Relationship of Serum Lipids to 10-year Deaths from All Causes and Cancer in Japanese Urban Dwellers Aged 40 Years and Over

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The present study aimed at examining relationships between baseline lipids to 10-year mortality from all causes and cancer. Subjects comprised 1202 men and 2054 women ranging in age from 40 to 80 years living in Toda City, an urban area of Japan. They were residents who had completed multiphasic health check-ups as the baseline survey between March 1979 and February 1981. Relationships of fasting lipids at baseline to 10-year deaths were analyzed using univariate and multivariate logistic regression analysis. One hundred and seventy-two died over the 10 years. Cancer was the most common cause of death, accounting for 44 percent of deaths, followed by stroke, and congestive heart failure. Total serum cholesterol (TC) at baseline was inversely related to all-cause mortality in men, even after adjustment of body mass index, systolic blood pressure, smoking habits, and drinking habits, with odds ratio showing 0.55 in 2nd tertile and 0.74 in 3rd tertile vs 1.00 in first tertile. In women, an inverse relationship of TC to 10-year all-cause mortality did not reach significant level either in crude or adjusted odds ratios. A significant inverse relationship between baseline high density lipoprotein cholesterol (HDL-C) and all-cause mortality in adjusted odds ratios was found in men alone. Serum triglyceride (TG) and (TC-HDL-C)/TC(atherosclerotic index, AI) showed no consistent relationship to mortalities from all causes in either men or women. A relationship of TC to cancer death was insignificant in both crude- and adjusted odds ratios in men. A significantly inverse relation of HDL-C to cancer death was recognized in adjusted odds ratios in men. The relation did not substantially differ according to observation period. An inverse relation of HDL-C with cancer death in women was not significant. Relationships of TG and AI to cancer death were diverse for both sexes. The present study thus revealed the inverse relationship of TC and HDL-C to all-cause and cancer mortalities in men.

Prospective study, all-cause mortality, cancer, HDL-cholesterol, total cholesterol

Recent epidemiological studies have related total serum cholesterol (TC) not only to coronary heart disease but also to cancer and all-cause mortality1-22. In Japan, research into TC has been mainly focused on stroke in rural areas23-25. There has been little information available concerning its contributions to all-cause mortality or occurrence of diseases in urban residents in Japan21, despite the fact that 70% of the Japanese population lives in urban areas according to Japanese census data.

The National Survey on Circulatory Disorders26 showed a fairly higher level of TC in urban areas than in rural areas on the basis of representative samples from the entire Japanese population. Prospective studies in urban areas are absolutely necessary in order to determine the significance of serum lipids as risk factors for mortality and disease incidences for all Japanese. Epidemiological studies in Japan greatly lagged behind the USA and European countries in incorporation of high density lipoprotein cholesterol (HDL-C) and triglyceride (TG) to baseline examinations25,27,28. The epidemiological roles of these lipids, therefore, have not yet been established in Japan. Even in the USA and western countries, the relationship of HDL-C to cancer has not yet been determined. The available data have been few and the results
were diverse\cite{13,16,19}. In light of this situation, the present study aimed at examining contributions of such lipids as serum TC, HDL-C, and TG to deaths from all causes and specific diseases based on a 10-year longitudinal observation of urban residents aged 40 years and over.

**MATERIALS AND METHODS**

**Enrollment of subjects**

As subjects of the present study, we enrolled residents of Toda city (1,202 men and 2,054 women) aged 40 years and over. Toda City (population 78,000) lies in the southernmost area of Saitama Prefecture facing Metropolitan Tokyo across the river Ara, and has been developed as a residential area for commuters to Metropolitan Tokyo and for the self-employed.

Toda City has been divided into 44 local communities for the convenience of public health activities for its citizens. Toda Municipal Health Care Center staffed by 50 personnel, established in 1971 for the promotion of public health, canvassed volunteers who wanted to undergo annual multiphasic health checkups from the 44 local communities. Subjects for the present study comprised volunteers who underwent the health checkups between March 1979 and February 1981. During the study period, two rounds of health checkups were carried out. Thirty percent of subjects underwent both checkups, of which the results from the first checkup were adopted for the present study.

Representativeness of subjects as a sample of the population was examined in three ways: comparison of demographic traits in municipal resident registration records, investigation of knowledge in terms of risk factors for chronic diseases in two local communities among the 44 local communities, and examination of serum lipids levels in the two local communities. In two local communities, 196 participants and 202 age-adjusted residents randomly sampled from 801 non-participants were investigated by home visits inquiring into knowledge and attitude towards prevention of chronic diseases in 1982. Further, the 202 residents were invited to undergo health checkups. Not only week days but also weekends were allocated for health checkups. When necessary, free transportation was provided to facilitate subjects availability for health checkups. A hundred and ninety-three persons responded to both interview surveys and health checkups.

The resident registration records of Toda City showed that subjects of the present study had lived in the city eight years longer than the entire population of the same age, and the participation rate in the National Health Insurance was higher in subjects (67%) than in the entire population (41%) in men alone, which implied the proportion of self-employed male subjects was higher than for the entire population.

An interview survey in 1982 among 196 subjects of the present study and 193 representative sample of non-participants of the same age revealed that subjects had little favorable knowledge and attitude towards prevention of chronic disease compared with non-participants. However, whether the difference was a cause or an effect of participation in our health checkups was unable to be determined. Levels of TC, HDL-C, and TG examined simultaneously in the 193 representative sample of non-participants did not differ from those of the 196 subjects at baseline.

**Examinations for baseline survey**

At Toda Municipal Health Care Center, subjects were invited to undergo annual multiphasic health-checkups on the morning of a day allocated to an individual local community. Subjects were provided with free bus transportation, and were also free to come to the Center on their own.

Anthropometric measurements, urine samples, blood pressure, electrocardiograms, retinal examinations, and blood samples were examined. Demographic data, habits of smoking and drinking were simultaneously investigated.

Height was measured with shoes off, and body weight was measured without their jackets. Blood pressure was taken on the right arm, sitting, after the subjects had been seated for five minutes. In the present study, direct values of blood pressure were adopted. Twelve-hour fasting blood samples were taken from cubital veins. MgCl2 and dextran sulfate were used to precipitate low density and very low lipoproteins. Cholesterol of the supernate, TC, and TG were measured by the enzymic method\cite{29}. Precision control of the measurement was carried out with a control serum (Moni-Trol, DADE, BAXTER) in the laboratory of Toda Municipal Health Care Center. Throughout the study period, coefficients of variation were maintained in ranges: 0.45-0.35% in TC, 2.73-3.96% in HDL-C, and 1.62-2.19% in TG.

Those who had stopped smoking over a year prior to the examination were regarded as non-smokers, and the rest as smokers. Average number of cigarettes smoked a day was inquired of smokers. Subjects were divided into three categories according to frequency of drinking: never or quit-drinking, several days per week, and everyday.

**Follow-up Procedure**

Subjects were followed up for 10 years between 1979-1981 and 1989-1991, during which time survivorship of subjects was investigated every month based on resident registration records in the municipality. Further, causes of death were referred to physicians who filled out death certificates for subjects who had lived in Toda City. Underlying causes of death were adopted in the present study. In most cases, information in terms of examina-
tions for making diagnosis was obtained. However, no revision was made to the original underlying causes of death described by physicians who filled out the death certificates. Diagnosis for malignant neoplasms were generally made in teaching hospitals of the Metropolitan Area. Eighty percent of stroke cases died in hospitals in Toda City or adjacent Warabi City. More than 60% underwent in-depth examinations including computer tomography. Validity of diagnosis for cardiac death was considered to be problematic in some cases. However, we did not look into the problem, because the number of cases was too small to analyze them separately. In terms of survivorship of subjects moving out of the City, mail or telephone surveys to themselves or their family members were employed once a year.

Survivorship of subjects which was unable to be identified by mail or telephone surveys was inquired into by the Toda Municipality, who contacted local governments of areas into which subjects had moved. Causes of death for these emigrants were enquired of their family members.

Analytical Method

Relationships of TC, HDL-C, TG, and (TC-HDL-C)/TC (atherosclerotic index, AI) at baseline examination to 10-year deaths from all causes, cancer, and stroke, were sought using multiple logistic analysis. Subjects of unknown survivorship (12 men and 22 women) were excluded from the analysis. All the continuous variables were categorized into tertile with the exception of age. Drinking habits were classified into 3 categories, and average number of cigarettes smoked a day as mentioned above was used for analysis. Crude odds ratios and adjusted odds ratios controlling for age, body mass index, systolic blood pressure, average number of cigarettes a day, and drinking habits were calculated. Odds ratios for the relationship between baseline variables and cancer or stroke were calculated using dead cases of targeted disease and living subjects. In terms of cancer, analysis was also performed for mortality during the former five years and the latter five years, separately, in order to examine whether the association of baseline variables was suggestive of an early sign or a risk factor. Further, the relation for the first two years was compared with that for the entire 10 years.

RESULTS

Table 1 shows characteristics of baseline variables by sex. Average age was similar between men and women, ranging in age 40-80 years and 40-79 years in men and women, respectively. Smoking and drinking habits showed marked sex difference with a predominance in men. Both TC and HDL-C were a little higher in women, whereas, TG was higher in men. Values at baseline lipids according to tertile are shown in Table 2.

Table 1. Characteristics of baseline variables by sex, Toda City, Japan, March 1979-February 1981.

|                      | Men        | Women      |
|----------------------|------------|------------|
|                      | N = 1190   | N = 2032   |
| Age (year)           | 51.8 ± 9.5 | 51.2 ± 8.5 |
| Body mass index†     | 22.7 ± 2.9 | 23.1 ± 3.2 |
| Systolic blood pressure (mmHg) | 133.4 ± 21.6 | 132.0 ± 19.9 |
| No. of cigarettes a day | 14.7 ± 13.1 | 2.1 ± 6.0 |
| Alcohol none (%)     | 26.0       | 81.4       |
| Alcohol several times a week (%) | 17.1 | 12.6 |
| Alcohol everyday (%) | 56.9       | 6.0        |
| Total cholesterol (mg/dl) | 194.1 ± 37.1 | 201.6 ± 38.7 |
| HDL cholesterol (mg/dl) | 48.2 ± 14.3 | 52.0 ± 13.3 |
| Triglyceride          | 150.9 ± 107.8 | 118.1 ± 68.3 |
| Atherosclerotic index² | 3.4 ± 1.5  | 3.1 ± 1.3  |

†Body mass index: weight (gm)/height (cm)² × 10
²Atherosclerotic index = (Total cholesterol - HDL cholesterol)/HDL cholesterol

Table 2. Values of serum lipids at baseline according to tertile by sex, Toda City, Japan, March 1979-February 1981.

|                | 1st tertile | 2nd tertile | 3rd tertile |
|----------------|-------------|-------------|-------------|
| Men            |             |             |             |
| Total cholesterol (mg/dl) | 90-176      | 177-206     | 207-419     |
| HDL cholesterol (mg/dl)     | 18-40       | 41-52       | 53-156      |
| Triglyceride (mg/dl)        | 40-99       | 100-153     | 154-178     |
| Atherosclerotic index       | 0.6-2.5     | 2.6-3.8     | 3.8-11.5    |
| Women           |             |             |             |
| Total cholesterol (mg/dl)   | 91-182      | 183-215     | 216-479     |
| HDL cholesterol (mg/dl)     | 20-44       | 45-57       | 58-114      |
| Triglyceride (mg/dl)        | 32-85       | 86-125      | 126-999     |
| Atherosclerotic index       | 0.7-2.4     | 2.5-3.4     | 3.5-20.1    |
12 men and 22 women which accounted for one percent of subjects investigated at baseline examinations (Table 3). Cancer was the most common cause of death accounting for 44 percent of all deaths, followed by stroke, congestive heart failure, and myocardial infarction. Causes of death were not ascertained in 18 cases (Table 4). Among the emigrants from the city, nine cases died over the 10-year period. Causes of death were identified only in two cases. In men, both crude and adjusted odds ratios revealed an inverse relationship between baseline TC and 10-year mortality from all causes. HDL-C in men also showed a similar relationship in adjusted odds ratios. TG did not show significant association to all-cause mortality. AI had an inverse effect in crude odds ratios, however, the significance disappeared in adjusted odds ratios (Table 5). In women, no consistent association was observed between all-cause mortality and levels of lipids at baseline examinations (Table 5).

Table 6 indicates odds ratios for association between lipids at baseline and 10-year mortality from cancer of all sites. In men, HDL-C was inversely related to cancer mortality. Significance of the relation increased in adjusted odds ratios, compared with crude odds ratios. In

| Table 3. Outcomes of subjects for 10 years by sex, Toda City, Japan, 1979-1991. |
|---------------------------------|-----------------|-----------------|
|                                  | Men             | Women           |
| Alive                           | %               | %               |
| in the City                     | 1000 (83.3)     | 1745 (84.9)     |
| moved out                       | 102 (8.5)       | 203 (9.9)       |
| Deceased                        | 88 (7.3)        | 84 (4.1)        |
| Unknown                         | 12 (0.9)        | 22 (1.1)        |
| Total                           | 1202 (100.0)    | 2054 (100.0)    |

| Table 4. Underlying causes of death in 172 cases by sex, Toda City, Japan, 1979-1991. |
|---------------------------------|-----------------|-----------------|
|                                  | Men             | Women           |
| Cancer                          | 37              | 39              | 76              |
| Stomach                         | (12) (6)        | (13) (6)        | (25) (14)       |
| Colon, rectum                   | (8) (6)         | (6) (4)         | (14) (8)        |
| Liver                           | (6) (5)         | (5) (3)         | (11) (8)        |
| Lung                            | (3) (5)         | (5) (8)         | (8) (11)        |
| Pancreas                        | (2) (2)         | (2) (2)         | (4) (2)         |
| Breast                          | -               | (2) (2)         | (2) (2)         |
| Uterus                          | -               | (2) (2)         | (2) (2)         |
| Others                          | (6) (4)         | (4) (10)        | (10) (3)        |
| Stroke                          | 15              | 15              | 30              |
| Cerebral infarction             | (7) (5)         | (5) (12)        | (12) (6)        |
| Cerebral hemorrhage             | (6) (5)         | (5) (11)        | (11) (7)        |
| Subarachnoid hemorrhage         | (2) (5)         | (5) (7)         | (7) (11)        |
| Congestive heart failure        | 8               | 10              | 18              |
| Myocardial infarction           | 4               | 2               | 6               |
| Other causes of death           | 14              | 10              | 24              |
| Unknown                         | 10              | 8               | 18              |
| Total                           | 88              | 84              | 172             |

Table 5. Crude and adjusted odds ratios for relationship between baseline variables and 10-year mortality from all causes, Toda City, Japan, 1979-1991.

|                          | crude OR1 | adjusted OR2 |
|--------------------------|-----------|--------------|
|                          | 1st tertile | 2nd tertile | 3rd tertile | 1st tertile | 2nd tertile | 3rd tertile |
|                          | (95% CI)   | (95% CI)     | (95% CI)   | (95% CI)   | (95% CI)   | (95% CI)   |
| Men                      |            |              |            |            |              |              |
| Total cholesterol        | 1.0        | 0.51**       | 0.57**     | 1.0        | 0.55**       | 0.74         |
| HDL cholesterol          | 1.0        | 0.51**       | 1.09       | 1.0        | 0.40***      | 0.54**       |
| (0.28-0.93)              | (0.34-0.95) | (0.67-1.78)  | (0.21-0.76) | (0.30-0.98) |              |              |
| Triglyceride             | 1.0        | 0.81         | 0.78       | 1.0        | 1.09         | 1.35         |
| (0.48-1.37)              | (0.46-1.32) | (0.62-1.92)  | (0.62-1.92) | (0.73-2.50) |              |              |
| Atherosclerotic index    | 1.0        | 0.42**       | 0.62       | 1.0        | 0.67         | 1.23         |
| (0.24-0.74)              | (0.37-1.02) | (0.36-1.24)  | (0.36-1.24) | (0.67-2.34) |              |              |
| Women                    |            |              |            |            |              |              |
| Total cholesterol        | 1.0        | 0.91         | 1.45       | 1.0        | 0.63         | 0.70         |
| (0.51-1.62)              | (0.86-2.44) | (0.35-1.15)  | (0.35-1.15) | (0.40-1.22) |              |              |
| HDL cholesterol          | 1.0        | 0.68         | 0.77       | 1.0        | 0.75         | 0.85         |
| (0.40-1.17)              | (0.46-1.30) | (0.43-1.30)  | (0.43-1.30) | (0.49-1.48) |              |              |
| Triglyceride             | 1.0        | 0.83         | 1.66*      | 1.0        | 0.59*        | 0.87         |
| (0.45-1.52)              | (0.99-2.79) | (0.31-1.10)  | (0.31-1.10) | (0.49-1.54) |              |              |
| Atherosclerotic index    | 1.0        | 0.76         | 1.49       | 1.0        | 0.62         | 0.92         |
| (0.42-1.37)              | (0.90-2.49) | (0.34-1.16)  | (0.34-1.16) | (0.53-1.61) |              |              |

1OR, odds ratio; CI, confidence interval. 2adjusted for age, body mass index, systolic blood pressure, smoking, and drinking.

*P<0.1 **P<0.05 ***P<0.01
Table 6. Crude and adjusted odds ratios for relationship between baseline variables and 10-year mortality from cancer, Toda City, Japan, 1979-1991.

|                | crude OR † |                          | adjusted OR ‡ |                          |
|----------------|------------|--------------------------|---------------|--------------------------|
|                | 1st tertile| 2nd tertile (95% CI ††) | 3rd tertile (95% CI ‡‡) | 1st tertile| 2nd tertile (95% CI ††) | 3rd tertile (95% CI ‡‡) |
| **Men**        |            |                          |               |                          |                          |
| Total cholesterol | 1.0        | 0.57                     | 0.81          | 1.0                      | 0.66                     | 1.10                       |
|                |            | (0.25-1.33)              | (0.38-1.72)   | (0.28-1.57)              | (0.49-2.44)              |
| HDL cholesterol | 1.0        | 0.42*                    | 0.79          | 1.0                      | 0.30**                   | 0.37**                     |
|                |            | (0.17-1.03)              | (0.38-1.63)   | (0.12-0.76)              | (0.16-0.88)              |
| Triglyceride   | 1.0        | 0.88                     | 0.88          | 1.0                      | 1.16                     | 1.34                       |
|                |            | (0.40-1.96)              | (0.40-1.95)   | (0.50-2.65)              | (0.54-3.35)              |
| Atherosclerotic index | 1.0        | 0.56                     | 0.83          | 1.0                      | 0.85                     | 1.67                       |
|                |            | (0.24-1.30)              | (0.39-1.77)   | (0.34-2.10)              | (0.67-4.16)              |
| **Women**      |            |                          |               |                          |                          |
| Total cholesterol | 1.0        | 0.82                     | 1.42          | 1.0                      | 0.60                     | 0.76                       |
|                |            | (0.35-1.92)              | (0.67-3.00)   | (0.25-1.43)              | (0.34-1.69)              |
| HDL cholesterol | 1.0        | 0.84                     | 0.76          | 1.0                      | 0.94                     | 0.92                       |
|                |            | (0.39-1.81)              | (0.35-1.65)   | (0.43-2.03)              | (0.41-2.07)              |
| Triglyceride   | 1.0        | 1.55                     | 1.78          | 1.0                      | 1.10                     | 0.99                       |
|                |            | (0.67-3.60)              | (0.78-4.05)   | (0.46-2.61)              | (0.40-2.43)              |
| Atherosclerotic index | 1.0        | 0.56                     | 1.24          | 1.0                      | 0.41**                   | 0.70                       |
|                |            | (0.23-1.35)              | (0.61-2.54)   | (0.17-1.01)              | (0.32-1.54)              |

‡ OR, odds ratio; CI, confidence interval. * adjusted for age, body mass index, systolic blood pressure, smoking, and drinking. **p<0.1 ***p<0.05

Table 7. Crude and adjusted odds ratios of baseline serum lipids to cancer mortality of the first five years, Toda City, Japan, 1979-1984.

|                | crude OR † |                          | adjusted OR ‡ |                          |
|----------------|------------|--------------------------|---------------|--------------------------|
|                | 1st tertile| 2nd tertile (95% CI ††) | 3rd tertile (95% CI ‡‡) | 1st tertile| 2nd tertile (95% CI ††) | 3rd tertile (95% CI ‡‡) |
| **Men**        |            |                          |               |                          |                          |
| Total cholesterol | 1.0        | 0.53                     | 0.41          | 1.0                      | 0.68                     | 0.65                       |
|                |            | (0.18-1.61)              | (0.13-1.34)   | (0.22-2.10)              | (0.19-2.20)              |
| HDL cholesterol | 1.0        | 0.24*                    | 0.90          | 1.0                      | 0.13**                   | 0.31**                     |
|                |            | (0.05-1.14)              | (0.34-2.43)   | (0.02-0.67)              | (0.10-0.96)              |
| Triglyceride   | 1.0        | 0.72                     | 0.47          | 1.0                      | 1.04                     | 1.00                       |
|                |            | (0.25-2.08)              | (0.14-1.58)   | (0.34-3.12)              | (0.27-3.68)              |
| Atherosclerotic index | 1.0        | 0.28*                    | 0.48          | 1.0                      | 0.49*                    | 1.31                       |
|                |            | (0.08-1.03)              | (0.16-1.41)   | (0.12-1.94)              | (0.38-4.58)              |
| **Women**      |            |                          |               |                          |                          |
| Total cholesterol | 1.0        | 0.99                     | 1.50          | 1.0                      | 0.74                     | 0.88                       |
|                |            | (0.32-3.09)              | (0.53-4.24)   | (0.23-2.37)              | (0.29-2.66)              |
| HDL cholesterol | 1.0        | 2.30                     | 1.56          | 1.0                      | 2.39                     | 1.73                       |
|                |            | (0.72-7.36)              | (0.45-5.34)   | (0.73-7.80)              | (0.49-6.15)              |
| Triglyceride   | 1.0        | 1.49                     | 0.99          | 1.0                      | 1.03                     | 0.57                       |
|                |            | (0.53-4.20)              | (0.32-3.08)   | (0.35-3.02)              | (0.16-1.96)              |
| Atherosclerotic index | 1.0        | 0.44                     | 0.90          | 1.0                      | 0.33*                    | 0.58                       |
|                |            | (0.14-1.43)              | (0.35-2.35)   | (0.10-1.11)              | (0.20-1.65)              |

‡ OR, odds ratio; CI, confidence interval. * adjusted for age, body mass index, systolic blood pressure, smoking, and drinking. **p<0.1 ***p<0.05
women, adjusted odds ratios across all lipids tended to be inversely related, however it did not reach significant level. Relationships of serum lipids to cancer mortality did not differ between the former five years and the latter five years of the 10-year follow-up (Tables 7, 8). Further, the direction and extent of the inverse relationship of serum lipids to first 2-year cancer mortality was not different from that to 10-year mortality although it is not tabulated.

**DISCUSSION**

In Japan, there is a certain regional difference in the level of TC. Urban areas tend to have a high level as compared with rural areas. The National Survey on Circulatory Disorders\(^26\) was conducted on a representative sample of the Japanese population in 1980, at the same period as the baseline survey of the present study. The survey showed a higher level of TC in 23 wards in the center of Metropolitan Tokyo than in the entire Japanese population. The level of subjects in the present study was close to that of the level in Tokyo, however, it was still lower than in the USA or European countries.

The low level of TC in Japanese may alter association of serum lipids with stroke. The Hisayama study revealed direct relationship of incidence from cerebral infarction (non embolic) with (TC-HDL-C)/TC, which implies a risk role of LDL-and/or VLDL cholesterol.\(^25\)

In terms of the association of serum lipids to cancer incidence and mortality, several questions have been raised. The first is whether inverse relation between baseline TC and cancer should be attributed to preclinical cancer effect. As McMichael et al.\(^13\) reviewed, there have been contradictory results between dietary cholesterol and serum cholesterol relating to cancer; excessive intake of cholesterol is risky, whereas a high level of serum cholesterol is protective. That contradiction sometimes warrants attributing the inverse relation found in serum cholesterol and cancer to a preclinical cancer effect. Some epidemiological studies have shown that the relationship was attributed to preclinical cancer effect, by separating analysis of cancer cases occurring in an earlier period from the baseline\(^13,12\). However, reports demonstrating the causal relationship between TC and cancer have been recently increasing. Evans County and Framingham Studies did not attribute the inverse relation between initial TC and total cancer present in men to preclinical cancer effect\(^3,4\). In studies from Honolulu and Yugoslavia, the relation is likely to differ according to sites of cancer\(^5,6,8\). The relation was of cause-effect in colon cancer, but not in total cancer.

The Puerto Rican Study\(^7\) demonstrated that the inverse
relation for total cancer was evident, after multivariate adjustment, and the inverse relation was not attributable to a preclinical cancer effect.

The present study confirmed that there was no difference in the relation of TC to cancer mortality between the first two years and 10 years, nor was there a difference in the direction and extent of the relationship of TC to cancer between the former five years and the latter five years. The present study thus shows a time-sequential relationship of TC to cancer. However, we should be prudent in determining its causal relationship. In Japan, two papers are available concerning the inverse relationship between TC and cancer mortality\(^\text{\textregistered}^{20,21}\). Both studies showed a significant relation even when the first 5-year deaths were excluded\(^\text{\textregistered}^{20,21}\).

Little has been known concerning association between HDL-C and cancer. Further, findings in available data are controversial. Keys stated that high HDL-C was a risk factor of cancer\(^\text{\textregistered}^{22}\). Cowan et al.\(^\text{\textregistered}^{16}\) recognized no significant relation to total cancer mortality, but a direct relation to gynecologic cancers with HDL-C. To the contrary, Hoyer et al.\(^\text{\textregistered}^{19}\) found an inverse association of HDL-C with breast cancer based on a prospective observation of 5,207 Danish women. The present study revealed an inverse association between HDL-C and cancer, even after adjustment of confounders, although the coefficients in women did not reach significant level. Further research is necessary to ascertain the relationship between HDL-C and cancer, in order to establish a causal relationship.

A U-shaped or an inverse relationship of TC to all-cause mortality is partly due to excess deaths in lower cholesterol levels as mentioned above. Pekkanen et al.\(^\text{\textregistered}^{33}\) observed that a longitudinal decline of TC was a risk of all-cause mortality, and ascribed it to a third factor, such as increased prevalence of chronic diseases or other changes associated with aging. Primary prevention trials to reduce coronary heart disease by lowering TC have sometimes shown an increase of deaths from suicide and violence. Engelberg\(^\text{\textregistered}^{40}\) thought it unlikely that these findings were due merely to chance alone. He hypothesized that a reduction in serum cholesterol may decrease brain-cell membrane cholesterol, lower the lipid microviscosity, and decrease the exposure of protein serotonin receptors on the membrane surface, resulting in a poorer uptake of serotonin from the blood and less serotonin entry into brain cells. Thus, risk roles of low TC on deaths are multifold.

An inverse association of HDL-C with total mortality has also been shown in the elderly. A high age group had a high level of HDL-C and HDL/TC ratio compared with a younger age group with or without coronary artery disease\(^\text{\textregistered}^{10}\).

The present study recognized an inverse relation of all-cause mortality not only with TC but also with HDL, controlling for confounders. However, the relation of HDL-C to total mortality is not necessarily consistent cross-culturally. A comparative study of correlates for total mortality between Russian and US women yielded a contradictory result; in US women, an inverse relation existed, but in Russian women it did not\(^\text{\textregistered}^{35}\). Thus, further investigation of HDL-C in relation to total mortality as well as to specific diseases is warranted.

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