



ORIGINAL CONTRIBUTIONS

Which Cholesterol Level Is Related to the Lowest Mortality in a Population with Low Mean Cholesterol Level: A 6.4-Year Follow-up Study of 482,472 Korean Men

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To evaluate the relation between low cholesterol level and mortality, the authors followed 482,472 Korean men aged 30–65 years from 1990 to 1996 after a baseline health examination. The mean cholesterol level of the men was 189.1 mg/100 ml at the baseline measurement. There were 7,894 deaths during the follow-up period. A low cholesterol level (<165 mg/100 ml) was associated with increased risk of total mortality, even after eliminating deaths that occurred in the first 5 years of follow-up. The risk of death from coronary heart disease increased significantly in men with the highest cholesterol level (≥ 252 mg/100 ml). There were various relations between cholesterol level and cancer mortality by site. Mortality from liver and colon cancer was significantly associated with a very low cholesterol level (<135 mg/100 ml) without any evidence of a preclinical cholesterol-lowering effect. With lengthening follow-up, the significant relation between a very low cholesterol level (<135 mg/100 ml) and mortality from stomach and esophageal cancer disappeared. The cholesterol level related with the lowest mortality ranged from 211 to 251 mg/100 ml, which was higher than the mean cholesterol level of study subjects. *Am J Epidemiol* 2000;151:739–47.

cholesterol; colonic neoplasms; coronary disease; liver neoplasms; mortality; neoplasms

Editor's note: An invited commentary on this paper appears on page 748 and the author's response, on page 752.

A high level of serum cholesterol is a well-known risk factor for coronary heart disease, and expert groups have advised people to lower their serum cholesterol level for the purpose of reducing coronary heart disease occurrence and mortality (1–3). There might still be the

possibilities, however, that cholesterol levels at the lower end of the distribution are also harmful and that a relation between a low serum cholesterol level and noncoronary mortality, especially cancer mortality, exists (4, 5). Most epidemiologic studies to explore the relation between a low serum cholesterol level and mortality were performed on Western populations whose mean cholesterol levels were relatively high. The results from those studies were not only insufficient to clarify the association of cholesterol level with mortality in populations having relatively low mean cholesterol levels but also conflicting (6–17). It would be worthwhile to examine the relation between serum cholesterol level and mortality from various causes of death, particularly in populations whose mean cholesterol levels are much lower than that usually observed in Western populations. Thus, we conducted a 6.4-year longitudinal study of 482,472 adult Korean men whose mean cholesterol level was relatively low in comparison with that of Western people.

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MATERIALS AND METHODS

Study population and variables

In Korea, medical insurance is provided to all people by the National Health Insurance System. The Korea Medical Insurance Corporation, one of two major national health insurance agencies, is in charge of medical insurance for all public service personnel, private school teachers and staffs, and their family members. The Korea Medical Insurance Corporation has provided the insured with the expenses for not only the diagnosis and treatment of diseases but also the biennial multiphasic health examination. To study the relation between cholesterol level and mortality in Korean men, we utilized the health examination data set of the Korea Medical Insurance Corporation accumulated since 1990. The study subjects were male public servants and teachers who had taken the multiphasic health examination and completed the questionnaire inquiring of health habits and past medical history in 1990. Women were not included in the study because the number of female public servants was too small compared with that of male public servants. The serum cholesterol level, blood pressure, body weight, and height were measured between March and July, 1990. Thereafter, these items were measured again at each biennial examination. After an overnight fast, venous blood was drawn in the morning in accordance with the health examination regulation of the Korea Medical Insurance Corporation. All blood samples were centrifuged to separate the serum. Cholesterol, glucose, aspartate aminotransferase, and alanine aminotransferase levels in the serum were measured using an automatic analyzer. All medical institutes that carried out the health examinations were equipped with standardized high quality laboratories authorized by the Korea Association of Clinical Pathology and the Korea Association of Quality Control over Clinical Laboratory Examination. The questionnaires inquiring of health habits were self-administered. For smoking status, study subjects were classified into four groups: nonsmoker, former smoker, light smoker (<20 cigarettes per day), and heavy smoker (≥ 20 cigarettes per day). Three classes were used to determine alcohol drinking habits: nondrinker, occasional drinker, and frequent drinker. Information on the exact frequency was not available. For physical exercise habit, two classes were used: doing exercise or not. From data on the basic monthly salary, economic status was classified into four levels: less than 734 dollars, 734–1,467 dollars, 1,468–2,201 dollars, and more than 2,202 dollars.

Among the 734,250 men who had taken the health examination in 1990, 251,778 persons belonging to any of the following categories were excluded: under 30

years or over 65 years of age (97,722 men); incomplete health examination or missing values in study variables (88,207 men); abnormally high levels of serum aspartate aminotransferase (over 50 units/liter) or serum alanine aminotransferase (over 45 units/liter), which might represent the presence of liver disease associated with affected cholesterol metabolism (18) (32,825 men); abnormally high level of serum glucose (over 120 mg/100 ml), which suggests the presence of altered glucose metabolism known to have a positive association with cholesterol level (19) (16,883 men); abnormally low level of hemoglobin (under 12 g/100 ml) (2,727 men); abnormal chest radiograph (12,826 men); and past history of cancer (598 men). Thus, 482,472 men were included in the study. Among the 1990 cohort, 90.8 percent (438,232 men) in 1992, 87.5 percent (422,322 men) in 1994, and 77.4 percent (373,535 men) in 1996 took the health examinations repeatedly.

The mean serum cholesterol level of the 482,472 men was 189.1 mg/100 ml (standard deviation, 36.0 mg/100 ml). Study subjects were divided into six discrete classes according to their distribution of cholesterol levels: <135 mg/100 ml (lower 5 percent), 135–164 mg/100 ml (lower 5–24 percent), 165–185 mg/100 ml (lower 25–49 percent), 186–210 mg/100 ml (upper 50–74 percent), 211–251 mg/100 ml (upper 75–94 percent), and ≥ 252 mg/100 ml (upper 5 percent). Body mass index, calculated as the weight (kg)/height (m)², was used as a measure of relative weight, classifying the men into groups of underweight (lower than 20 kg/m²), normal weight (20–24 kg/m²), and overweight (25 kg/m² or more).

Mortality follow-up

The vital status of the subjects studied was checked through the death registry of the Korea National Statistical Office and the death benefit record of the Korea Medical Insurance Corporation from October 1990 to December 1996. Usually, the complete vital information of the Korean people is available because all deaths are reported to the Korea National Statistical Office by submitting death certificates. Unfortunately, however, a part of the death record from the Korea National Statistical Office between 1990 and 1991 had some errors in resident registration number, which made the complete data linkage difficult. Thus, we had to utilize the death benefit record of the Korea Medical Insurance Corporation complementarily in ascertainment of the vital status. Using these two record systems, we could follow up on the vital status of 97.0 percent of the subjects. To evaluate the accuracy of the code for cause of death according to the death certificate, we compared the cause of death with medical service utilization records of the study subjects between

June 1995 and December 1995. The code of deaths tabulated by the Korea Medical Insurance Corporation was 72.6 percent accurate (326 of 446 cases were concordant) for the deaths from all causes, whereas the code of deaths from cancers was 97.2 percent accurate (171 of 176 cases were concordant). The code of deaths obtained from the Korea National Statistical Office was 74.6 percent accurate (641 of 859 cases were concordant) for the deaths from all causes and 91.6 percent accurate (347 of 379 cases were concordant) for the deaths from cancers. There was no significant difference, however, in accuracy of the causes of deaths among the classes of cholesterol level ($p > 0.05$).

Statistical analysis

Age-adjusted mortality rates (per 100,000 person-years) from all-cause, cancer, coronary heart diseases, stroke, violent causes, and noncardiovascular non-cancer nonviolent causes by the six classes of cholesterol level were calculated using the direct standardization method. Relative risks and their 95 percent confidence intervals were estimated by Cox proportional hazard regression analysis using the SAS version 6.02 software program (SAS Institute, Inc., Cary, North Carolina) to investigate the relation between serum cholesterol level and mortality. The cholesterol level was used in quadratic term for computation. Dummy variables were defined for six classes of cholesterol using 165–186 mg/100 ml as the comparison

group. Age by 5 years, relative body weight (underweight, normal, overweight), diastolic blood pressure by 1 mmHg, economic status (four levels), smoking habits (nonsmoker, former smoker, light smoker, heavy smoker), drinking habits (nondrinker, occasional drinker, frequent drinker), and exercise habit (doing exercise or not) were added for multivariate analysis. To identify the preclinical disease effect, we repeated the Cox proportional hazard regression analysis several times, progressively excluding the deaths that occurred earlier during the period.

RESULTS

During the 6.4-year follow-up period, 7,894 deaths were identified. Of these, 3,136 deaths (39.7 percent) occurred from cancer. Another 744 deaths (9.4 percent) were attributable to stroke, 394 deaths (5.0 percent) to coronary heart diseases, 1,752 deaths (22.2 percent) to violent causes, and 1,341 deaths (17.0 percent) to noncardiovascular noncancer nonviolent causes. The 10 leading cancer sites among the subjects were the stomach (821 cases), liver (756 cases), lung (511 cases), pancreas (161 cases), biliary tract (123 cases), anorectum (95 cases), esophagus (89 cases), colon (85 cases), leukemia (66 cases), and brain (60 cases). Table 1 shows the baseline serum cholesterol level in relation to certain other baseline variables. Subjects with higher cholesterol levels were slightly older and accordingly had higher diastolic and systolic blood pressure levels than did those with lower cho-

TABLE 1. Selected variables in 482,472 men aged 30–65 years at the baseline examination by cholesterol level, Korea, 1990–1996

Cholesterol level (mg/100 ml)	Mean age (years)*	Former smoker (%)**	Smoker, <20 cigarettes/ day (%)**	Smoker, ≥20 cigarettes/ day (%)**	Alcohol drinker, occasional (%)**	Alcohol drinker, frequent (%)**	Doing exercise (%)**
<135 (n = 23,890)	40.0	13.1	45.0	14.2	51.2	21.3	18.8
135–164 (n = 95,060)	40.7	13.8	43.9	15.0	52.1	21.7	19.6
165–185 (n = 118,283)	41.7	13.9	43.0	15.7	51.8	22.9	20.5
186–210 (n = 123,754)	42.7	14.3	42.1	16.6	51.2	23.6	20.5
211–251 (n = 96,511)	43.8	14.9	41.6	17.3	50.7	24.8	20.9
≥252 (n = 24,974)	45.0	15.4	40.7	18.6	50.0	25.7	21.1

	Mean systolic blood pressure (mmHg)*	Mean diastolic blood pressure (mmHg)*	Body mass index (%)**		Basic monthly salary (%)**			
			<20 kg/m ²	≥25 kg/m ²	\$<734	\$734– 1,467	\$1,468– 2,201	≥2,202
<135 (n = 23,890)	121.0	79.0	13.2	13.9	8.3	43.8	35.4	12.6
135–164 (n = 95,060)	121.7	79.5	11.3	16.2	7.8	40.5	36.7	15.1
165–185 (n = 118,283)	122.7	80.2	9.0	19.6	7.5	36.9	37.4	18.2
186–210 (n = 123,754)	123.8	81.0	7.3	22.9	7.6	33.8	38.4	20.3
211–251 (n = 96,511)	125.4	82.3	5.4	27.4	7.4	30.9	38.2	23.4
≥252 (n = 24,974)	127.7	83.7	3.9	32.0	7.3	28.1	38.6	26.1

* $p < 0.01$ (analysis of variance test); ** $p < 0.01$ (chi-square test).

lesterol levels. While smoking was less prevalent compared with other, the proportion of heavy smokers was larger in the group with higher cholesterol levels. Physical exercise and alcohol consumption were more prevalent among subjects with higher cholesterol levels. Among the subjects with higher cholesterol levels, the proportion of persons belonging to a higher socioeconomic status and overweight was larger than that of the subjects with lower cholesterol levels.

The cause-specific, age-adjusted mortality rate by classes of cholesterol level is presented in figure 1. The curve for all-cause mortality by cholesterol levels was U-shaped. The all-cause mortality rate was highest among men with the lowest cholesterol levels (<135 mg/100 ml) and lowest among men with cholesterol levels between 211 and 251 mg/100 ml. This inverse relation was also observed between cholesterol level and mortality from cancer, violent causes, and noncardiovascular noncancer nonviolent causes. The mortality rate from stroke was highest among men with the lowest cholesterol levels (<135 mg/100 ml), followed by the group with the highest cholesterol levels (≥ 252 mg/100 ml) comprising the second rank in stroke deaths. On the other hand, coronary heart disease mortality and cholesterol level revealed a J-shaped relation. Although the mortality rate of coronary heart diseases was much higher among men with the highest cholesterol levels (≥ 252 mg/100 ml) than among those with lower cholesterol levels, the mortality rate was very low compared with the mortality rate from cancer.

Multivariate analysis applying the Cox proportional hazard model showed an inverse relation between all-cause mortality and cholesterol level (table 2). The greater risk of death for the men with cholesterol levels below 165 mg/100 ml compared with those with cholesterol levels between 165 and 185 mg/100 ml persisted throughout the first 5 years of follow-up. The risk of death for the men with cholesterol levels between 211 and 251 mg/100 ml was significantly lower than that of other groups, although it disappeared when the deaths occurring during the first 4 years were excluded. Men with the highest cholesterol levels seemed to have higher risk of death without statistical significance. A significant inverse relation between the blood cholesterol level and cancer death was observed (table 2). The greatest risk of cancer death was confined to those men with the lowest cholesterol level, but the magnitude of risk decreased gradually over the follow-up period and finally lost statistical significance. Significantly increased risk of death from coronary heart diseases was evident among men with the highest cholesterol levels (≥ 252 mg/100 ml) throughout the whole follow-up period. No association was found between cholesterol level and mortality from stroke and violent causes. Significantly increased risk of mortality from noncardiovascular noncancer nonviolent causes was observed in men with a lower cholesterol level (<165 mg/100 ml).

Multivariate analysis performed in order to determine cancer site-specific differences in the relation

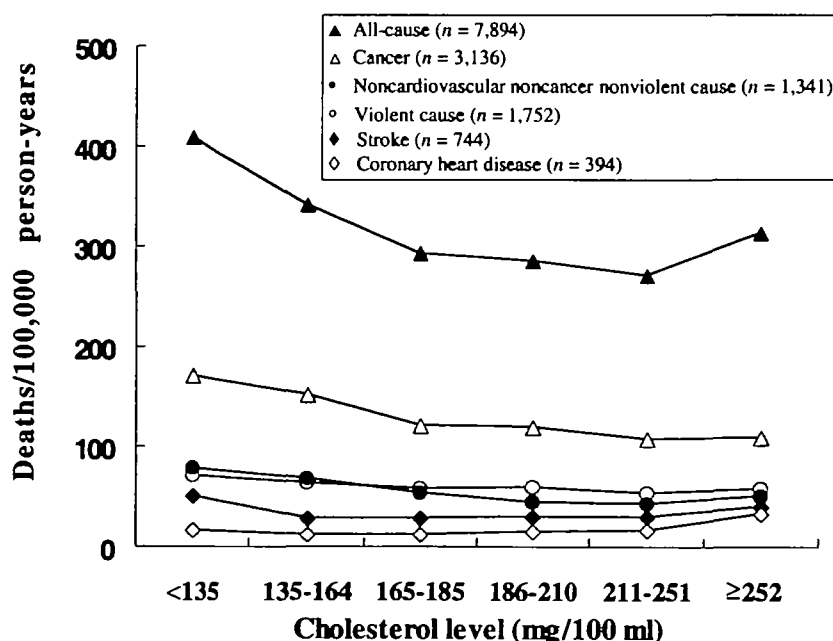


FIGURE 1. Age-adjusted rate of cause-specific mortality among 482,472 men aged 30–65 years by baseline cholesterol level, Korea, 1990–1996.

TABLE 2. Multivariate adjusted relative risks† for mortality from all-cause, cancer, stroke, coronary heart disease, violent cause, and noncardiovascular noncancer nonviolent causes of 482,472 men aged 30–85 years by cholesterol level according to the follow-up period, Korea, 1990–1996

Follow-up period	No. of cases	Cholesterol level (mg/100 ml)					
		<135	135–164	165–185	186–210	211–251	≥252
All-cause death							
All study subjects	7,894	1.30 (1.18, 1.45)**‡	1.11 (1.04, 1.19)**	1	0.99 (0.93, 1.05)	0.92 (0.86, 0.98)*	1.03 (0.94, 1.14)
>2 years	6,272	1.29 (1.15, 1.46)**	1.12 (1.04, 1.21)**	1	0.98 (0.91, 1.05)	0.90 (0.83, 0.97)**	1.05 (0.94, 1.18)
>3 years	5,036	1.27 (1.11, 1.45)**	1.09 (1.00, 1.19)*	1	0.98 (0.91, 1.06)	0.92 (0.84, 1.00)*	1.04 (0.92, 1.18)
>4 years	3,584	1.30 (1.11, 1.53)**	1.14 (1.03, 1.26)**	1	1.03 (0.94, 1.13)	0.95 (0.86, 1.05)	1.02 (0.87, 1.18)
>5 years	2,060	1.36 (1.11, 1.68)**	1.21 (1.06, 1.38)**	1	1.08 (0.95, 1.22)	1.00 (0.88, 1.14)	1.01 (0.83, 1.24)
Cancer							
All study subjects	3,136	1.42 (1.21, 1.68)**	1.16 (1.05, 1.30)**	1	0.97 (0.88, 1.07)	0.87 (0.78, 0.97)*	0.91 (0.77, 1.07)
>2 years	2,554	1.35 (1.12, 1.62)**	1.14 (1.02, 1.29)*	1	0.95 (0.85, 1.06)	0.85 (0.76, 0.96)**	0.92 (0.77, 1.10)
>3 years	2,069	1.31 (1.06, 1.61)*	1.10 (0.96, 1.26)	1	0.96 (0.85, 1.08)	0.87 (0.76, 0.99)*	0.92 (0.75, 1.12)
>4 years	1,487	1.28 (1.00, 1.64)*	1.07 (0.91, 1.25)	1	0.96 (0.83, 1.11)	0.90 (0.77, 1.05)	0.90 (0.71, 1.15)
>5 years	872	1.26 (0.91, 1.75)	1.11 (0.90, 1.36)	1	0.95 (0.79, 1.15)	0.92 (0.76, 1.12)	0.81 (0.58, 1.12)
Stroke							
All study subjects	744	1.42 (0.99, 2.03)	1.07 (0.84, 1.36)	1	1.14 (0.93, 1.41)	1.06 (0.85, 1.32)	1.20 (0.89, 1.63)
>2 years	617	1.38 (0.93, 2.05)	1.15 (0.89, 1.49)	1	1.15 (0.91, 1.44)	0.99 (0.78, 1.26)	1.18 (0.84, 1.64)
>3 years	513	1.53 (1.00, 2.33)*	1.17 (0.88, 1.55)	1	1.18 (0.92, 1.51)	1.00 (0.77, 1.31)	1.16 (0.80, 1.68)
>4 years	382	1.36 (0.80, 2.29)	1.25 (0.90, 1.74)	1	1.27 (0.95, 1.70)	1.04 (0.76, 1.42)	1.33 (0.88, 2.03)
>5 years	216	1.62 (0.83, 3.15)	1.21 (0.78, 1.90)	1	1.35 (0.91, 1.99)	1.07 (0.71, 1.64)	1.53 (0.89, 2.64)
Coronary heart disease							
All study subjects	394	1.44 (0.87, 2.38)	0.98 (0.69, 1.39)	1	1.17 (0.87, 1.57)	1.33 (0.99, 1.79)	2.42 (1.69, 3.48)**
>2 years	320	1.34 (0.78, 2.31)	0.86 (0.59, 1.26)	1	0.96 (0.69, 1.32)	1.15 (0.83, 1.60)	2.20 (1.49, 3.25)**
>3 years	250	1.23 (0.66, 2.30)	0.76 (0.49, 1.18)	1	0.87 (0.60, 1.25)	1.19 (0.84, 1.70)	2.02 (1.30, 3.15)**
>4 years	164	0.95 (0.40, 2.26)	0.68 (0.39, 1.19)	1	0.94 (0.60, 1.47)	1.12 (0.72, 1.74)	2.17 (1.28, 3.68)**
>5 years	83	1.30 (0.44, 3.83)	0.76 (0.36, 1.64)	1	0.81 (0.42, 1.56)	1.06 (0.57, 1.99)	2.43 (1.19, 4.96)*
Violent cause							
All study subjects	1,752	1.04 (0.83, 1.31)	1.07 (0.93, 1.23)	1	1.02 (0.89, 1.16)	0.93 (0.80, 1.07)	1.08 (0.86, 1.34)
>2 years	1,402	1.08 (0.84, 1.39)	1.05 (0.90, 1.23)	1	1.04 (0.90, 1.20)	0.93 (0.80, 1.10)	1.06 (0.82, 1.36)
>3 years	1,082	1.04 (0.78, 1.40)	1.02 (0.85, 1.22)	1	1.03 (0.87, 1.22)	0.93 (0.77, 1.11)	0.98 (0.73, 1.32)
>4 years	736	1.29 (0.92, 1.80)	1.23 (0.99, 1.52)	1	1.07 (0.87, 1.32)	0.95 (0.76, 1.20)	0.93 (0.64, 1.35)
>5 years	398	1.25 (0.78, 2.01)	1.31 (0.98, 1.75)	1	1.14 (0.86, 1.50)	0.97 (0.71, 1.32)	0.84 (0.49, 1.42)
Noncardiovascular non-cancer nonviolent causes							
All study subjects	1,341	1.40 (1.10, 1.79)**	1.21 (1.04, 1.42)*	1	0.89 (0.77, 1.04)	0.81 (0.69, 0.96)*	0.85 (0.66, 1.11)
>2 years	1,019	1.30 (0.98, 1.73)	1.22 (1.02, 1.46)*	1	0.89 (0.74, 1.06)	0.79 (0.66, 0.96)*	0.91 (0.68, 1.21)
>3 years	832	1.35 (0.99, 1.85)	1.20 (0.98, 1.47)	1	0.91 (0.75, 1.11)	0.85 (0.69, 1.05)	1.02 (0.75, 1.40)
>4 years	610	1.46 (1.01, 2.12)*	1.30 (1.02, 1.66)*	1	1.05 (0.84, 1.32)	0.94 (0.74, 1.20)	0.98 (0.67, 1.44)
>5 years	368	1.58 (0.97, 2.56)	1.42 (1.04, 1.95)*	1	1.21 (0.90, 1.63)	1.03 (0.75, 1.42)	1.13 (0.70, 1.84)

* $p < 0.05$; ** $p < 0.01$.

† Relative risk compared with the cholesterol level between 165 and 185 mg/100 ml after adjustment for age, basic monthly salary, diastolic blood pressure, body mass index, smoking, alcohol drinking, and exercise.

‡ Numbers in parentheses, 95% confidence interval.

showed various results (table 3). Of the 10 most common cancers by site, only the mortality from liver cancer had a persistently strong association with cholesterol level. The risk of death from liver cancer decreased progressively with increasing cholesterol levels, which was persistently significant throughout the follow-up period. A significantly higher risk of death from colon cancer was observed among men with the lowest cholesterol levels (<135 mg/100 ml) when the deaths occurring during the first 5 years were excluded, which was quite peculiar to colon cancer and not observed among other cancers. Risks of death from cancers of the stomach and esophagus among the men with the lowest cholesterol levels (<135 mg/100 ml) were significantly higher than among the men with

higher cholesterol levels, although the strength of the associations lost its statistical significance when the deaths occurring during the earlier study period were excluded. No significant trends in the relation between cholesterol level and mortality were observed in cancers of the lung, anorectum, pancreas, biliary tract, or brain. The risk of mortality from leukemia was high among the men with low cholesterol levels and low among the men with high cholesterol levels. However, the relation was not significant statistically.

We quantified the changes in the mean cholesterol levels over the period between the baseline and last follow-up examination by the cause of death (table 4). The proportion of subjects having taken follow-up measurement of the cholesterol level was 95.1 percent

TABLE 3. Multivariate adjusted relative risks† for mortality from 10 common cancers of 482,472 men aged 30–65 years by cholesterol level according to the follow-up period, Korea, 1990–1996

Follow-up period	No. of cases	Cholesterol level (mg/100 ml)					
		<135	135–164	165–185	186–210	211–251	≥252
Stomach cancer							
All study subjects	821	1.81 (1.33, 2.44)**‡	1.12 (0.90, 1.40)	1	1.12 (0.92, 1.37)	1.06 (0.86, 1.31)	1.08 (0.78, 1.48)
>2 years	648	1.47 (1.02, 2.10)*	1.06 (0.83, 1.35)	1	1.05 (0.85, 1.31)	1.01 (0.80, 1.27)	1.02 (0.71, 1.45)
>5 years	212	1.55 (0.80, 3.00)	1.14 (0.73, 1.79)	1	1.31 (0.88, 1.93)	1.28 (0.85, 1.92)	1.22 (0.65, 2.27)
Liver cancer							
All study subjects	756	1.74 (1.30, 2.33)**	1.38 (1.13, 1.68)**	1	0.83 (0.68, 1.02)	0.84 (0.51, 0.81)**	0.39 (0.24, 0.62)**
>2 years	597	1.78 (1.28, 1.47)**	1.43 (1.15, 1.79)**	1	0.80 (0.64, 1.01)	0.65 (0.50, 0.85)**	0.38 (0.22, 0.66)**
>5 years	196	1.92 (1.09, 3.38)*	1.55 (1.05, 2.27)*	1	0.70 (0.46, 1.07)	0.79 (0.51, 1.21)	0.25 (0.09, 0.80)*
Lung cancer							
All study subjects	511	0.81 (0.48, 1.36)	1.05 (0.80, 1.38)	1	1.00 (0.78, 1.27)	0.92 (0.71, 1.19)	1.18 (0.82, 1.70)
>2 years	441	0.76 (0.43, 1.36)	1.06 (0.79, 1.42)	1	0.98 (0.75, 1.27)	0.92 (0.70, 1.22)	1.31 (0.90, 1.90)
>5 years	152	0.48 (0.15, 1.55)	0.99 (0.61, 1.62)	1	0.88 (0.57, 1.37)	0.80 (0.50, 1.28)	0.98 (0.50, 1.92)
Pancreatic cancer							
All study subjects	161	1.25 (0.56, 2.82)	1.30 (0.80, 2.12)	1	1.31 (0.85, 2.02)	0.94 (0.58, 1.52)	0.65 (0.27, 1.55)
>2 years	126	1.13 (0.44, 2.93)	1.22 (0.70, 2.11)	1	1.24 (0.76, 2.03)	0.96 (0.58, 1.63)	0.81 (0.33, 1.96)
>5 years	38	2.14 (0.43, 10.6)	0.99 (0.28, 3.51)	1	1.66 (0.61, 4.50)	2.33 (0.89, 6.10)	0.60 (0.07, 5.02)
Biliary tract cancer							
All study subjects	123	0.76 (0.27, 2.15)	0.93 (0.54, 1.61)	1	0.95 (0.59, 1.54)	0.83 (0.49, 1.39)	0.59 (0.23, 1.51)
>2 years	109	0.92 (0.32, 2.62)	1.02 (0.57, 1.84)	1	1.04 (0.62, 1.74)	0.95 (0.55, 1.65)	0.74 (0.28, 1.93)
>5 years	41		0.48 (0.13, 1.78)	1	1.55 (0.68, 3.55)	1.67 (0.72, 3.88)	
Anorectal cancer							
All study subjects	95	1.25 (0.52, 3.01)	0.74 (0.40, 1.39)	1	0.52 (0.28, 0.95)*	0.86 (0.50, 1.49)	0.85 (0.35, 2.06)
>2 years	87	1.11 (0.43, 2.89)	0.74 (0.39, 1.42)	1	0.52 (0.28, 0.98)*	0.85 (0.48, 1.50)	0.77 (0.29, 2.00)
>5 years	37		0.45 (0.16, 1.22)	1	0.36 (0.14, 0.91)*	0.55 (0.24, 1.30)	0.53 (0.12, 2.32)
Esophageal cancer							
All study subjects	89	2.33 (1.08, 5.04)*	0.81 (0.41, 1.60)	1	1.00 (0.56, 1.75)	0.40 (0.19, 0.87)*	1.64 (0.78, 3.46)
>2 years	72	2.80 (1.20, 6.48)*	0.76 (0.34, 1.71)	1	1.08 (0.56, 2.06)	0.54 (0.24, 1.22)	1.99 (0.88, 4.49)
>5 years	32	0.98 (0.12, 8.17)	1.19 (0.36, 3.91)	1	1.55 (0.56, 4.27)	0.87 (0.27, 2.86)	3.24 (0.98, 10.7)
Colon cancer							
All study subjects	85	1.99 (0.79, 5.01)	1.66 (0.89, 3.12)	1	0.73 (0.36, 1.47)	1.27 (0.68, 2.40)	1.15 (0.42, 3.11)
>2 years	78	1.99 (0.79, 5.03)	1.51 (0.79, 2.88)	1	0.73 (0.37, 1.48)	1.04 (0.53, 2.02)	0.93 (0.31, 2.75)
>5 years	26	4.01 (1.13, 14.3)*	1.20 (0.36, 3.92)	1	0.79 (0.24, 2.59)	1.10 (0.35, 2.59)	
Leukemia							
All study subjects	66	1.68 (0.62, 4.61)	1.18 (0.58, 2.42)	1	1.17 (0.60, 2.27)	0.75 (0.34, 1.67)	0.60 (0.14, 2.63)
>2 years	54	1.53 (0.50, 4.66)	1.05 (0.48, 2.32)	1	0.99 (0.47, 2.07)	0.78 (0.34, 1.81)	0.70 (0.16, 3.08)
>5 years	19	1.14 (0.13, 9.78)	1.39 (0.40, 4.81)	1	0.96 (0.28, 3.33)	0.46 (0.09, 2.38)	0.90 (0.10, 7.74)
Brain cancer							
All study subjects	60	0.88 (0.18, 3.51)	1.15 (0.54, 2.47)	1	1.05 (0.52, 2.10)	0.49 (0.20, 1.21)	1.82 (0.74, 4.49)
>2 years	47	1.00 (0.22, 4.49)	1.32 (0.58, 3.00)	1	1.08 (0.50, 2.33)	0.35 (0.11, 1.08)	1.29 (0.41, 4.02)
>5 years	13		1.89 (0.42, 8.45)	1	1.50 (0.36, 6.29)		1.18 (0.12, 11.5)

* $p < 0.05$; ** $p < 0.01$.

† Relative risk compared with the cholesterol level between 165 and 185 mg/100 ml after adjustment for age, basic monthly salary, diastolic blood pressure, body mass index, smoking, alcohol drinking, and exercise.

‡ Numbers in parentheses, 95% confidence interval.

among subjects who were alive at the end of the study. Considering the subjects (1,622 men) who died within 2 years after the baseline examination and could not take the follow-up health examination, the proportion of subjects who measured the follow-up cholesterol level (5,348 men) was 85.3 percent among those who died. For those who died during the study period, the mean time interval between the last follow-up examination and death was 19.7 months (standard deviation, 11.5 months). While the mean cholesterol level of men alive at the end of the follow-up period increased significantly when compared with the initial

level, there was a 0.31-mg/100 ml decrease from the level of the deceased. The mean cholesterol level of men who died from cancer showed a 3.25-mg/100 ml decrease on average ($p < 0.05$). Among those who died from stomach cancer and leukemia, the mean cholesterol levels also showed a significant decrease. Although the initial cholesterol level of the people who died from liver cancer was much lower than that of other study subjects, the degree of decrease during the follow-up period was very small. Apart from other cancer deaths, increases of cholesterol level were observed among men who died from cancers of the

TABLE 4. Mean cholesterol levels measured at baseline and last follow-up examination according to the vital status at the end of study and specific causes of death, Korea, 1990–1998

Vital status and cause of death	Cholesterol level (mg/100 ml)								
	At baseline examination			At last examination if alive			Change between two periods†		
	No. of cases	Mean	SE‡	No. of cases	Mean	SE	No. of cases	Mean	SE
Alive	474,578	189.0	0.05	451,414	193.2	0.05	451,414	4.26**	0.06
All-cause death	7,894	190.8	0.43	5,348	190.4	0.57	5,348	−0.31	0.58
Stroke	744	195.6	1.47	500	195.4	1.75	500	0.83	1.84
Coronary heart disease	394	201.5	2.15	294	198.8	2.23	294	0.14	2.28
Violent causes	1,752	189.6	0.89	1,331	192.3	1.04	1,331	2.80**	1.07
Noncardiovascular noncancer nonviolent causes	394	187.3	1.29	849	186.7	1.51	849	−0.42	1.55
All cancer	3,136	189.7	0.67	2,080	186.8	0.90	2,080	−3.25**	0.89
Stomach cancer	821	191.4	1.32	526	186.8	1.61	526	−4.86*	1.74
Liver cancer	756	180.7	1.25	505	181.0	1.62	505	−0.44	1.74
Lung cancer	511	195.3	1.67	352	191.9	2.23	352	−4.40	1.99
Pancreatic cancer	161	189.5	2.70	103	188.3	3.98	103	−3.10	3.95
Biliary tract cancer	123	191.6	2.97	95	193.0	4.00	95	0.85	3.97
Rectal cancer	95	191.4	3.93	69	189.7	4.52	69	1.74	5.25
Esophageal cancer	89	190.7	4.61	60	188.6	5.82	60	−1.73	4.99
Colon cancer	85	189.3	4.72	61	193.3	6.63	61	3.54	5.16
Leukemia	66	184.4	4.34	44	172.2	6.66	44	−14.93*	5.87
Brain cancer	60	194.7	5.59	37	185.3	6.35	37	−4.49	6.02

* $p < 0.05$; ** $p < 0.01$.† Statistical significance of the change between two periods was evaluated by paired t test.

‡ SE, standard error.

colon (4.23 mg/100 ml), anorectum (1.74 mg/100 ml), and biliary tract (0.85 mg/100 ml).

DISCUSSION

When compared with that of other studies, the follow-up period of our study might be too short to give a clear conclusion about the relation between cholesterol level and mortality. Even with this limitation, the larger proportion of the study population with low cholesterol levels than in previous studies and the sufficient number of deaths made it possible to examine the relation between cholesterol level and mortality.

This study indicates that the cholesterol level is a useful predictive variable for death, having a U-shaped relation with mortality among Korean adult males. Results of previous studies on the relation varied by the values of mean cholesterol level in the population studied. Studies done in populations with relatively high mean cholesterol levels reported a U- or J-shaped relation between cholesterol level and mortality (10–12, 17, 20), while studies in populations with low mean cholesterol levels reported an inverse relation (16, 21). In this study, the cholesterol level with the lowest risk of death was between 211 and 251 mg/100 ml, which was higher than not only the mean cholesterol level of the study subjects and but also the cholesterol levels with lowest risk of death reported from other studies. In Western populations with high cho-

lesterol levels, the ranges of cholesterol level with the lowest mortality risk were lower than the mean cholesterol level of the population (6, 13, 17, 20). The discrepancy between the Korean and Western study results might be attributed to the differences in the main causes of death and in the proportion of people exposed to the risk factors contributing to the main causes of deaths among populations.

Although the mortality rate from coronary heart disease among Korean men with high cholesterol levels was much lower (10, 17) and also the proportion of people with high cholesterol levels in our study subjects was much smaller than that observed among Western populations (6, 13, 17, 20), the cholesterol level that abruptly increased the risk of mortality from coronary heart disease was very similar to the level reported from the studies done in Western and Japanese-American populations (6, 10, 13, 20, 22). Thus, our study findings again confirmed high cholesterol as a significant risk factor of coronary heart disease and at the same time also suggested that the impacts of a risk factor can be different by the prevalence of disease and the distribution of the risk factor in a population.

Like previous studies that reported inverse associations between cholesterol level and cancer death, we also observed a similar pattern of association in the risk of cancer death. However, the level that signifi-

cantly increases the risk of cancer death was lower than that reported from other studies (15, 23, 24). There have been discussions concerning the possibility that the inverse relation between cholesterol level and cancer death might not be a real causal relation but an effect-cause relation due to the preclinical cancer effect on cholesterol level (10, 13, 25, 26). In order to minimize the possibility of a preclinical cancer effect, we tried to exclude all subjects who had been diagnosed as having cancer or who had abnormal health examination outcomes suspicious of possible pre-diagnosed cancer. In addition, the changing pattern of the relation between cholesterol level and cancer death during the entire follow-up period was observed. The inverse relation between cholesterol level and cancer death remained significant for the 5-year follow-up period. The relative risk for cancer death, however, among the people with a very low cholesterol level decreased progressively with the lengthening of the follow-up period, as reported from previous studies (10, 13). The mean cholesterol level of the people who died from cancer in our study also showed a remarkable decrease during the follow-up period, as shown in other studies (27, 28). In this aspect, our study findings seem to indicate a preclinical cancer effect on cholesterol level.

On the other hand, the mortality from liver and colon cancer associated with cholesterol level in our study presents a different view from other study results. Previously Chen et al. (21) and Kagan et al. (29) reported the significant inverse relation between cholesterol level and mortality from liver cancer. This relation, however, lost its statistical significance when the deaths that occurred during the first 2 years were excluded (29). In our study analysis, in which a relatively sufficient number of deaths occurred late in the period, the deaths from liver cancer revealed a consistent significant inverse relation with cholesterol level. This result might support the true association of cholesterol level with liver cancer death. Considering that the initial cholesterol level was relatively low and that there was very little decrease in cholesterol level over the follow-up period in men who died from liver cancer, we cannot rule out the role that other factors that act on both the cholesterol level and liver cancer might have. Although we tried to exclude the subjects with chronic liver disease at the baseline examination by detecting abnormally elevated levels of serum aspartate aminotransferase and serum alanine aminotransferase, healthy chronic carriers of hepatitis B and hepatitis C with normal liver function test results may have been included in our study. In some Asian countries with a high prevalence rate of hepatitis B infection, liver cancers are known to develop largely from

liver cirrhosis associated with hepatitis B and hepatitis C viral infections (30, 31). Chen et al. (32) suggested that prolonged infection with hepatitis B virus might produce an inverse association between cholesterol concentration and the risk of liver cancer through the lowering of cholesterol level in adulthood.

Study results on the relation between colon cancer and cholesterol level vary. Törnberg et al. (33) reported a positive association, while Stemmermann et al. (34) reported a significant inverse association. Other study results suggested the preclinical cholesterol-lowering effect of colon cancer (35, 36). The study finding that the inverse relation became stronger progressively as the follow-up period was getting longer may indicate a causal association between cholesterol level and colon cancer. Moreover, the increase of mean cholesterol level among men who died from colon cancer over the follow-up period, which negates the preclinical cholesterol-lowering effect of cancer, supports the above implication. However, considering that the small number of cases with colon cancer occurred 5 years after the baseline cholesterol measurement, further studies might be needed to confirm the true association between colon cancer and cholesterol.

There was no consistency in the patterns of relation between cholesterol level and other cancer deaths such as gastric and esophageal cancer, although we could observe a somewhat increased risk of death from these cancers among men with a very low cholesterol level. This finding and a decrease in the mean cholesterol level of the people who died from these cancers over the follow-up period do not support the true association between these cancers and cholesterol, which may imply a possible preclinical cancer effect. Despite the inverse associations with serum cholesterol level reported for lung, pancreatic, biliary tract, and hematopoietic cancers in many previous studies (11, 15, 17, 29), no notable evidence of association was found in our study.

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