Consumption of Plant Foods and Stomach Cancer Mortality in the Seven Countries Study. Is Grain Consumption a Risk Factor?

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Abstract: Plant foods are generally considered to be beneficial for health. A higher consumption of fruits, and to a lesser extent vegetables, is consistently associated with a lower risk of stomach cancer. Results on the association between stomach cancer and grain consumption are less clear. We associated plant food consumption with 25-year stomach cancer mortality at population level in the Seven Countries Study. Around 1960, >12,000 men aged 40–59 years from 7 countries and 16 cohorts were enrolled. In each cohort, dietary information was collected in small random samples. Crude and adjusted associations were calculated for a change of 10% of mean intake. Results differed for the plant foods studied: an inverse association was observed for fruits (adjusted rate ratio = 0.96, 95% confidence interval = 0.91–0.99), a positive relation for refined grains (adjusted rate ratio = 1.07, 95% confidence interval = 1.03–1.12), and no association for total plant foods, vegetables, whole grains, and potatoes. A high intake of refined grains was correlated with a low consumption of fruits. In conclusion, high intake of refined grains may increase stomach cancer risk. However, because adjustment could only be limited in this study, high intake of refined grains may just reflect the deleterious effect of a diet low in fruits or other characteristics associated with low fruit consumption.

Introduction

Although rates of stomach cancer are declining, this cancer remains a major health problem throughout the world, inasmuch as it is second in rank of incidence and mortality among cancers. Stomach cancer has a distinct geographic variation, with high rates in Japan and low rates in the United States (1), and is more incident among lower socioeconomic groups (2). Diet and other environmental factors are assumed to be most important in the etiology of stomach cancer. High fruit and vegetable consumption is consistently associated with low risk. Consumption of grains and high-carbohydrate/starch diets are postulated to increase risk; however, results are not consistent (3). Furthermore, intake of whole grains and dietary fiber is mostly inversely associated with risk (4,5). Salt/salted foods and N-nitroso compounds are thought to increase risk, although findings vary (3). Finally, smoking and Helicobacter pylori infection are risk factors for stomach cancer, whereas alcohol intake seems not related to risk in most studies (3).

In a cross-cultural analysis in the Seven Countries Study, an inverse association was observed between vitamin C and stomach cancer mortality (6). Using the same data and study design, we investigated the association at food group level for the consumption of plant foods, i.e., fruits, vegetables, potatoes, and grains, with 25-year stomach cancer mortality.

The Seven Countries Study covers a wide range of food intake, and this ecological study is unique, in that food consumption data were gathered in random subsamples at the individual level and cohort members were followed for 25 years.

Subjects and Methods

Study Design and Participants

The study design and participants of the Seven Countries Study have been described in detail elsewhere (7,8). Briefly, 12,763 men aged 40–59 years in 16 cohorts from 7 countries were enrolled between 1958 and 1964. The number of men per cohort and the countries are mentioned in Table 1. Most
Table 1. Baseline Cohort Size, Mean Age, Prevalence of Smoking, Energy Intake, Number of Men From Whom Dietary Information Was Gathered, and 25-Year Total and Stomach Cancer Mortality of the Seven Countries Study, 1958–89

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Country</th>
<th>Cohort Size</th>
<th>Mean Age, yrs</th>
<th>Smokers, %</th>
<th>Energy Intake, MJ/day</th>
<th>No. Dietary Information</th>
<th>Total Mortality, %</th>
<th>n</th>
<th>Stomach Cancer Mortality Rate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>US Railroad USA</td>
<td>2,571</td>
<td>49.8</td>
<td>59.0</td>
<td></td>
<td>9.6</td>
<td>30</td>
<td>45.1</td>
<td>13</td>
<td>0.5</td>
</tr>
<tr>
<td>East Finland</td>
<td>Finland</td>
<td>817</td>
<td>49.0</td>
<td>68.5</td>
<td>14.7</td>
<td>30</td>
<td>59.7</td>
<td>23</td>
<td>2.9</td>
</tr>
<tr>
<td>West Finland</td>
<td>Finland</td>
<td>860</td>
<td>50.1</td>
<td>57.2</td>
<td>14.4</td>
<td>30</td>
<td>50.3</td>
<td>21</td>
<td>2.3</td>
</tr>
<tr>
<td>Zutphen</td>
<td>Netherlands</td>
<td>878</td>
<td>50.1</td>
<td>74.5</td>
<td>11.3</td>
<td>45</td>
<td>48.0</td>
<td>15</td>
<td>1.7</td>
</tr>
<tr>
<td>Crevalcore Italy</td>
<td>993</td>
<td>50.0</td>
<td>62.6</td>
<td></td>
<td>15.2</td>
<td>29</td>
<td>49.8</td>
<td>32</td>
<td>3.2</td>
</tr>
<tr>
<td>Montegiorgio</td>
<td>Italy</td>
<td>719</td>
<td>49.6</td>
<td>58.7</td>
<td>12.1</td>
<td>35</td>
<td>46.2</td>
<td>29</td>
<td>4.0</td>
</tr>
<tr>
<td>Rome Railroad</td>
<td>Italy</td>
<td>768</td>
<td>48.7</td>
<td>65.2</td>
<td>11.0</td>
<td>49</td>
<td>39.7</td>
<td>10</td>
<td>1.6</td>
</tr>
<tr>
<td>Dalmatia</td>
<td>Croatia</td>
<td>671</td>
<td>50.6</td>
<td>58.7</td>
<td>15.8</td>
<td>24</td>
<td>43.3</td>
<td>7</td>
<td>1.0</td>
</tr>
<tr>
<td>Slavonia</td>
<td>Croatia</td>
<td>696</td>
<td>50.5</td>
<td>60.3</td>
<td>15.5</td>
<td>24</td>
<td>61.0</td>
<td>27</td>
<td>3.8</td>
</tr>
<tr>
<td>Velika Krsna</td>
<td>Serbia</td>
<td>511</td>
<td>49.9</td>
<td>49.2</td>
<td>14.3</td>
<td>21</td>
<td>50.0</td>
<td>14</td>
<td>2.6</td>
</tr>
<tr>
<td>Zrenjanin</td>
<td>Serbia</td>
<td>516</td>
<td>49.2</td>
<td>63.2</td>
<td>13.4</td>
<td>40</td>
<td>57.9</td>
<td>10</td>
<td>1.8</td>
</tr>
<tr>
<td>Belgrade</td>
<td>Serbia</td>
<td>536</td>
<td>47.8</td>
<td>43.7</td>
<td>11.4</td>
<td>41</td>
<td>29.5</td>
<td>2</td>
<td>0.2</td>
</tr>
<tr>
<td>Crete</td>
<td>Greece</td>
<td>686</td>
<td>49.2</td>
<td>57.3</td>
<td>11.8</td>
<td>31</td>
<td>31.4</td>
<td>3</td>
<td>0.5</td>
</tr>
<tr>
<td>Corfu</td>
<td>Greece</td>
<td>529</td>
<td>49.8</td>
<td>63.5</td>
<td>11.3</td>
<td>37</td>
<td>40.4</td>
<td>7</td>
<td>1.3</td>
</tr>
<tr>
<td>Tanushimaru</td>
<td>Japan</td>
<td>508</td>
<td>50.7</td>
<td>70.7</td>
<td>10.0</td>
<td>24</td>
<td>39.4</td>
<td>28</td>
<td>5.1</td>
</tr>
<tr>
<td>Ushibuka</td>
<td>Japan</td>
<td>502</td>
<td>50.0</td>
<td>77.8</td>
<td>10.2</td>
<td>8</td>
<td>51.5</td>
<td>26</td>
<td>5.1</td>
</tr>
</tbody>
</table>

* Age-adjusted.

cohorts were situated in rural areas, except for two railroad cohorts, the large agroindustrial cooperative Zrenjanin, faculty members of Belgrade University, Zutphen with inhabitants of a commercial market town, and the fishing village Ushibuka in Japan. The overall participation rate was >90%.

Participants were followed for 25 years, and during that period, 5,974 men died. Data on vital status and causes of death were collected by means of death certificates, medical records, and interviews of physicians and relatives of the deceased. Overall, only 56 men (0.4%) were lost to follow-up. Underlying cause of death was coded by two central reviewers (9) according to the Eighth Revision of the International Classification of Diseases (ICD). The end point in the present study is mortality from stomach cancer (ICD 151).

Dietary Information

During the baseline survey, the record method was used to collect dietary information in small random samples (8–49 men) of each of the cohorts (Table 1). Diet was recorded for seven days, except in the Ushibuka (4 days) and US Railroad (1 day) cohorts. Collection took place between 1959 and 1964, with the exception of the Rome Railroad and Ushibuka cohorts (around 1970). The dietary data were recoded in a standardized way by one dietitian in 1986, and the average daily food intake per cohort was calculated (10). However, by then, the Greek records were no longer available and had to be reconstructed by results of Greek dietary surveys (11) and food balance sheets from Greece in 1961–65. Furthermore, food equivalent composites representing the baseline average food intake in each of the 16 cohorts were collected locally and chemically analyzed in a central laboratory according to a strict protocol in 1987 (12). Chemical analyses for oligosaccharides, starch, and dietary fiber were performed at the laboratory of the Department of Human Nutrition, Wageningen Agricultural University (Wageningen, The Netherlands). Vitamins were measured at the State Institute for Quality Control of Agricultural Products (Wageningen, The Netherlands). All methods of analysis were according to standard methodology of that time and have been described in detail elsewhere (13).

We investigated the role of total plant foods (vegetable oils and alcoholic beverages not included) and several plant food groups. Citrus and noncitrus fruits were examined separately. Grains were divided into whole grains and refined grains and as eaten in bread vs. other sources. Intakes of legumes and fruit preserves and fruit juices were included in consumption of plant foods and fruits, respectively, but not investigated as separate groups.

Statistical Analysis

Poisson regression was used to examine associations between dietary intake and stomach cancer mortality (PROC GENMOD, SAS statistics version 6.12) (14). Number of stomach cancer cases per cohort was the dependent variable. To adjust for differences in cohort size and survival time, the log of the total survival time per cohort was used as the offset variable. Cohort mean daily intakes were the independent variables. Analyses were carried out for a change in intake of 10% of the mean consumption, both crude and adjusted for potential confounders. Because the number of cohorts was small (n = 16), adjustments were made for only two variables at a time. On the basis of the literature and univariate analyses (data not shown), it was decided to adjust for smoking (prevalence) and energy intake (cohort mean daily intake). Alcohol consumption was not related to 25-year stomach cancer mortality (data not shown). Moreover,
there was no adjustment for age, because the range in this study is very narrow (Table 1). Baseline data on smoking were collected by a standardized questionnaire (8). Information on intakes of energy and alcohol was derived from the dietary record method described above.

Two-sided P values < 0.05 were considered statistically significant. Spearman correlation coefficients are presented.

Results

Baseline cohort size, mean age, smoking prevalence, energy intake, number of men from whom dietary information was collected, and 25-year total and stomach cancer mortality of the 16 cohorts of the Seven Countries Study are shown in Table 1. Stomach cancer mortality was highest in both Japanese cohorts (5.1%) and lowest in the Belgrade cohort (0.2%). Baseline mean daily consumption of plant foods and several components as measured in the food composites are given in Table 2. The Seven Countries Study covers a wide range on intake of plant foods, especially for fruits and grains, and to a lesser extent for vegetables (Table 2).

Table 3 shows results, crude and adjusted for energy intake and smoking, of the Poisson regression analyses for consumption of plant foods, vitamin C, carbohydrates, starch, oligosaccharides, and dietary fiber. Total plant food consumption was not related to stomach cancer risk, whereas

Table 2. Baseline Daily Mean Consumption of Several Plant Food Groups and Baseline Representative Daily Intake of Several Components Analyzed in the Food Composites of the Seven Countries Studya

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Plant Foods</th>
<th>Fruits</th>
<th>Vegetables</th>
<th>Grains</th>
<th>Whole Grains</th>
<th>Refined Grains</th>
<th>Potatoes</th>
<th>Carbohydrates</th>
<th>Starch</th>
</tr>
</thead>
<tbody>
<tr>
<td>US Railroad</td>
<td>652</td>
<td>233</td>
<td>170</td>
<td>124</td>
<td>24</td>
<td>100</td>
<td>124</td>
<td>182</td>
<td>63</td>
</tr>
<tr>
<td>East Finland</td>
<td>874</td>
<td>40</td>
<td>108</td>
<td>451</td>
<td>288</td>
<td>163</td>
<td>273</td>
<td>411</td>
<td>94</td>
</tr>
<tr>
<td>West Finland</td>
<td>897</td>
<td>34</td>
<td>104</td>
<td>455</td>
<td>268</td>
<td>187</td>
<td>296</td>
<td>453</td>
<td>245</td>
</tr>
<tr>
<td>Zutphen</td>
<td>833</td>
<td>82</td>
<td>227</td>
<td>270</td>
<td>64</td>
<td>206</td>
<td>252</td>
<td>293</td>
<td>126</td>
</tr>
<tr>
<td>Crevalcore</td>
<td>864</td>
<td>191</td>
<td>140</td>
<td>48</td>
<td>0</td>
<td>498</td>
<td>30</td>
<td>384</td>
<td>207</td>
</tr>
<tr>
<td>Montegiorgio</td>
<td>827</td>
<td>28</td>
<td>194</td>
<td>528</td>
<td>0</td>
<td>528</td>
<td>56</td>
<td>355</td>
<td>235</td>
</tr>
<tr>
<td>Rome Railroad</td>
<td>807</td>
<td>150</td>
<td>260</td>
<td>362</td>
<td>8</td>
<td>354</td>
<td>29</td>
<td>258</td>
<td>147</td>
</tr>
<tr>
<td>Dalmatia</td>
<td>925</td>
<td>6</td>
<td>200</td>
<td>499</td>
<td>202</td>
<td>298</td>
<td>214</td>
<td>361</td>
<td>227</td>
</tr>
<tr>
<td>Slavonia</td>
<td>928</td>
<td>1</td>
<td>198</td>
<td>560</td>
<td>76</td>
<td>485</td>
<td>129</td>
<td>401</td>
<td>236</td>
</tr>
<tr>
<td>Velika Krsna</td>
<td>990</td>
<td>1</td>
<td>115</td>
<td>823</td>
<td>686</td>
<td>137</td>
<td>28</td>
<td>462</td>
<td>369</td>
</tr>
<tr>
<td>Zrenjanin</td>
<td>1,090</td>
<td>185</td>
<td>245</td>
<td>509</td>
<td>399</td>
<td>110</td>
<td>136</td>
<td>358</td>
<td>207</td>
</tr>
<tr>
<td>Belgrade</td>
<td>715</td>
<td>145</td>
<td>179</td>
<td>293</td>
<td>131</td>
<td>162</td>
<td>86</td>
<td>272</td>
<td>123</td>
</tr>
<tr>
<td>Crete</td>
<td>1,285</td>
<td>464</td>
<td>191</td>
<td>410</td>
<td>380</td>
<td>30</td>
<td>190</td>
<td>323</td>
<td>223</td>
</tr>
<tr>
<td>Corfu</td>
<td>1,328</td>
<td>462</td>
<td>191</td>
<td>495</td>
<td>450</td>
<td>45</td>
<td>150</td>
<td>331</td>
<td>221</td>
</tr>
<tr>
<td>Tanushimarui</td>
<td>973</td>
<td>26</td>
<td>174</td>
<td>575</td>
<td>0</td>
<td>575</td>
<td>95</td>
<td>442</td>
<td>334</td>
</tr>
<tr>
<td>Ushibuka</td>
<td>888</td>
<td>42</td>
<td>222</td>
<td>511</td>
<td>0</td>
<td>511</td>
<td>34</td>
<td>404</td>
<td>315</td>
</tr>
</tbody>
</table>

a: Values are expressed in grams.

Table 3. Relations for 25-Year Mortality From Stomach Cancer in Men in the Seven Countries Study With Baseline Mean Daily Consumption of Food Groups and Baseline Representative Daily Intake of Components Analyzed in Food Compositesa

<table>
<thead>
<tr>
<th>10% of Mean Intake</th>
<th>Crude</th>
<th>Adjusted for Energy and Smoking</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate ratio</td>
<td>95% CI</td>
<td>Rate ratio</td>
</tr>
<tr>
<td>Plant foods</td>
<td>93.0 g</td>
<td>1.06</td>
</tr>
<tr>
<td>Fruits and vegetables</td>
<td>31.3 g</td>
<td>0.89</td>
</tr>
<tr>
<td>Fruits</td>
<td>13.1 g</td>
<td>0.94</td>
</tr>
<tr>
<td>Citrus</td>
<td>1.8 g</td>
<td>0.95</td>
</tr>
<tr>
<td>Noncitrus</td>
<td>10.1 g</td>
<td>0.97</td>
</tr>
<tr>
<td>Vegetables</td>
<td>18.2 g</td>
<td>0.96</td>
</tr>
<tr>
<td>Grains</td>
<td>46.0 g</td>
<td>1.15</td>
</tr>
<tr>
<td>Whole</td>
<td>18.6 g</td>
<td>0.99</td>
</tr>
<tr>
<td>Refined</td>
<td>27.4 g</td>
<td>1.09</td>
</tr>
<tr>
<td>Bread</td>
<td>14.8 g</td>
<td>1.03</td>
</tr>
<tr>
<td>Other sources</td>
<td>12.6 g</td>
<td>1.03</td>
</tr>
<tr>
<td>Potatoes</td>
<td>13.3 g</td>
<td>0.98</td>
</tr>
<tr>
<td>Vitamin C</td>
<td>7.4 mg</td>
<td>0.89</td>
</tr>
<tr>
<td>Carbohydrates</td>
<td>35.6 g</td>
<td>1.30</td>
</tr>
<tr>
<td>Starch</td>
<td>21.7 g</td>
<td>1.15</td>
</tr>
<tr>
<td>Oligosaccharides</td>
<td>11.1 g</td>
<td>1.00</td>
</tr>
<tr>
<td>Dietary fiber</td>
<td>3.3 g</td>
<td>1.01</td>
</tr>
</tbody>
</table>

a: Poisson regressions are shown for a 10% change in mean intake. CI, confidence interval.
the intake of fruits was inversely associated to risk. After removal of the two cohorts with the highest fruit intake, i.e., Crete and Corfu, the inverse association found for fruits was still statistically significant (data not shown). Our results indicated that citrus fruits were most responsible for the inverse relation with fruits. However, one-half of the cohorts consumed no or a very low amount of citrus fruits per day. Six cohorts ate <2 g, whereas three cohorts consumed no citrus fruits. Adjustment for energy intake and prevalence of smoking did not materially change the results. Intake of vegetables was not related to risk, whereas the adjusted association found for potatoes was of borderline significance. Grain consumption was positively related to stomach cancer risk. Separating this consumption into whole grains and refined grains revealed only a positive association for the latter group and, in particular, for grains from sources other than bread, e.g., rice and pasta.

At the nutrient level, carbohydrates and starch were positively associated with stomach cancer mortality, whereas oligosaccharides and dietary fiber were not related to risk. As reported elsewhere (8), vitamin C intake was inversely associated to risk (Table 3).

The inverse association of fruit consumption with age-adjusted 25-year stomach cancer mortality is shown in Figure 1A. Some cohorts ate almost no fruits (Slavonia and Velika Kršna), and others had a very high consumption (Crete and Corfu). Figure 1B depicts the positive relation between intake of refined grains and stomach cancer mortality. Compared with fruit intake, refined grain consumption has a wider range and is better distributed along the range. Cohorts with a high fruit consumption ate little refined grains; the same is true in the opposite direction. Investigating whether associations for fruits and refined grains were independent was not considered feasible, because both intakes were highly correlated ($r = -0.56, p < 0.01$).

Discussion

Cross-cultural analyses in the Seven Countries Study relating 25-year stomach cancer mortality with plant food con-

Figure 1. Association between baseline fruit (A) and refined grain (B) consumption and age-adjusted 25-yr stomach cancer mortality in Seven Countries Study, 1958–89. US, US Railroad; EF, East Finland; WF, West Finland; ZU, Zutphen; CR, Crevalcore; MO, Montegiorgio; RO, Rome Railroad; DA, Dalmatia; SL, Slavonia; VK, Velika Kršna; ZR, Zrenjanin; BE, Belgrade; CT, Crete; CF, Corfu; TA, Tanushimaru; UB, Ushibuka.

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assumption revealed an inverse association with fruits, a positive relation with refined grains, and no association with total plant foods, vegetables, whole grains, and potatoes.

Ecological analysis for testing etiological hypotheses has its limitations, mainly by the potential for substantial bias in effect estimation. The central problem is known as "ecological fallacy" (15). Associations at the population level are not necessarily the same as those at the individual level. This depends mainly on the distribution of other risk factors within populations. The advantages of this design are a large variation in exposure and outcome and relatively small measurement errors in the exposure. Furthermore, in our study, dietary intake was assessed in small random samples, and cohort members were followed for 25 years. Yet, our study did have some disadvantages: 16 cohorts is a small number; dietary records were kept only by a subgroup of the cohort; food consumption around 1960 may not be an appropriate indicator for average food consumption during 25 years of follow-up. Regarding the last disadvantage, although differences in food consumption patterns have diminished, characteristic differences between the cohorts were still present after 20 years (10).

In our study, smoking and energy intake seemed to be the most important variables for which to adjust. We had very limited information on intake of salt and salted foods. Therefore, we decided not to adjust risk estimates on plant foods for these intakes. Furthermore, univariate analyses between salt intake and stomach cancer mortality did not show an association. *Helicobacter pylori* infection is positively associated with stomach cancer in most studies, and infection rates vary throughout the world. Information on this factor, however, was lacking, and we could not evaluate its potential confounding effect.

We calculated risk estimates for a difference of 10% of the mean intake, because such a change is assumed to be a feasible and realistic goal in public health. For evaluating the magnitude of the associations, it should be noticed that this contrast is small compared with differences generally used in etiological studies.

Although generally considered a consistent finding, most cross-cultural correlation studies did not observe an inverse association between stomach cancer and fruit intake (16–20). Using per capita disappearance data, not using an appropriate lag time, and the fact that exposure and outcome did not apply to the same population may have influenced these results. We did find an inverse relationship for fruits, perhaps because of the features of our ecological study. Correlation studies within countries and case-control and cohort studies did consistently find inverse associations for fruits with stomach cancer (3). Fruits are the richest source of vitamin C in the diet. However, other foods, e.g., potatoes, can contribute substantially to intake. Vitamin C may protect against stomach cancer by inhibiting the formation of carcinogenic *N*-nitroso compounds (3). Furthermore, fruits contain bioactive compounds other than vitamin C that may be responsible, separately or in combination, for the protective effect observed.

Vegetable intake was not associated with stomach cancer mortality in our study. Also other correlation studies did not report an association (16–20). We found a smaller variance in intake for vegetables than for fruits. This may explain why fruits were inversely associated, whereas vegetables were not. Moreover, case-control studies on stomach cancer showed a more pronounced inverse association for fruits than for vegetables (21).

Epidemiological studies investigated the relationship of grains, high-carbohydrate/starch diets, whole grains, rice, pasta, bread, and components such as carbohydrates, starch, and dietary fiber to stomach cancer. Associations observed for these dietary items are not consistent. In line with our study, cross-cultural correlation studies found a positive association between grain consumption and stomach cancer mortality (17–19,22,23). A Japanese correlation study also observed a positive relationship (24), whereas in Spain no correlation was found (25). Ecological findings on bread (17,25,26), rice (20,25–29), and pasta (25,26) were inconsistent. A review of case-control studies on consumption of grains (30) suggested an increased stomach cancer risk: in seven of eight studies, of which five were statistically significant (31–35), risk was found to increase. Some recent case-control studies on grain consumption (36,37) did not show an association with stomach cancer. For rice and pasta, variable results from case-control studies were reported (30). Case-control studies on bread revealed no association, and whole-grain bread may decrease stomach cancer risk (4,5). Only a few cohort studies on grain consumption have been published, and moderate, mostly nonsignificant, increased risks or no associations were reported (30).

Several mechanisms have been proposed for how grains or a high-carbohydrate/starch diet can increase stomach cancer risk. First, there may be physical irritation of the gastric mucosa. Second, such diets are generally low in proteins, leading to a reduced gastric mucus production facilitating carcinogen absorption (38). However, protein intake has never been related to a decreased risk in case-control or cohort studies (30) and was not associated in the present study (data not shown). Another possibility hypothesized is that diets high in starch are also high in salt and that salt is the risk factor in such a diet (39). Furthermore, it is suggested that a high-starch diet is generally a monotonous diet, low in fruits, vegetables, and whole grains; such a diet is low in bioactive components thought to be anticarcinogenic (30).

We observed a positive association for grains that could be attributed to refined grains. No association for refined bread intake was observed, whereas consumption of refined grains from sources other than bread was associated with an increased stomach cancer risk. At the nutrient level, we found the strongest positive association for intake of carbohydrates. When divided into starch, oligosaccharides, and dietary fiber, only an association for starch was present.

It seems that the suggestion of increased risk with grain consumption is mainly based on case-control studies on broad groups of grains. However, not all these studies adjusted for all relevant potential confounders. For instance, studies did
not control for intake of fruits and/or vegetables (31,34), for
total energy intake (31,32), or for smoking and socioeco-
nomic status (34). Socioeconomic status is correlated with
several dietary and other lifestyle factors that are associated
with stomach cancer itself (40), e.g., monotonous diets (2) and
use of refrigerators (30). In one study (35), a statistically
significant positive trend was observed for grain consump-
tion; however, this trend was no longer significant after
further adjustment for education, smoking, energy, and vita-
min C.

Given that not all these studies adjusted the risk estimates
appropriately, the epidemiological evidence supporting the
idea that grain consumption is a risk factor for stomach
cancer is not as firm as sometimes stated. Furthermore,
because associations differ for grain items studied, results for
broad groups of grains may not be informative enough. This
may have implications for the choice and/or design of dietary
assessment methods.

Although we emphasized the need for appropriate adjust-
ment, our ability to adjust our own study was limited. Fruit
consumption was highly correlated with intake of refined
grains in our study. Because of the small number of cohorts
and the fact that adjustment for confounders can only be
done crudely in this ecological study design, we could not
examine whether both associations were independent. How-
ever, taking the evidence together, we hypothesize that the
consumption of refined grains did not elevate the risk, but
a high intake of these grains was an indicator for a diet low
in fruits. Such a diet provides a low amount of bioactive
compounds thought to protect against cancer. Furthermore,
other nonmeasured factors correlated with a refined grain
intake could be responsible for the observed association.

In case-control and cohort studies, multicollinearity is
expected to be a smaller problem, so that after adequate
adjustment, the independent effect of dietary factors can be
evaluated. These types of studies may further elucidate
whether grain consumption itself can be seen as a risk factor
for stomach cancer.

Briefly, on the basis of our study, we cannot rule out the
possibility that refined grain consumption is a risk factor
for stomach cancer. However, we hypothesize that the
consumption of refined grains did not elevate the risk, but
a high intake of these grains was an indicator for a diet poor
in fruits. Such a diet is low in bioactive compounds that
may exert an anticarcinogenic effect on the development of
stomach cancer.

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