RESEARCH ACTIVITIES OF EPIDEMIOLOGY IN JAPAN

Cardiovascular Disease

A Brief Review of Epidemiological Studies on Ischemic Heart Disease in Japan

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The age-adjusted death rate from ischemic heart disease in Japan is the lowest among developed countries and the rates have decreased since 1970. The incidences of myocardial infarction in selected populations ranged between 0.12 and 2.56 per 1,000 for middle-aged males, and between 0.00 and 1.52 per 1,000 for females. The incidences of sudden death within 24 hours were from 0.00 to 1.58 per 1,000 for males and from 0.00 to 0.76 per 1,000 for females. The incidences in Japanese populations appeared to be far below those in Western populations. In the Cox proportional hazard regression model, hypertension and smoking were selected as independent risk factors for myocardial infarction in an agricultural district. It was noteworthy that the level of serum cholesterol was not associated with development of myocardial infarction in rural areas. No positive relation between dietary fat and serum cholesterol was observed in school children, suggesting that growth, sexual maturation and others might be confounding variables between them. The levels of serum cholesterol for females were more affected by menopause than those of blood pressures and body mass index. Although some polymorphisms in selected candidate genes appeared to be associated with some serum lipids and apolipoproteins, the effect of individual RFLP on the inter-individual variations in serum traits was relatively subtle in comparison with that of lifestyle factors. *J Epidemiol*, 1996 ; 6 : S49-S59.

ischemic heart disease, mortality, morbidity, risk factors, RFLP, Japanese story

The death rate from ischemic heart disease in Japan is the lowest among developed countries and the rates have been decreasing since 1970^{1,2)}. In addition, frequency of ischemic heart disease is much lower than that of cerebrovascular disease³⁾. Thus, less emphasis has been laid on epidemiology of ischemic heart disease than that of stroke, and its risk factors have been examined under the observation of stroke. However, it is much concerned that both mortality and morbid-

ity of ischemic heart disease may shift to the increasing trends soon or later, because the intake of fat has been increasing with lifestyle westernization.

In this brief review, we deal with descriptive and analytic epidemiology of ischemic heart disease in Japan.

DEATH RATES FROM ISCHEMIC HEART DISEASE

This section presents the pattern of mortality from ischemic

Received and accepted January 8, 1996.

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Table 1 Trends in crude and age-adjusted death rates per 100,000 from ischemic heart disease by sex, 1950-1993, Japan

		1950	1955	1960	1965	1970	1975	1980	1985	1990	1993
Crude rate	Total	9.9	11.6	21.3	28.5	37.9	39.4	41.6	41.1	41.9	41.9
	Males	12.6	14.3	26.0	34.1	44.3	44.0	47.0	45.5	45.4	45.1
	Females	7.4	9.0	16.7	23.1	31.7	34.9	36.3	36.9	38.6	38.9
Age-adjusted rate	Males	24.6	26.9	48.7	61.7	75.7	70.4	65.5	54.7	46.3	41.9
	Females	13.0	14.8	26.4	35.0	43.7	42.8	37.4	30.9	25.6	22.6

Note : The age-adjusted death rates were computed on the Japanese "model" population for 1985

Source : Statistics and Information Department, Minister's Secretariat, Ministry of Health and Welfare : Vital Statistics of Japan 1993, Vol. 1. Health and Welfare Statistics Association, Tokyo, 1995 : 294-295

Figure 1-1 . Secular trends in age-adjusted death rates from ischemic heart disease for males in selected countries, 1950-1989

Figure 1-2 . Secular trends in age-adjusted death rates from ischemic heart disease for males in selected countries, 1950-1989

heart disease by sex during the period from 1950 to 1993³⁾. During this period, the International Statistical Classification of Diseases, Injuries and Cause of Death (ICD) was revised four times : the 6th revision for 1950 to 1957, the 7th for 1958 to 1967, the 8th for 1968 to 1978 and the 9th for 1979 to 1993 in Japan. The changes in the 7th and the 8th revision were very large because degenerative heart disease was excluded from ischemic heart diseases in the 8th revision. Therefore, a marked decrease in the death rate from ischemic heart disease was artificially observed between 1967 and 1968.

Trends in mortality from ischemic heart disease are shown in Table 1³⁾. The age-adjusted rate increased during the period from 1950 to 1970, and decreased after 1970. The increasing trends from 1950 to 1970 appear to be affected by mortality from senility without mention of psychosis in the elderly

Japanese^{4,5)}. Previously, family members of the aged patient were liable to expect physicians to mention the cause of death as "senility" (not dementia but aging) in the death certificate, even if the cause was clear, in order to customarily idealize the death of the elderly people. For example, 40.8% of the total number of deaths in the age of 80 years and over were recorded as the death from "senility" in 1950³⁾. The percentage, however, decreased afterwards : 30.3% in 1960 and 19.9% in 1970. In these elderly persons, the recorded mortality from ischemic heart disease increased markedly between 1950 and 1970, showing the inverse correlation with mortality from "senility". Assuming that many of the "true" causes of deaths when reported as "senility" were from ischemic heart disease, the mortality curve for the aged may not have showed such an increase as recorded. It may have been sliding along or on the decrease.

As for the decreasing trends in age-adjusted death rate from ischemic heart disease after 1970, there has been considerable discussion in the literatures, some of which, particularly those from clinicians, suggest that many deaths which would previously have been attributed to ischemic heart disease are now coded to some other forms of heart disease, which would account for a substantial part of the decline^{1,6)}. According to some surveys of the diagnostic accuracy of all forms of heart disease, however, the number which was erroneously diagnosed as ischemic heart disease among the coded deaths from ischemic heart disease was almost the same as the number which of the "true" causes of deaths when reported as other forms of heart disease was from ischemic heart disease^{1,7,8)}. As the results, the diagnostic fashion would not affect the trends in age-adjusted death rate from ischemic heart disease after 1970. Although some of the trends at least may well have arisen from internal reassignments within the heart diseases group, it is generally accepted that the rate has been decreasing since 1970.

Figures 1-1 and 1-2 show secular trends in age-adjusted death rates from ischemic heart disease for males in selected countries during the period from 1950 through 1989¹⁾ (since the data for females are similar to those for males, they are not presented here). As shown in Figure 1-1, the rates tended to decrease after the 1960s in the United States of America, Australia and Western and Southern European countries, excluding Spain and France where no marked change was observed. In Eastern European countries (Figure 1-2), conversely, the rates tended to increase. Some of the rise may be due to having diagnostic and certification practices, i.e. a preference among physicians in these countries for less specific diagnoses other than ischemic heart disease¹⁾.

To the extent that the trends largely reflect real changes in mortality, what have been the underlying causes? Explanations that have been proposed emphasize the role of improved medical care or better community wide measures such as hypertension control on the one hand, and lifestyle modification with respect to the principal etiological factors for the disease on the other hand. The relative contribution of these various influences is still very much under debate¹⁾.

INCIDENCE OF MYOCARDIAL INFARCTION AND SUDDEN DEATH

Definition of Myocardial Infarction and Sudden Death

In incidence studies in Japan, acute myocardial infarction and sudden death are measured, but any other form, i.e. angina pectoris, is not included⁹⁾. Acute myocardial infarction is defined as a clinical syndrome resulting from sudden and persistent curtailment of the myocardial blood supply. It is characterized by severe and prolonged (at least half an hour) cardiac pain and other symptoms and signs of cardiac damage, and by electrocardiographic and laboratory evidence of myocardial necrosis (Q waves and CPK, GOT and LDH). Although the chest pain which lasts for more than 30 minutes is described for all of the

patients, the findings of ECG and serum enzymes are available for 60 to 70%. Thus, about one third of "myocardial infarction" in epidemiological studies is considered to be "possible", but not "probable".

In Japan, only those subjects who have been observed in apparent good health but who expire within 24 hours of such observation are included in the category of sudden death. It should be unexpected from any known pathological condition already present. In Japan where the 24-hour definition is usually used, all of the sudden deaths would not be attributed to ischemic heart disease, but a relatively higher percentage of deaths could be attributed to stroke or other diseases. According to Baba et al¹⁰⁾, 33% of the sudden deaths within 24 hours died within one hour.

Case Ascertainment

The occurrence of possible myocardial infarction and sudden death within 24 hours is determined using both active surveillance and registry⁹⁾. Under the surveillance system, all of the residents aged 40 years and over are examined annually. Those who survive and fail to undergo the examination are contacted by telephone or visited at their home by a staff member to determine whether or not a myocardial infarction occurred.

The myocardial infarction and sudden death registration system is established in community-based studies. Suspected patients are referred to the registry by all general practitioners and by hospitals and the nearby hospitals in the area. Patients are also referred by visiting public health nurses and by lay personnel in charge of health services in the area. Other sources of notification may be ambulance personnel, medical authorities etc. The national health insurance records are also regularly reviewed by staff physicians. Information about fatal myocardial infarctions and sudden deaths is obtained by review of all death certificates with supplementary clinical data obtained from the certifying physicians.

Verification of Diagnosis

Clinical histories of the patients who are alive at the time of referral to the study are reviewed by staff physicians⁹⁾. If the patient is dead at the referral time, the staff members collect clinical information from the relatives and the certifying physician.

Information collected includes identifying information, personal health status and treatment received prior to myocardial infarction and death, early stages of the present attack, and clinical and laboratory findings at the first medical examination. This information and the review of hospital records are considered jointly by two or three staff physicians to determine if the patient meets the criteria as a myocardial infarction or a sudden death case.

Incidence

Table 2 shows the incidences of possible myocardial infarction and sudden death within 24 hours for the middle-aged per-

sons in selected populations^{6,9,11}). The incidences of myocardial infarction ranged between 0.12 and 2.56 per 1,000 (median=0.57) for males, and between 0.00 and 1.52 per 1,000 (median=0.15) for females. The incidences of sudden death ranged from 0.00 to 1.58 (median=0.42) for males, and from

0.00 to 0.76 (median=0.09) for females.

According to a meta-analysis of the incidences of myocardial infarction and sudden death for the middle-aged males in selected populations in the US and Northern European countries, the rates were between 3.74 and 13.1 per 1,000 (medi-

Table 2 Average annual incidence of myocardial infarction and sudden death per 1,000 population aged 40-69 years in selected populations, Japan

Population Group	Prefecture	Geographical and occupational feature	Observation periods	Average annual incidence per 1,000			
				Myocardial infarction		Sudden death	
				Males	Females	Males	Females
1	Hokkaido I	flatland+mountain, stock and dairy farmers	1975-1984	2.56	0.38	0.64	0.00
2	Hokkaido II	flatland+mountain, farmers (potato and vegetable cultivation)	1975-1984	1.47	0.00	1.05	0.58
3	Akita I	flatland, farmers (rice cultivation) day laborers	1965-1974	0.42	0.00	0.42	0.09
			1975-1984	0.54	0.08	0.46	0.08
4	Akita II	mountain+flatland, farmers (rice cultivation), day laborers	1975-1983	0.63		1.58	
5	Niigata	mountain+flatland, farmers (rice cultivation, orchard)	1975-1983	0.12		0.35	
			1985-1989	0.40	0.36	0.20	0.00
6	Ibaraki	flatland, farmers	1975-1983	0.77		1.54	
7	Nagano	mountain+flatland, farmers (rice cultivation), blue-collar workers	1975-1983	0.43		0.22	
8	Toyama	mountain+flatland, farmers	1975-1983	0.66		0.88	
9	Osaka I	flatland, a residential and farming district in the suburbs of Osaka City, salaried employees, gardeners, farmers	1965-1974	0.44	0.11	0.50	0.17
			1975-1984	0.59	0.07	0.44	0.25
			1985-1989	0.49	0.15	0.27	0.26
10	Osaka II*	white-collar workers in a company	1965-1969	0.35		0.52	
			1975-1984	0.83		0.19	
			1985-1989	0.72		0.12	
11	Osaka III*	blue-collar workers in the production line of machineries in a factory	1965-1969	0.24		0.36	
			1975-1984	0.39		0.08	
			1985-1989	0.71		0.00	
12	Osaka IV	mountain, woodcutters, farmers, salaried employees	1975-1983	0.68		0.41	
13	Kochi	flatland, farmers (vegetable cultivation in greenhouses)	1975-1983	0.41		1.11	
14	Fukuoka	a town in the suburbs of Fukuoka City, farmers, salaried employees	1962-1974	2.32	0.71	0.36	0.00
			1975-1987	1.89	1.13	0.32	0.08

* aged 40-59 years, The groups include only males.

an=5.76) for probable myocardial infarction, and between 1.00 and 3.60 per 1,000 (median=1.03) for sudden death, usually defined as death within 1 or 2 hours, after 1975⁶⁾. Before 1975, the rates were between 2.10 and 17.79 (median=5.72) for myocardial infarction⁶⁾. The Framingham Study, USA, reported that the average annual incidence of myocardial infarction in the males aged 55-64 years was 10.3 per 1,000 in 1953-63, 11.6 in 1963-73 and 12.0 in 1973-83 : as for females, the rate was 0.38, 0.50 and 0.45 respectively¹²⁾. The incidence per 1,000 males aged 50-59 years of non-fatal myocardial infarction was reported to be 4.99 in 1970-74, 4.74 in 1975-1979 and 4.76 in 1980-84 in Gothenburg, Sweden : 0.91, 1.04 and 1.35 for females¹³⁾. In three WHO MONICA Project regions of Germany, the incidences of myocardial infarction were 0.68-0.92 per 1,000 males aged 35-44, 2.54-2.93 for those aged 45-54 and 6.51-7.73 for those aged 55-64 : 0.03-0.12, 0.23-0.65, and 1.36-2.03 respectively in females¹⁴⁾. Thus, the incidences of myocardial infarction in Japanese populations appear to be far below those in Western populations.

Since the population size of the groups in Table 2 is small, almost less than 5,000, and the incidence of ischemic heart disease is very low, only one case which developed myocardial infarction would effect the incidence seriously. Therefore, it is not clear whether secular trends in the incidence of myocardial infarction or sudden death have a tendency to increase or to decrease in Japan.

PROGNOSIS OF MYOCARDIAL INFARCTION

A Japanese epidemiological research group sponsored by the National Cardiovascular Center registered all of the patients

Figure 2. Sex- and age-adjusted survival rates within 5 years after myocardial infarction. Pooled data of 5 populations in Osaka, Hiroshima and Niigata Prefectures, Japan (Cox proportional hazard regression model)

with the first-ever myocardial infarction and followed them prospectively for up to 10 years in 5 populations in Osaka, Hiroshima and Niigata Prefectures¹¹⁾. As seen in Figure 2, the sex- and age-adjusted survival rates within 5 years after myocardial infarction improved from 1965-1974 to 1985-1990. Although the major contributors to the increase in the survival rates appeared to be the decline in the number of patients with severe myocardial infarction in addition to improved medical care, we do not have any information about which factor is more important. In a hospital-based study, however, the rates improved at the beginning when the coronary care unit (CCU) was introduced to the hospital¹⁵⁾. There have been very few studies of long-term prognosis after the attack of myocardial infarction using the life-table method in Japan. The prognosis and its contributors are the subjects for future studies.

RISK FACTORS

A Prospective Study

The authors report the results of a 15.5-year cohort study for occurrence of possible myocardial infarction (PMI) and sudden death within 24 hours (24SD) in A-I district, Shibata City, Niigata Prefecture¹⁶⁾.

The city of Shibata is located in the northern part of Niigata Prefecture and includes a commercial and an agricultural area around it. A-I district belongs to the agricultural area. Although the majority of the families used to be farmers who supplemented their income with side-jobs in other occupations, they are now regularly hired employees in factories and offices who are engaged in farming works only in the rice-planting and harvesting seasons.

Using all the residents aged 40 years and over, that is, 1,182 males and 1,469 females as the population eligible, a baseline examination was conducted in July, 1977. The response rate for the examination was 84.5% for males and 92.6% for females. Nine hundred and sixty males and 1,339 females who were initially free of ischemic heart disease were followed from July 1977 through December 1992.

As shown in Table 3, in the sex- and age-stratified univariate analyses by the Cox proportional hazard regression model, statistically significant relative risk, hazard ratio, of PMI was observed for systolic (SBP), diastolic (DBP), and mean (MBP) blood pressures, body mass index (BMI) and smoking. For 24SD, DBP and albuminuria were selected as significant risk factors. In the multivariate analyses, MBP and smoking were selected as independent risk factors for PMI. No significant association of any factor with 24SD was detected. It is noteworthy that the influence of serum cholesterol on development of PMI appeared to be small.

According to some cohort studies conducted in rural Japanese populations^{9,17)}, no relationship or a slight inverse relationship was observed between the level of serum cholesterol and occurrence of myocardial infarction, as seen in our

Table 3. Relative risks of possible myocardial infarction and sudden death within 24 hours, A-I district, Shibata City, Niigata Prefecture, 1977-1992

Variable	Myocardial infarction		Sudden death	
	Sex, age-stratified univariate	Multivariate	Sex, age-stratified univariate	Multivariate
	Relative risk 95% CI (p value)	Relative risk 95% CI (p value)	Relative risk 95% CI (p value)	Relative risk 95% CI (p value)
Systolic blood pressure (+21mmHg)	1.55 1.12-2.16 (0.007)	-	1.20 0.85-1.69 (0.30)	-
Diastolic blood pressure (+12mmHg)	1.49 1.04-2.14 (0.028)	-	1.46 1.05-2.04 (0.025)	-
Mean blood pressure (+14mmHg)	1.63 1.13-2.35 (0.010)	1.71 1.15-2.55 (0.008)	1.39 0.97-1.98 (0.072)	***
Total cholesterol (+47mg/dl [1.21mmol/l])	1.25 0.84-1.86 (0.27)	***	0.88 0.57-1.37 (0.56)	***
Body Mass Index (+3kg/m ²)	1.42 1.01-2.01 (0.047)	***	0.97 0.68-1.41 (0.89)	***
ECG abnormality (definite/none)	1.96 0.85-4.52 (0.12)	***	1.45 0.65-3.24 (0.37)	***
Urinary albumin (+, ++, +++/-, ±)	2.01 0.59-6.89 (0.27)	***	2.87 1.06-7.75 (0.038)	***
Urinary glucose (±, +, ++, +++/-)	2.96 0.66-13.23 (0.16)	***	1.50 0.20-11.27 (0.70)	***
Optic fundus abnormality (definite/none)	1.98 0.26-15.10 (0.51)	***	uncalculable	***
Daily cigarettes (≥20/<20)	3.57 1.08-11.76 (0.037)	4.07 1.26-13.11 (0.019)	1.33 0.44-4.00 (0.61)	***
Daily alcohol drinking (≥2 drinks/<2 drinks)	1.08 0.36-3.26 (0.88)	***	0.95 0.33-2.70 (0.92)	***

CI denotes confidence interval; ECG electrocardiographic.

Mean blood pressure = 1/3 systolic blood pressure + 2/3 diastolic blood pressure.

ECG abnormality is defined as high R and/or ST-T change, and optic fundus abnormality is defined as Keith-Wegener class 2-4

Each multivariate model includes age, mean blood pressure, total cholesterol, BMI, hematocrit, ECG abnormality, urinary albumin, urinary glucose, daily cigarettes and alcohol drinking. 1 drink = 12g ethanol.

Relative risks and 95% CI estimated on basis of Cox regression coefficients (sex and total cholesterol are forced into each multivariate stepwise model).

For continuous variables, risks are given for an increase in the variable of 1 standard deviation.

- : not entered into model, *** : entered into model but not selected in the final model.

study. In an urban population in Japan¹⁸⁾ and many populations in the US and European countries¹⁹⁻²²⁾, however, hypercholesterolemia is regarded as one of the strongest risk factors for ischemic heart disease. The heterogeneity of patients with myocardial infarction is presumably one of the reasons for the discrepant findings on the pathogenic effect of serum cholesterol. According to some autopsy studies in Japan^{23,24)}, the massive type of myocardial infarction was closely related to hypercholesterolemia, smoking and other atherogenic factors measured before death, but the scattered type was related only to hypertension. An inverse relationship was clearly observed between the scattered type and serum cholesterol levels prior to death. In addition, there was no relationship between myocardial infarction as a single entity and serum cholesterol in a rural Japanese population, as A-I district, where the scattered type

(ca.70% of MI) was more frequent than the massive type, but a clear positive relationship between overall myocardial infarction and serum cholesterol was observed in a large city where the westernization of lifestyle, particularly dietary intake, advanced much more than in rural areas and the massive type (ca.90% of MI) was predominant, probably as in the US and European countries. If the ratio of the massive to scattered type increase with increasing in the level of serum cholesterol in Japanese rural populations, a significantly positive association of serum cholesterol with overall myocardial infarction would be seen.

Serum Cholesterol in School Children

After World War II, Japanese lifestyle, particularly diet and physical activity, moved towards westernization in concert

Table 4 The average value of serum total cholesterol and dietary intake of fat in school children (14 years old)

	Japan			USA (Bogalusa)	
	Osaka	Shibata	Gunma	White	Black
Serum total cholesterol (mg/dl)	145.7	147.5	170.0	150.2	156.1
Energy (kcal)	2,782	2,577	2,538	2,254	2,148
Total fat (g)	88.1	75.3	64.5	97.2	93.5
Animal fat (g)	43.7	34.5	32.2	61.3	60.5
P/S	1.00	1.19	0.93	0.31	0.30

Dietary intake was assessed by 24-hour recall method.

with the socioeconomic changes, especially during the rapid economic growth period from 1960 to 1975. Epidemiological studies of cardiovascular disease were initiated around 1965. On the basis of the findings from these studies, community-based control of cardiovascular disease, particularly stroke, was conducted in several communities, spreading throughout the country during the first half of the 1970s under legislation aimed at prevention of chronic non-communicable diseases.

The lifestyle modernization and community-based control program of cardiovascular disease resulted in a decrease of hypertension, and therefore in a marked decrease of stroke. Although the level of serum cholesterol and the frequency of obesity increased, especially in agricultural areas, increasing trends in mortality and morbidity of myocardial infarction have not been observed yet. This may be because the generation experienced the period of national privation before 1950 for a long time. During the period, their diet was expressed as high carbohydrate and salt, and extremely low fat and animal protein, their labor intensity was very heavy, and their working hours were very long.

However, the Japanese in their teens and 20s who were born and grew up at the time of slow economic growth while lifestyle westernization advanced are at risk of developing hypercholesterolemia and, therefore, myocardial infarction. As shown in Table 4, the Japanese school children had a tendency to show almost the same levels of serum cholesterol as or higher than American children²⁵⁾. However, no positive relation between fat intake and serum total cholesterol level was observed, suggesting there were some confounding variables between them. For example, A group children whose growth rate decreased showed a little increasing trend in serum cholesterol (Figure 3). The levels of serum cholesterol in B and C groups whose growth rates increased tended to decrease markedly.

Thus, in Japan, young persons must be put under surveillance for dietary intake and cardiovascular risk factors, and the need to establish hypercholesterolemia control programs for school children is very large. However, the effect of growth, sexual maturation, exercise and other factors on the levels of serum cholesterol must be taken into account, and the dietary reduction program of serum cholesterol in Japanese school children must be designed and performed very carefully.

- A : The group whose growth rate in height decreases during the 3 years
 B : The group whose growth rate in height increases up to the 2nd grade then decreases
 C : The group whose growth rate in height increases during the 3 years

Figure 3. Growth and serum total cholesterol in school children, A-I district, Shibata City, Niigata Prefecture

Serum Cholesterol and Menopause

In A-I district, a mass-screening examination has been conducted annually since 1972 for the early detection of cardiovascular risk factors. Using the data except those who were in menopause at the initial examination and those who had regular menstruation at the final examination, annual changes in systolic and diastolic blood pressures, serum total cholesterol and body mass index ($BMI = \text{weight}/\text{height}^2$) were longitudinally observed during 10 years before and after menopause (Figure 4)²⁶⁾. The comparison group was a group of age-matched males, matching age to within 2 years, who underwent the examination in the same year (the reference year for males) as his matching female. The changes in cardiovascular risk factors for males were considered to be mainly due to aging.

Figure 4. Annual changes in systolic and diastolic blood pressures, serum total cholesterol and body mass index during 10 years before and after menopause (reference year for males), A longitudinal study in A-I district, Shibata City, Niigata Prefecture

The levels of both systolic and diastolic blood pressure were higher in males than in females, and the trend curves for both sexes were parallel. Therefore, the effect of menopause on the blood pressure levels appeared to be relatively small. The levels of serum total cholesterol decreased about five years before the reference year and leveled off afterwards in males. On the other hand, the levels increased markedly before and after menopause in females. The difference between males and females was not large 4 to 9 years before the reference year or menopause, but the difference was getting larger after the reference year, e.g. 12.3mg/dL at the reference year, 32.6mg/dL after five years and 33.6mg/dL after 10 years. Although a declining trend in BMI was observed for males, it was not seen for females, suggesting that menopause appeared to preserve

adiposity. The curve of BMI was similar to that of diastolic blood pressure in females.

Molecular Epidemiology of Hyperlipidemia

The level of serum lipid or apolipoprotein at any given time is a result of interactions of genetic endowment with lifestyle over the entire lifespan. For the serum lipid levels, however, the relative contributions of genetic and lifestyle factors are not clear; it is very difficult to arrive at an assignment of weights.

The authors quantitatively estimated the relative contributions of selected genetic and lifestyle factors to the inter-individual variations in serum lipid and apolipoprotein levels in a rural Japanese population, H-Y district, Shiso County, Hyogo Prefecture, using the multiple regression model²⁷⁾. Serum total

cholesterol (TC), low density lipoprotein cholesterol (LDL-C), triglycerides (TG), apolipoprotein B (apo B), high density lipoprotein cholesterol (HDL-C), apo AI, apo AII and apo CIII levels were determined as the dependent variables of the function. On the basis of established or putative roles of the candidate gene products in lipoprotein metabolism, four restriction fragment length polymorphisms (RFLPs) were selected with Xba I and EcoR I at the apo B, and Msp I and Sac I at the apo AI-CIII gene loci as the genetic independent variables. As for lifestyle factors, dietary intake, cigarette smoking, alcohol consumption and physical activity were also entered into the model. An index, P_i , for estimating the relative contribution of a specific independent variable, X_i , was employed and given by $P_i = R^2 - R_{-i}^2$

where R was the multiple correlation coefficient from the model with all of the selected independent variables ($X_1, \dots, X_p$) and R_{-i} was that of the model excluding X_i from the independent variables.

As shown in Figure 5, the contribution, P_i , of individual RFLP to inter-individual variation in serum TC was 0.08% to 1.60%, 0.06% to 1.69% in LDL-C, 0.04% to 0.89% in log TG,

0.06% to 1.99% in apo B, 0.05% to 2.59% in HDL-C, 0.54% to 2.73% in apo AI, 0.12% to 1.96% in apo AII and 0.09% to 0.48% in log apo CIII. In general, P_i for a RFLP did not appear to be larger than that for a lifestyle factor within the model: 2.67% for Keys dietary score (largest among lifestyle factors selected) and 1.69% for Sac I (largest among the RFLPs tested) in LDL-C, 2.60% for smoking and 0.89% for Xba I in log TG, 2.18% for dietary fiber and 1.99% for EcoR I in apo B, 3.15% for drinking and 2.59% for Xba I in HDL-C, 4.53% and 4.48% respectively for drinking and physical activity and 2.73% for Sac I in apo AI, 5.99% and 4.26% respectively for drinking and physical activity and 1.96% for EcoR I in apo AII, and 2.96% for drinking and 0.48% for Msp I in log apo CIII, although P_i for Sac I (1.60%) was almost as large as that for Keys dietary score (1.53%) in TC.

In conclusion, some polymorphisms in selected candidate genes appeared to be associated with some serum lipids or apolipoproteins, but the effect of individual RFLP on the inter-individual variations in serum lipids was relatively subtle. There was no marked difference between the contribution of individual RFLP and that of individual lifestyle factor to any

Figure 5. Relative contributions ($P_i \times 100\%$) of selected genetic and lifestyle factors to the inter-individual variations in serum lipid and apolipoprotein levels. $P_i = R^2 - R_{-i}^2$, where R is the multiple correlation coefficient from the model with x_1, x_2 , and x_{13} as the independents and R_{-i} is that of the model excluding x_i from the independents. The graph shows only the attributed part of the total variation. TC=total cholesterol; LDL-C=low density lipoprotein cholesterol; TG=triglycerides; HDL-C=high density lipoprotein cholesterol; APO=apolipoprotein; Carbo=carbohydrate; n-3 FA=n-3 fatty acids; Keys=Keys dietary score; PA=physical activity.

serum trait in our study. We did not find out any convincing evidence that the role of the genetic factors was more important than that of the environmental factors in lipoprotein metabolism in our study population, although many researchers reported that the environmental factors were less important than the genetic factors in Western populations²⁸⁾.

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