Review

Explanation for the Japanese Paradox: Prevention of Increase in Coronary Heart Disease and Reduction in Stroke

Hirotsugu Ueshima

Department of Health Science, Shiga University of Medical Science

Japan's age-adjusted rate for mortality from stroke increased after the Second World War until 1965 and then showed a significant decline until 1990; however, the age-adjusted rate for mortality from all heart disease and coronary heart disease (CHD) increased until 1970 and then declined slowly. A puzzling question is why the rate of mortality from CHD declined in spite of an increase in serum total cholesterol level following an increase in fat consumption.

It was confirmed that CHD incidence was far lower in several Japanese populations compared to Western countries in the "Monitoring Trends and Determinants in Cardiovascular Disease" (MONICA) project; therefore, the lower CHD mortality in Japan stems from the lower CHD incidence. CHD risk factors based on epidemiologic cohort studies in Japan were no different from those of other industrialized countries: hypertension, hypercholesterolemia, smoking and diabetes mellitus (DM). So, how can we explain this phenomenon?

There are three possible explanations. One is the decline in population blood pressure level and the prevalence of hypertension during the years 1965-1990; the second is the decline in smoking rate in men and women; the third is that the serum total cholesterol level for middle-aged and elderly populations remains 5-15 mg/dL lower than that of the US elderly counterpart, although men aged 40-49 in Japan and the US had similar serum total cholesterol levels. It was also noted that elderly people in Japan, as observed in the Seven Countries Study, had far lower serum total cholesterol levels in midlife, i.e., around 160 mg/dL in the 1960s. This was not the case for elderly in the US where a higher serum total cholesterol level was observed in midlife.

In conclusion, the lower serum cholesterol level in the past of Japanese middle-aged and elderly people compared to Western counterparts helps to maintain the low CHD incidence and mortality supported by the declining trend in blood pressure level and smoking rate for both men and women.

J Atheroscler Thromb, 2007; 14:278-286.

Key words; Coronary heart disease, Epidemiology, Serum total cholesterol, Hypertension, Blood pressure, Smoking rate, Diabetes mellitus

Introduction

The high life expectancy rate in Japan has led the world for over 20 years[1]. This position has been maintained since the mid-1980s by overcoming the highest stroke mortality rate in the world and also preventing an increase in coronary heart disease (CHD)[2-5]. The question raised is why Japanese people have lower CHD mortality and incidence than other industrialized countries in spite of an increase in serum total cholesterol following an increase in fat consumption and a high smoking rate[6].

This review article discusses the possible reasons for this phenomenon after reviewing trends in stroke and CHD mortality, and associated risk factors.

Address for correspondence: Hirotsugu Ueshima, Department of Health Science, Shiga University of Medical Science, Tsukinowa-cho Seta, Otsu, Shiga, 520-2192 Japan.
E-mail: hueshima@belle.shiga-med.ac.jp
Received: June 25, 2007
Accepted for publication: July 7, 2007

Trends in Stroke and Heart Disease Mortality

Age-adjusted all-stroke mortality in Japan increased after the Second World War until 1965 and then

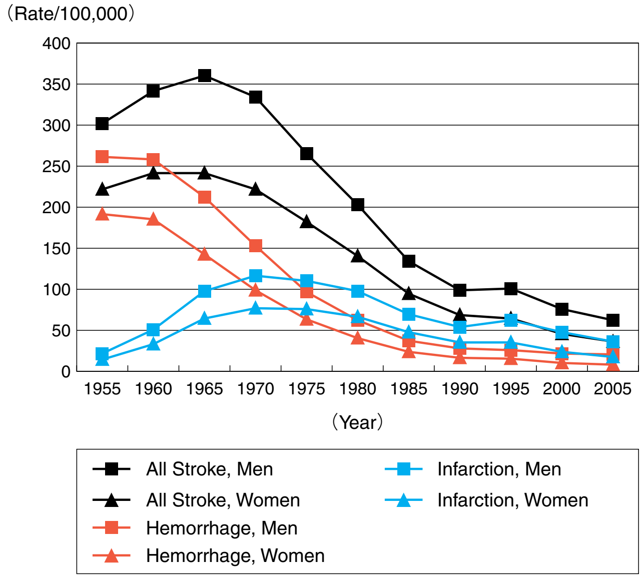


Fig. 1. Change in age-adjusted stroke mortality in Japan by gender.

Age-adjusted all-stroke mortality for men and women peaked in 1965 and then declined substantially until 1990. Cerebral hemorrhage was higher than cerebral infarction when all-stroke mortality was highest. Although cerebral infarction showed a peak in 1970, this was later than that of all-stroke mortality, and it declined thereafter. Age-adjusted all-stroke mortality has slowed down since around 1990.

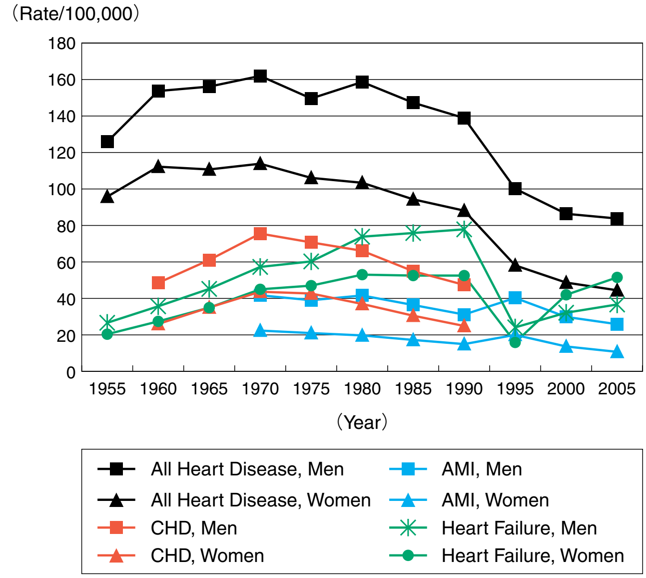


Fig. 2. Change in age-adjusted heart disease mortality in Japan by gender.

Age-adjusted all heart disease and coronary heart disease mortality peaked around 1970, 5 years later than that of all-stroke mortality. This has also declined steadily. The sudden change in mortality from the all heart disease and heart failure before and after 1995 was due to the change in the diagnostic approach for heart failure. Age-adjusted mortality from acute myocardial infarction maintained a low rate with a slightly downward trend. A slight increase in 1995 for acute myocardial infarction was also due to the diagnostic change.

showed a significant decline until 1990 (**Fig. 1**)[4]. In fact, an approximately 80% reduction in age-adjusted all stroke mortality occurred during 1965-1990. On the other hand, age-adjusted mortality from all heart disease and CHD increased until 1970 and then gradually declined (**Fig. 2**)[2-6]. Even in 1970, age-adjusted mortality from all heart disease, CHD and acute myocardial infarction (AMI) was far lower than that of stroke (**Fig. 2**)[2-4]. Age-adjusted all-stroke mortality in 1965 in Japan was recorded as the highest rate in the world[2, 4] whereas age-adjusted CHD and/or AMI mortality around 1970 was one of the lowest rates among industrialized countries, as in some Mediterranean countries[5].

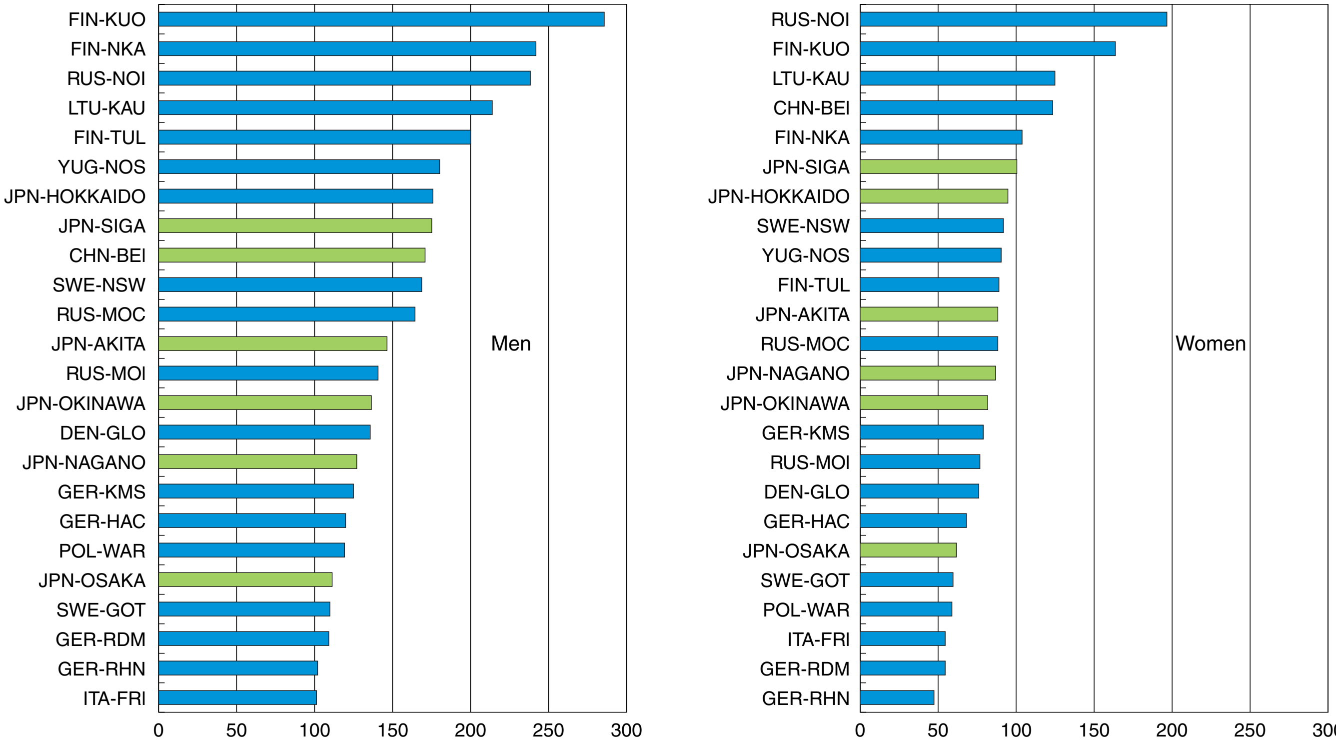
The high stroke rate and low CHD mortality rate is a specific feature of Japan among industrialized countries and it continues to the present day, although we were able to greatly reduce stroke mortality during 1965-2000.

A number of arguments remain regarding the diagnostic approach in Japan's lower CHD mortality compared to other industrialized countries, because the diagnosis of heart failure has a higher proportion in Japan than in the US[6]; however, even if heart failure is combined with mortality from ischemic heart disease, the rate is still lower in Japan than in the US[6]. In addition, mortality from all heart disease is also lower[6].

Validation studies on the incidence rate of myocardial infarction were carried out in Osaka and Kyushu[7, 8]. The two studies examined the extent to which heart failure should be classified as AMI, and concluded that the myocardial infarction rate did not change significantly due to misclassification of heart failure[7, 8]. Some incidences of heart failure should be classified as myocardial infarction, while some incidences of myocardial infarction should be excluded. Therefore, mortality from all heart disease as well as from CHD was lower in Japan than in the US and other Western countries.

Trends in Incidence of Stroke and Myocardial Infarction

The incidence of stroke, either thrombotic or hemorrhagic, has declined in accordance with stroke mortality[9-15]. Epidemiologic studies reveal that more than half the decline in stroke mortality can be explained by the decline in its incidence[9-15]. It is also



Source: MONICA, Circulation, 1994; 90:583-612 and K Isomura, Report of NCVC No.19-20.

(Rate per 100,000/year)

Fig. 3. Age-adjusted (35-64 years) stroke incidence for MONICA and a Japanese study.

Age-adjusted (35-64 years) stroke incidence was compared between the MONICA study in 1985-87 and a Japanese study in 1989-92. The diagnostic criteria of the MONICA study were used for the Japanese study. Stroke incidence for the six Japanese populations showed that the rate was in the middle of these populations and definitely lower than that of Finland.

true that the decline in CHD mortality since 1970 brought about the decline in the incidence of acute myocardial infarction[9-16].

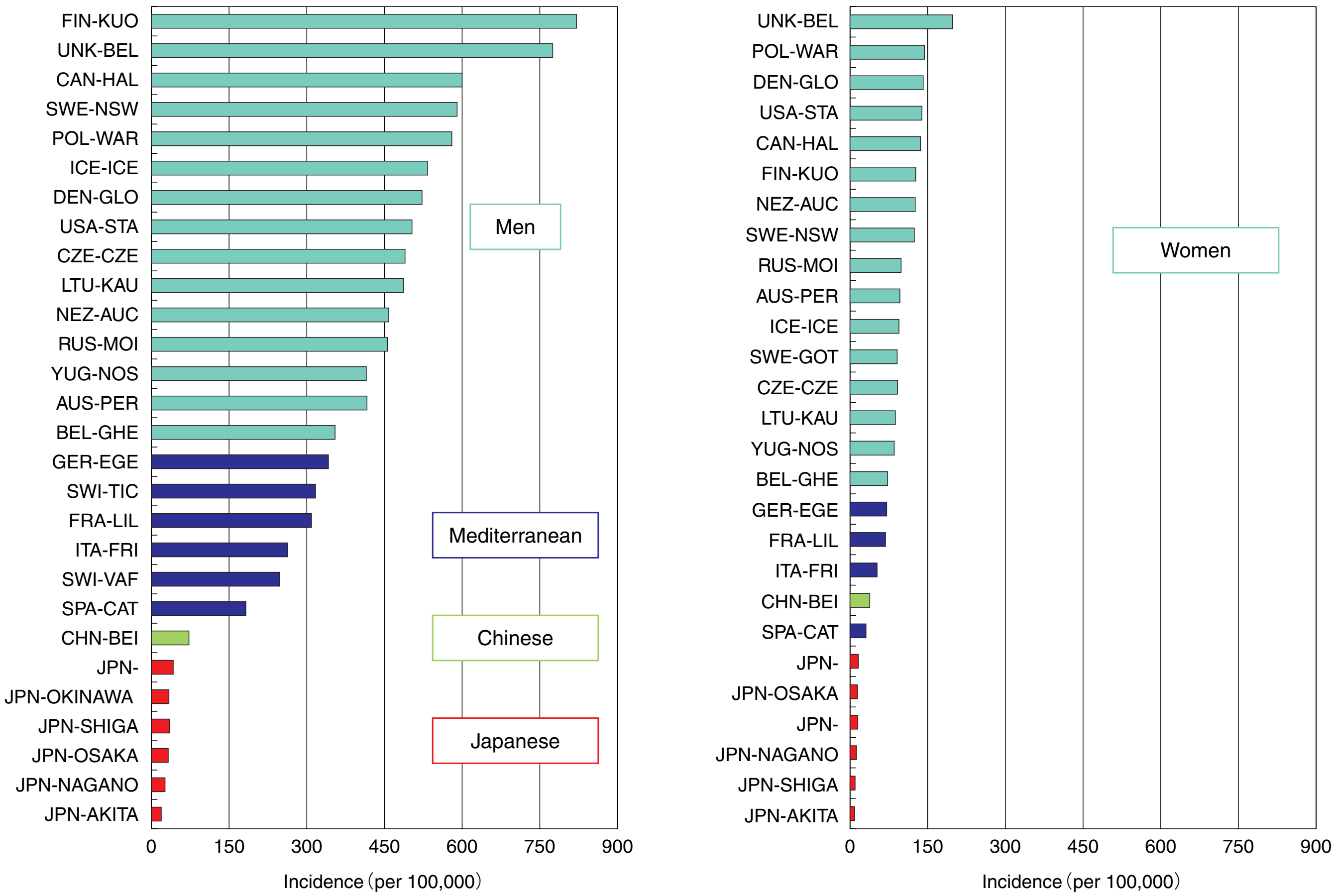
The Hisayama Study compares the incidence of CHD as well as AMI, asymptomatic myocardial infarction and sudden death among three cohorts; the oldest is a survey taken during 1961-73, the second one during 1974-1986, and the latest during 1988-2000[10]. Since the Hisayama Study is a long-term cohort study with around 80% autopsy cases, it is suitable for determining trends in CHD[9, 10]. The trend in CHD incidence in the Hisayama Study showed a decline between the second cohort and the third latest cohort, which is compatible with the trend in CHD mortality in Japan. The Hiroshima/Nagasaki Study also found that the trend in incidence of AMI was similar to that in CHD mortality in Japan[13].

International Comparison of the Incidence of Stroke and Myocardial Infarction

Six Japanese cohorts are available for comparing the incidence of AMI with that of the MONICA Project (multinational monitoring of trends and determinants in cardiovascular disease) conducted by WHO[15-18]. The MONICA Project started monitoring trends in AMI and stroke incidence, and their risk factors in 1985[19, 20]. Shortly afterwards, six Japanese cohort studies were conducted using the same registration criteria for stroke and AMI, making it possible to compare data with that of the MONICA Project[15-20] (**Fig. 3, 4**).

For stroke incidence, six Japanese populations were included among the MONICA populations. The data show that the Japanese populations did not have a higher incidence rate of stroke compared to MONICA populations in the world; in fact, the Osaka population had a considerably lower incidence of stroke. These results are compatible with those of stroke mortality world statistics, as shown in **Fig. 1**.

As for AMI, all six Japanese populations showed the lowest incidence rates among these populations (**Fig. 4**). The incidence in Finnish and British populations for men was 10 to 15 times higher than that



Circulation, 1994; 90:583-612 and K Isomura, Report of NCVC No.19-20.

Fig. 4. Age-adjusted (35-64 years) incidence of acute myocardial infarction in MONICA and a Japanese study.

Age-adjusted (35-64 years) incidence of acute myocardial infarction was compared between the MONICA study in 1985-87 and a Japanese study in 1989-92. The diagnostic criteria of the MONICA study were used for the Japanese study. The incidence of acute myocardial infarction in six Japanese populations was far lower than that in other MONICA populations followed by China and Mediterranean countries' populations.

of Japanese populations. China and Mediterranean countries were also lower than other countries but higher than Japanese populations. This incidence pattern is also similar to that of CHD mortality in the world[1-5, 15-20]; therefore, the lower CHD mortality in Japan stems from the lower CHD incidence compared to other industrialized countries.

Risk Factors for Stroke and CHD in Japan

The most potent risk factor for stroke, either cerebral hemorrhagic or infarction, is high blood pressure[21-25], although hypertension is more specific to cerebral hemorrhage than to cerebral infarction. The higher the blood pressure, the higher the risk ratio. There is no threshold between blood pressure and stroke occurrence[22-24] and this holds true for the young and old[23].

Smoking was not found to be a risk factor for stroke in the past[26, 27]; however, recent large cohort studies in Japan, i.e. NIPPON DATA80, show a clear graded relationship between smoking and stroke[28-30], as has been found in Western countries[31, 32]. One explanation is that the magnitude of hypertension as a strong risk factor weakened due to the decline in population blood pressure level[3-5]. Since the smoking rate for Japanese men is around 50% in spite of a substantial decline, the population smoking risk contributable to stroke in men is around 30%; this means that 30% of strokes in men would be prevented by smoking cessation[21]. In addition, it is estimated based on Japanese cohort studies that a 1% reduction in the smoking

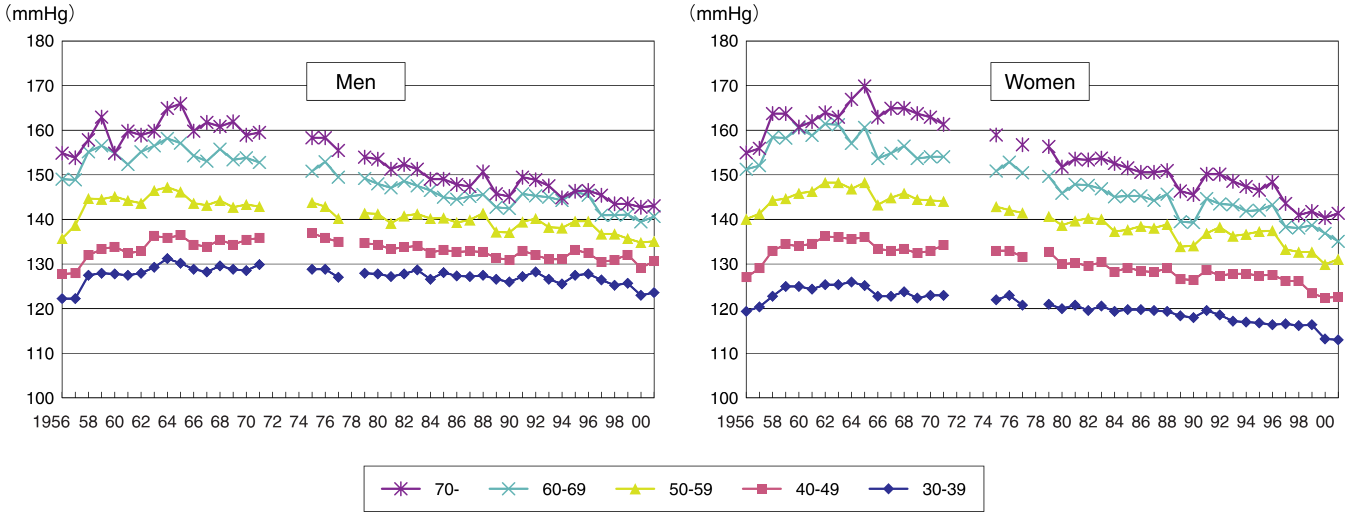


Fig. 5. Trends in systolic and diastolic blood pressures for men and women in Japan, 1956-2001.

Systolic and diastolic blood pressure levels for men and women have declined substantially since around 1965, whereas the rate of stroke mortality was highest in Japan. In particular, those in men and women aged over 60 years were much higher and evident compared to those for men and women in their 30s to 50s. The lowering trend in systolic and diastolic blood pressure has slowed down since around 1990 and is compatible with that of the similar slowdown phenomenon of stroke mortality.

rate in Japan would result in about a 1.3% reduction in stroke[21]; therefore, it is reasonably concluded than the recent decline in the smoking rate in men contributed to the decline in stroke mortality and incidence.

Serum total cholesterol is not a risk factor for stroke, either cerebral hemorrhage or cerebral infarction, in Japan[29, 33-37] because most incidents of cerebral infarction in Japan are caused by hypertension and smoking[11, 21-30, 33]. Although atherosclerosis of large vessels in the brain is caused by hypercholesterolemia[38], the proportion caused by hypercholesterolemia is quite low in Japan[33].

The most important risk factors for CHD are hypertension, hypercholesterolemia, smoking and diabetes mellitus[21, 29]. These are no different from the findings in the USA and European countries[39].

Trends in Population Blood Pressure Level and the Prevalence of Hypertension

The National Nutrition Survey of Japan has been conducted since the Second World War for the purpose of monitoring the population's nutrition intake through the random selection of families in government statistical areas throughout Japan. Blood pressure measurement was also introduced in 1956 in this National Nutrition Survey of about 10,000 men and women in randomly selected families[40]. Japan is an exceptional country in the world for monitoring its population's blood pressure level as well as for the prevalence of high blood pressure during the long period since 1956[3-5, 40].

Fig. 5 shows the trend in systolic blood pressure (SBP) level for men and women in 10-year age groups. The figures for both men and women show that SBP levels have declined since around 1965 for men aged 50 years and older and for women in all age groups. The level in men aged 40-49 and 30-39 has also declined since 1965. These declining trends are compatible with the declining trends in age-adjusted stroke mortality, that is, stroke mortality has also declined since 1965[4] (**Fig. 1**). For men aged 60-69, SBP declined by around 15 mmHg during 1965-1990[5].

The prevalence of severe hypertension, defined as SBP$\geqq$180 mmHg, in men and women has also declined since 1965 and shows almost a similar pattern to that of SBP[4]. For example, the prevalence of severe hypertension in men aged 60-69 was around 21% in 1965 and only 4% in 1990.

Trends in Smoking Rate

The average smoking rate in men was 82.3% in 1965, which had decreased by 45.5% in 2005[41]. The absolute decline in the smoking rate in men during 1965-1990 was around 20% (**Fig. 6**). The smoking rate in men in all age groups is continuously declining. In particular, the smoking rate in elderly men aged 60 years and over has declined considerably from 74.6% in 1965 to 49.4% in 1990 and to 31.4% in

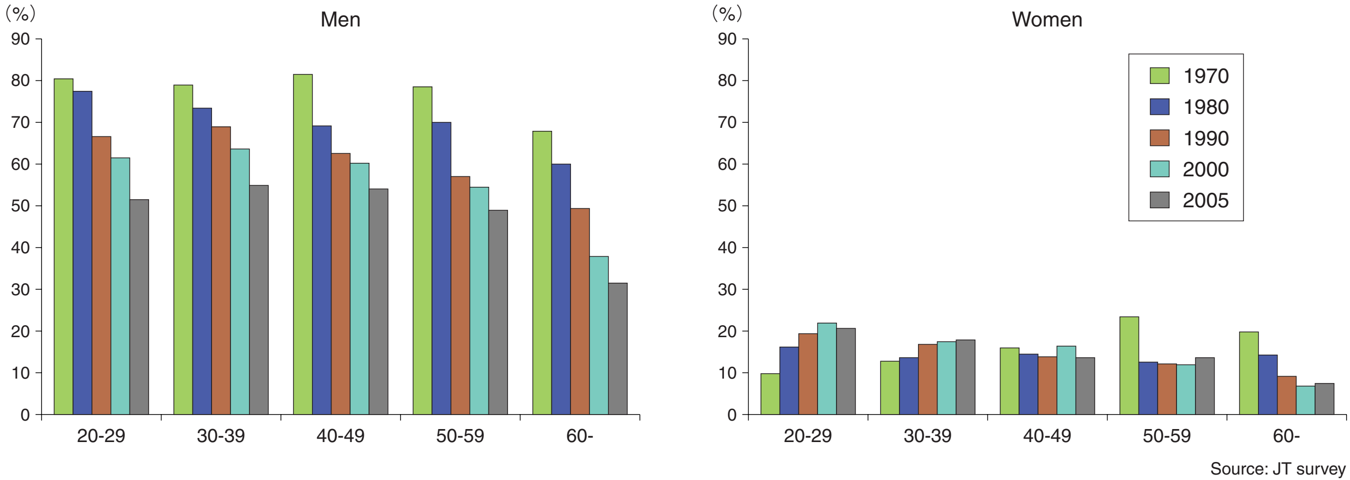


Fig. 6. Trend in smoking rate for men and women by 10-year age groups in Japan, 1970-2005.

The smoking rate in Japanese men was very high at around 80%, except for men aged 60 years and older, in 1970, while that of Japanese women was far lower. The high smoking rate in men has declined considerably, especially in men aged 60 years and over. On the other hand, that for young women aged 20-29 years has increased to 20%.

2005[41]. For women, the smoking rate is generally low in all age groups and that of elderly women aged 60 years and older was 23.0% in 1965, 9.4% in 1990 and 5.5% in 2005[41]. Therefore, the absolute decline in the smoking rate in men and women aged 60-69 during the years 1965-1990 was 15.2% and 13.6%, respectively.

Trends in Serum Total Cholesterol Level

Serum total cholesterol increased substantially in Japan following an increase in dietary fat intake. The daily dietary fat intake for adults in 1950 was around 10% kcal of total energy intake; however, it increased greatly to around 25% kcal in 1990[3, 4, 40, 42].

The Seven Countries Study recorded an average serum total cholesterol level of around 160 mg/dL in 1956 for men in Ushibuka and Tanushimaru in Kyushu, and around 250 mg/dL for men in Kuopio, Finland[43, 44]. The Cerebro-Cardiovascular Survey in 1980 and 1990 of a representative Japanese population showed a serum total cholesterol of around 190 mg/dL and 200 mg/d, respectively, in middle-aged men[5, 42] (**Fig. 7**). These national trends were compatible with the findings of a review paper on serum total cholesterol for many cohort studies in Japan[45]. The increasing trend in serum total cholesterol stems from the increase in dietary fat intake in populations since Keys's dietary factor[46] defined by fat intake in Japanese populations was confirmed to be well correlated with serum total cholesterol in populations[46]. Furthermore, the recent slowdown of dietary fat intake in

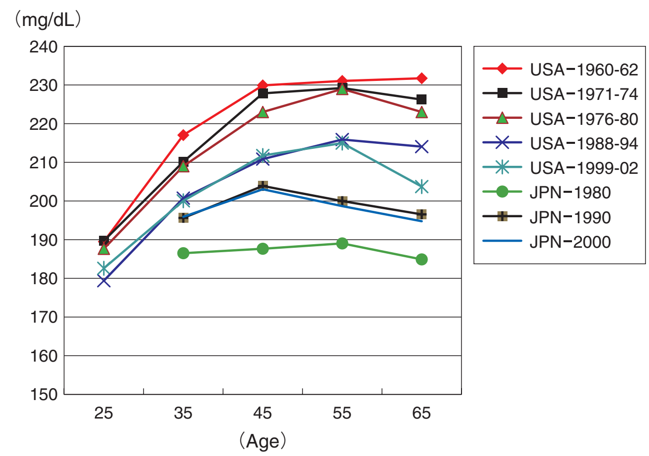


Fig. 7. Trend in serum total cholesterol for Japanese men compared with Americans.

Serum total cholesterol levels in Japan increased during 1980-1990, while those in America decreased gradually during around 1960-1980. In the 1980s, there was a 40 mg/dL difference between Japanese and American men aged 50-59 years, but this difference had lowered to 15 mg/dL by 1990. For men aged 30-49 years, the difference in serum total cholesterol level was around 5-8 mg/dL. There were no changes in Japanese men and American men during 1990-2000, except for American men aged 60 years and over. The data on American men aged 65 is for men aged 60 years and older, but for Japanese men it is for 60-69 years.

Japanese populations[42] is also compatible with the halt in the increase of serum total cholesterol level with some effect from treatment for hypercholesterolemia in Japanese populations[5].

Possible Explanation for the Decline in Stroke and Coronary Heart Disease

Hypertension and smoking are potent risk factors for CHD and stroke[11, 21-37]. The higher the population blood pressure, the higher the risk of CHD and stroke[21-24, 29]. As estimated in "Health Japan 21", if the population SBP were lowered by 2 mmHg, the estimated reduction in CHD and stroke would be 4.8% and 6.4%, respectively, based on Japanese cohort studies[21]. Similarly, a 1% reduction in the smoking rate is estimated to result in a 1.3% decrease in CHD and stroke[21].

Therefore, it is reasonably concluded that a reduction in population blood pressure level and also a substantial reduction in the prevalence of severe hypertension contributed greatly to the decline in CHD mortality as well as stroke[3-5]. Since the average blood pressure reduction in men aged 30-69 was around 7.4 mmHg and smoking rate reduction was approximately 20% during the years 1965-1990, it is expected that CHD and stroke reduction would be 44% and 50%, respectively. The actual reduction in CHD and stroke mortality for men aged 30-69 was 51% and 79%, respectively, during the same period. Therefore, more than 80% of the observed reduction in CHD mortality for men aged 30-69 can be explained by the decrease in population blood pressure level and smoking rate. Similarly, 63% of the reduction in stroke mortality can be explained by the same factors.

It is true in Japanese populations that serum total cholesterol is a risk factor for CHD[21, 29, 35, 36]; therefore, the increase in population serum total cholesterol level directly contributes to increasing CHD in the Japanese population. However, the increase in serum total cholesterol appears mainly in young to middle-aged populations[5] (**Fig. 7**), and its adverse effects may surface in later years. In contrast, elderly people as a high risk group for CHD continue to maintain a level lower than 200 mg/dL, similar to their lower level in the past[5]. In addition, there was also a 5-15 mg/dL difference in serum total cholesterol level between middle-aged to elderly men in Japan and the USA[5] (**Fig. 7**); therefore, the adverse influence of raised total cholesterol on CHD in the elderly is considered to be overcome by the reduction in both population blood pressure and smoking rate[3, 5]. In addition, the increase in serum total cholesterol is not related to the risk of stroke[21, 29, 35, 36]; it had no effect on stroke mortality reduction. It is also worth noting that the elderly in the USA in 1990-2000 had a higher serum total cholesterol level when they were younger in 1960-70 than when they were older (**Fig. 7**).

Trends in Diabetes Mellitus

The trend in the prevalence of diabetes mellitus (DM) is not precisely known, especially for age-adjusted and/or age-specific data. DM prevalence was estimated for half the subjects of the National Nutrition Survey in 1997 and 2002[47]. Age-specific prevalence of DM did not differ greatly except for elderly people aged 70 years and over; however, with the rapidly aging Japanese population, we have not determined the extent to which the prevalence of DM in the age group of 70 years and older increased in the past 5 years[47]. Although conclusive data are not available to confirm any trend in DM prevalence over the past three decades, it is reasonably estimated that DM prevalence in Japan increased somewhat following BMI increase in men and elderly women. It is well known that DM and glucose intolerance are a risk factor for stroke and CHD in Japan; i.e., relative risk is 2-3[29, 48-51]. Therefore, the increasing prevalence of DM and glucose intolerance may contribute in part to an increased adverse influence on stroke and CHD.

Conclusions

A significant reduction in stroke mortality and incidence has been achieved since 1965 as well as the prevention of increased CHD mortality and incidence. This phenomenon stems from the reduction in population SBP and the smoking rate. On the other hand, although the serum cholesterol level in Japanese people in both genders and all age groups increased greatly following the increase in dietary fat intake, it is reasonably concluded that its adverse effects on CHD were overcome by the decline in SBP level and the smoking rate in men and women. Nevertheless, the present younger generation with a higher serum total cholesterol level compared to that of past young generations, may face higher CHD incidence and mortality in the future. Therefore, we should carefully monitor the new generations as well as the general population for CHD incidence[14-16, 51, 52].

References

1) Life expectancy in Japan. http://www.mhlw.go.jp/toukei/saikin/hw/life/life05/index.html (access on May 7, 2007)
2) Uemura K and Piza Z: Trends in cardiovascular disease mortality in industrialized countries since 1950. World Health Statist Quart, 1988; 41:155-178
3) Ueshima H, Tatara K, and Asakura S: Declining mortality from ischemic heart disease and changes in coronary risk factors in Japan, 1956-1980. Am J Epidemiol, 1987; 125:62-72

4) Ueshima H: Changes in dietary habits, cardiovascular risk factors and mortality in Japan. Acta Cardiol, 1990; 45:311-327
5) Ueshima H: Trends in Asia. In “Coronary Heart Disease Epidemiology: From Aetiology to Public Health” (2nd ed.), Marmot M and Elliott P (eds.), pp 102-112, Oxford University Press, Oxford, UK, 2005
6) Sekikawa A, Kuller LH, Ueshima H, Park JE, Shu I, Jee SH, and Pan WH: Coronary heart disease mortality trends in men in the post World War II birth cohorts aged 35-44 in Japan, South Korea and Taiwan compared with the United States. Int J Epidemiol, 1999; 28:1044-1049
7) Baba S, Ozawa S, Sakai Y, Terao A, Konishi M, and Tatara K: Heart disease deaths in a Japanese urban area evaluated by clinical and police records. Circulation, 1994; 89:109-115
8) Yamashita T, Ozawa H, Aono H, Hosokawa H, Saito I, and Ikebe T: Heart disease deaths on death certificates re-evaluated by clinical records in a Japanese city. Jpn Circ J, 1997; 61:331-338
9) Ueda K, Omae T, Hirota Y, Takeshita M, Katsuki S, Tanaka K, and Enjoji M: Decreasing trend in incidence and mortality from stroke in Hisayama residents, Japan. Stroke, 1981; 12:154-160
10) Kubo M, Kiyohara Y, Kato I, Tanizaki Y, Arima H, Tanaka K, Nakamura H, Okubo K, and Iida M: Trends in the incidence, mortality, and survival rate of cardiovascular disease in a Japanese community: the Hisayama study. Stroke, 2003; 34:2349-2354
11) Shimamoto T, Komachi Y, Inada H, Doi M, Iso H, Sato S, Kitamura A, Iida M, Konishi M, Nakanishi N, Terao A, Naito Y, and Kojima S: Trends for coronary heart disease and stroke and their risk factors in Japan. Circulation, 1989; 79:503-515
12) Morikawa Y, Nakagawa H, Naruse Y, Nishijo M, Miura K, Tabata M, Hirokawa W, Kagamimori S, Honda M, Yoshita K, and Hayashi K: Trends in stroke incidence and acute case fatality in a Japanese rural area: the Oyabe study. Stroke, 2000; 31:1583-1587
13) Kodama K, Sasaki H, and Shimizu Y: Trend of coronary heart disease and its relationship to risk factors in a Japanese population: a 26-year follow-up, Hiroshima/Nagasaki study. Jpn Circ J, 1990; 54:414-421
14) Kitamura A, Iso H, Iida M, et al: Trends in the incidence of coronary heart disease and stroke and the prevalence of cardiovascular risk factors among Japanese men from 1963 to 1994. Am J Med, 2002; 112:104-109
15) Kita Y, Okayama A, Ueshima H, Wada M, Nozaki A, Choudhury SR, Bonita R, Inamoto Y, and Kasamatsu T: Stroke incidence and case fatality in Shiga, Japan 1989-1993. Int J Epidemiol, 1999; 28:1059-1065
16) Yoshida M, Kita Y, Nakamura Y, Nozaki A, Okayama A, Sugihara H, Kasamatsu T, Hirose K, Kinoshita M, and Ueshima H: Incidence of acute myocardial infarction in Takashima, Shiga, Japan. Circ J, 2005; 69:404-408
17) Isomura K: 3A-1 Study on the development of the community-based long-term follow-up system for cardio-cerebrovascular diseases. 1993 Annual Report of the Research on Cardiovascular Diseases, Osaka, National Cardiovascular Center, 1994
18) Fukiyama K, Kimura Y, Wakugami K, and Muratani H: Incidence and long-term prognosis of initial stroke and acute myocardial infarction in Okinawa, Japan. Hypertens Res, 2000; 23:127-135
19) WHO MONICA Project. Myocardial infarction and coronary deaths in the World Health Organization MONICA Project. Registration procedures, event rates, and case-fatality rates in 38 populations from 21 countries in four continents. Circulation, 1994; 90:583-612
20) WHO MONICA Project. Stroke incidence and mortality correlated to stroke risk factors in the WHO MONICA Project. An ecological study of 18 populations. Stroke, 1997; 28:1367-1374
21) Health Japan 21. http://www1.mhlw.go.jp/topics/kenko21_11/b8f.html (in Japanese, access on May 12, 2007)
22) NIPPON DATA Research Group. Impact of elevated blood pressure on mortality from all causes, cardiovascular diseases, heart disease and stroke among Japanese: 14 year follow-up of randomly selected population from Japanese–Nippon Data80. J Hum Hypertens, 2003; 17:851-857
23) Okayama A, Kadowaki T, Okamura T, Hayakawa T, Ueshima H, for the NIPPON DATA80 Research Group: Age-specific effects of systolic and diastolic blood pressures on mortality due to cardiovascular diseases among Japanese men (NIPPON DATA80). J Hypertens, 2006; 24:459-462
24) Asia Pacific Cohort Studies Collaboration. Blood pressure and cardiovascular disease in the Asia Pacific region. J Hypertens, 2003; 21:707-716
25) Takagi S, Saitoh S, Nakano M, Hayashi Y, Obara F, Onishi H, and Shimamoto K: Relationship between blood pressure level and mortality rate: an 18-year study conducted in two rural communities in Japan. J Hypertens, 2000; 18:139-144
26) Toshima H, Koga Y, Menotti A, Keys A, Blackburn H, Jacobs DR, and Seccareccia F: The seven countries study in Japan. Twenty-five-year experience in cardiovascular and all-causes deaths. Jpn Heart J, 1995; 36:179-189
27) Kiyohara Y, Ueda K, and Fujishima M: Smoking and cardiovascular disease in the general population in Japan. J Hypertens Suppl, 1990; 8:S9-15
28) Ueshima H, Choudhury SR, Okayama A, Hayakawa T, Kita Y, Kadowaki T, Okamura T, Minowa M, and Iimura O: Cigarette smoking as a risk factor for stroke death in Japan: NIPPON DATA80. Stroke, 2004; 35:1836-1841
29) NIPPON DATA Research Group. Risk assessment chart for death from cardiovascular disease based on a 19-year follow-up study of a Japanese representative population. Circ J, 2006; 70:1249-1255
30) Mannami T, Iso H, Baba S, Sasaki S, Okada K, Konishi M, Tsugane S, for the Japan Public Health Center-based Prospective Study on Cancer and Cardiovascular Disease Group: Cigarette smoking and risk of stroke and its subtypes among middle-aged Japanese men and women: the JPHC Study Cohort I. Stroke, 2004; 35:1248-1253
31) Abbott RD, Yin Y, Reed DM, and Yano K: Risk of stroke in male cigarette smokers. N Engl J Med, 1986; 315:717-720
32) Wolf PA, D’Agostino RB, Kannel WB, Bonita R, and Belanger AJ: Cigarette smoking as a risk factor for stroke.

The Framingham Study. JAMA, 1988; 259:1025-1029
33) Tanizaki Y, Kiyohara Y, Kato I, Iwamoto H, Nakayama K, Shinohara N, Arima H, Tanaka K, Ibayashi S, and Fujishima M: Incidence and risk factors for subtypes of cerebral infarction in a general population: the Hisayama study. Stroke, 2000; 31:2616-2622
34) Ueshima H, Iida M, Shimamoto T, Konishi M, Tsujioka K, Tanigaki M, Nakanishi N, Ozawa H, Kojima S, and Komachi Y: Multivariate analysis of risk factors for stroke. Eight-year follow-up study of farming villages in Akita, Japan. Prev Med, 1980; 9:722-740
35) Okamura T, Kadowaki T, Hayakawa T, Kita Y, Okayama A, Ueshima H, for the NIPPON DATA80 Research Group: What cause of mortality can we predict by cholesterol screening in the Japanese general population? J Intern Med, 2003; 253:169-180
36) Okumura K, Iseki K, Wakugami K, Kimura Y, Muratani H, Ikemiya Y, and Fukiyama K: Low serum cholesterol as a risk factor for hemorrhagic stroke in men: a community-based mass screening in Okinawa, Japan. Jpn Circ J, 1999; 63:53-58
37) Nakayama T, Date C, Yokoyama T, Yoshiike N, Yamaguchi M, and Tanaka H: A 15.5-year follow-up study of stroke in a Japanese provincial city. The Shibata Study. Stroke, 1997; 28:45-52
38) Konishi M, Iso H, Komachi Y, Iida M, Shimamoto T, Jacobs DR Jr., Terao A, Baba S, Sankai T, and Ito M: Associations of serum total cholesterol, different types of stroke, and stenosis distribution of cerebral arteries. The Akita Pathology Study. Stroke, 1993; 24:954-964
39) Stamler J: Established major coronary risk factors: historical overview. In “Coronary Heart Disease Epidemiology: From Aetiology to Public Health” (2nd ed.), Marmot M and Elliott P (eds.), pp. 18-31, Oxford University Press, Oxford, 2005
40) Ueshima H, Tatara K, Asakura S, and Okamoto M: Declining trends in blood pressure level and the prevalence of hypertension, and changes in related factors in Japan, 1956-1980. J Chronic Dis, 1987; 40:137-147
41) Smoking Rate Surveillance. Japan Tobacco Company. http://www.health-net.or.jp/tobacco/product/pd090000.html#top (access on June 9, 2007.)
42) Ueshima H: Dietary habits and disease patterns in the Japanese elderly. Nippon Ronen Igakkai Zasshi, 2007; 44:17-22 (in Japanese)
43) Kimura N and Keys AX: Rural Southern Japan. In “Coronary Heart Disease in Seven Countries”, Monograph I, Keys A (ed.), Circulation, 1970; Supple I; I-101-I-112
44) Karvonen MJ, Orma E, Punsar S, Kallio V, Arstila M, Luomanmaki K, and Takkunen J: VI. Five-year experience in Finland. In “Coronary Heart Disease in Seven Countries”, Monograph I, Keys A (ed.), Circulation, 1970; supple I; I-52-I-62
45) Okayama A, Ueshima H, Marmot MG, Nakamura M, Kita Y, and Yamakawa M: Changes in total serum cholesterol and other risk factors for cardiovascular disease in Japan 1980-1989. Int J Epidemiol, 1993; 22:1038-1047
46) Ueshima H, Iida M, Shimamoto T, Konishi M, Tanigaki M, Doi M, Nakanishi N, Takayama Y, Ozawa H, and Komachi Y: Dietary intake and serum total cholesterol level: their relationship to different lifestyles in several Japanese populations. Circulation, 1982; 66:519-526
47) National Survey on Diabetes Mellitus Prevalence in Japan. URL http://www.mhlw.go.jp/shingi/2004/03/s0318-15.html (access on May 13, 2007)
48) Fujishima M, Kiyohara Y, Kato I, Ohmura T, Iwamoto H, Nakayama K, Ohmori S, and Yoshitake T: Diabetes and cardiovascular disease in a prospective population survey in Japan: The Hisayama Study. Diabetes, 1996; 45:S14-16
49) Kadota A, Hozawa A, Okamura T, Kadowaki T, Nakamura K, Murakami Y, Hayakawa T, Kita Y, Okayama A, Nakamura Y, Kashiwagi A, and Ueshima H: Relationship between metabolic risk factor clustering and cardiovascular mortality stratified by high blood glucose and obesity: NIPPON DATA90, 1990-99. Diabetes Care, 2007; 30:1533-1538
50) Iso H, Imano H, Kitamura A, Sato S, Naito Y, Tanigawa T, Ohira T, Yamagishi K, Iida M, and Shimamoto T: Type 2 diabetes and risk of non-embolic ischaemic stroke in Japanese men and women. Diabetologia, 2004; 47:2137-2144
51) Nakamura Y, Saitoh S, Takagi S, Ohnishi H, Chiba Y, Kato N, Akasaka H, Miura T, Tsuchihashi K, and Shimamoto K: Incidence of type 2 diabetes in individuals with central obesity in a rural Japanese population: The Tanno and Sobetsu study. Diabetes Care, 2006; 29:1128-1129
52) Sekikawa A, Ueshima H, Zaky WR, Kadowaki T, Edmundowicz D, Okamura T, Sutton-Tyrrell K, Nakamura Y, Egawa K, Kanda H, Kashiwagi A, Kita Y, Maegawa H, Mitsunami K, Murata K, Nishio Y, Tamaki S, Ueno Y, and Kuller LH: Much lower prevalence of coronary calcium detected by electron-beam computed tomography among men aged 40-49 in Japan than in the US, despite a less favorable profile of major risk factors. Int J Epidemiol, 2005; 34:173-179