Dietary Antioxidant Intake and Risk of an Amyotrophic Lateral Sclerosis in Japan

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Abstract

The Background of the Study
Several studies have suggested that dietary antioxidants may play a protective role against the development of Amyotrophic Lateral Sclerosis (ALS). In general, however, various dietary antioxidants may be interactive or synergistic rather than isolated. Therefore, the purpose of this study is to investigate the relationship between dietary antioxidant intake and the risk of ALS using population-based case-control study conducted in Japan.

Materials and Methods
A case-control study was conducted with incident 143 ALS cases and 385 controls. An antioxidant intake score was calculated for individual values for each food group (green-yellow vegetables, fruits, mushroom, seaweed, dairy products) collected by a self-administered food frequency questionnaire. Those who had one or more of five-food group almost every day were grouped into high-intake category. Those who consumed all food group once a week or less were grouped into low-intake category. A value of 1, 2 and 3 was assigned to food group categories, low medium and high-intake. The antioxidants intake score totaled a value in each food groups. This score was then classified into approximate tertiles based on intake scores among control group.

Results
Higher antioxidant intake score and greater number of food group consumed daily or almost daily (high-intake category) were inversely associated with the risk of ALS, even after adjusting for confounding factors.

Conclusion
The present studies suggest that the frequent intake of various kinds of dietary antioxidants may be associated with a decreased risk of ALS.

Keywords
Amyotrophic Lateral Sclerosis; Antioxidants; Nutrition; Epidemiology; Case-control study

Introduction
Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease of unclear etiology involving spinal cord motor neurons, leading to atrophy of skeletal muscles, paralysis and rapidly-progressive death. Most of the patients are sporadic cases (SALS), while 5-10% of the patients have a family history of ALS (familial ALS or FALS) [1]. Several studies have been reported that high intake of antioxidants may play a protective role against the
development of Amyotrophic Lateral Sclerosis (ALS) [2-8].

We previously reported that green-yellow vegetable as antioxidants was significantly associated with reduced risk of ALS. The relationship between carotenoid intake and ALS risk has been examined in only 3 previous case-control studies [5]. Dietary intake of vitamin E was also associated with a lower risk of ALS in case-control studies [6-7] and five cohorts 7. However, we take antioxidants in food items, not only antioxidants. Moreover, since we consume various foods in combination, not alone, the effects of various dietary antioxidants in food items on the risk of ALS may be also interactive or synergistic rather than isolated.

To the best of knowledge, few studies have examined the relationship between items with antioxidants and the risk of ALS.

Therefore, we conducted a case–control study to examine the relationship between antioxidants intake score as index of intake frequencies of various antioxidant-rich foods and the risk of sporadic ALS in Japan.

Materials and Methods

Study Populations

Our methods were previously described in detail [6-7]. In brief, we conducted a case-control study of ALS and lifestyle factors. Case subjects were all definite or probable ALS [9]. Patients aged from 18 to 81 years in the medical centers located in the Tokai area. All cases of progressive bulbar palsy [PBP] were included for this study, but familial progressive muscular atrophy was excluded. There was no evidence of coexisting Parkinson disease and related disorders including multisystem atrophy. The institutional review board of Aichi Prefectural College of Nursing and Health approved the present study.

We set up community controls consisting of subjects, matching to each patient for age [±2 years], gender and residence [based on electoral districts]. They were selected by a proportional simple random sampling with stratification by sex and age groups, using the basic register of residents.

Data Collection

A structured self-administered questionnaire specifically designed for this case-control study was distributed and collected by mail in both patients and controls. We asked patients to recall their lifestyle within the 3 years before the onset of ALS, and controls within the 3 years before the survey. When the patients were unable to provide any information on their lifestyle and exposures because of early death or too impaired conditions, proxies (mainly spouses) were interviewed.

The questionnaire yielded information on demographic characteristics (sex, age, height, and present and past weight, occupation and work environment held the longest), a history of bone fracture, vigorous physical activity, hate to lose, self-reported stress, type A behavior pattern, smoking and drinking habits, body pliability by nature, and frequency of green-vegetable intake.

Type a behavior pattern was measured by ten-item scale designed for Japanese persons by Maeda [10]. Subjects who scored between 0 and 16 considered as non-type A, while those who scored 17 or greater were considered as type A. Smoking status was classified as current smokers or nonsmokers (including ex-smokers). Drinking status was classified as current drinkers or nondrinkers (including ex-drinkers).

Dietary information was obtained by a self-administered food frequency questionnaire (FFQ) [11-12]. Consisting of 97 commonly eaten food and beverage items. Subjects were asked intake frequencies of foods and nutrients with five response options as follows: “never/occasionally,” “less than once a week,” “1-2 times per week,” “3-4 times per week,” and “daily or almost daily.

To avoid multiple comparison, food items were classified into five groups; green-yellow vegetables (carrots, spinach, pumpkins, sweet peppers, tomato and others), fruits (apple, orange, watermelon, strawberries, banana, grapefruits), mushroom, seaweed, dairy products (yogurt, cheese). Those who had one or more of the above-mentioned six vegetables, six fruits, two dairy products, mushroom and seaweed daily or almost daily were grouped into high-intake category. Those who consumed all food group never/occasionally, or “less than once a week,” were grouped into low-intake category. A value of 1, 2 and 3 was assigned to each food group, low and medium and high-intake. An antioxidant intake score (range from 1 to 15) was calculated by the sum of value in each food group (green-yellow vegetables, fruits, mushroom, seaweed, dairy products) together. This score was then classified into approximate tertiles based on intake scores among control group.

Statistical Analysis

Estimation of odds ratios [ORs] and their 95% confidence intervals [CIs] were carried out by means of
multiple conditional logistic regression analysis. Tests for trend in logistic regression analysis was performed by the exposure variables and treating the scored variables as a continuous one. Two-sided p values less than 0.05 were considered statistically significant. Statistical analyses were conducted by use of SPSS ver 24.0 [SPSS IBM Inc] was used.

**Results**

Table 1 shows the characteristics of the 143 ALS patients (Cases) and 385 controls. Cases had significantly higher proportions of type A behavior pattern and lower mean of BMI in comparison with controls. Table 2 shows the antioxidant intake score was inversely associated with the risk of ALS, even after adjusting for confounding factors (lowest vs highest score adjusted OR: 0.31 95% CI; 0.17-0.57). Table 3 shows that greater number of food group consumed daily or almost daily (high-intake category) was inversely associated with the risk of ALS, even after adjusting for confounding factors (≥2 vs none adjusted OR: 0.33 95% CI; 0.18-0.60).

### Table 1: Comparison of selected characteristics of cases and controls

<table>
<thead>
<tr>
<th></th>
<th>Cases (n=143)</th>
<th>Controls (n=385)</th>
<th>p for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>% or Mean</td>
<td>% or Mean</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men (%)</td>
<td>60.8</td>
<td>59.1</td>
<td></td>
</tr>
<tr>
<td>Mean age (SD)</td>
<td>63.7±9.2</td>
<td>63.4±10.6</td>
<td>N.S</td>
</tr>
<tr>
<td>Use of proxy respondents (%)</td>
<td>67.5</td>
<td>67.5</td>
<td>N.S</td>
</tr>
<tr>
<td>Body Mass index (BMI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>22.2 ± 0.2</td>
<td>23.3 ± 0.3</td>
<td>p=0.04</td>
<td></td>
</tr>
<tr>
<td>Type A behavior pattern (%)</td>
<td>44.2</td>
<td>19.6</td>
<td>p=0.000</td>
</tr>
<tr>
<td>Smoking habit (%)</td>
<td>58.1</td>
<td>54.1</td>
<td>N.S</td>
</tr>
<tr>
<td>Drinking habit (%)</td>
<td>35.3</td>
<td>31.4</td>
<td>N.S</td>
</tr>
</tbody>
</table>

### Table 2: Adjusted OR* and 95% CI for ALS according to antioxidant intake score

<table>
<thead>
<tr>
<th>Dietary antioxidants score</th>
<th>Cases (n=143)</th>
<th>Controls (n=385)</th>
<th>Crude odds ratio</th>
<th>95%CI</th>
<th>Adjusted odds ratio</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lowest</td>
<td>32.9%</td>
<td>20.5%</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Medium</td>
<td>38.5</td>
<td>35.3</td>
<td>0.9</td>
<td>0.59-1.37</td>
<td>0.84</td>
<td>0.54-1.33</td>
</tr>
<tr>
<td>Highest</td>
<td>28.7</td>
<td>44.2</td>
<td>0.3</td>
<td>0.16-0.54</td>
<td>0.31</td>
<td>0.17-0.57</td>
</tr>
<tr>
<td>P for trend</td>
<td>p=0.0001</td>
<td></td>
<td></td>
<td></td>
<td>p=0.0001</td>
<td></td>
</tr>
</tbody>
</table>

*Adjusted for sex, age, Type a behavior pattern

### Table 3: Odds ratios and 95% confidence interval according to the number of food group consumed daily or almost daily

<table>
<thead>
<tr>
<th>Number of food group</th>
<th>Cases (n=143)</th>
<th>Controls (n=385)</th>
<th>Crude odds ratio</th>
<th>95%CI</th>
<th>Adjusted odds ratio</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>67.80%</td>
<td>49.9%</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>One</td>
<td>21.7</td>
<td>25.2</td>
<td>0.63</td>
<td>0.39-1.02</td>
<td>0.65</td>
<td>0.40-1.06</td>
</tr>
<tr>
<td>Two or more</td>
<td>10.5</td>
<td>24.9</td>
<td>0.31</td>
<td>0.17-0.56</td>
<td>0.33</td>
<td>0.18-0.61</td>
</tr>
<tr>
<td>P for trend</td>
<td>p=0.0001</td>
<td></td>
<td></td>
<td></td>
<td>p=0.0001</td>
<td></td>
</tr>
</tbody>
</table>
Discussion

In this study, we found that higher antioxidant intake score as an index of intake frequency and number of food group with antioxidant rich-food was significantly associated with a decreased risk of ALS, approximately 70% reduction in ALS risk.

Therefore, higher antioxidant intake score means high intake frequency and great number of food group with antioxidant rich-food. These results are the first epidemiological finding that not only higher intake frequency, but also greater number of food group with antioxidants rich-food, not alone may have stronger protective activity against the development of ALS.

In this study, we also found that higher intake frequency of dairy products, green-yellow vegetables, mushroom, seaweed used to construct the antioxidants intake score was associated with a decreased risk of ALS.

Dietary antioxidants may effect on health status in combination, not individual. The food groups and items selected in the present study contain a wide range of antioxidants such as lipophilic (conjugated linoleic acid, α-tocopherol, β-carotene, vitamins A and D3, coenzyme Q10, phospholipids in dairy products [13], β-carotene, and vitamins C and E in green-yellow vegetables and fruits [6-7]. Phenolic and flavonoids in mushroom [14], 1, 1-diphenyl-2-picrylhydrazyl (DPPH) total phenolic compounds in seaweed [15]. Moreover, we found that proportion of subjects with daily intake of various food groups were significantly higher in cases than in controls.

These findings indicated that these antioxidant activities appear to be the result of a combination of those different compounds acting in synergic and interactive manners, not alone. The inverse association detected between higher antioxidants intake score and risk of ALS can be explained by the synergic and interactive effects according to intakes of various food groups with antioxidants rich-food. Accordingly, higher antioxidants intake score considered as an index of not only higher intake frequency, but also greater number of food group of antioxidants rich-food, suggesting that higher antioxidants intake score may increase an anti-oxidative effects, and result in decreased the development of ALS.

There are several limitations to this study. First, we used prevalent patients whose diagnosis was made within 3 years before the present study, which would result in some difficulty in recalling their conditions before the onset of ALS. It is quite likely that prevalent cases often take the influence of the recall bias in comparison with incident cases. According to Swan et al. [16] it is difficult to assess reporting bias because of the absence of a reference criterion against which to compare self-reported, retrospectively collected information in case-control studies. In this study, the association of the studied variables and the risk of ALS remained even after we reanalyzed for the subjects within one year before the onset of ALS, although the number of cases were small (n=64).

Second, our questionnaire asked several information 3 years before recruitment into study. This was because we examine the causality between lifestyle factors before the onset of ALS and the risk of one. Accordingly, the possibility could arise that lifestyle exposure might have occurred after initiation of ALS development. Therefore, we have confirmed that all of cases and controls had no significant change in their lifestyle between 3 years at interview and 10 years prior to disease onset. Reliability and validity on information collected among latent interval for symptom to appear have been pointed out as a methodological issue in research that involves interviews or questionnaires as case-control study. To avoid these problems, therefore, we are now planning relatively large population-based prospective study. Third, we used the self-administered questionnaire to collect information both cases and controls. The authors have demonstrated no significant difference in the responses to questions related to lifestyle factors such as physical activity, general life stress and dietary habit between self- and interviewer-administered questionnaires [17]. Marshall et al. reported that 90% of the estimates by spouses and by respondents to food-frequency, questionnaires are within one frequency category of each other [18]. Fourth, in this study, we examined based on information of food frequency within the 3 years before the onset of ALS, although it is highly likely that kind or degree of severity of chief complainants such as muscle weakness and difficulty swallowing at onset affect dietary intake. Therefore, we need to collect that information to provide more detail information on the manner of food intake against the development of ALS.

In summary, higher antioxidants intake score as index of intake frequency and number of food group with antioxidants rich-food consumed was associated with a reduced risk of ALS. Further interventional or longitudinal studies are necessary to confirm our finding.

References


Citation: Kazushi Okamoto (2017) Dietary Antioxidant Intake and Risk of An Amyotrophic Lateral Sclerosis in Japan. SF J Pub Health 1:2.