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 1926 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-
shima and Nagasaki atomic bombings, which began in 1950, from June to November 1979. A mail survey was conducted among the 55,650 Life Span Study participants who were alive on September 1, 1978, who were 40 to 79 years old, of whom 40,349 persons returned a completed questionnaire (response rate, 72.5%). The nonrespondents did not differ from the respondents in terms of sex (38% men in both groups), age (mean age: nonrespondents, 53 years; respondents, 54 years), city of radiation exposure (nonrespondents, 74% in Hiroshima; respondents, 73% in Hiroshima), and stroke death rate during the follow-up (5% in both groups). After exclusion of self-reported history of stroke, the study population consisted of 39,337 participants (14,966 men and 24,371 women). The mean age at baseline was 54 years (range, 34 to 97 years) for men and 58 years (range, 35 to 103 years) for women.

**Dietary Assessment**

The mail questionnaire included items regarding sociodemographic information, lifestyle factors, past medical history, and a 22-item food frequency questionnaire.17 Food items referred to beef and pork, chicken, pork products, dairy products, milk, eggs, fish (except broiled and dried), broiled fish, dry fish, green-yellow vegetables, fruit, seaweed, tofu, miso soup, salted foods, confectionery, rice, bread, black tea, coffee, fizzy drinks, and green tea. The validity of the food frequency questionnaire has been reported previously, and vegetable and fruit items showed a moderate correlation with a 24-hour diary.18 On the questionnaire, vegetable intake was limited to green-yellow vegetables, and fruit intake represented total fruit consumption. Each food had a 4-level precoded answer: “once or less per week,” “2 to 4 times a week,” “almost daily,” and “do not eat.” Since those who responded “do not eat” were few for both green-yellow vegetables (n=2286 for fruit) because the food frequency questionnaire validation study found the mean intake of those with missing data was also included in this category (n=2286 for fruit) due to these previous results, relative risks were first adjusted for smoking habits (never, current, past), then for additional potential confounders: city (Hiroshima, Nagasaki), radiation dose (continuous), alcohol habits (never, current, past), education level (junior high school or less, high school, junior college or more), self-reported body mass index (continuous), history of myocardial infarction (yes, no), history of diabetes (yes, no), and history of hypertension (yes, no). Additional adjustments were also made for dietary factors found to be independent risk factors for intracerebral hemorrhage mortality, such as animal products, eggs, dairy products, and fish, the results of which are presented elsewhere.21 A test for trend was used to assess statistical significance across exposure categories by including ordinal terms for each of the 3 categories and entering the variable as a continuous term in the model. Relative hazards of stroke death compared with staying alive were calculated with the SAS PHREG procedure.22

**Follow-up and Ascertainment of Stroke Death Cases**

Stroke 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). Associations between dietary factors and stroke mortality were examined with a Cox proportional hazards model with age as the primary time scale and stratified by sex and birth cohort. In a previous study we examined the nondietary risk factors of total stroke mortality and its 2 main subtypes among the present population.21 Significantly increased risks of stroke death were observed among current smokers, past alcohol drinkers, and those with a self-reported history of hypertension and diabetes. Body mass index presented an L-shaped relationship with stroke mortality. According to these previous results, relative risks were first adjusted for smoking habits (never, current, past), then for additional potential confounders: city (Hiroshima, Nagasaki), radiation dose (continuous), alcohol habits (never, current, past), education level (junior high school or less, high school, junior college or more), self-reported body mass index (continuous), history of myocardial infarction (yes, no), history of diabetes (yes, no), and history of hypertension (yes, no). Additional adjustments were also made for dietary factors found to be independent risk factors for intracerebral hemorrhage mortality, such as animal products, eggs, dairy products, and fish, the results of which are presented elsewhere.21 A test for trend was used to assess statistical significance across exposure categories by including ordinal terms for each of the 3 categories and entering the variable as a continuous term in the model. Relative hazards of stroke death compared with staying alive were calculated with the SAS PHREG procedure.22

**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).

**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>Men</th>
<th>Women</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>9th Revision</td>
<td>10th Revision</td>
<td>No. %</td>
<td>No. %</td>
</tr>
<tr>
<td>Subarachnoid hemorrhage</td>
<td>430</td>
<td>160, 169.0</td>
<td>31</td>
<td>4.5</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>
</tr>
<tr>
<td>Cerebral infarction</td>
<td>433, 434</td>
<td>163, 169.3</td>
<td>348</td>
<td>50.3</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>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>692</td>
<td>35.9</td>
</tr>
</tbody>
</table>

**TABLE 2. Baseline Characteristics by Fruit and Vegetable Consumption**

<table>
<thead>
<tr>
<th>Fruit and Vegetable Intake</th>
<th>Men</th>
<th>Women</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low or moderate education</td>
<td>723</td>
<td>1234</td>
<td>1957</td>
</tr>
<tr>
<td>High school or less</td>
<td>32</td>
<td>79</td>
<td>111</td>
</tr>
<tr>
<td>Junior college or more</td>
<td>166</td>
<td>24</td>
<td>190</td>
</tr>
</tbody>
</table>

**TABLE 3. Trends in Cardiovascular Disease Mortality by Dietary Factors**

<table>
<thead>
<tr>
<th>Dietary Factor</th>
<th>Cerebral Infarction</th>
<th>Intracerebral Hemorrhage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vegetable intake</td>
<td>0.0007</td>
<td>0.03</td>
</tr>
<tr>
<td>Fruit intake</td>
<td>0.01</td>
<td>0.01</td>
</tr>
</tbody>
</table>

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 vasomotoricity, 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
carotene may reduce lipid oxidation of LDL cholesterol, preventing atherogenesis and its progression. However, a study among the elderly showed that the plasma level of antioxidant vitamins was not clearly associated with extracranial 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, 1 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.\(^4\)

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.\(^14,43\) 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,\(^18\) 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

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References


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