Vegetable and Fruit Intake and Stroke Mortality in the Hiroshima/Nagasaki Life Span Study

C. Sauvaget, MD; J. Nagano, MD; N. Allen, PhD; K. Kodama, MD

Background and Purpose—Fruits and vegetables are known for their beneficial effects on chronic diseases. The purpose of the present study was to investigate the protective effect of a diet rich in fruits and vegetables on total stroke mortality and its 2 main subtypes in men and women separately.

Methods—A prospective cohort study of 40,349 Japanese men and women was initiated in 1980–1981 and followed until 1998. Fruit and vegetable intake was assessed at baseline on the basis of the response to a food frequency questionnaire. During the 18-year follow-up period, deaths from stroke were registered.

Results—A total of 1,926 stroke deaths were identified during the follow-up period. An increasing frequency of intake of green-yellow vegetables and fruit was associated with a reduced risk of death from intracerebral hemorrhage and cerebral infarction. Daily intake of green-yellow vegetables was associated with a significant 26% reduction in the risk of death from total stroke in men and women compared with an intake of once or less per week. The protective effect associated with daily fruit and vegetable intake was observed for both cerebral infarction and intracerebral hemorrhage mortality but was slightly stronger and clearer for infarction than for hemorrhage, with a 32% reduction in men and a 30% reduction in women. Daily fruit intake was associated with a significant 35% reduction in risk of total stroke in men and a 25% reduction in women and was equally strong for both intracerebral hemorrhage and cerebral infarction.

Conclusions—Daily consumption of green-yellow vegetables and fruits is associated with a lower risk of total stroke, intracerebral hemorrhage, and cerebral infarction mortality. The protective effects are similar in both men and women.

Key Words: cerebrovascular disorders • fruit • Japan • longitudinal studies • mortality • vegetables

Stroke incidence and mortality rates have declined dramatically in the past 3 decades in Japan. The age-standardized mortality rate in Japan is now comparable to the rates observed in Western countries (Japan, 56.7/100,000 per year; United Kingdom, 51.8/100,000 per year; United States, 34.8/100,000 per year).1 Stroke is a heterogeneous disease2; the 2 most common subtypes are intracerebral hemorrhage and cerebral infarction, and with the exception of increasing age and high blood pressure, they do not share the same risk factors. Risk factors for cerebral infarction have been well established and include diabetes mellitus, atrial fibrillation, elevated serum cholesterol level, and hypertension, leading to cerebral atherosclerosis.3 In contrast, little is known about the etiology of intracerebral hemorrhage, although a low serum cholesterol level and a low intake of animal protein and fat are hypothesized to be risk factors.4 Unlike in Western countries, tobacco smoking has not been identified as a strong determinant of total stroke mortality in Japanese populations.5,6 The trend toward a more Western-style dietary pattern7 is consistent with the 20% reduction in total stroke mortality rates observed over the past 20 years, largely due to a dramatic decline in hemorrhagic stroke, associated with a concomitant, although slow, increase in the rates of cerebral infarction.8 Indeed, as in Western countries, cerebral infarction is now the most common stroke subtype diagnosed in Japan.

The beneficial effects of a high intake of vegetables and fruits on chronic diseases, especially on the prevention of cancer, have been studied extensively.9 Recently, some prospective studies have reported a possible protective effect of vegetable and fruit consumption on stroke.10–14 However, the study populations tended to be limited to either 1 sex,10,11 total stroke,12,13 or 1 stroke subtype.14 One study in Japan suggested that both vegetables and fruits might be protective against the incidence of cerebral infarction as well as hemorrhagic stroke.15

The aim of the present study was to investigate the effect of a diet rich in fruits and vegetables on the risk of stroke mortality and its main subtypes, in men and women separately, in a large cohort in Japan.

Subjects and Methods

Study Population

The Life Span Study is an ongoing longitudinal cohort study of 120,321 persons exposed and not exposed to radiation from Hiro-
assessed by the Radiation Effects Research Foundation for all deceased Life Span Study participants in Japan. Copies of death certificates are regularly obtained by the Japan’s family registration system, since the mortality ascertainment procedure has been described previously.19

Follow-up and Ascertainment of Stroke Death Cases
Stoke death cases were ascertained by linkage with the nationwide family registration system in Japan,19 since the mortality ascertainment was complete for the Life Span Study participants residing in Japan. Copies of death certificates are regularly obtained by the Radiation Effects Research Foundation for all deceased Life Span Study participants, and trained coders enter the appropriate codes into the database. Causes of death were coded according to the International Classification of Diseases, Ninth Revision, and International Statistical Classification of Diseases, Tenth Revision.20 The follow-up was started on January 1, 1980, for men and February 1, 1981, for women and continued until the date of death or March 31, 1998, whichever came first.

Statistical Analysis
Characteristics at baseline were compared according to green-yellow vegetable and fruit intake with the χ² test (for categorical variables) and ANOVA (for continuous variables).

Table 1: Distribution of Cerebrovascular Deaths in Men and Women

<table>
<thead>
<tr>
<th>Type of Cerebrovascular Disease</th>
<th>Assigned ICD Codes</th>
<th>9th Revision</th>
<th>10th Revision</th>
<th>Men No.</th>
<th>%</th>
<th>Women No.</th>
<th>%</th>
<th>Total No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subarachnoid hemorrhage</td>
<td>430</td>
<td>160, 169.0</td>
<td>31</td>
<td>4.5</td>
<td>121</td>
<td>9.8</td>
<td>152</td>
<td>7.9</td>
<td></td>
</tr>
<tr>
<td>Intracerebral hemorrhage</td>
<td>431, 432</td>
<td>161, 162, 169.1, 169.2</td>
<td>166</td>
<td>24.0</td>
<td>287</td>
<td>23.3</td>
<td>453</td>
<td>23.5</td>
<td></td>
</tr>
<tr>
<td>Cerebral infarction</td>
<td>433, 434</td>
<td>163, 169.3</td>
<td>348</td>
<td>50.3</td>
<td>572</td>
<td>46.4</td>
<td>920</td>
<td>47.8</td>
<td></td>
</tr>
<tr>
<td>Other cerebrovascular diseases</td>
<td>435 to 438</td>
<td>164 to 168, 169.4, 169.8</td>
<td>147</td>
<td>21.2</td>
<td>254</td>
<td>20.6</td>
<td>401</td>
<td>20.8</td>
<td></td>
</tr>
</tbody>
</table>

Total 692 35.9 1234 64.1 1926 100.0

**Results**
During the median follow-up period of 16 years, there were 1926 stroke deaths, comprising 920 deaths from cerebral infarction (48%), 453 deaths from intracerebral hemorrhage (24%), 152 deaths from subarachnoid hemorrhage (8%), and 401 deaths from other cerebrovascular diseases (21%) (Table 1). Baseline characteristics by fruit and vegetable consumption are shown in Table 2. In general, women consumed green-yellow vegetables and fruits more frequently than men. Green-yellow vegetable and fruit intake was less frequent among current smokers and drinkers and among those with a low or moderate education level. Radiation dose was not associated with fruit and vegetable consumption. No appreciable difference was observed for body mass index across the consumption levels of green-yellow vegetables and fruits.

The association between green-yellow vegetable and fruit intake and risk of stroke mortality in men and women is shown in Table 3. Overall, an increasing frequency of both green-yellow vegetables and fruits was associated with a reduced age-stratified risk of mortality from total stroke, as well as intracerebral hemorrhage and cerebral infarction. The dose-response relationships were significant for all these associations, except for vegetable intake and hemorrhagic stroke mortality. Compared with consumption of vegetables and fruits once or less per week, a daily consumption of...
vegetables and fruits was associated with a risk reduction of between 20% and 40%; this was equally strong for both men and women. Adjustment for smoking status did not alter the associations appreciably. Additionally, these protective associations remained after we controlled for other potential confounders such as radiation dose, city, body mass index, education level, alcohol drinking, and past history of hypertension, diabetes, and myocardial infarction. Additional adjustment for intake of animal products slightly attenuated the association between vegetable consumption and intracerebral hemorrhage, but the associations between fruit consumption and the risk of death from stroke remained unchanged. Furthermore, mutual adjustment for intake of fruits and green-yellow vegetables did not alter the relationships (data not shown).

Exclusion of individuals with missing information on green-yellow vegetable and fruit intake did not alter the associations materially. Fruits and vegetables remained protective factors against stroke mortality and its 2 main subtypes in men and women, although the association between vegetable intake and total stroke and 2 main subtypes was not statistically significant among men (Table I, available online at http://stroke.ahajournals.org).

Discussion

This cohort study in Japan, with a median follow-up time of 16 years and a total of 1926 deaths from stroke, showed that daily intake of fruits was significantly associated with a lower risk of mortality from total stroke as well as from cerebral infarction and intracerebral hemorrhage. Daily intake of green-yellow vegetables was significantly related to a decrease risk of total stroke and infarction. However, the relation between vegetable intake and intracerebral hemorrhage was less clear, especially in men. The protective effects of green-yellow vegetable and fruit consumption appeared to be similar for both men and women.

Compared with Western populations, Japanese people have different exposures to potential dietary and lifestyle risk factors and have different stroke subtypes and etiopathology. However, longitudinal studies in both Japanese and American populations have consistently shown fruit and vegetable consumption to be inversely associated with stroke incidence and mortality, although these studies have not considered potential differences between men and women or between stroke subtypes. The present study adds to evidence that vegetable and fruit consumption is protective against intracerebral hemorrhage and cerebral infarction in both men and women.

The potential protective effects of fruits and vegetables are thought to be mediated through their effects on lowering blood pressure and/or their antioxidant effects. Fruits and vegetables are rich sources of vitamins and minerals such as vitamin C, beta carotene, potassium, magnesium, and calcium, in addition to other nutrients such as folate and fiber. Potassium has been shown to increase natriuresis and vasomotoric, thereby lowering blood pressure. High serum vitamin C levels have also been associated with a reduced risk of stroke among hypertensive men, and fiber may be involved in lowering blood pressure. Magnesium, calcium, and other minerals may also play a role in preventing hypertension, and randomized controlled trials have shown fruit and vegetable consumption to significantly lower systolic and diastolic blood pressure. Consequently, vitamins and phytochemicals from fruits and vegetables may help to prevent and control high blood pressure, thus preventing both hemorrhagic and infarction strokes.

Although other mechanistic effects of vegetable and fruit consumption on the prevention of intracerebral hemorrhage are unclear, there is additional evidence on their preventive association with cerebral infarction, in particular through their ability to reduce atherosclerosis. For example, potassium has been shown to inhibit platelet aggregation and arterial thrombosis. High folate levels may lower serum homocysteine levels, a risk factor for arterial endothelial dysfunction, and fiber may have effects that act to lower cholesterol. Antioxidants such as vitamin C and beta...
TABLE 3. Relative Hazards and 95% CI According to the Level of Consumption of Green-Yellow Vegetables and Fruits by Sex and Stroke Subtype

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th></th>
<th>Women</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0–1/ Week 2–4/ Week Daily</td>
<td></td>
<td>0–1/ Week 2–4/ Week Daily</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total Cases, n RH* RH* 95% CI† RH* RH* 95% CI†</td>
<td>P Value for Trend</td>
<td>Total Cases, n RH* RH* 95% CI† RH* RH* 95% CI†</td>
<td>P Value for Trend</td>
</tr>
<tr>
<td>Green-yellow vegetables</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total stroke</td>
<td>Cases 692 310 242 140</td>
<td>1.00 0.78 (0.85–0.92) 0.74 (0.60–0.91) 0.0015</td>
<td>1234 421 511 302</td>
<td>1.00 0.88 (0.77–1.01) 0.73 (0.62–0.85) 0.0001</td>
</tr>
<tr>
<td>Age-stratified risk</td>
<td>1.00 0.78 (0.85–0.92) 0.74 (0.60–0.91) 0.0015</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age-stratified and smoking-adjusted risk</td>
<td>1.00 0.78 (0.86–0.93) 0.76 (0.62–0.94) 0.0034</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age-stratified and multivariate-adjusted risk 1†</td>
<td>1.00 0.82 (0.69–0.98) 0.77 (0.62–0.94) 0.0068</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age-stratified and multivariate-adjusted risk 2‡</td>
<td>1.00 0.83 (0.69–0.99) 0.77 (0.62–0.96) 0.0113</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebral hemorrhage</td>
<td>Cases 166 75 53 38</td>
<td>1.00 0.65 (0.45–0.95) 0.74 (0.49–1.11) 0.0785</td>
<td>287 94 120 73</td>
<td>1.00 0.87 (0.66–1.15) 0.74 (0.54–1.02) 0.0834</td>
</tr>
<tr>
<td>Age-stratified risk</td>
<td>1.00 0.65 (0.45–0.95) 0.74 (0.49–1.11) 0.0785</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age-stratified and smoking-adjusted risk</td>
<td>1.00 0.67 (0.46–0.97) 0.86 (0.57–1.30) 0.2685</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age-stratified and multivariate-adjusted risk 1†</td>
<td>1.00 0.68 (0.47–0.99) 0.84 (0.56–1.29) 0.2596</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age-stratified and multivariate-adjusted risk 2‡</td>
<td>1.00 0.72 (0.49–1.06) 0.90 (0.58–1.40) 0.4685</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebral infarction</td>
<td>Cases 348 156 131 61</td>
<td>1.00 0.67 (0.69–1.11) 0.71 (0.53–0.96) 0.0256</td>
<td>572 210 225 137</td>
<td>1.00 0.79 (0.65–0.96) 0.64 (0.52–0.80) 0.0001</td>
</tr>
<tr>
<td>Age-stratified risk</td>
<td>1.00 0.67 (0.69–1.11) 0.71 (0.53–0.96) 0.0256</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age-stratified and smoking-adjusted risk</td>
<td>1.00 0.90 (0.71–1.10) 0.73 (0.54–0.98) 0.0458</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age-stratified and multivariate-adjusted risk 1†</td>
<td>1.00 0.90 (0.70–1.15) 0.70 (0.51–0.95) 0.0265</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age-stratified and multivariate-adjusted risk 2‡</td>
<td>1.00 0.88 (0.68–1.14) 0.68 (0.50–0.94) 0.0223</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fruits</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total stroke</td>
<td>Cases 692 371 222 199</td>
<td>1.00 0.81 (0.67–0.97) 0.62 (0.51–0.75) 0.0001</td>
<td>1234 345 348 541</td>
<td>1.00 0.92 (0.79–1.07) 0.69 (0.60–0.79) 0.0001</td>
</tr>
<tr>
<td>Age-stratified risk</td>
<td>1.00 0.81 (0.67–0.97) 0.62 (0.51–0.75) 0.0001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age-stratified and smoking-adjusted risk</td>
<td>1.00 0.79 (0.96–0.95) 0.64 (0.53–0.78) 0.0001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age-stratified and multivariate-adjusted risk 1†</td>
<td>1.00 0.81 (0.67–0.98) 0.66 (0.54–0.80) 0.0001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age-stratified and multivariate-adjusted risk 2‡</td>
<td>1.00 0.81 (0.67–0.99) 0.65 (0.53–0.80) 0.0001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebral hemorrhage</td>
<td>Cases 166 65 60 41</td>
<td>1.00 0.78 (0.54–1.12) 0.54 (0.36–0.81) 0.0025</td>
<td>287 74 93 120</td>
<td>1.00 0.91 (0.74–1.32) 0.61 (0.45–0.82) 0.0002</td>
</tr>
<tr>
<td>Age-stratified risk</td>
<td>1.00 0.78 (0.54–1.12) 0.54 (0.36–0.81) 0.0025</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age-stratified and smoking-adjusted risk</td>
<td>1.00 0.79 (0.94–1.15) 0.61 (0.41–0.91) 0.0160</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age-stratified and multivariate-adjusted risk 1†</td>
<td>1.00 0.83 (0.57–1.22) 0.61 (0.40–0.93) 0.0202</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age-stratified and multivariate-adjusted risk 2‡</td>
<td>1.00 0.91 (0.61–1.34) 0.63 (0.41–0.97) 0.0381</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebral infarction</td>
<td>Cases 348 131 111 106</td>
<td>1.00 0.90 (0.70–1.17) 0.63 (0.48–0.82) 0.0006</td>
<td>572 163 152 257</td>
<td>1.00 0.84 (0.67–1.06) 0.68 (0.56–0.83) 0.0001</td>
</tr>
<tr>
<td>Age-stratified risk</td>
<td>1.00 0.90 (0.70–1.17) 0.63 (0.48–0.82) 0.0006</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age-stratified and smoking-adjusted risk</td>
<td>1.00 0.90 (0.89–1.17) 0.66 (0.50–0.88) 0.0020</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age-stratified and multivariate-adjusted risk 1†</td>
<td>1.00 0.88 (0.68–1.15) 0.64 (0.49–0.85) 0.0016</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age-stratified and multivariate-adjusted risk 2‡</td>
<td>1.00 0.86 (0.65–1.13) 0.63 (0.47–0.83) 0.0012</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Relative hazards (RH).  †95% confidence intervals.  ‡Relative hazards 1: age-stratified, and adjusted for radiation dose, city, BMI, smoking status, alcohol habits, education level, and medical history of hypertension, myocardial infarction, and diabetes.
§Relative hazards 2: age-stratified, and adjusted for radiation dose, city, BMI, smoking status, alcohol habits, education level, medical history of hypertension, myocardial infarction, diabetes, and consumption of animal products (egg, dairy, fish).

Missing data on vegetable and fruit consumption were considered as zero consumption.

carotene may reduce lipid oxidation of LDL cholesterol, preventing atherosclerosis and its progression. However, a study among the elderly showed that the plasma level of antioxidant vitamins was not clearly associated with extra cranial carotid atherosclerosis status. Moreover, intervention studies of intake of vitamins A, C, and E, carotenoids, and beta carotene have failed to show any beneficial effect on total stroke incidence or mortality. This may be because...
the mixture of phytochemicals contained in fruits and vegetables has a greater effect than a single antioxidant. Indeed, a study has demonstrated that nearly all of the antioxidant activity of fresh apples on cell proliferation was derived from a mixture of phytochemicals rather than vitamin C alone.42

It is well established that a diet rich in fruits and vegetables is associated with lower rates of smoking, higher levels of physical exercise, better health management, and a relatively low intake of cholesterol, saturated fat, and dietary sodium.18,43 However, adjustment for potential confounders of stroke such as body mass index, smoking habits, drinking habits, education level, animal products, and history of high blood pressure did not alter the protective association of vegetable and fruit consumption, suggesting that vegetable and fruit intake may have independent effects on stroke prevention.

Limitations of the study relate to the baseline dietary assessment. Although the questionnaire used had some validity, its reproducibility has not been examined, and it assessed only 1 point in time. The absence of information on portion size and the limited number of foods included in the questionnaire meant that total energy intake could not be calculated or adjusted for in the analysis and may have therefore caused an underestimation of the present results. On the other hand, during the present study period, the 1980s and 1990s, the use of CT scanning for diagnosis of stroke was widespread in Japan, and therefore the death certificate information is likely to be reliable not only for total stroke but also for stroke subtypes.44

Although the study participants are unique in the fact that they were exposed to the atomic bombings of Hiroshima and Nagasaki in 1945, no association was observed between stroke mortality and radiation exposure in the Life Span Study cohort.19 Additionally, dietary patterns were not related to radiation dose.17 Consequently, the present results are likely to be generalizable to the whole Japanese population. In conclusion, the results suggest that daily consumption of fruits and vegetables has a protective effect against both cerebral hemorrhage and infarction and that these effects are seen in both men and women. Future research needs to clarify the mechanisms through which a high intake of vegetables and fruits may protect against stroke.

Acknowledgments

This publication is based on research performed at the Radiation Effects Research Foundation (RERF), Hiroshima and Nagasaki, Japan. RERF is a private nonprofit foundation funded equally by the Japanese Ministry of Health, Labor, and Welfare and the US Department of Energy through the National Academy of Sciences. We are indebted to the persons in charge of the Life Span Study. We are also grateful to the staff of the Master File Sections in Hiroshima and Nagasaki for data collection and mortality coding and to Mikiko Hayashi for data set preparation.

References


Vegetable and Fruit Intake and Stroke Mortality in the Hiroshima/Nagasaki Life Span Study

C. Sauvaget, J. Nagano, N. Allen and K. Kodama

Stroke. 2003;34:2355-2360; originally published online September 18, 2003;
doi: 10.1161/01.STR.0000089293.29739.97

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2003 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://stroke.ahajournals.org/content/34/10/2355

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published
in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office.
Once the online version of the published article for which permission is being requested is located, click
Request Permissions in the middle column of the Web page under Services. Further information about this
process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/