A Case-Cohort Study of Diet and Stomach Cancer

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ABSTRACT

In this case-cohort study, from 1965 to 1968, 8006 Hawaiian men of Japanese ancestry were interviewed with a 24-h dietary recall questionnaire. After a follow-up period of 18 years, 111 stomach cancer incident cases were identified. Dietary data from these patients and from 361 cancer-free men were analyzed for intake of selected foods, food groups, and nutrients. We found that the consumption of all types of vegetables was protective against stomach cancer. Specifically, subjects in the highest group of vegetable consumption (≥80 g/day) had a relative risk of 0.6 (95% confidence interval, 0.3–0.9) in comparison with nonconsumers. This statistically significant inverse trend persisted after adjustment for age at examination and cigarette-smoking status. Similar but weaker protective effects from consumption of green and cruciferous vegetables were also observed. In addition, an inverse association between stomach cancer risk and intake of fruits was noted (P = 0.05), but this inverse trend was weakened after the effect of cigarette smoking was taken into account. There were no other dietary factors significantly associated with the risk of gastric cancer.

INTRODUCTION

Researchers suspect that diet affects the risk of stomach cancer. Past dietary studies strongly suggest that a high intake of various types of vegetables is protective against stomach cancer (1–9). Epidemiological studies in different countries have also found that frequent ingestion of fruits (2, 6, 8, 10–12) and vitamin C (1, 2, 6, 11) is inversely associated with gastric cancer risk. On the other hand, the results from several other reports have not supported these findings (13–15).

Observational studies have also shown that increased risk of gastric cancer is associated with the high intake of dried/salted fish (3, 13), pickled vegetables (3, 10, 13), cured meats (2, 11), and carbohydrate (7, 11, 16, 17). However, other investigators have not been able to substantiate these observations (5, 8, 9, 14, 17).

Due to the discrepant findings in past dietary investigations, we undertook the present study. Previously, we reported the results of a prospective study of stomach cancer and its relation to diet in our study population of Japanese men (15). At that time, a brief food frequency questionnaire obtained at time of examination was analyzed. We found that cases had more frequent intakes of pickles and cured meats but less frequent intakes of fruits and fried vegetables than did noncases. None of these differences was statistically significant. The computerized 24-h diet recall questionnaire data were limited to the intakes of major nutrients, so we were unable to report findings concerning the consumption of other specific foods or food groups recorded in the questionnaire. Subsequently, we recoded in detail the 24-h intake data from this population to assess further the relation of diet to gastric cancer risk by means of this case-cohort study.

MATERIALS AND METHODS

The population base for this study consisted of 8006 American men of Japanese ancestry who were born from 1900 to 1919. The median year of birth was 1913. They were interviewed and examined from 1965 to 1968 on the Hawaiian island of Oahu. Since then, newly diagnosed cases of stomach cancer have been identified through continuous surveillance of the major Oahu hospitals. To reduce the possibility of missing incident cases, computer linkage was periodically done with data files from the Hawaii Tumor Registry, which is a population-based cancer registry and a member of the Surveillance, Epidemiology, and End Results Program of the National Cancer Institute. From 1966 to July 1983, 115 incident stomach cancer cases [International Classification of Diseases, Rev. 8, code 151] with histological tissue confirmation of their diagnoses were identified. Based on a separate 19-year follow-up survey of the study subjects since their examination, we found that only 1.3% of the men could not be located on Oahu. Consequently, the surveillance for incident cases of stomach cancer should be nearly complete.

To identify a suitable control group for this investigation, we chose a random sample of 391 cancer-free men to represent the large cohort, using the case-cohort study design approach (18).

Four cases and 30 noncases were excluded because their previous 24-h dietary intake was self-reported as atypical, leaving 111 stomach cancer cases and 361 noncases for further data analysis.

Based on the Lauren histopathological classification (19), there were 83 cases with the intestinal-mixed-other type, 23 with the diffuse type, and 5 with unknown type. Because of their small number, the diffuse cases were not analyzed separately.

A 24-h dietary recall questionnaire was administered at the time of examination of the cohort subjects. The interviewing and coding methods have been described in detail elsewhere (20). Briefly, to prepare the recall data for analysis at the time of examination, a set of precoded forms was used in transcribing the 24-h dietary information. The nutritionists tallied the consumption frequencies of predefined units of 54 common food items grouped on the form on the basis of similarity of macronutrients. For example, vegetables were grouped as starchy, cooked, or raw and coded according to number of half-cup portions, while beef items were grouped and coded as number of ounces eaten. For specific foods other than the 54 items that were consumed over the past 24 h, the nutritionists recorded the data and calculated by hand the nutrients consumed. The original nutrient data bank included only calories, carbohydrate, fat, protein and their components, cholesterol, and sodium.

For the present study, we recoded the 24-h recalls, recording actual items consumed such as tomatoes, carrots, oranges, etc. This was done so that specific foods and food groups, as well as the intakes of vitamins and minerals, could be analyzed, using our updated comprehensive food consumption data base. In this data base, information for more than 1000 items, 50 nutrients, and other dietary components is available in 100-g units. Sources include United States Department of Agriculture Handbook 8 (21), United States Department of Agriculture Handbook supplements (22), food composition tables from Japan (23, 24), and other publications.

The age-adjusted mean intakes of selected nutrients and various generic food groups were calculated for cases and noncases. A test based on one-way, unbalanced analysis of covariance methods was used to determine whether there was a statistically significant difference (P ≤ 0.05) between cases and noncases in mean intakes of individual nutrients and food groups (25).

For the food groups which showed statistically significant or border-
RESULTS

The mean age at time of examination was 57.7 years for the 111 gastric cancer cases and 57.6 years for the 361 noncases. Seventy-eight percent of the cases and 81% of the noncases were born in Hawaii or elsewhere in the United States. Of the 111 cancer cases, 33 (29.7%) were diagnosed from 1966 to 1973, another 37 (33.3%) were identified from 1974 to 1978, and the remaining 41 (37%) were diagnosed during the last 5 years of follow-up from 1979 to 1983.

The age-adjusted mean intakes of selected nutrients for cases and noncases are listed in Table 1. The cases consumed smaller amounts of β- and other carotenes, vitamin C, and vitamin D than did noncases, but none of the differences were statistically significant at P = 0.05. The intakes of vitamin A and retinol did not differ markedly between the two groups of subjects. They were also similar in their consumption of carbohydrate, fat, protein, and sodium.

Table 2 summarizes the comparison between cases and noncases in their mean intakes of selected food groups, as well as their intakes of nitrate, nitrite, and dimethylnitrosamine. The cases consumed fewer vegetables and fruits than the noncases. Statistically significant differences were observed in the intakes of all vegetables (P < 0.01) and green vegetables (P = 0.02). There were also borderline differences in the consumption of cruciferous vegetables and all fruits. The cases and noncases did not differ greatly in their consumption of dried fish, processed meats, pickles, grains, and nitrate-related compounds.

The relative risks by increasing amounts of consumption of different vegetables are shown in Table 3. There was a statistically significant inverse trend in the age-adjusted relative risk of stomach cancer with the intake of green, cruciferous, and all vegetables. However, after adjustment for current smoking status, only the association with all vegetables remained significant (P = 0.001).

The relative risk of gastric cancer by increasing intake of all fruits is presented in Table 4. There was an inverse linear trend in risk that was statistically significant (P = 0.05), but it did not persist after adjustment for cigarette smoking.

The analyses in Tables 3 and 4 were repeated for the 83 intestinal-mixed-other histopathological cases of stomach cancer. The results were similar. The relative risks were 0.8 for the high consumers of all vegetables (for linear trend, P = 0.01) and 0.6 for the high consumers of all fruits (for linear trend, P = 0.06) with adjustment for age at the time of examination and current smoking status.

To determine whether the high consumption of both vegetables and fruits had an additive protective effect, the subjects were classified into four categories in which those with less than the median intake of both foods were chosen as the baseline

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* To compare the two mean values, adjustment for age at the time of examination was by analysis of covariance.

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Table 1 Age-adjusted mean daily intake of selected nutrients for stomach cancer cases and noncases

<table>
<thead>
<tr>
<th>Nutrient (units/day)</th>
<th>Cases (n = 111)</th>
<th>Noncases (n = 361)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calories</td>
<td>2126.4</td>
<td>60.1</td>
<td>0.52</td>
</tr>
<tr>
<td>Carbohydrate (g)</td>
<td>3384</td>
<td>7.8</td>
<td>0.43</td>
</tr>
<tr>
<td>Fat (g)</td>
<td>76.1</td>
<td>3.2</td>
<td>1.15</td>
</tr>
<tr>
<td>Protein (g)</td>
<td>89.1</td>
<td>3.1</td>
<td>0.17</td>
</tr>
<tr>
<td>Sodium (g)</td>
<td>3.0</td>
<td>0.3</td>
<td>0.06</td>
</tr>
<tr>
<td>Vitamin A (IU)</td>
<td>6155.2</td>
<td>1465.6</td>
<td>0.19</td>
</tr>
<tr>
<td>Retinol (µg)</td>
<td>672.0</td>
<td>156.3</td>
<td>0.28</td>
</tr>
<tr>
<td>β-Carotene (µg)</td>
<td>1944.4</td>
<td>695.4</td>
<td>0.13</td>
</tr>
<tr>
<td>Other carotene (µg)</td>
<td>802.7</td>
<td>249.8</td>
<td>0.11</td>
</tr>
<tr>
<td>Vitamin C (mg)</td>
<td>101.3</td>
<td>9.3</td>
<td>0.02</td>
</tr>
<tr>
<td>Vitamin D (IU)</td>
<td>27.6</td>
<td>6.1</td>
<td>0.04</td>
</tr>
<tr>
<td>Vitamin E (IU)</td>
<td>6.2</td>
<td>0.4</td>
<td>0.07</td>
</tr>
<tr>
<td>Calcium (mg)</td>
<td>607.0</td>
<td>33.3</td>
<td>0.42</td>
</tr>
</tbody>
</table>

Table 2 Age-adjusted mean daily intake of selected food groups and nitrate-related compounds for stomach cancer cases and noncases

<table>
<thead>
<tr>
<th>Food group (units/day)</th>
<th>Cases (n = 111)</th>
<th>Noncases (n = 361)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>All vegetables (g)</td>
<td>45.3</td>
<td>8.2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Green vegetables (g)</td>
<td>73.0</td>
<td>5.8</td>
<td>0.02</td>
</tr>
<tr>
<td>Cruciferous vegetables (g)</td>
<td>10.4</td>
<td>4.3</td>
<td>0.06</td>
</tr>
<tr>
<td>Yellow vegetables (g)</td>
<td>4.2</td>
<td>5.7</td>
<td>0.09</td>
</tr>
<tr>
<td>All fruits (g)</td>
<td>174.2</td>
<td>21.2</td>
<td>0.07</td>
</tr>
<tr>
<td>Yellow fruits (g)</td>
<td>86.7</td>
<td>12.6</td>
<td>0.32</td>
</tr>
<tr>
<td>Citrus fruits (g)</td>
<td>52.9</td>
<td>12.0</td>
<td>0.70</td>
</tr>
<tr>
<td>Dried fish (g)</td>
<td>4.0</td>
<td>1.3</td>
<td>0.44</td>
</tr>
<tr>
<td>Processed meats (g)</td>
<td>32.7</td>
<td>4.0</td>
<td>0.28</td>
</tr>
<tr>
<td>Peaches (g)</td>
<td>15.7</td>
<td>2.4</td>
<td>0.97</td>
</tr>
<tr>
<td>Breakfast cereals (g)</td>
<td>9.8</td>
<td>4.5</td>
<td>0.77</td>
</tr>
</tbody>
</table>

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* To compare the two mean values, adjustment for age at the time of examination was by analysis of covariance.

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Table 3 Adjusted relative risk of stomach cancer by level of intake of all vegetables, green vegetables, and cruciferous vegetables

Cutoff points for daily intakes were as follows. All vegetables: 0; none; <40, low; <80, medium; 80+, high. Green vegetables: 0; none; <30, low; <60, medium; 80+, high. Cruciferous vegetables: 0; none; >0, consumer.

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Table 4 Adjusted relative risk of stomach cancer by level of intake of all vegetables

* Current smoking status: yes/no.

* Referent group.
The consumption of all types of vegetables was found to be protective against stomach cancer in this investigation. The highest consumers (>80 g/day) of vegetables had an age-adjusted relative risk of 0.6 (CI 0.4–1.0) compared with nonconsumers, but the trend was only of borderline statistical significance. The association diminished too with adjustment for current smoking status. The correlation (Spearman’s) coefficient between fruit intake and pack-years of cigarette smoking was −0.17, indicating fruit intake and cigarette smoking are weakly related. Earlier studies done in five countries all showed a protective effect of fruit intake against stomach cancer (2, 6, 8, 10, 11). Moreover, two of these studies (8, 11) found a clear dose-response relationship. Yet, other investigators (3, 9, 13) did not support this finding.

The subjects in our study consumed 54 different fruits. Papayas, oranges, apples, guavas, and mangoes accounted for 66% of the total amount of fruits consumed. These fruits (except apples) are rich in vitamin A or vitamin C. Vitamin A has been found to be protective against tumor promotion in laboratory animals (32), and vitamin C inhibits the formation of N-nitroso compounds (33), which have been suspected to play a role in gastric carcinogenesis (34). Noncases consumed more vitamin A, β- and other carotenes, and vitamin C than cases in our study. However, none of these nutrients was found to be significantly protective against stomach cancer (P > 0.10).

Although this study has the advantage of obtaining the dietary data prospectively before the cases of stomach cancer were identified, one limitation is that the dietary intake was based only on a 24-h diet recall. A 7-day diet record completed by 329 men in the cohort was done to assess the within-person variability of the 24-h data. Similar levels of nutrient intakes were recorded by both methods (35). Thirty-four subjects, whose dietary intake on the previous day was atypical, were excluded from the study to improve the representativeness of the 24-h dietary recall. Nonetheless, the possibility exists that intraindividual variation in daily diet could decrease the statistical power to detect specific differences of the nutrient intakes between the two groups of subjects. Consequently, associations found in this study may actually be stronger than reported.

The consumption of dried fish, processed meats, pickles, and foods rich in nitrate-related compounds was relatively low in these subjects. This low consumption in persons, aged 45–68 years at time of interview, may have partially contributed to the lack of any association of these foods with stomach cancer risk. Some past studies have found that persons who consume foods high in precursors of N-nitroso compounds are at increased risk for gastric cancer (1, 3, 34, 36–38), although other investigators have not supported this association (5, 8–10, 14, 17).

In conclusion, the results of our investigation support the potential importance of vegetable and probably fruit intake in reducing the risk of stomach cancer. Further research is required to identify the specific vegetables and their components which may be protective agents. Furthermore, we would rec-
ommend that future epidemiological studies in populations at high risk of developing gastric cancer be conducted. Quantitative diet histories covering a longer time should be included in the study design to estimate the usual intakes of foods associated with gastric cancer risk.

REFERENCES


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