Animal Protein, Animal Fat, and Cholesterol Intakes and Risk of Cerebral Infarction Mortality in the Adult Health Study

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Background and Purpose—A traditional diet that is poor in animal products is thought to explain the high rate of stroke in Asian populations. The purpose of the present study was to examine the effect of a diet rich in animal protein, animal fat, and cholesterol on the risk of cerebral infarction mortality in a Japanese population.

Methods—A prospective study of 3731 Japanese men and women aged 35 to 89 years was conducted from 1984 to 2001. Nutrient intake was estimated at baseline from the responses to a 24-hour diary. During the follow-up period, cases of cerebral infarction deaths (as entered on death certificates) were monitored.

Results—During the follow-up period, 60 deaths were attributed to cerebral infarction. A high intake of animal fat and cholesterol was significantly associated with a reduced risk of cerebral infarction death. The risk was reduced by 62% (CI, 82% to 18%) for those in the third tertile of animal fat intake, compared with those in the first tertile, with a significant linear dose-response relationship ($P=0.0073$). The risk of death from infarction was reduced by 63% (CI, 82% to 22%) in the high cholesterol consumption group, compared with the low consumption group. A significant linear dose–response relationship was observed. Animal protein was not significantly associated with infarction mortality after adjustment for animal fat and cholesterol.

Conclusions—This study suggests that in Japan, where animal product intake is lower than in Western countries, a high consumption of animal fat and cholesterol was associated with a reduced risk of cerebral infarction death. (Stroke. 2004;35:000-000.)

Key Words: cerebral infarction ■ cholesterol ■ diet ■ epidemiology ■ Japan ■ models, animal ■ mortality

The decline in mortality rates from total stroke in Japan started 3 decades ago, with cerebral infarction becoming the most frequent stroke subtype.1 It has been hypothesized that the recent westernization of the Japanese lifestyle, particularly of diet, accounts for the dramatic changes in stroke incidence and mortality.2,3

Based on studies among Japanese populations living in Japan or in Hawaii, the protective dietary factors of stroke included a low intake of salt and a high intake of fruit and vegetables,4 total and saturated fats,5–7 and animal protein.2,8 Those results, however, were related to all stroke subtypes or to intracerebral hemorrhage, the most prevalent death subtype in Japan in the 1960s and 1970s.

We previously showed that in ≈40,000 members of the Life Span Study (LSS), a cohort including atomic bomb survivors in Hiroshima and Nagasaki, a high intake of animal products (determined by a food frequency questionnaire) was associated with a decreased risk of stroke and intracerebral hemorrhage mortality. The risk of cerebral infarction death declined with fish and dairy product intake, but not to a level of statistical significance.9

In the present study, which is modeled after the previous one, we analyzed the relationship between the intake of animal protein, animal fat, and cholesterol, and the risk of mortality from cerebral infarction using the responses to a 1-day dietary diary among a subcohort of the LSS population.

Study Population

Participants were members of the Adult Health Study (AHS), a clinical study subcohort of the LSS. The LSS is a cohort of 120,000 persons (93,000 atomic bomb survivors and 27,000 unexposed individuals) who were residents of Hiroshima and Nagasaki in the early 1950s.10 The AHS participants are examined biennially in an ongoing investigation of the long-term effects of A-bomb radiation on health and cause of death.11 Between 1983 and 1985, 6743 AHS members were invited to respond to a 24-hour dietary survey; 6179 (91.6%) accepted, and 3731 (1436 men and 2295 women) returned a completed diary.12 Those who returned the diary (R) did not differ from those who did not (non-R) in terms of sex (91.6% women, non-R=57% women), place of living (R=59% in Hiroshima, non-R=58% in Hiroshima), mean age (R=57 years old, non-R=56 years old), and stroke death during the study period (3% in both R and non-R). The mean age was 57 years old (range: 35 to 89).

Dietary Information

A trained nurse provided the participants with instructions for completing the diary and with a measuring spoon for weighing...
foods. The subjects chose a day to record their usual meals and wrote down the names of the foods along with the amount consumed at each meal. A dietician then checked and coded the diaries and contacted the subjects if entries needed clarification. Nutrient consumption was estimated from the Japan Food Composition Tables.13,14 Participants also answered a diet questionnaire that included items on vitamin supplements, type of work, and body measurements. Diaries were provided and completed by the AHS participants equally throughout the week and the year.15

Outcome
Vital status was ascertained by linkage to the nationwide family registration system of Japan.16 Copies of death certificates were obtained on a regular basis by the Radiation Effects Research Foundation for all AHS participants. Death certificates were available for all participants who had lived in Japan. Because the number of emigrants was low (less than 0.1%), death ascertainment was virtually complete. Trained coders entered codes into the database. Cause of death followed the International Classification of Diseases codes (9th and 10th revisions).16,17 Cerebral infarction death was defined in the 9th revision as codes 433 and 434, and in the 10th revision as codes I63 and I69.3. Follow-up was started on Nov 1, 1983, and continued until the date of death or July 31, 2001, whichever came first.

Potential Confounding Variables
Because the study participants were atomic bomb survivors, brain radiation dose was considered as a potential confounder, even though previous reports of the same cohort did not indicate that radiation exposure increased the risk of stroke mortality.10 Individual dose estimates were based on the survivor’s location and shielding situation at the time of the bombing. The dosimetry system, introduced in 1986 (DS86), is based on modern nuclear physics theory and validated by the measurement of existing exposed materials, such as brick and tiles.18 DS86 provides estimates of gamma ray and neutron doses to 15 organs. We considered radiation dose received by the brain in the present study. We also considered the city of residence, Hiroshima or Nagasaki, as a possible confounder because the 2 cities differ in terms of environmental factors.

Data on height and weight, smoking and drinking habits, and degree of physical activity needed for work were based on the anamnesis. Body mass index was calculated as weight (kg) divided by square of height (m2). Information on vitamin supplements, type of work, and body measurements. 

Statistical Analysis
We used a Cox proportional hazards model to examine the risk of stroke mortality and Wald statistics to test hypotheses and determine confidence intervals. Age was the primary time scale in all analyses, and baseline rates were stratified by sex and birth cohort. All nutrients were categorized into tertiles according to intake distribution. The nutrients examined were total fat and protein, animal fat and protein, vegetable fat and protein, animal saturated fatty acids (SFAs), animal monounsaturated fatty acids (MUFA), animal polyunsaturated fatty acids (PUFAs), and cholesterol. We adjusted multivariate analyses for possible confounding variables as follows: radiation dose (continuous), city of exposure (Hiroshima, Nagasaki), smoking and drinking status (never, current, past), body mass index (<19, 19 to 22, 22 to 25, >25), and history of hypertension and diabetes (yes, no). Consecutive adjustments were made, including for various potential confounders such as fruit and vegetable intake (up to once per week, 2 to 4 times a week, daily); markers of nutritional status; lymphocyte count (396 to 1786, 1787 to 2331, 2332 to 11766 cells/microl) and blood cholesterol level (75 to 185, 186 to 215, 216 to 450 mg/dL); total energy intake (345 to 1607, 1608 to 1982, 1983 to 4775 Kcal/d); and weight (continuous). We also performed tests for linear trend across the tertiles.

Risks of cerebral infarction deaths associated with animal protein, animal fat, and cholesterol intakes were estimated, after mutual adjustments. The nutrient variable was treated as continuous. The independent effects of animal fat and cholesterol were estimated by categorizing each variable into 2 classes according to the median value of the cerebral infarction cases. Those with low intakes of both animal fat and cholesterol represented the reference group. The effects of cholesterol intake only (low fat/high cholesterol category) and animal fat consumption solely (high fat/low cholesterol category) were calculated.

The PHREG procedure (SAS Institute) was used to calculate the relative hazard (RH) of cerebral infarction death compared with staying alive.19

Results
During a mean follow-up period of 14 years, 90 stroke deaths were monitored, of which 60 were attributed to cerebral infarction. As shown in Table 1, those subjects with high animal protein intake, as compared with those with low animal protein intake, were more likely to be young, male, current smokers and current drinkers, and to have a high intake of vegetables; they were less likely to live in Hiroshima and have a history of hypertension. Those with high fat intake, in comparison to those with low fat intake, were more likely to be young, male, to live in Hiroshima, be current drinkers and have high vegetable intake; they were less likely to have a history of hypertension or diabetes.

Table 2 shows the relative hazard of cerebral infarction according to the consumption level of protein and fat consumed from animal and vegetal products as well as those associated with cholesterol and 3 types of fatty acid. A high intake of total protein was significantly associated with a decreased risk of cerebral infarction, but when the protein source was considered, only animal protein was protective. Among fats, only animal fat intake was significantly associated with reduced risk. The associations did not change after controlling for potential confounders.

Cholesterol was significantly associated with reduced cerebral infarction risk. SFA and PUFA also seemed to be associated with reduced risk, but to a lesser degree and without statistical significance. When the risks were adjusted for cholesterol intake, however, the protective effect was not observed (SFA in the third tertile RR = 1.49 [0.70 to 3.17], P for trend = 0.2721; PUFA in the third tertile RR = 0.99 [0.48 to 2.02]; P = 0.9969), suggesting that the SFA and PUFA effects were confounded by the cholesterol effect.

Table 3 shows the associations between cerebral infarction mortality risk and the 3 nutrients that were significantly associated with the risk. Additional adjustments for known or possible confounders were made. We included vegetable intake and fruit intake in the “multivariate 1” set of covariates because they were found to significantly reduce risk of stroke mortality in the Life Span Study cohort (the full cohort, which includes the present subcohort).4 We also considered lymphocyte count and blood cholesterol level, total energy intake, and body weight as potential confounders. None of those 3 adjustments, however, materially changed the association of risk with the dietary factors, except that adjustment for total energy intake attenuated the association of risk with animal protein to a nonsignificant level.
The relative hazards of cerebral infarction death after mutual adjustment are shown in Table 4. For animal protein, the protective effect disappeared when the risks were adjusted for animal fat and cholesterol intake, suggesting an absence of effect of animal protein consumption. The protective effect of animal fat intake remained after adjustment for cholesterol. The results also suggested that cholesterol may be a protective factor (RH = 0.65, after adjustment for animal fat), but we lost precision, though the confidence intervals became larger.

In Table 5, the effect of cholesterol intake only (low fat/high cholesterol category) showed a significant reduced risk of cerebral infarction as compared with those in the low fat and low cholesterol intakes category. Animal fat consumption solely (high fat/low cholesterol category) was also associated with a significant reduced risk of cerebral infarction. Finally, those in the high category intake of both cholesterol and animal fat had a risk of cerebral infarction reduced significantly by 71%, as compared with those in the low fat and low cholesterol intakes category. These findings suggested that the effects of cholesterol and animal fat were neither additive, nor multiplicative, because the presence of 1 of the 2 factors seemed sufficient to reduce the risks of cerebral infarction.

**Discussion**

This prospective study among Japanese people shows that a low intake of animal fat and cholesterol was significantly associated with an increased risk of cerebral infarction mortality. Protein and vegetable fat were not associated with risk of infarction mortality. Adjustment for lymphocyte count and blood cholesterol level (general markers of good nutritional status) or for weight (a marker of energy intake) did not modify the results.

Meat products are rich in SFAs, which are thought to be a risk factor for cerebral infarction through their atherogenic effects. Conversely, fish products, a rich source of PUFA, are thought to protect against cerebral infarction through their hypolipidemic, hypotensive, antiatherogenic, and antithrombotic effects. In the present study, however, SFAs were not found to be a risk factor for cerebral infarction mortality. Moreover, neither SFA nor PUFA were related to cerebral infarction death.

Westernization of the lifestyle in Japan during the 1960s brought considerable changes in dietary habits. Per capita consumption of meat, milk, and dairy products rose dramatically from 1955 to 1975 and is still rising, although more slowly. Between 1960 and 1985, the intake of animal protein increased by 13%, and the intake of animal fat increased by 130%. Compared with other industrialized countries, however, Japan consumes low amounts of protein and fat from animal sources. In 1986, animal products represented only 18% of the total energy consumed in Japan (20% in the present study), whereas the figure reached 37% in the present study, although more slowly. Moreover, the current mean animal protein intake and mean saturated fat intake in Japan usually correspond to the low consumption categories in Western countries. It should also be noted that the increased consumption of animal protein and animal fat was concomitant with a decline of salt consumption in the early 1970s in Japan. Dietary salt is highly correlated with hypertension, an established determinant of stroke.

Our present findings are in line with the results of previous studies among Japanese, Japanese-Americans, and Americans. The Ni-Hon-San study, a longitudinal study on Japanese men living in Hiroshima and Nagasaki and Japanese-American men living in Honolulu and San Francisco, showed that the subjects with cerebral infarction had a significantly
<table>
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<tr>
<th>Nutrient from animal and vegetal products</th>
<th>Consumption Level</th>
<th>Tertile 1</th>
<th>Tertile 2</th>
<th>Tertile 3</th>
<th>P for Trend</th>
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<td>Mean intake (g/day)</td>
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<td><strong>Polyunsaturated fatty acids</strong></td>
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<td>Mean intake (g/day)</td>
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<td>0.34 (0.16–0.69)</td>
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<td>0.57 (0.31–1.05)</td>
<td>0.34 (0.16–0.70)</td>
<td>0.0023</td>
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</table>

Relative Hazards stratified by sex and age, and adjusted for radiation dose, city, BMI, smoking status, alcohol habits, and medical history of hypertension and diabetes. Tertile 1 refers to the low consumption group; Tertile 2, the moderate consumption group; and Tertile 3 for the high consumption group. BMI indicates body mass index.
lower mean intake of animal fat than the disease-free controls in both Japanese and Hawaiian cohorts.5,27 In the Honolulu Heart Program, a prospective study of cardiovascular disease among men of Japanese ancestry, Reed and colleagues reported that consumption of animal fat was inversely associated with cerebral infarction mortality.28 Finally, the findings from the Framingham Study, a follow-up study among American men aged 45 to 65 years, showed that the risk of incidence of ischemic stroke declined significantly with the increased intake of total fat, SFA, and MUFA, but not PUFA.29 The associations with SFA and MUFA, however, might have been confounded by the effect of cholesterol or other animal fat nutrients intake. The recent findings from a prospective study in male US healthcare professionals reported no association between intake of animal fat and cholesterol and the risk of ischemic stroke.30

Cerebral infarction is not a single entity. Infarction may occur in large or small vessels, each with a specific pathogenesis. In Japan, cerebral infarction caused by small vessel lesions makes up 76% of the cases in autopsy studies,31 whereas in Western countries, it makes up only 20%.32 Small vessel pathogenesis differs from the atheroma process in large vessels, and cholesterol may protect small vessel endothelium.29,32,33 Thus, in the Honolulu Heart Program study, protein and fat from animal sources were risk factors for atherosclerosis in large arteries, but not in the small cerebral vessels.28

Nevertheless, in spite of accumulated data on the protective effect of blood cholesterol level on stroke incidence or death,34,35 we did not observe any significant correlation between dietary cholesterol and total serum cholesterol levels (correlation coefficient = −0.01, P = 0.40).

Artery walls comprise several layers, including (from the lumen) the endothelium, tunica intima, smooth muscle, tunica media, and tunica adventitia. Intracerebral artery disease may be due to either a focal injury to the endothelial layer, which

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Tertile 1 (95% CI)</th>
<th>Tertile 2 (95% CI)</th>
<th>Tertile 3 (95% CI)</th>
<th>P for Trend</th>
</tr>
</thead>
</table>

**TABLE 3. Relative Hazards and 95% CI of Cerebral Infarction Death, by Consumption Level of Animal Protein, Animal Fat, and Cholesterol.**

Nutrient | Consumption Level | P for Trend |
----------|-------------------|------------|
Animal protein | | |
Age/sex-stratified and multivariate 1-adjusted risk | 1.00 | 0.55 (0.28−1.06) | 0.50 (0.25−1.00) | 0.0401 |
Age/sex-stratified and multivariate 2-adjusted risk | 1.00 | 0.58 (0.30−1.13) | 0.46 (0.23−0.92) | 0.0230 |
Age/sex-stratified and multivariate 3-adjusted risk | 1.00 | 0.60 (0.30−1.17) | 0.54 (0.26−1.12) | 0.0864 |
Age/sex-stratified and multivariate 4-adjusted risk | 1.00 | 0.50 (0.26−0.97) | 0.47 (0.24−0.92) | 0.0212 |
Animal fat | | |
Age/sex-stratified and multivariate 1-adjusted risk | 1.00 | 0.53 (0.28−0.99) | 0.38 (0.18−0.82) | 0.0073 |
Age/sex-stratified and multivariate 2-adjusted risk | 1.00 | 0.49 (0.27−0.92) | 0.33 (0.15−0.71) | 0.0019 |
Age/sex-stratified and multivariate 3-adjusted risk | 1.00 | 0.53 (0.28−1.01) | 0.39 (0.17−0.88) | 0.0130 |
Age/sex-stratified and multivariate 4-adjusted risk | 1.00 | 0.49 (0.26−0.90) | 0.36 (0.17−0.76) | 0.0032 |
Cholesterol | | |
Age/sex-stratified and multivariate 1-adjusted risk | 1.00 | 0.61 (0.32−1.15) | 0.37 (0.18−0.78) | 0.0071 |
Age/sex-stratified and multivariate 2-adjusted risk | 1.00 | 0.56 (0.30−1.04) | 0.33 (0.16−0.68) | 0.0019 |
Age/sex-stratified and multivariate 3-adjusted risk | 1.00 | 0.60 (0.32−1.13) | 0.38 (0.18−0.84) | 0.0117 |
Age/sex-stratified and multivariate 4-adjusted risk | 1.00 | 0.57 (0.31−1.06) | 0.36 (0.17−0.76) | 0.0045 |

**Multivariate 1:** radiation dose, city, BMI, smoking status, alcohol habits, medical history of hypertension and diabetes, fruit and vegetable intake
**Multivariate 2:** multivariate 1 plus lymphocyte count and blood cholesterol level
**Multivariate 3:** multivariate 1 plus total energy intake
**Multivariate 4:** multivariate 1 plus body weight

Tertile 1 refers to the low consumption group; Tertile 2, the moderate consumption group; and Tertile 3, the high consumption group.

**TABLE 4. Associations of Cerebral Infarction Risk With the Intakes of Animal Protein, Animal Fat, and Cholesterol, With Additional Mutual Adjustment.**

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>None</th>
<th>Animal Protein</th>
<th>Animal Fat</th>
<th>Cholesterol</th>
<th>2 Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Animal protein (per unit of 30 g/d)</td>
<td>0.45 (0.26−0.80)</td>
<td>—</td>
<td>0.80 (0.40−1.62)</td>
<td>0.63 (0.31−1.26)</td>
<td>0.92 (0.43−1.95)</td>
</tr>
<tr>
<td>Animal fat (per unit of 30 g/d)</td>
<td>0.21 (0.08−0.51)</td>
<td>0.26 (0.08−0.81)</td>
<td>—</td>
<td>0.28 (0.10−0.81)</td>
<td>0.30 (0.09−0.97)</td>
</tr>
<tr>
<td>Cholesterol (per unit of 450 mg/d)</td>
<td>0.37 (0.19−0.74)</td>
<td>0.53 (0.23−1.23)</td>
<td>0.65 (0.29−1.45)</td>
<td>—</td>
<td>0.68 (0.28−1.61)</td>
</tr>
</tbody>
</table>

Risks stratified by sex and age, and adjusted for radiation dose, city, BMI, smoking status, alcohol habits, medical history of hypertension and diabetes, fruit and vegetable intake. Unit intake indicates mean intake of third tertile — mean intake of first tertile.
results in a weakening of the artery wall or even lacunar infarcts, or necrosis of the medial muscle layer, which results in arterio-occlusion and fibromuscular lesions. Although persistent high blood pressure is necessary to arteriopathy, other determinants, such as low intake of cholesterol and animal protein, may be involved.2,31,36,37 When Reed and colleagues examined lesions in small intracerebral arteries in a series of cerebral autopsies among men of the present cohort and Japanese men living in Hawaii, they found that medial fibrosis was the most prevalent lesion.36 Asian diet was positively associated with small arterial lesions. In particular, SFA consumption was inversely associated with lacunar infarcts and medial fibrosis, but intake of animal protein, PUFA, and cholesterol did not increase the risk of small artery disease.36 Therefore, this pathology study adds to the evidence that dietary factors might be involved in intracerebral arteriopathy, although the findings were not as strong as those of epidemiological studies.

One of the limitations of this study was the use of a single 24-hour diary, which is not a precise measure of usual diet. The use of several 24-hour diaries would have shown stronger associations. Moreover, a single assessment does not consider changes in the diet pattern. The National Nutrition Survey, however, has reported that since the 1980s, the average consumption of animal products (such as meat, fish, milk, egg, and dairy products) has remained constant among Japanese.23

The traditional Japanese diet is low in fat, high in salt, and, in men, high in cigarette consumption associated with heavy ethanol drinking2; all of which, it has been suggested, may increase the risk of stroke. Further adjustment for smoking and drinking habits, however, did not materially alter the protective association of animal fat and cholesterol on the risk of cerebral infarction death.

The information on cerebral infarction death was likely to be reliable because computerized tomography diagnosis was already in use when the study was initiated, and thus, the quality of death certificate information was likely to be sufficient.38

The present study population is unique in that all the subjects had been exposed to ionizing radiation. No association was found, however, between stroke risk and radiation exposure in the present study or in previous ones,39 nor has an association been found between diet and radiation exposure.39 The present findings are therefore applicable to the Japanese population as a whole.

In conclusion, this long follow-up community-based cohort study suggests that in Japan, where animal product intake is still generally low and small arteries disease remains the first subtype of cerebral infarction, consumption of both animal fat and cholesterol may reduce the risk of mortality from cerebral infarction.

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References


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