
	control	187.9	36.1						
Cancer									
	case	177.3*	34.0	0.91	(0.83-1.00)	0.89	(0.81-0.98)	0.87	(0.78-0.97)
	control	190.5	37.3						
Women									
All									
	case	195.8	35.5	0.92	(0.76-1.10)	0.92	(0.76-1.10)	0.93	(0.75-1.14)
	control	202.7	32.0						
All except suicide and accident									
	case	196.4	35.7	0.93	(0.77-1.12)	0.93	(0.77-1.12)	0.92	(0.74-1.15)
	control	202.6	33.4						
Cancer									
	case	204.3	42.2	0.99	(0.79-1.24)	0.98	(0.78-1.25)	1.03	(0.74-1.42)
	control	205.5	35.1						

* ; p<0.05 : tested by t-test

¹⁾ Adjusted A : adjusted for BMI²⁾ Adjusted B : adjusted for BMI, smoking and drinking habits³⁾ OR : odds ratios per 10 mg/dl increment of serum cholesterol

Table 4. Means and standard deviations of serum cholesterol with its odds ratios for deaths from specific sites of cancer (in men).

Site of cancer		N	Mean (mg/dl)	S.D.	Crude		Adjust A ¹⁾		Adjust B ²⁾	
					OR ³⁾	(95% CI)	OR ³⁾	(95% CI)	OR ³⁾	(95% CI)
Lung cancer	case	11	196.8	35.4	1.06	(0.87-1.28)	1.07	(0.87-1.31)	1.04	(0.83-1.30)
	control	22	188.6	40.0						
Stomach cancer	case	12	185.1	36.2	0.94	(0.78-1.14)	0.94	(0.78-1.14)	0.89	(0.69-1.14)
	control	24	193.5	37.7						
Digestive organ cancers ⁴⁾	case	23	183.1	31.6	0.92	(0.81-1.05)	0.90	(0.77-1.04)	0.86	(0.73-1.02)
	control	46	196.9	40.9						
Smoking related cancers ⁵⁾	case	19	182.2	34.0	0.92	(0.79-1.06)	0.95	(0.81-1.11)	0.94	(0.79-1.11)
	control	38	194.4	34.9						

¹⁾ Adjusted A : adjusted for BMI²⁾ Adjusted B : adjusted for BMI, smoking and drinking habits³⁾ OR : odds ratios per 10 mg/dl increment of serum cholesterol⁴⁾ Digestive organ cancers ; esophagus, stomach, colon and rectum⁵⁾ Smoking related cancers ; lung, mouth, larynx, esophagus, pancreas, bladder, and leukemia**Table 5.** Means and standard deviations of serum cholesterol with its odds ratios for total cancer mortality by follow-up period (in men).

Follow-up year		N	Mean (mg/dl)	S.D.	Crude		Adjust A ¹⁾		Adjust B ²⁾	
					OR ³⁾	(95% CI)	OR ³⁾	(95% CI)	OR ³⁾	(95% CI)
2~ 5	case	17	187.0	35.6	1.06	(0.19-1.23)	1.03	(0.87-1.21)	1.09	(0.89-1.34)
	control	34	178.4	38.3						
6~ 8	case	15	166.1*	29.5	0.86	(0.72-1.02)	0.82	(0.67-1.00)	0.77	(0.60-0.99)
	control	29	188.6	36.3						
9~11	case	22	177.5*	34.7	0.84	(0.71-0.98)	0.85	(0.72-1.00)	0.83	(0.69-1.00)
	control	44	201.1	34.9						

* ; p<0.05 : tested by t-test

¹⁾ Adjusted A : adjusted for BMI²⁾ Adjusted B : adjusted for BMI, smoking and drinking habits³⁾ OR : odds ratios per 10 mg/dl increment of serum cholesterol

Risk of cancer death with serum cholesterol was separately evaluated by follow-up period in men (Table 5). For the first period (follow-up 2-5 years), no association was obvious. For the second (follow-up 6-8 years) and the last period (follow-up 9-11 years), mean serum cholesterol were significantly lower in the cases, and an inverse association was statistically significant, when adjusted for BMI, and smoking and drinking habits. In women, however, no significant associations were noted in any follow-up periods between serum cholesterol level and cancer mortality (not shown in the text).

DISCUSSION

At first, we will discuss a few methodological shortcomings in our study and how we overcame them. First, the present study was based on relatively small numbers of cancer death. When case-control study is conducted based on small numbers of cases and controls, significant associations are not likely to be obtained. When a significant association is found, however, it may not be a distorted relationship between a given disease and a risk factor, unless cases and controls were selected with biases. Second, we could not trace all individuals in the study population up to September 1, 1991 to identify all dead subjects.

The missed individuals were more likely to be women by sex, younger in men and older in women by age, compared to those who could be successfully traced. Thus, non-respondent bias could possibly exist in the present study, but we could not exclude this bias. Since some deaths were likely to be missed, we adopted the study design of a nested case-control study, in which cases were limitedly identified, and controls were definitely confirmed as survivors. This means, accordingly, that missclassification of cases and controls is not likely at all. Third, some studies have revealed an U-shape association of total mortality with serum cholesterol¹⁻⁹⁾. According to our separate analysis by categorizing serum cholesterol into four levels, we found no U-shape association, but dose-response relationship with total mortality in men. We then handled serum cholesterol as a continuous variable, but not as a categorical variable, in our analysis.

As many other studies^{2,10-13,17-20)}, we found an inverse association between serum cholesterol and cancer mortality in men, but not in women. No apparent association in women might possibly be due to small numbers of cancer death in women, and partly to sex differentials in predominant sites of cancer¹⁸⁾.

In several studies, low serum cholesterol was found to be inversely associated with colon cancer^{1,2,14,15,18,23,50-52)}, lung cancer^{5,6,12,14,15,23,25,32,33)} or smoking-related cancer^{6,18-20)}. Our study, however, failed to demonstrate any significant associations between serum cholesterol level and specific sites of cancer, possibly because of small numbers of death from individual sites of cancer. A positive association with lung cancer deaths and negative association with deaths from smoking related cancers in our study, could not be readily explainable due to small number of deaths in these sites.

An association of low serum cholesterol level with cancer deaths was found in most reports^{3,5,11,20-23,25-32)}, when cancer deaths which occurred within a few years after cholesterol measurement were analyzed. This short-term association is believed to reflect an effect of preclinical cancer⁵⁾ which lowered serum cholesterol. In our study all deaths which occurred in less than 2 years after examination were intentionally excluded. But in male patients who died in less than 2 years after cholesterol measurement, mean serum cholesterol was apparently lower by about 20 mg/dl when compared to their controls. This short-term effect was probably ascribable to increased catabolism resulting from enhanced low density lipoprotein (LDL)-receptor activity in malignant cells⁵³⁾. Henriksson and his colleagues⁵⁴⁾, who compared prostatic cancer patients with and without metastasis and their controls, found that the patients with metastasis cleared LDL faster than those without metastasis and controls. According to

this finding that indicates faster catabolism of LDL, a mechanism by which cancer reduces serum cholesterol is theoretically plausible.

In several studies^{4,10-18)}, a long-term inverse association of serum cholesterol level with cancer was also obtained likewise our study. This long-term inverse association could not be explained by preclinical cancer, though implications of this association have not been fully understood. There are three possible explanations for the long-term inverse relationship between low serum cholesterol level and cancer. The first, it is just a chance observation; the second, a third factor will exist which lowers serum cholesterol and simultaneously increases the probability of cancer development; and the third, low serum cholesterol itself actually causes cancer^{10,12,55-57)}.

First, long-term association was found in 10^{4,10-18)} reports out of 29^{1-5,10-33)} cohort studies in which an inverse association of serum cholesterol level with cancer was reported. Law and Thompson⁴⁵⁾, who reviewed 33 published prospective studies by meta-analysis, confirmed a long-term association of low serum cholesterol with cancer. It may be, therefore, unlikely to be observed only by chance.

Second, a possible third factor may include smoking habits or beta-carotene. Since serum cholesterol is known to be pharmacologically lowered by smoking⁴⁵⁾, serum cholesterol level could possibly be confounded by smoking habits. It is, however, found in most studies^{1,4,11-15,18,19,22-26,31,32)} including ours that an inverse association between serum cholesterol and cancer persisted even after statistical adjustment for smoking habits. Smoking is also known to lower high density lipoprotein (HDL) cholesterol⁵⁸⁻⁶¹⁾. Most prospective studies have examined an association of cancers with total serum cholesterol except a few studies^{18,62,63)}, in which an inverse association of serum HDL cholesterol with cancer was not consistently demonstrated. In our study, the relation with HDL cholesterol was examined as well, but no association with cancer mortality was found (unpublished data). Another possibility is that beta-carotene is a third factor to influence both cancer mortality and serum cholesterol level. Shekelle and his colleagues⁶⁴⁾ reported that the association between low serum cholesterol level and increased risk of lung cancer did appear to be stronger in strata with low intake of beta-carotene than in the total cohort. And they hypothesized that beta-carotene mediated the association between low serum cholesterol and increased risk of lung cancer. Though beta-carotene may possibly play an important role in a serum cholesterol-cancer relationship, there have been few prospective studies⁶⁴⁾, which examined the inter-relationship between serum cholesterol level and serum

beta-carotene level or dietary intake of beta-carotene. There were also potential confounding factors which have been taken into account in previous studies; systolic blood pressure^{1,12-14,16,23}, relative weight^{14,15,24,25,32}, educational level^{11,24,32}, alcohol consumption^{4,11,14,18,19,23}, hematocrit²⁴, physical activity²⁴, or social class^{1,12,15}. When adjusted for these variables, significant inverse associations between serum cholesterol and cancer were not altered⁶⁵.

Third, if an association is real, a mechanism by which low serum cholesterol causes cancer should be rational. Isles and his colleagues¹² indicated the theoretical possibility that low cholesterol concentration predisposes directly to cancer, as cholesterol is an essential component of cell membranes. Kark and his colleagues¹⁵ also discussed that serum cholesterol levels may be associated predictively with a risk of developing certain cancers, possibly through an effect of serum cholesterol concentration on the characteristics of cell membranes, or by serum cholesterol levels reflecting membrane cholesterol levels. It is also possible that "malnutrition" expressed as "low serum cholesterol" may promote cancer development in some populations. According to Lowell and his colleagues⁶⁹, laboratory studies have documented detrimental effects of malnutrition on host defenses and immune function by decreasing functions of lymphocytes, granulocytes, and macrophages. Since immune effector cells are known to mediate antitumor effects *in vitro*⁶⁷, malnutrition may possibly be implicated in oncogenesis and/or the body's ability to control the development and spread of cancer by immune depression, though the overall mechanisms remain unknown.

Increasing dietary intake of saturated fat and cholesterol is known to increase serum cholesterol level⁶⁸⁻⁷¹, and international correlation was positive between per capita consumption of diets high in saturated fat and animal fat and cancer risk^{72,73}. This positive correlation is quite contradictory to low serum cholesterol-cancer association. In 1992, Kritchevsky¹⁷, who examined the role of dietary fat and cholesterol, found that diet cannot explain the low serum cholesterol-cancer association. Based on these discussions, it may probably be hypothesized that men with naturally occurring low levels of cholesterol are at an increased risk of cancer^{18,74}. To resolve this hypothesis, such researches as intervention trials of increasing serum cholesterol in low-serum-cholesterol populations may be needed.

In conclusion, we found a statistically significant inverse association between serum cholesterol level and cancer mortality in men. This inverse association was most apparent in 6 years or later after serum measurement. This finding was believed not to be ascribable

to an effect of preclinical cancer.

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