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Relationship Between Serum Cholesterol and the Risk of Acute Myocardial Infarction in a Screened Cohort in Okinawa, Japan

Kiyoshi Wakugami, MD; Kunitoshi Iseki, MD*; Yorio Kimura, MD;
Koichiro Okumura, MD; Yoshiharu Ikemiya, MD**;
Hiromi Muratani, MD; Koshiro Fukiyama, MD

Coronary heart disease (CHD) is rare in Japanese subjects and serum cholesterol levels are low. However, no data have been published relating the effect of serum cholesterol levels to the incidence of acute myocardial infarction (AMI) in Japan. Data from a large community-based mass screening registry are available for the geographically isolated island of Okinawa, Japan (1980 census, 1.11 million). A total of 38,053 participants (17,859 men and 20,194 women) whose serum cholesterol levels were determined in the 1983 mass screening were examined to determine whether they had experienced AMI. Every case of AMI that occurred during a 3-year period (1 April 1988 to March 1991) throughout Okinawa was recorded in a separate registry. The total number of cases of AMI was 1,021 (674 men and 347 women). Of these, 65 patients (41 men and 24 women) were identified by name, sex, birth date, and zip code in the mass screening registry. The cumulative incidence of AMI increased with the serum level of cholesterol: 42.1 (serum cholesterol ≤167 mg/dl), 133.5 (serum cholesterol 168−191 mg/dl), 188.9 (serum cholesterol 192−217 mg/dl), and 323.0 (serum cholesterol ≥218 mg/dl) per 100,000 screened subjects. Multiple logistic analysis was conducted to examine the effect of serum cholesterol on the risk of AMI with adjustment for other variables such as sex, age, systolic and diastolic blood pressure, and proteinuria. The adjusted odds ratio (95% confidence interval) of the observed serum levels of cholesterol was 1.66 (1.29−2.15) with a reference serum cholesterol level of ≤167 mg/dl. The risk of AMI increased in proportion to the serum level of cholesterol. Serum cholesterol is an independent predictor of AMI in Okinawa, Japan.

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Hypercholesterolemia is an established risk factor for coronary heart disease (CHD) in many populations[1−9] The risk of CHD is continuous from the lowest to the highest serum levels of cholesterol studied. Most dietary trials designed to lower serum cholesterol levels have shown negative or equivocal results[4,5,10] However, lipid-lowering drugs, prescribed to reduce the risk of CHD, have proved to be effective in treating patients with hypercholesterolemia[11,12] Although there have been a few studies of hypercholesterolemia as a risk factor for CHD in the Japanese population, the results are inconclusive[13−15] CHD is relatively rare in Japanese population and serum cholesterol levels are generally low[3,16] However, as the life expectancy of Japanese subjects increases[17] so too does the risk of developing CHD.

Data are presented here from the 1983 mass screening registry (n=38,053) and subsequent acute myocardial infarction (AMI) registry in Okinawa, whose population has the longest life expectancy and the lowest rate of deaths from cardiovascular disease in Japan. Our hypothesis was that in this Japanese population the serum level of cholesterol is an independent predictor of AMI. We examined the associa-

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*Third Department of Internal Medicine and *Dialysis Unit, University of The Ryukyus, and **Okinawa General Health Maintenance Association, Okinawa, Japan*
Mailing address: Kiyoshi Wakugami, MD, Third Department of Internal Medicine, University of The Ryukyus, 207 Uehara, Okinawa 903-01, Japan

tion between the incidence of AMI and serum cholesterol levels recorded at the 1983 mass screening.

Methods

Study Design

An epidemiologic study of the risk factors for AMI was conducted in the prefecture of Okinawa, a subtropical island in southernmost Japan. According to the census, the population of this island was 1.11 million in 1980 and 1.22 million in 1990. All individuals over 18 years of age who participated in the 1983 mass health screening and whose serum cholesterol levels had been recorded were eligible for the study. Details of the registry of the Okinawa General Health Maintenance Association (OGHMA) have been reported previously[18,19] Subjects whose birth date and serum cholesterol level were not in the computer file were excluded from evaluation in the present study.

An independent registry of AMI that also covered the entire area of Okinawa was available[20] The period covered by this registry was the 3 years between April 1988 and March 1991.

Subjects with AMI who were included among the participants of the 1983 mass screening were identified by using the data compiled in the 2 registries. The subjects' identities were verified by name, sex, birth date, zip code, and, as required, by reviewing their medical records. The cumulative incidence of AMI was calculated and the risk factors for AMI were determined by logistic analysis by using the Statistical Analysis System (SAS) package.

Mass Screening Registry

A large, community-based health examination program is conducted annually by the OGHMA, under the direction of Dr Y. Ikemiya. OGHMA staff visit sites throughout Okinawa where people live or work. Clinical and laboratory data were recorded in the computer file for the fiscal year from 1 April 1983 to 31 March 1984. Blood pressure was measured by a nurse or doctor using a standard mercury sphygmomanometer. Dipstick urinalysis (Ames dipstick) was performed using spontaneously voided fresh urine, morning or afternoon. The blood test was optional as the cost was not covered by the public sector. Fasting serum cholesterol was measured at the OGHMA laboratory by the enzymatic oxidase method using a commercially available kit. Information regarding various lipoprotein particles, drug use, or smoking habits is not available in the data file. A total of 107,192 inhabitants over 18 years of age participated in the mass screening in 1983. The estimated population was 13.7% of the 1983 adult population in Okinawa[18] The present analysis was based on a total of 38,053 participants (17,859 men and 20,194 women) whose serum cholesterol and other clinical variables are recorded in the computer data file.

AMI Registry

Cases of AMI were identified from the registry of the Co-operative Study Group of Morbidity and Mortality of Cardiovascular Disease in Okinawa (COSMO registry). A description of this registry has been published[20] Briefly, every case of AMI that occurred in Okinawa during the 3 years between 1 April 1988 and 31 March 1991 was recorded. We visited 9 public hospitals, 25 main private hospitals, and 7 public health centers with the collaboration of the Okinawa Medical Association. These medical facilities covered more than 95% of cases of systemic lupus erythematosus registered in the entire area of Okinawa[21] Because of the geographic location of Okinawa, AMI patients seek medical advice exclusively on that island. The health care system covers nearly all of the residents. The environment and health department of the Okinawa prefecture government and the department of legal medicine of the University of The Ryukyus also participated in this study to identify AMI patients. Therefore, we believe this hospital-based registry covered virtually all of the cases of AMI in the period studied. Criteria for the diagnosis of AMI were based on those in the World Health Organization (WHO) MONICA project[22] and both definite and possible AMI were included. Medical record data including history, electrocardiogram, and laboratory data were examined and included.

Statistical Analysis

Two methods, the paired t test and the equivalent non-parametric test, and the Wilcoxon rank-sum test were used to compare continuous variables. Fisher's exact test was used to compare differences among the groups of discrete variables. Subjects in the 1983 mass screening were categorized according to age at the time of screening, the results of urinalysis, blood pressure, and serum cholesterol[18] The cumulative incidence of AMI was calculated as the ratio of the number of AMI to the number of screened subjects at risk, being expressed per 100,000 screened subjects. The relative risk was calculated by dividing the incidence rate by the corresponding rate in the reference category. Serum cholesterol-adjusted rates were calculated for age and other variables simultaneously with multiple logistic analysis using the SAS package[23] The dependent variable in the model was binary, that

Table 1 Number of Screened Subjects Based on Age at the Mass Screening and the Quartile of Serum Cholesterol. Mass Screening was Performed From 1 April 1983 to 31 March 1984

Serum cholesterol (mg/dl)	*Age at mass screening (years)*						
	18–29	*30–39*	*40–49*	*50–59*	*60–69*	*70+*	*Total*
Men							
≤167	*705*	*995*	*971*	*711*	*660*	*613*	*4,655*
168–191	*382*	*939*	*1,269*	*818*	*745*	*589*	*4,742*
192–217	*251*	*869*	*1,303*	*982*	*696*	*451*	*4,552*
≥218	*161*	*688*	*1,249*	*959*	*533*	*320*	*3,910*
Total	*1,499*	*3,491*	*4,792*	*3,470*	*2,634*	*1,973*	*17,859*
Women							
≤167	*708*	*1,246*	*1,344*	*637*	*483*	*425*	*4,843*
168–191	*278*	*741*	*1,328*	*1,051*	*844*	*753*	*4,995*
192–217	*139*	*390*	*1,022*	*1,328*	*1,149*	*951*	*4,979*
≥218	*53*	*203*	*680*	*1,610*	*1,564*	*1,267*	*5,377*
Total	*1,178*	*2,580*	*4,374*	*4,626*	*4,040*	*3,396*	*20,194*

To convert values for cholesterol to mmol/L, multiply by 0.026.

is AMI or non-AMI, during the study period. For all relative risks we calculated 95% confidence limits. Data are expressed as means±SD.

Results

Mass Screening

Serum cholesterol levels varied widely among the screened subjects, from 66 mg/dl to 748 mg/dl (median 180–189 mg/dl in both sexes). The screened subjects were grouped into quartiles according to their basal serum cholesterol level: ≤167 mg/dl (n=9,498), 168–191 mg/dl (n=9,737), 192–217 mg/dl (n=9,531), and ≥218 mg/dl (n=9,287). The mean serum cholesterol level in each quartile was 149.3 mg/dl, 179.8 mg/dl, 203.7 mg/dl, and 245.3 mg/dl, respectively.

Table 1 summarizes the number of screened subjects in each quartile of serum cholesterol by sex and by age at screening. Other demographic factors such as blood pressure and urinalysis have been reported previously[18,19]

AMI Registry

A total of 1,059 cases of AMI in 1,021 patients (674 men, 347 women) were registered during the study period. Among them, 152 patients (99 men, 53 women) were identified among the recipients of the 1983 mass screening (n=107,192). The number of identified AMI cases who had participated in the 1983 screening was 44 (total 320) in 1988, 54 (total 366) in 1989, and 54 (total 335) in 1990. The proportion of first-ever AMI was 88.2% of the total (87 men and 47 women). The clinical demographics at the mass screening of these AMI cases are shown in Table 2. In the present study, 65 (41 men and 24 women) cases of AMI in screened subjects were investigated. The proportions of men among the screened AMI patients (63.1%) and the AMI patients (66.7%) who had not been screened were similar. Similarly, the mean (SD) age at onset of AMI was not different: 69.8 (11.4) years in the former and 68.9 (12.5) years in the latter.

The cumulative incidence of AMI in each quartile of serum cholesterol is summarized in Table 3. The cumulative incidence of AMI increased from 42.1 to 323.0 per 100,000 screened subjects from the 1st to 4th quartile. In any level of serum cholesterol, men had a higher incidence of AMI than women (Fig 1).

Risk Factors for AMI

The relationship between the cumulative incidence of AMI and both systolic and diastolic blood pressure among all screened subjects is shown in Figs 2 and 3. There was a linear relationship between them in both men and women.

Table 4 shows the results of the multiple logistic analysis of the risk of AMI. The odds ratio (95% confidence interval) was 1.77 (1.38–2.26) in the univariate analysis and 1.66 (1.29–2.15) in the multivariate analysis with adjustment for age, sex, proteinuria, and systolic and diastolic blood pressure. The risk ratio (RR) increased to 1.14 (serum cholesterol 167–191 mg/dl), 1.30 (192–217 mg/dl), and 1.48 (≥218 mg/dl) when compared with the reference level of serum cholesterol (≤167 mg/dl, RR=1.00).

Table 2 Characteristics of the Acute Myocardial Infarction (AMI) Patients at 1983 Mass Screening. Mass Screening was Performed From 1 April 1983 to 31 March 1984

	Present analysis (n=38,053)	*Total number of screened subjects (N=107,192)*	
	Case AMI	*Non-case AMI*	*Total AMI*
Number of patients			
Total	65	87	152
Men/women	41/24	58/29	99/53
Age at screening (years)			
Mean	63.7	62.7	63.1
SD	11.4	12.5	12.0
Range	43–88	33–84	33–88
Age at onset of AMI (years)			
Mean	69.8	68.7	69.2
SD	11.4	12.5	12.0
Range	50–95	36–90	36–95
Serum cholesterol (mg/dl)			
Mean	218.5		
SD	38.9		
Range	144–320		
Systolic blood pressure (mmHg)			
Mean	146.2	141.7	143.6
SD	20.8	19.0	19.8
Range	96–190	86–206	86–206
Diastolic blood pressure (mmHg)			
Mean	85.5	83.4	84.3
SD	11.9	12.2	12.1
Range	58–110	60–138	58–138
Proteinuria			
Normal	58	83	141
Abnormal	6	4	10

Abnormal urinalysis denotes 1+ and over by dipstick.

A comparison of serum cholesterol levels observed at the 1983 mass screening and at the onset of AMI (n=44) is shown in Fig 4. The mean serum level of cholesterol at the onset of AMI (209.5±33.5 mg/dl) was slightly lower than that at the mass screening (225±41.2 mg/dl), and the difference was significant ($p<0.002$).

Discussion

The annual incidence of AMI in Okinawa, Japan, adjusted by age and sex to the standard Japanese population was 26 per 100,000 subjects[20] The incidence among the subjects screened in 1983 was 27 per 100,000 screened subjects, suggesting that the sample size and the distribution of sex and age in this screening registry was adequate and representative of the

Table 3 Cumulative Incidence of Acute Myocardial Infarction (AMI) During the Study Period in Each Quartile of Basal Serum Cholesterol Level at 1983 Mass Screening. Mass Screening was Performed From 1 April 1983 to 31 March 1984

	Quartile of serum cholesterol (mg/dl)			
	1st	*2nd*	*3rd*	*4th*
Serum cholesterol				
Range	≤167	168–191	192–217	≥218
Mean	149.3	179.8	203.7	245.3
Screened subjects				
Number	9,498	9,737	9,531	9,287
Men (%)	49.0	48.7	47.8	42.1
Acute myocardial infarction				
Total	4	13	18	30
Men	3	10	10	18
Women	1	3	8	12
Cumulative incidence per 100,000 screened subjects				
Total	42.1	133.5	188.9	323.0
Men	64.5	210.9	219.5	460.4
Women	20.6	60.1	160.8	223.2

To convert values for cholesterol to mmol/L, multiply by 0.026.

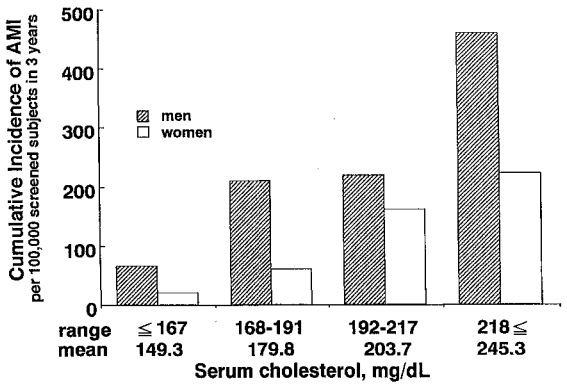

Fig 1. Cumulative incidence of AMI in each quartile of basal serum cholesterol, expressed per 100,000 screened subjects in 3 years. Serum cholesterol was measured between 1 April 1983 and 31 March 1984. To convert values for cholesterol to mmol/L, multiply by 0.026.

entire adult population of Okinawa. The number of screened subjects was 13.9% of the total adult population in Okinawa[18] As AMI occurs mostly in adults, the expected number of cases of AMI was estimated by multiplying the total number of patients registered with an AMI (n=1,022) by 0.139 to obtain 142. The number of cases actually observed was 152.

Serum cholesterol levels are often measured in subjects who participate in mass screenings. To our knowledge, this is the first population-based study in Japan that has attempted to address the issue of the

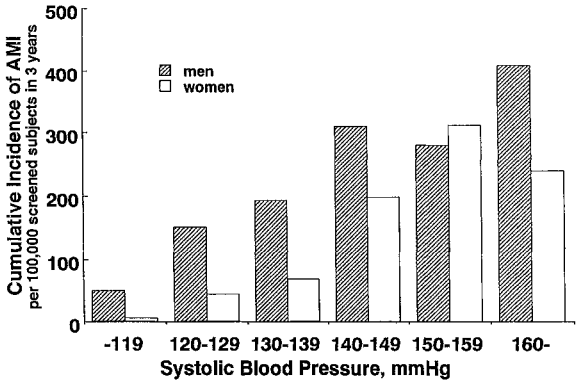

Fig 2. Cumulative incidence of AMI, expressed per 100,000 screened subjects in 3 years as related to the systolic blood pressure recorded between 1 April 1983 and 31 March 1984.

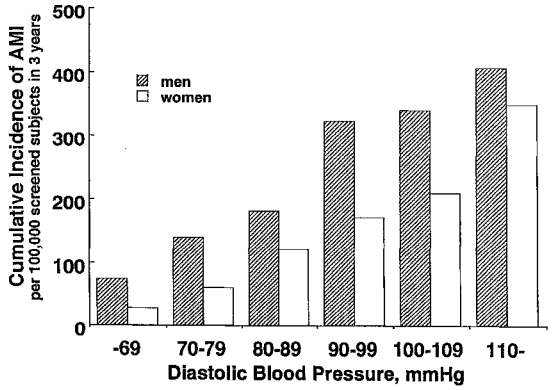

Fig 3. Cumulative incidence of AMI, expressed per 100,000 screened subjects in 3 years as related to the diastolic blood pressure recorded between 1 April 1983 and 31 March 1984.

relationship between baseline serum cholesterol levels and the subsequent incidence of AMI. The mean serum cholesterol levels in Okinawa did not differ significantly from that in national population-based samples recorded in 1980[24] although they were slightly higher on average. In women, the highest quartile of serum cholesterol was observed after age 50 (Table 1). This is probably related to the effect of the menopause[25] Our findings strongly support the results of the epidemiologic studies conducted outside Japan[1-9] However, the lower incidence of AMI in Japan may not be explained solely by the difference in basal serum cholesterol levels[26] Changes in lifestyle and diet have greatly influenced the mortality rates from CHD and stroke[27]

The present study used only 1 measurement of serum cholesterol. Therefore, the duration of the elevated serum cholesterol level was not known. The effects of dietary control or of drug use were not

Table 4 Logistic Analysis on the Risk of Acute Myocardial Infarction by Serum Cholesterol Among the Participants of the 1983 Mass Screening

Variables	*Odds Ratio*	*95% confidence interval*
Serum cholesterol	*1.77*	*1.38 to 2.26*
Serum cholesterol, age, sex	*1.72*	*1.34 to 2.22*
Serum cholesterol, age, sex, proteinuria, systolic and diastolic blood pressure	*1.66*	*1.29 to 2.15*

Systolic blood pressure (mmHg) was categorized as: <120, 120–129, 130–139, 140–149, and 150 and over. Diastolic blood pressure (mmHg) was categorized as: <<70, 70–79, 80–89, 90–99, and 100 and over.

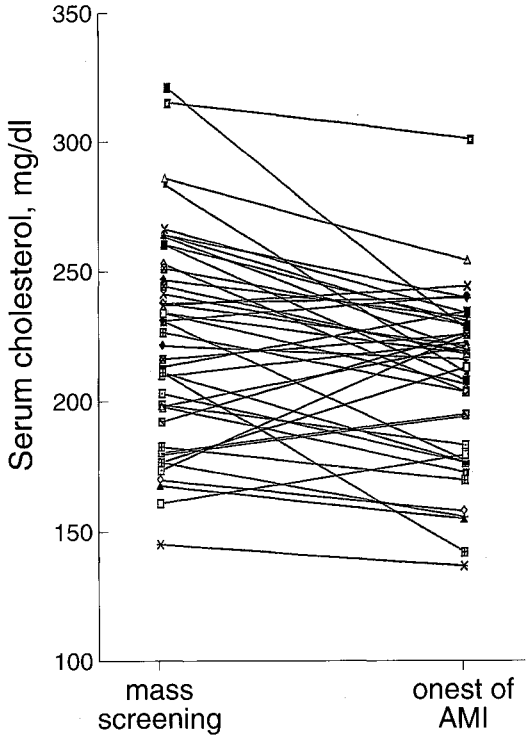

Fig 4. Comparison of observed serum levels of cholesterol between the 1983 mass screening and the onset of AMI (n=44). Mass screening was performed between 1 April 1983 and 31 March 1984. The mean cholesterol level was 15.6 mg/dl lower at the onset of AMI than that at screening ($p<0.002$, paired t test). To convert values for cholesterol to mmol/L, multiply by 0.026.

considered. However, the use of baseline data, rather than time-averaged data, is recommended in a prospective study conducted to determine the risk factors for an event[28] The mean serum cholesterol level was 218.5 mg/dl for subjects who experienced a heart attack in the present study (Table 2), which was lower than the average level of 244 mg/dl observed

in the Framingham study[3] Furthermore, the mean serum cholesterol level was slightly lower at the onset of AMI (Fig 4). We believe that the patients were in a state of slight malnutrition at the onset of the AMI.

Several limitations of this study should be addressed. First, we did not investigate the cases of AMI that occurred in the 4 years after the screening, from April 1984 to March 1988. However, this deficiency would not affect the relationship between serum cholesterol and AMI if the other risk factors for AMI were constant, at least from 1983 to 1991. There were no appreciable changes in lifestyle, dietary habits, or treatment strategy in Okinawa during that specific period, except for the introduction of HMG-CoA reductase inhibitors[29] in August 1989. If used appropriately, the effect of these drugs on serum cholesterol would be evident in 6 months![11] The benefit of treating hypercholesterolemia by pravastatin was shown with an average follow-up of 4.9 years![11] At one institute, only 33% of the patients who were treated with HMG-CoA reductase inhibitors had serum cholesterol levels at or below the levels recommended by the National Cholesterol Education Program (NCEP)[30] A significant rise in the serum cholesterol level and passage of time are required before mass atherosclerosis is observed or the overall incidence of AMI is increased. Second, the AMI registry used in this study is basically a hospital-based registry; therefore, one might argue that some AMI cases may have been missed because of non-compliance or unknown reasons. We think that the likelihood of this is negligible, as the incidence of AMI in this study is no smaller than that in other reports from Japan, and we carefully reviewed both hospital and legal records for cases of suspected cardiac death or sudden death[20] The medical facilities we used for our study are considered to cover more than 95% of the area's population[21] Third, information was not available regarding other risk factors such as smoking habits, alcohol intake, lipid profile, family history, past medical history, and drug use. In Japan, the national prevalence of individuals who currently smoke, considering men (women) aged 20 and over, was 80% (16%) in 1965, 76% (15%) in 1975, and 65% (14%) in 1980[31] The prevalence of smoking has not decreased since 1980[32] Of the total AMI cases in our study, 67.2% were smokers. Fourth, whether the association between serum cholesterol levels and the incidence of AMI was due to the progression of pre-existing atherosclerotic processes was not clear in this study. Whether further decreases in serum cholesterol levels will reduce the incidence of AMI in our population remains to be proved. However, based on the present study, any decrease will not be substantial, as the adjusted odds ratio was only 1.66 (Table 4).

Reducing the serum cholesterol levels with pravastatin has been reported to reduce the risk of CHD events in asymptomatic subjects with hypercholesterolemia![11] In that study the reported mean baseline serum cholesterol was 272 mg/dl. Reduction of serum cholesterol by 20% was associated with a 30% reduction in CHD incidence. All these changes in serum cholesterol were in the range of the highest quartile for the present study. Recently, it was shown that coronary events can be prevented by cholesterol-lowering drugs in patients who do not have hypercholesterolemia[33] However, lipid-lowering drugs may increase the risk of death from non-cardiovascular causes[34,35] and are not free of adverse effects[36] The Japanese population has a relatively high incidence of stroke![17,37,38] Low serum cholesterol may be a risk factor for stroke if accompanied by malnutrition. Thus, further prospective studies are needed to establish a target level of serum cholesterol that will reduce CHD but not increase mortality from other causes in this country.

In conclusion, the present study demonstrates that the level of serum cholesterol is an independent predictor of AMI, even in people living in Okinawa, Japan. The risk of AMI increased progressively from the lowest to the highest level of serum cholesterol. Medical advice about lowering cholesterol is necessary for screened subjects with high serum cholesterol levels. Use of non-pharmacologic strategies are warranted to lower or to prevent increases in serum cholesterol levels. Based on the low incidence of AMI and low serum cholesterol level in Japan, the benefit of lipid-lowering drugs in reducing the overall death rate remains to be determined.

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