Association of vegetable, fruit, and grain intakes with colorectal cancer: the Multiethnic Cohort Study*

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ABSTRACT

Background: It is uncertain whether or not vegetables, fruit, or grains protect against colorectal cancer.

Objective: In a large prospective study, we investigated the association of vegetable, fruit, and grain intakes with colorectal cancer risk.

Design: Between 1993 and 1996, 85,903 men and 105,108 women completed a quantitative food-frequency questionnaire that included ≈180 foods and beverages in the Multiethnic Cohort Study. A diagnosis of colorectal cancer was made in 1138 men and 972 women after an average follow-up of 7.3 y. Cox proportional hazards models were used to calculate multivariate-adjusted relative risks and 95% CIs for colorectal cancer.

Results: In men, multivariate adjustment for energy intake, dietary, and nondietary variables resulted in relative risks in the highest quintile group of 0.74 (95% CI: 0.59, 0.93; \( P \) for trend = 0.02) for vegetables and fruit combined, 0.80 (95% CI: 0.64, 0.99; \( P \) for trend = 0.09) for fruit alone, and 0.85 (95% CI: 0.69, 1.05; \( P \) for trend = 0.05) for vegetables alone. When colon and rectal cases were separated among men, the inverse associations were stronger for colon than for rectal cancer. In women, none of the associations with vegetables, fruit, or vegetables and fruit combined were significant. Grain intake was not associated with colorectal cancer for either men or women.


INTRODUCTION

There has been much interest over the years in the possible protective effect of vegetables, fruit, and grains against colorectal cancer. These plant foods contain potential anticarcinogenic agents, such as antioxidants, flavonoids, isothiocyanates, phenols, and protease inhibitors (1). Nevertheless, the findings from epidemiologic cohort studies have produced inconsistent results.

The National Institutes of Health (NIH) and the AARP Diet and Health Study reported an inverse association of vegetable intake with colorectal cancer among men, but not among women; there was no association with fruit intake in either sex (2). The Cancer Prevention Study II by the American Cancer Society found that men with a very low intake of vegetables and women with a very low intake of fruit were at an increased risk of colon cancer (3). However, the Netherlands Cohort Study on Diet and Cancer reported an inverse association between colon cancer and the combined intake of vegetables and fruit among women but not among men (4).

Other investigations have not supported these findings. The Health Professionals Follow-Up Study and the Nurses’ Health Study reported an inverse association with vegetable or fruit consumption (even in subgroups of vegetables or fruit) with colorectal cancer among men and women (5). There was no relation between vegetable or fruit intake and colorectal cancer risk in the Women’s Health Study (6). The Japan Public Health Center study also reported no reduction in colorectal cancer risk with vegetable or fruit consumption (7).

In an earlier investigation, our results supported an inverse association of dietary fiber with colorectal cancer mainly in men (8). There was a suggestion that the association was primarily with vegetable and fruit fiber intakes. Because plant foods are rich sources of dietary fiber, and because of the equivocal results of past studies, we decided to conduct this investigation into the association of vegetables, fruit, grains, and certain subgroups of vegetables and fruit with colorectal cancer in our Multiethnic Cohort Study.

SUBJECTS AND METHODS

Study design and population

The Multiethnic Cohort Study in Hawaii and Los Angeles was designed to investigate the association of dietary, lifestyle, and genetic factors with the incidence of cancer and other chronic diseases. Its study design, questionnaire development, subject recruitment, and data collection were described elsewhere (9). Briefly, >215,000 men and women aged 45–75 y and living in Hawaii or in California (mainly in Los Angeles County) completed a 26-page self-administered mailed questionnaire between 1993 and 1996. The primary sampling frame for the study was 215,000 men and women aged 45–75 y and living in Hawaii or in California (mainly in Los Angeles County) completed a 26-page self-administered mailed questionnaire between 1993 and 1996.
was the driver’s license files in both states, because they included
the names of most adult residents, contained information on age,
and encompassed all socioeconomic strata.

Study participants provided information on their diet, body
weight and height, demographic factors, lifestyle practices (in-
cluding smoking and physical activity), history of medical con-
ditions, use of medications (including aspirin), use of dietary
supplements, a family history of common cancers, and, for
women, reproductive history and use of hormone replacement
therapy. All questionnaire data were checked for consistency and
legibility before scanning and stored in a secured database.
The institutional review boards at the University of Hawaii and at
the University of Southern California approved the study protocol.

Study exclusion criteria

For this analysis, we limited the study participants to the 5
major ethnic groups recruited into the study (African Americans,
Japanese Americans, Latinos, Native Hawaiians, and whites).
Latinos were defined as persons of Mexican or South or Central
American ancestry, including immigrants from those countries.
We excluded relatively small numbers of Chinese, Filipinos, and
members of other ethnic groups (n = 13 994). In addition, we
excluded individuals with implausible diets (n = 8265) in each of
the 5 remaining ethnic groups. Implausible diets were defined as
those with energy intakes >3 Modified SDs from the mean,
where the MSD was calculated after individuals in the top and
bottom 10% tails of the log energy distribution by ethnicity were
excluded and a truncated normal distribution was assumed. Sim-
ilar exclusions were made for fat, carbohydrate, and protein
intakes with the use of a range of mean ± 3.5 MSD to further
identify individuals who failed to complete the quantitative food-
frequency questionnaire (FFQ), but whose energy levels were
reasonable. Subjects with a colorectal cancer diagnosis before
baseline that was either self-reported in the FFQ or identified by
registry linkages (n = 2561) were also excluded. Persons with
other bowel diseases were not excluded from the cohort. As a
result, 191 011 participants remained in the analysis.

Dietary assessment

Dietary intake was assessed at baseline by using a compre-
hensive questionnaire especially designed and validated for use
in this multiethnic population. The development of the self-
administered quantitative FFQ (QFFQ) was described elsewhere
(9, 10). Briefly, the collection of 3-d measured dietary records
from ≈60 men and women of each ethnic group served as the
basis for the selection of food items for the QFFQ. The minimum
set of food items contributing ≥85% of the intake of a specific list
of nutrients for each ethnic group was selected and supplemented
by the inclusion of food items that were common in the diet of a
particular ethnic group, irrespective of their nutrient contribu-
tions (9). The QFFQ inquired about the usual frequency, based on
8 or 9 categories, and on the amount of food consumed, based on
3 portion sizes per food item. The portion size and gram weight
of each portion size were derived from the 3-d measured dietary
records. The amount listed for each portion size of each food was
weighed and average weights were used to convert the portion
sizes to grams. Photos showing examples of portion sizes were
used to assist the responder and examples of portion sizes were
described. As an example, the 3 choices of portion sizes for
hamburgers (on a bun) were 1 regular size burger, 1 quarter-
pound burger, or 1 large double burger. There were ≈180 foods
and beverages included in the questionnaire.

For processing dietary intake data, we used a food-
composition database that has been developed and maintained at
the Cancer Research Center of Hawaii. The Cancer Research
Center of Hawaii food-composition table includes a large recipe
database and many unique foods consumed by the 5 multiethnic
populations included in this analysis (9). For questionnaire items
covering more than one food, nutrient profiles of the items were
calculated by using a weighted average of the specific foods
based on the frequency of use in the 24-h recalls obtained as part
of a calibration study (10). Food intake measured by the QFFQ
was linked to the Cancer Research Center of Hawaii food-
composition table to convert daily grams to daily nutrients con-
sumed from that food. Before food group intake was calculated,
the food mixtures from the QFFQ were disaggregated to the
ingredient level by using a customized recipe database. For ex-
ample, the tomatoes on pizza were counted toward the vegetable
group. Food group intake was calculated as grams per day of the
basic food commodities. Food groups and foods included in this
analysis were the following: total fruit and total vegetables com-
bed; total fruit separately, citrus and yellow-orange fruit; total
vegetables separately, light green, dark green, yellow-orange,
and cruciferous vegetables, including broccoli; and grains. Fruit
juices were included only in the total fruit categories, but not with
citrus or yellow-orange fruit. Some vegetables were included in
multiple categories. For example, broccoli is both a dark green
and a cruciferous vegetable. Grains included rice, cereals,
breads, and pasta—all in cooked form.

For validation and calibration purposes, a substudy was incor-
porated into the initial dietary assessment. Details about this
calibration study were published previously (10). In total, 1606
study participants, who were randomly chosen out of subgroups
defined by sex and ethnicity, completed 3 unannounced 24-h
dietary recalls via telephone during a period of ≈3 mo and an
additional QFFQ 3 mo afterward. Correlation coefficients be-
tween the dietary recall measurement and the QFFQ were 0.31
and 0.25 for vegetables, 0.58 and 0.52 for fruit, and 0.67 and 0.66
for grains among men and women, respectively. The instruments
led to different levels of energy estimates, with correlations of
0.31 for men and 0.20 for women. Therefore, the correlations,
based on density measurements (g·1000 kcal−1·d−1, adjusted
for energy intake), were higher: 0.43 and 0.36 for vegetables,
0.60 and 0.60 for fruit, and 0.70 and 0.72 for grains among men
and women, respectively.

Surveillance

Since 1993, the cohort has been under surveillance for col-
rectal cancer incidence and mortality by record linkages to the
Hawaii Tumor Registry, the Cancer Surveillance Program for
Los Angeles County, and the California State Cancer Registry in
addition to the death certificate files in Hawaii and California and
to the National Death Index. All 3 cancer registries are members
of the NCI’s Surveillance, Epidemiology and End Results Pro-
gram (11). The out-migration rate in the cohort has been low at
3.7% after 7 y of follow-up; therefore, few cases should be
missed through passive follow-up. Case ascertainment was com-
plete through 31 December 2001. Information was available on
the histologic type of the tumor, its anatomical location, and the
stage of the cancer. The identification of cases in this study was
limited to patients with a diagnosis of invasive adenocarcinoma of the large bowel (n = 2110 cases). Colorectal cancer patients, who did not have adenocarcinoma of the large bowel (n = 111) or who had a diagnosis of carcinoma in situ (n = 183), were not included as cases. Colon cancer cases had an International Classification of Disease (ICD)-02 code of C18.0–C18.9 or C26.0. Rectal cancer cases had an ICD-02 code of C19.9 or C20.9. Stage of disease was based on the following categories: localized, regional, distant, and unstaged. Tumors with regional or distant spread of the disease were considered advanced tumors. In all, there were 1571 colon and 515 rectal cancer cases, whereas there were 24 cases of synchronous tumors at both sites.

Statistical analysis

We applied Cox proportional hazards models using age as the time metric to calculate relative risks. Person-times were calculated beginning at the date of cohort entry, defined as questionnaire completion, or, for the few individuals (n = 1113) who were slightly younger than 45 y of age when they completed the baseline questionnaire, as the date the participant turned 45 y of age. Person-times ended at the earliest of the following dates: date of colorectal cancer diagnosis, date of death, or 31 December 2001—the closure date of the study. Tests of proportional hazards assumptions, based on plotting the sum of scaled Schoenfeld residuals and parameter estimates against time, showed no violations for any analysis (12). All Cox models were stratified by follow-up time, categorized as ≤2, 2–5, and >5 y. Food groups were investigated in disease models in terms of quintiles. Four dummy variables were created to represent the sex-specific quintiles, which were based on the distribution of each exposure across the entire cohort of men or women. Trend variables assigned the sex- and ethnic-specific median values for the appropriate sex-specific quintiles were used in the respective models to test for dose-response. In a subsequent analysis, separate regression parameters were computed for colon cancer and rectal cancer, using competing risk techniques described in (12) and compared using a Wald test.

The following adjustment factors were used in the multivariate model: age at cohort entry, ethnicity (indicator variables), family history of colorectal cancer (indicator variable), history of colorectal polyph (indicator variable), pack-years of cigarette smoking, body mass index (weight in kg divided by the square of height in meters), physical activity (hours of vigorous activity in a week), aspirin use (indicator variable for at least twice a week for ≥1 mo), multivitamin use (indicator variable for at least once a week during the past year), use of hormone replacement therapy for women (indicator variable for current or past user of estrogen, with or without progesterone), energy intake (logarithmically transformed to reduce the correlation between the variability and the magnitude of values), alcohol, red meat, folate (food and supplements), vitamin D (food), and calcium (food and supplements). All adjustment variables were entered in the model as continuous measures, unless otherwise indicated. In a sensitivity analysis, the dietary adjustment variables were modeled by a variety of techniques, such as nutrient densities and by the method of residuals; however, the results for vegetables and fruit were unchanged. Anyone with missing data for any of the adjustment variables was excluded in the multivariate analysis. Multiple imputation was used to verify that the results were not biased by the pattern of missing data (data not shown).

To reduce measurement error in the dietary assessments, we analyzed food intakes in terms of densities, ie, adjusted for energy intake by creating ratios of amount per 1000 kcal per day. As noted above, in the validation study we found that energy-adjusted intake (by the methods of residuals or using densities) produced substantially higher correlation coefficients with the reference instrument than did crude intake (10). This phenomenon has also been reported in other studies (13). All analyses were performed by using SAS Statistical Software, version 9 (SAS Institute Inc, Cary, NC), and all statistical tests were 2-sided.

RESULTS

There were 85 903 men and 105 108 women included in this study. The mean duration of follow-up was 7.3 y, with a total of >1.4 million person-years of observation. During that time, 1138 men and 972 women were diagnosed with colorectal cancer. The mean age at diagnosis was 68.5 y for men and 68.0 y for women.

Baseline characteristics of colorectal cancer cases and the total study population by sex are shown in Table 1. The cases were older at the time of study entry, more likely to have a family history of colorectal cancer, more likely to be ever smokers, less likely to use multivitamins, and less physically active than were the study population (both men and women). In women, cases were also heavier and less likely to report the use of replacement hormones.

The relative risk of colorectal cancer by intake of vegetables and fruit combined, vegetables (alone), fruit (alone), and grains is presented separately for men and women in Table 2. First, there was a strong inverse trend in colorectal cancer risk with adjustment for age and ethnicity among men for the intake of vegetables and fruit combined, vegetables alone, and fruits alone, but not for grains. After multivariate adjustment for energy intake and dietary and nondietary variables, the relative risks for the highest compared with the lowest quintiles were 0.74 for vegetables and fruit combined and 0.80 for fruit alone, whereas the inverse trend for vegetables alone was of borderline significance (P = 0.052).

For women, there was an inverse trend with adjustment for age and ethnicity for fruit intake, but not for vegetables, vegetables and fruit combined, or grains. The highest quintile group had a relative risk of 0.79 for fruit. After multivariate adjustment, the inverse trend was no longer significant for fruit intake.

To reduce the chances that undiagnosed preclinical colorectal cancer could affect the results, we repeated the multivariate analysis for vegetables and fruit combined, excluding cases diagnosed within 2 y of their study enrollment. For the remaining subgroups, relative risks for the highest compared with the lowest quintiles were 0.72 (95% CI: 0.56, 0.93; P for trend = 0.03) for men and 1.08 (95% CI: 0.81, 1.46; P for trend = 0.84) for women (based on 763 and 601 cases, respectively). After reanalysis of the data including only advanced tumors with either regional or distant spread as endpoint events, the relative risks for the highest quintiles after multivariate adjustment were 0.77 (95% CI: 0.57, 1.05; P for trend = 0.08) for men and 1.18 (95% CI: 0.84, 1.66; P for trend = 0.75) for women (based on 555 and 440 cases, respectively).

Next, the analysis in Table 2 for men was done separately for colon and rectal cancer cases. With multivariate adjustment,
there was a significant trend between colon cancer and vegetables alone and vegetables and fruit combined, as shown in Table 3. Also, the highest quintile of fruit intake had a relative risk of 0.75 for colon cancer. However, none of the trends were significant for rectal cancer. The Wald test based on competing-risk analysis for a difference in the effect of fruit and vegetable intake by cancer site suggested that the reduced risk was stronger for colon cancer risk and on rectal cancer was not significant ($P = 0.13$). Similar analyses were done for women (Table 3). There were no significant trends in colon or rectal cancer risk with the intake of vegetables, fruit, vegetables and fruit combined, or grains.

Because of the possible importance of the type of vegetables and fruit consumed, we determined the risk of colorectal cancer according to the consumption of 7 specific foods or food groups among men and women (Table 3). After multivariate adjustment, none of the trends was significant for either sex.

To examine the stability of the overall findings for men and women, relative risks in the highest quintiles for the combined intake of vegetables and fruit were determined for each of the 10 sex-ethnic-specific groups after adjustment for energy intake and dietary and nondietary variables. The results are shown in Figure 1. The relative risk among all men combined was significant (Table 2), and the relative risks were <1 in each of the 5 ethnic groups. For women, the relative risks were <1 for Latinos and Native Hawaiians, but the CIs were wide.

The median intake of vegetables and fruit combined was higher for Latinos and Native Hawaiians (range of intake from 600 to 679 and 665 to 707 g/d, respectively, for men and women) and lower for African Americans, Japanese Americans, and whites (range of intake from 513 to 582 and 573 to 606 g/d, respectively, for men and women).

### DISCUSSION

In our study, high consumers of vegetables had a reduced risk of colorectal cancer among men but not among women. Analysis by cancer site suggested that the reduced risk was stronger for colon than for rectal cancer. The NIH-AARP Study (2) and the Cancer Prevention Study II (3) also reported a low colon cancer risk with vegetable consumption among men. However, there was no association with vegetable intake among men in other cohort studies (5, 7, 14). The NIH-AARP Study found its inverse relationship with vegetable consumption among men. However, there was no association with vegetable intake among men in other cohort studies (5, 7, 14). The NIH-AARP Study found its inverse relationship with vegetable consumption among men.

## TABLE 1
Baseline characteristics of the colorectal cancer cases and the study population by sex

<table>
<thead>
<tr>
<th></th>
<th>Men (n = 1138)</th>
<th></th>
<th>Women (n = 972)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of cohort at entry (y)</td>
<td>64.7 ± 7.6</td>
<td>60.2 ± 8.9</td>
<td>64.1 ± 7.9</td>
<td>59.7 ± 8.8</td>
</tr>
<tr>
<td>Race-ethnicity (%)</td>
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<tr>
<td>African American</td>
<td>15.6 ± 1.1</td>
<td>13.9 ± 0.1</td>
<td>27.7 ± 1.4</td>
<td>19.8 ± 0.1</td>
</tr>
<tr>
<td>Japanese American</td>
<td>38.0 ± 1.4</td>
<td>29.5 ± 0.2</td>
<td>30.8 ± 1.5</td>
<td>27.2 ± 0.1</td>
</tr>
<tr>
<td>Latino</td>
<td>18.9 ± 1.2</td>
<td>24.4 ± 0.2</td>
<td>15.4 ± 1.2</td>
<td>21.5 ± 0.1</td>
</tr>
<tr>
<td>Native Hawaiian</td>
<td>7.1 ± 0.8</td>
<td>7.0 ± 0.1</td>
<td>6.2 ± 0.8</td>
<td>7.4 ± 0.1</td>
</tr>
<tr>
<td>White</td>
<td>20.4 ± 1.2</td>
<td>25.3 ± 0.2</td>
<td>20.0 ± 1.3</td>
<td>24.1 ± 0.1</td>
</tr>
<tr>
<td>Family history of colorectal cancer (%)</td>
<td>11.2 ± 0.9</td>
<td>7.2 ± 0.1</td>
<td>13.4 ± 1.1</td>
<td>8.5 ± 0.1</td>
</tr>
<tr>
<td>History of colorectal polyps (%)</td>
<td>5.9 ± 0.7</td>
<td>6.8 ± 0.1</td>
<td>5.3 ± 0.7</td>
<td>4.3 ± 0.1</td>
</tr>
<tr>
<td>Cigarette smoking status</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Nonsmoker</td>
<td>23.4 ± 1.3</td>
<td>30.0 ± 0.2</td>
<td>52.7 ± 1.6</td>
<td>55.7 ± 0.1</td>
</tr>
<tr>
<td>Past smoker</td>
<td>58.2 ± 1.5</td>
<td>51.9 ± 0.2</td>
<td>33.9 ± 1.5</td>
<td>30.0 ± 0.1</td>
</tr>
<tr>
<td>Current smoker</td>
<td>18.4 ± 1.2</td>
<td>18.2 ± 0.1</td>
<td>13.4 ± 1.2</td>
<td>14.4 ± 0.1</td>
</tr>
<tr>
<td>Pack-years of cigarette smoking $^2$</td>
<td>23.5 ± 17.9</td>
<td>20.6 ± 16.6</td>
<td>16.7 ± 14.8</td>
<td>15.4 ± 14.4</td>
</tr>
<tr>
<td>BMI (kg/m$^2$)</td>
<td>26.0 ± 4.2</td>
<td>26.1 ± 4.2</td>
<td>26.5 ± 6.1</td>
<td>26.0 ± 5.7</td>
</tr>
<tr>
<td>Vigorous physical activity (h/wk)</td>
<td>3.0 ± 5.9</td>
<td>4.1 ± 7.1</td>
<td>0.9 ± 2.3</td>
<td>1.5 ± 3.8</td>
</tr>
<tr>
<td>Aspirin use (%)</td>
<td>40.0 ± 1.4</td>
<td>41.3 ± 0.2</td>
<td>38.9 ± 1.6</td>
<td>37.6 ± 0.2</td>
</tr>
<tr>
<td>Multivitamin use (%)</td>
<td>42.0 ± 1.5</td>
<td>47.7 ± 0.2</td>
<td>48.4 ± 1.6</td>
<td>54.0 ± 0.2</td>
</tr>
<tr>
<td>Replacement hormone use (%)</td>
<td></td>
<td></td>
<td>42.6 ± 1.6</td>
<td>46.6 ± 0.2</td>
</tr>
<tr>
<td>Energy intakes (kcal/d)</td>
<td>2329 ± 1044</td>
<td>2380 ± 1105</td>
<td>1854 ± 924</td>
<td>1947 ± 949</td>
</tr>
<tr>
<td>Alcohol (g/d)</td>
<td>17.3 ± 35.9</td>
<td>14.6 ± 32.6</td>
<td>5.6 ± 23.9</td>
<td>4.3 ± 14.9</td>
</tr>
<tr>
<td>Red meat (g·1000 kcal$^{-1}$·d$^{-1}$)</td>
<td>29.1 ± 15.7</td>
<td>29.5 ± 17.1</td>
<td>25.0 ± 16.4</td>
<td>24.4 ± 15.9</td>
</tr>
<tr>
<td>Folate intake (µg/d)</td>
<td>503 ± 330</td>
<td>548 ± 369</td>
<td>502 ± 357</td>
<td>528 ± 358</td>
</tr>
<tr>
<td>Vitamin D (IU·kcal$^{-1}$·d$^{-1}$)</td>
<td>61.9 ± 37.5</td>
<td>62.9 ± 40.6</td>
<td>68.4 ± 44.0</td>
<td>69.6 ± 45.1</td>
</tr>
<tr>
<td>Calcium (mg/d)</td>
<td>887 ± 513</td>
<td>965 ± 564</td>
<td>954 ± 653</td>
<td>1059 ± 700</td>
</tr>
</tbody>
</table>

$^2$ All values are $\bar{x} \pm$ SD or percentage ± SE.

$^2$ For current and past smokers only.
Women, we found no association with fruit intake after adjustment for nondietary and dietary variables. Six other cohort studies (2, 5–7, 15, 16) also reported no relation between fruit and colorectal cancer among women. In contrast, the Swedish Mammography Screening Cohort Study (17) and the Cancer Prevention Study II (22) reported an inverse association with fruit intake among men (14) or cereal fiber in women (17). Others have suggested that there are differences in risk factors between men and women with regard to colorectal neoplasia (21), but the issue still needs to be resolved. The consumption of grains, which included both refined and whole grains, was not related to colorectal cancer in our cohort. Previously, we found no association with whole grains in men (14) or cereal fiber in women (17), and women with the intake of high-fiber grains (23). However, in a subsequent report, the researchers found no association with whole grain intake (3). A similar lack of association was reported by others with regard to the consumption of whole-grain cereals in men (14) or cereal fiber in women (17).

It is uncertain why the association with vegetables and fruit was weaker in women than in men in our cohort. Others have noted that sex differences in bile acid synthesis and composition may account for differences in colorectal cancer risk (18). Past studies have reported that estrogen replacement therapy among women protects against colorectal cancer (19, 20); we also found this inverse relation in the Multiethnic Cohort Study (data not shown). Nevertheless, when we separated hormone replacement therapy users from nonusers, relative risks in the highest quintile of total fruit and vegetable intake were 1.08 for users and 1.00 for nonusers, which suggested no effect. Some researchers have

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**TABLE 2**

Relative risk (95% CI) of colorectal cancer by quintile (Q) of vegetable, fruit, and grain intakes

<table>
<thead>
<tr>
<th>Food group</th>
<th>No. of cases</th>
<th>Q1 (low)</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
<th>Q5 (high)</th>
<th>P for trend$^d$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vegetables and fruit</td>
<td></td>
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</tr>
<tr>
<td>Median intake (g·1000 kcal$^{-1}$·d$^{-1}$)</td>
<td>134.7</td>
<td>205.3</td>
<td>267.7</td>
<td>343.2</td>
<td>483.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted$^a$</td>
<td>1138</td>
<td>1</td>
<td>0.79 (0.66, 0.94)</td>
<td>0.75 (0.63, 0.89)</td>
<td>0.71 (0.59, 0.85)</td>
<td>0.57 (0.47, 0.69)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Multivariate adjusted$^d$</td>
<td>1023</td>
<td>1</td>
<td>0.88 (0.72, 1.06)</td>
<td>0.84 (0.69, 1.02)</td>
<td>0.84 (0.69, 1.03)</td>
<td>0.74 (0.59, 0.93)</td>
<td>0.018</td>
</tr>
<tr>
<td><strong>Vegetables</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median intake (g·1000 kcal$^{-1}$·d$^{-1}$)</td>
<td>71.9</td>
<td>105.5</td>
<td>134.2</td>
<td>168.9</td>
<td>236.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted$^a$</td>
<td>1138</td>
<td>1</td>
<td>1.04 (0.88, 1.24)</td>
<td>0.83 (0.69, 0.99)</td>
<td>0.80 (0.67, 0.96)</td>
<td>0.76 (0.63, 0.91)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Multivariate adjusted$^d$</td>
<td>1023</td>
<td>1</td>
<td>1.07 (0.89, 1.28)</td>
<td>0.86 (0.71, 1.05)</td>
<td>0.91 (0.75, 1.11)</td>
<td>0.85 (0.69, 1.05)</td>
<td>0.052</td>
</tr>
<tr>
<td><strong>Fruit</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median intake (g·1000 kcal$^{-1}$·d$^{-1}$)</td>
<td>30.1</td>
<td>73.6</td>
<td>118.9</td>
<td>179.9</td>
<td>295.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted$^a$</td>
<td>1138</td>
<td>1</td>
<td>0.79 (0.66, 0.95)</td>
<td>0.70 (0.58, 0.84)</td>
<td>0.66 (0.55, 0.79)</td>
<td>0.63 (0.53, 0.76)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Multivariate adjusted$^d$</td>
<td>1023</td>
<td>1</td>
<td>0.86 (0.71, 1.05)</td>
<td>0.76 (0.64, 0.95)</td>
<td>0.79 (0.64, 0.97)</td>
<td>0.80 (0.64, 0.99)</td>
<td>0.089</td>
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<tr>
<td><strong>Grains</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Median intake (g·1000 kcal$^{-1}$·d$^{-1}$)</td>
<td>73.4</td>
<td>106.1</td>
<td>140.6</td>
<td>192.8</td>
<td>290.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted$^a$</td>
<td>1138</td>
<td>1</td>
<td>0.84 (0.69, 1.02)</td>
<td>0.97 (0.80, 1.17)</td>
<td>0.92 (0.75, 1.12)</td>
<td>0.85 (0.68, 1.05)</td>
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<tr>
<td>Multivariate adjusted$^d$</td>
<td>1023</td>
<td>1</td>
<td>0.94 (0.76, 1.16)</td>
<td>1.13 (0.92, 1.39)</td>
<td>1.08 (0.86, 1.35)</td>
<td>0.98 (0.76, 1.26)</td>
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<td></td>
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</tr>
<tr>
<td>Vegetables and fruit</td>
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<td></td>
<td></td>
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<tr>
<td>Median intake (g·1000 kcal$^{-1}$·d$^{-1}$)</td>
<td>176.3</td>
<td>267.3</td>
<td>346.2</td>
<td>440.0</td>
<td>608.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted$^a$</td>
<td>972</td>
<td>1</td>
<td>0.97 (0.79, 1.19)</td>
<td>0.95 (0.77, 1.16)</td>
<td>0.85 (0.69, 1.05)</td>
<td>0.90 (0.73, 1.10)</td>
<td>0.191</td>
</tr>
<tr>
<td>Multivariate adjusted$^d$</td>
<td>802</td>
<td>1</td>
<td>1.04 (0.82, 1.30)</td>
<td>1.04 (0.83, 1.31)</td>
<td>0.94 (0.74, 1.20)</td>
<td>1.04 (0.81, 1.33)</td>
<td>0.995</td>
</tr>
<tr>
<td><strong>Vegetables</strong></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Median intake (g·1000 kcal$^{-1}$·d$^{-1}$)</td>
<td>85.5</td>
<td>125.8</td>
<td>160.5</td>
<td>202.7</td>
<td>286.5</td>
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</tr>
<tr>
<td>Adjusted$^a$</td>
<td>972</td>
<td>1</td>
<td>0.89 (0.73, 1.08)</td>
<td>0.81 (0.66, 0.99)</td>
<td>0.95 (0.78, 1.15)</td>
<td>0.85 (0.70, 1.04)</td>
<td>0.277</td>
</tr>
<tr>
<td>Multivariate adjusted$^d$</td>
<td>802</td>
<td>1</td>
<td>0.87 (0.70, 1.09)</td>
<td>0.85 (0.68, 1.07)</td>
<td>0.94 (0.76, 1.17)</td>
<td>0.94 (0.75, 1.17)</td>
<td>0.920</td>
</tr>
<tr>
<td><strong>Fruit</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median intake (g·1000 kcal$^{-1}$·d$^{-1}$)</td>
<td>47.5</td>
<td>108.5</td>
<td>168.5</td>
<td>243.4</td>
<td>381.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted$^a$</td>
<td>972</td>
<td>1</td>
<td>0.85 (0.69, 1.04)</td>
<td>0.94 (0.77, 1.15)</td>
<td>0.88 (0.72, 1.07)</td>
<td>0.79 (0.64, 0.97)</td>
<td>0.046</td>
</tr>
<tr>
<td>Multivariate adjusted$^d$</td>
<td>802</td>
<td>1</td>
<td>0.85 (0.68, 1.08)</td>
<td>1.00 (0.80, 1.25)</td>
<td>0.97 (0.77, 1.22)</td>
<td>0.83 (0.65, 1.06)</td>
<td>0.272</td>
</tr>
<tr>
<td><strong>Grains</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median intake (g·1000 kcal$^{-1}$·d$^{-1}$)</td>
<td>73.4</td>
<td>106.5</td>
<td>138.3</td>
<td>182.8</td>
<td>266.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted$^a$</td>
<td>972</td>
<td>1</td>
<td>1.12 (0.93, 1.36)</td>
<td>1.11 (0.91, 1.36)</td>
<td>0.84 (0.67, 1.05)</td>
<td>0.93 (0.74, 1.18)</td>
<td>0.221</td>
</tr>
<tr>
<td>Multivariate adjusted$^d$</td>
<td>802</td>
<td>1</td>
<td>1.12 (0.90, 1.40)</td>
<td>1.19 (0.95, 1.49)</td>
<td>0.96 (0.75, 1.24)</td>
<td>1.05 (0.80, 1.38)</td>
<td>0.913</td>
</tr>
</tbody>
</table>

$^a$ P value for Wald test of trend variables, assigned the median for the appropriate quintile.

$^b$ Estimated from Cox regression in which age is the time metric, adjusted for ethnicity and time since cohort entry as strata variables and age at cohort entry as an independent variable in the log linear model component.

$^c$ Estimated from Cox regression in which age is the time metric, adjusted for ethnicity and time since cohort entry as strata variables and age at cohort entry as an independent variable in the log linear model component.
minimize these potential limitations by rigorously designing our QFFQ, by including a comprehensive group of food items, and by using nutrient densities in the analyses, which resulted in better correlations between the questionnaire and more accurate measurements of diet (10, 13). We assumed that the relative ranking of participants with regard to intake of vegetables, fruit, and grains remained stable during surveillance. There is some assurance that this assumption may be appropriate (5, 25).

TABLE 4
Multivariate-adjusted relative risk (95% CI) of colorectal cancer by intake of types of fruit and vegetables!

<table>
<thead>
<tr>
<th>Type of fruit and vegetables</th>
<th>Q1 (low)</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
<th>Q5 (high)</th>
<th>P for trend2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yellow-orange fruit</td>
<td>0.97</td>
<td>0.87</td>
<td>0.89</td>
<td>0.83</td>
<td>0.81</td>
<td>0.081</td>
</tr>
<tr>
<td>Citrus fruit</td>
<td>0.91</td>
<td>0.96</td>
<td>0.72</td>
<td>0.85</td>
<td>0.95</td>
<td>0.082</td>
</tr>
<tr>
<td>Light-green vegetables</td>
<td>1.10</td>
<td>1.01</td>
<td>1.00</td>
<td>0.93</td>
<td>0.93</td>
<td>0.234</td>
</tr>
<tr>
<td>Dark-green vegetables</td>
<td>0.88</td>
<td>0.81</td>
<td>0.81</td>
<td>0.88</td>
<td>0.88</td>
<td>0.380</td>
</tr>
<tr>
<td>Yellow-orange vegetables</td>
<td>0.97</td>
<td>0.94</td>
<td>0.83</td>
<td>0.90</td>
<td>0.90</td>
<td>0.248</td>
</tr>
<tr>
<td>Cruciferous vegetables</td>
<td>0.93</td>
<td>0.88</td>
<td>0.90</td>
<td>0.87</td>
<td>0.87</td>
<td>0.291</td>
</tr>
<tr>
<td>Broccoli</td>
<td>1.10</td>
<td>0.95</td>
<td>0.98</td>
<td>0.94</td>
<td>0.94</td>
<td>0.300</td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yellow-orange fruit</td>
<td>0.81</td>
<td>0.99</td>
<td>0.91</td>
<td>0.83</td>
<td>0.91</td>
<td>0.354</td>
</tr>
<tr>
<td>Citrus fruit</td>
<td>0.95</td>
<td>0.90</td>
<td>1.08</td>
<td>1.04</td>
<td>1.04</td>
<td>0.368</td>
</tr>
<tr>
<td>Light-green vegetables</td>
<td>0.99</td>
<td>0.79</td>
<td>0.79</td>
<td>1.04</td>
<td>1.04</td>
<td>0.911</td>
</tr>
<tr>
<td>Dark-green vegetables</td>
<td>0.85</td>
<td>0.76</td>
<td>0.73</td>
<td>0.85</td>
<td>0.85</td>
<td>0.344</td>
</tr>
<tr>
<td>Yellow-orange vegetables</td>
<td>0.74</td>
<td>0.86</td>
<td>0.84</td>
<td>0.90</td>
<td>0.90</td>
<td>0.891</td>
</tr>
<tr>
<td>Cruciferous vegetables</td>
<td>0.91</td>
<td>0.76</td>
<td>0.79</td>
<td>0.91</td>
<td>0.91</td>
<td>0.787</td>
</tr>
<tr>
<td>Broccoli</td>
<td>0.93</td>
<td>0.85</td>
<td>0.72</td>
<td>0.92</td>
<td>0.652</td>
<td></td>
</tr>
</tbody>
</table>

1 Estimated from Cox regression in which age is the time metric, adjusted for other covariates as strata variables, age, and other variables.
2 P value for Wald test of trend variables, assigned the median for the appropriate quintile.
The relative risks and 95% CIs of the highest quintiles of the combined intake of vegetables and fruit compared with the lowest quintiles for colorectal cancer are represented as squares and horizontal lines by sex for the 5 ethnic groups. The relative risks were estimated from Cox regression, where age is the time metric, and adjusted for time since cohort entry as strata variables and age, family history of colorectal cancer, history of colorectal polyp, pack-years of cigarette smoking, BMI, hours of vigorous activity, aspirin use, multivitamin use, replacement hormone use (women), log energy intake, alcohol, red meat, folate, vitamin D, and calcium as independent variables in the log linear model component.

Another concern is that FFQs, out of practical necessity, may omit many foods (15). Vegetable and fruit intake was based on 9 items in the Japan Public Health study (7), 12 in the Swedish Mammography Screening Study (17), and 19 in the Breast Cancer Detection Demonstration Project (15). The more comprehensive questionnaire, the more likely it will record intake of all vegetables and fruit. The Nurses’ Health Study had 15 fruits and 28 vegetables in its questionnaire (5). The Women’s Health Study used a 131-item questionnaire, which included ≥ 16 fruits and 34 vegetables (6). Our questionnaire recorded the intake of 15 fruits, 22 vegetables, and 15 items with fruit or vegetables in soups, mixed dishes, or desserts.

Past studies have noted that the amount of vegetables and fruit consumed may be insufficient to produce an effect, or the range of intake may be too narrow between the lowest and highest quintile groups. In the Breast Cancer Detection Demonstration Project, the authors stated that they and other investigators may not have observed an inverse association between vegetable intake and colorectal cancer because of the consumption of insufficient quantities to show a reduction in risk (15). In the Iowa Women’s Health Study, 29 vegetables and 15 fruits were in the questionnaire, but the researchers noted that the range of vegetable and fruit consumption was relatively narrow, which limited the ability to have contrasts between extremes of consumption (16).

Because of the comprehensiveness of our questionnaire, the recorded amounts were sizable. The median daily intake of vegetables and fruit was 293 and 259 g, respectively, for men and 286 and 298 g, respectively, for women. In addition, the range of intake of these foods was wide. There was a 3.4-fold difference in vegetable intake to a 9.8-fold difference in fruit intake between the lowest and highest quintile groups. In the Netherlands Cohort Study (4), the mean daily intake of vegetables and fruit was 187 and 154 g, respectively, for men and 191 and 196 g, respectively, for women. There was a 2.9-fold difference in vegetable intake to an 8.4-fold difference in fruit intake between the lowest and highest quintile groups.

In conclusion, we found an inverse relation of vegetable and fruit intake to colorectal cancer risk in men and not in women. The association appeared consistent across the different ethnic groups in the study and was stronger for colon cancer. Separation according to the different sources of vegetables and fruit did not identify specific food groups that accounted for the association. There was no association of grain intake with colorectal cancer for either men or women.

The authors’ responsibilities were as follows—AMYN: drafted the article and revised it for important content and contributed to the conception and design of the study, acquisition of the data, and the analysis and interpretation of the data; LRW: assisted in the revision of the article for important content and contributed to the conception and design of the study, acquisition of the data, and analysis and interpretation of the data; SPAM and MCP: contributed to the design of the study and the analysis and interpretation of its data and assisted with the revision of the article for important content; JHH: assisted with the revision of the article for important content and contributed to the conception of the study, acquisition of the data, and interpretation of the results; BEH: contributed to the conception of the study and acquisition of the data and assisted with the revision of the article for important content; and LNK: assisted with the revision of the article for important content and contributed to the conception and design of the study, acquisition of the data, and interpretation of the results. None of the authors had a personal or financial interest with the organization (National Cancer Institute) sponsoring the research.

REFERENCES