Vegetable Intake, but Not Fruit Intake, Is Associated with a Reduction in the Risk of Cancer Incidence and Mortality in Middle-Aged Korean Men1–3

Yuni Choi,4,5,12 Jung Eun Lee,4,5,12 Jong-Myon Bae,6 Zhong-Min Li,7 Dong-Hyun Kim,8 Moo-Song Lee,9 Yoon-Ok Ahn,10 and Myung-Hee Shin11*

4Women’s Health Research Institute and 5Department of Food and Nutrition, Sookmyung Women’s University, Seoul, Republic of Korea; 6Department of Preventive Medicine, Cheju National University College of Medicine, Jeju, Republic of Korea; 7Department of Epidemiology and Statistics, School of Public Health Sciences, Jilin University, Changchun, China; 8Department of Social and Preventive Medicine, Hallym University College of Medicine, Chuncheon, Republic of Korea; 9Department of Preventive Medicine, University of Ulsan College of Medicine, Seoul, Republic of Korea; 10Department of Preventive Medicine, Seoul National University College of Medicine, Seoul, Republic of Korea; and 11Department of Social and Preventive Medicine, Sungkyunkwan University School of Medicine, Suwon, Republic of Korea

Abstract

Background: Few prospective studies have examined the preventive role of fruit and vegetable intakes against cancer in Asian populations.

Objective: This prospective study evaluated the associations between total fruit intake, total vegetable intake, and total fruit and vegetable intake and total cancer incidence and mortality.

Methods: This prospective cohort study included 14,198 men 40–59 y of age enrolled in the Seoul Male Cohort Study from 1991 to 1993. Fruit and vegetable intakes were assessed by a validated food-frequency questionnaire. We used Cox proportional hazard regression models to compute RR ratios and 95% CIs.

Results: During the follow-up period from 1993 to 2008, 1343 men were diagnosed with cancer, and 507 died of cancer. Total vegetable intake was linearly associated with cancer incidence but was nonlinearly associated with cancer mortality; by comparing ≥500 g/d with <100 g/d of total vegetable intake, the multivariable-adjusted RR for total cancer incidence was 0.72 (95% CI: 0.58, 0.90; P-trend: 0.02; P-nonlinearity: 0.06). For total cancer mortality, the multivariable-adjusted RRs comparing 100 to <200 g/d, 200 to <300 g/d, 300 to <500 g/d, and ≥500 g/d with <100 g/d of total vegetable intake were 0.68 (95% CI: 0.53, 0.88), 0.75 (95% CI: 0.57, 0.98), 0.72 (95% CI: 0.54, 0.95), and 0.67 (95% CI: 0.47, 0.95), respectively (P-trend: 0.09; P-nonlinearity: 0.01). No associations were found between total fruit intake and total cancer incidence and mortality; ≥300 g/d vs. <50 g/d, RR: 1.04 (95% CI: 0.87, 1.25; P-trend: 0.56) for incidence and RR: 0.89 (95% CI: 0.66, 1.21; P-trend: 0.71) for mortality.

Conclusions: Our findings suggest that total vegetable intake is linearly associated with cancer incidence but nonlinearly associated with total cancer mortality in middle-aged Korean men. However, total fruit intake is not associated with total cancer incidence or mortality.

Keywords: cancer, fruits, prospective study, vegetables, incidence, mortality, diet, Asian

Introduction

A diet rich in fruits and vegetables has been suggested to decrease cancer risk, and this hypothesis was extensively examined in epidemiologic studies in Western populations (1). In the 1990s, the WHO and the World Cancer Research Fund and the American Institute for Cancer Research (WCRF/AICR) emphasized the beneficial effect of fruit and vegetable intake on cancer prevention because a relatively large number of case–control studies supported this hypothesis (2, 3). The first report by the WCRF/AICR (1997) concluded that the preventive effects of high fruit and vegetable consumption against cancer risk were convincing, showing at least a 20% reduction in total cancer risk with ≥400 g/d of fruit and vegetable intake (3). However, the evidence was limited because most of the reviewed studies were case-control studies, which are susceptible to recall and selection...
bias. Because the cumulative results from prospective cohort studies have not provided similar evidence of the benefits of fruit and vegetable intake in cancer prevention as the previous case-control studies, the second WCRC/AICR report downgraded the level of evidence for several cancer types from convincing to probable, limited, or suggestive in 2007 (4, 5–13, 27). Large prospective studies have shown weaker evidence, such as weak or null associations (5–8). A meta-analysis that evaluated the association between total fruit and vegetable intake and colorectal cancer risk showed no overall significance (9); however, the study also suggested that a reduction in risk was consistent with a 100–200 g/d threshold, and there was no further benefit of increasing the intake above this level (9). Previous prospective studies on the relation between total fruit and/or vegetable intake and total cancer mortality have shown inconsistent results (10–13).

Fruit and vegetable intake varies markedly across various geographic locations, and Asian populations are estimated to consume a diet with a relatively high content of vegetables (14). To the best of our knowledge, this investigation is the first study to evaluate the associations between total fruit and vegetable intake (combined and separately) and total cancer incidence and mortality in a prospective study of middle-aged Korean men.

Methods

Study cohort. The study population consisted of participants in the Seoul Male Cohort Study, a prospective cohort study designed to investigate the association between lifestyle and dietary factors and the incidence and mortality of cancer and additional chronic disease outcomes (15). Between 1991 and 1993, we mailed a baseline questionnaire to a random sample of 29,918 healthy men residing in Seoul who received regular biennial general health screenings in 1990 as beneficiaries of the Korea Medical Insurance Corporation. A total of 14,533 men 40–59 y of age returned the baseline self-administered comprehensive questionnaires. Of these men, we excluded those who did not complete the FFQs (n = 4), those who were diagnosed with cancer before enrolling in the study (n = 22), those who had an implausible total energy intake (>3 SDs from the log-transformed mean energy intake; n = 100), or those with missing information about the main exposures (n = 209). After these exclusions, 14,198 men were included in the analysis. The Institutional Review Board of the Seoul National University approved the protocol for this study, and all of the study subjects provided written informed consent.

Dietary assessment. Habitual dietary intake was assessed at baseline by using an 84-item self-administered FFQ designed and validated for use in Korea (16). Participants were asked to report how often, on average, they consumed food or beverage items during the previous year, using 3 standard serving sizes. The FFQ included 8 possible responses about frequency of consumption, ranging from “never or less than once per month” to “two or more times per day.” Average daily fruit and vegetable intake (in g/d) was calculated by multiplying intake frequency (servings of food per day) with serving size (grams per serving), and the sum was calculated from all relevant items. In the present analysis, we included 13 vegetables (green vegetables, lettuce, Chinese cabbage, boiled vegetables, raw green vegetables, tomato, garlic, onion, ginseng, kimchi, kimchi soup, white kimchi, or radish or cucumber seasoned with soy sauce) and 12 fruits (tangerine, orange, peach, apple, plum, banana, pear, melon, watermelon, strawberry, grape, kiwi). We excluded potatoes from the vegetable group because of their high-starch and -protein content (17). Total fruit intake only considered fresh fruit, not fruit juice.

Assessment of nondietary factors. At baseline, participants completed a questionnaire on demographics, lifestyle, anthropometry, use of dietary supplements, medical and family history, educational level, socioeconomic status, and occupational factors. BMI (in kg/m²) was calculated on the basis of directly measuring height and weight collected during their health examination. Pack-years of smoking were calculated by multiplying the reported average number of cigarettes smoked per day by the number of years of smoking and dividing by 20.

Ascertainment of cancers and cause of death. Men were followed from the date of study entry until the date of cancer diagnosis, date of death, or the end of follow-up period (31 December 2008). The incidence of cancer was ascertained through unique 13-digit personal identification numbers in the Seoul Cancer Registry, a population-based cancer registry, and the National Cancer Registration Program, a nationwide hospital-based cancer registry (18). Incident cancer cases were coded and classified according to the International Classification of Diseases for Oncology, 2nd edition (19) and converted according to the International Classification of Diseases, 10th edition (20). The dates and underlying causes of death were identified through data linkage to Korean death certificate data (21).

Statistical analysis. We used Cox proportional hazards regression models to estimate the RRs and 95% CIs of the associations between total fruit intake, total vegetable intake, and total fruit and vegetable intake with total cancer incidence. In this prospective cohort study, we also evaluated site-specific cancer risks in relation to total combined fruit and vegetable intake, focusing on the following common types of cancers in Korean men: stomach, colorectal, liver and bile duct, and lung cancers. In the cancer incidence analyses, the number of person-years of follow-up was calculated from the date of study entry until the date of cancer diagnosis, death, or the end of the follow-up period, whichever occurred first. For total cancer mortality, the number of person-years of follow-up was calculated from the date of study entry until the date of death from cancer, death from any other cause, or the end of the follow-up period, whichever occurred first. The participants were classified into categories of absolute intake. The following cutoffs were used to identify the intake categories: <50, 50 to <100, 100 to <200, 200 to <300, and ≥300 g/d for fruit intake; <100, 100 to <200, 200 to <300, 300 to <500, and ≥500 g/d for vegetable intake; and >200, 200 to <300, 300 to <400, 400 to <600, 600 to <800, and ≥800 g/d for total combined fruit and vegetable intake in the main analysis. In analyzing the common sitespecific cancers (22), we combined the two highest categories of total combined fruit and vegetable intake because of the small number of cases. We also chose different intake levels as the reference category because of the small sample size.

All of the models were stratified by age at baseline and were further adjusted for vigorous physical activity (<1, 1–2, or ≥3 h/wk), total calorie intake (kcal/d, continuous), alcohol intake (<1, 0.1 to <1.5, 1.5 to <30, or ≥30 kcal/d), red meat intake (g/d, continuous or missing indicator), multivitamin use (none, 1–6 times/wk, daily, 2–3 times/d, or missing), pack-years of smoking (<0.1, 0.1 to <20, 20 to <40, or ≥40 pack-years), BMI (<18.5, 18.5 to <23, 23 to <25, ≥25, or missing), educational level (less than high school, high school graduate or higher, or missing), family history of cancer (yes or no), and history of diabetes or cardiovascular disease at baseline (yes or no). In the additional analyses, we simultaneously adjusted for total fruit and vegetable intake in analyzing total vegetable intake or total fruit intake. If needed, missing indicator variables were used to impute missing responses for each measured covariate (red meat 0.5%, multivitamin use 2.4%, BMI 0.7%, education level 2.6%). A test for linear trends across fruit and vegetable intake categories was conducted by fitting the median value of each category as a continuous variable in the model and evaluating the relation by using the Wald test. To examine for a possible nonlinear relation, we examined the nonparametric regression curve by using restricted cubic splines. Tests for nonlinearity were performed by using the likelihood ratio test and comparing the model that only included the linear term with the model that included the linear and cubic spline terms. The models were visually inspected by using the restricted cubic spline graphs (23, 24). In addition, we repeated the analyses after excluding kimchi (a traditional fermented Korean dish prepared with cabbage, radishes, onions, and a variety of seasonings) from the primary analyses. We also
analyzed the associations between kimchi intake and total cancer incidence and mortality.

We stratified the analyses for the total combined fruit and vegetable intake and total vegetable intake by BMI (≥25 and <25), smoking habits (never or ever), or history of diabetes or cardiovascular disease at baseline (yes and no) and tested the statistical significance of the cross-product terms with an effect modifier variable in the multivariable models by using the likelihood ratio test. We conducted a sensitivity analysis by excluding cancer cases or cancer deaths that occurred during the first 2 years of follow-up to examine the possibility of reverse causality. All of the analyses were conducted with SAS version 9.3 (SAS Institute, Inc.). All P values were 2-sided and were considered to be statistically significant at a level of <0.05.

Results

The mean intake of total fruits and vegetables was 449.0 g/d (191.8 g/d and 257.2 g/d of total fruit intake and total vegetable intake, respectively). During the 15.3 years of follow-up for total cancer incidence and 15.6 years for total cancer mortality among 14,198 men, we ascertained a total of 1343 total cancer cases and 507 cancer deaths. Compared with men who consumed <200 g/d of fruits and vegetables combined, men who consumed ≥800 g/d were more likely to be educated, perform vigorous physical activity, and take multivitamins and were less likely to smoke and have a history of cardiovascular disease or diabetes (Table 1). Men who consumed larger amounts of total combined fruits and vegetables tended to consume more total energy, alcohol, red meat, fish, dietary calcium, and dietary fiber than men who consumed smaller amounts of fruits and vegetables.

We found a significant risk reduction of total cancer incidence only for 600–799 g/d of fruit and vegetable intake combined (Table 2); the multivariable-adjusted RR of total cancer incidence that compared 600–799 g/d with <200 g/d of fruit and vegetable intake combined was 0.80 (95% CI: 0.65, 0.99; P-trend: 0.67). To minimize the potential influence of preclinical disease on diet, we conducted additional analyses after excluding 67 men who had a cancer diagnosis within the first 2 years of follow-up. The results were similar to the results of the main analysis (data not shown). No association was found between combined total fruit and vegetable intake and the risk of total cancer mortality (≥600 to <800 g/d vs. <200 g/d, RR: 0.79; 95% CI: 0.56, 1.12; P-trend: 0.80).

After excluding kimchi, which comprised 36.9% of the fruit and vegetable intake (mean intake: 166 g/d), we found no associations for total cancer incidence or mortality; ≥500 g/d vs. <100 g/d, RR: 0.96 (95% CI: 0.80, 1.15; P-trend = 0.94) for incidence and RR: 0.84 (95% CI: 0.62, 1.14; P-trend = 0.49) for mortality. However, when we analyzed the associations between kimchi intake and total cancer incidence and mortality, we found significant inverse associations (Supplemental Table 1). The multivariable-adjusted RR of total cancer incidence that compared 300 g/d with <50 g/d of kimchi intake was 0.73 (95% CI: 0.59, 0.91; P-trend: 0.004). For total cancer mortality, the multivariable-adjusted RRs that compared 50 to <100, 100 to <150, 150 to <200, and ≥200 g/d with <50 g/d of kimchi intake were 0.60 (95% CI: 0.43, 0.79), 0.65 (95% CI: 0.51, 0.84), 0.60 (0.46, 0.79), and 0.67 (95% CI: 0.48, 0.94; P-trend: 0.12), respectively. The age-adjusted Spearman correlation coefficient between kimchi and non-kimchi vegetable intake was 0.32 (P < 0.001).

Total vegetable intake, but not total fruit intake, was associated with a reduction in the risk of total cancer incidence (Table 3); by comparing ≥500 g/d with <100 g/d of total vegetable intake, the multivariable-adjusted RR of total cancer incidence was 0.72 (95% CI: 0.58, 0.90; P-trend: 0.02, model 2). A reduction in the risk of total cancer incidence was produced between 100 and 199 g/d in the cubic spline curve, which corresponded to the results from the multivariable regression analyses (Figure 1A). For total cancer mortality, the multivariable-adjusted RRs that compared 100 to <200, 200 to <300, 300 to <500, and ≥500 g/d with <100 g/d of total vegetable intake were 0.68 (95% CI: 0.53, 0.88), 0.75 (95% CI: 0.57, 0.98), 0.72 (95% CI: 0.54, 0.95), and 0.67 (95% CI: 0.47, 0.95), respectively (model 2); both multivariable proportional hazards models (P-trend: 0.09) and the cubic spline curve (P-nonlinearity: 0.01; Figure 1B) showed a nonlinear relation between total vegetable intake and total cancer mortality.

We examined whether the associations between total vegetable intake (Table 4) and combined fruit and vegetable intake...
In this prospective study of Korean middle-aged men, we observed that vegetable intake was linearly associated with a decrease in total cancer incidence or mortality and that this association was independent of other dietary factors, lifestyle factors, and other potential confounders. This finding is consistent with previous studies that have shown a protective effect of dietary vegetables on cancer incidence and mortality, even after adjusting for other factors.

(Supplemental Table 2) varied by BMI, smoking habits, or history of diabetes and cardiovascular disease at baseline. We found an apparent inverse association between total vegetable intake and total cancer incidence and mortality among ever-smokers, whereas no association was found among never-smokers (P-interactions were 0.04 and 0.01, respectively). Among ever-smokers, the multivariable-adjusted RR of total cancer incidence and mortality that compared ≥500 g/d with <100 g/d of total vegetable intake was 0.73 (95% CI: 0.57, 0.93; P-trend: 0.08) and 0.68 (95% CI: 0.46, 0.99; P-trend: 0.18), respectively. Among never-smokers, the corresponding RRs were 0.55 (95% CI: 0.28, 1.07; P-trend: 0.09) and 0.58 (95% CI: 0.21, 1.59; P-trend: 0.23), respectively. We found that the associations between total combined fruit and vegetable intake and total cancer incidence or mortality did not vary by these characteristics.

In the site-specific analysis of common cancers in Korea (stomach, colorectal, liver and bile duct, and lung cancers), we did not observe a statistically significant inverse association of total combined fruit and vegetable intake with any specific cancer incidence or mortality (Supplemental Table 3).

**Discussion**

In this prospective study of Korean middle-aged men, we observed that vegetable intake was linearly associated with a decrease in total cancer incidence or mortality and that this association was independent of other dietary factors, lifestyle factors, and other potential confounders. This finding is consistent with previous studies that have shown a protective effect of dietary vegetables on cancer incidence and mortality, even after adjusting for other factors.

(Supplemental Table 2) varied by BMI, smoking habits, or history of diabetes and cardiovascular disease at baseline. We found an apparent inverse association between total vegetable intake and total cancer incidence and mortality among ever-smokers, whereas no association was found among never-smokers (P-interactions were 0.04 and 0.01, respectively). Among ever-smokers, the multivariable-adjusted RR of total cancer incidence and mortality that compared ≥500 g/d with <100 g/d of total vegetable intake was 0.73 (95% CI: 0.57, 0.93; P-trend: 0.08) and 0.68 (95% CI: 0.46, 0.99; P-trend: 0.18), respectively. Among never-smokers, the corresponding RRs were 0.55 (95% CI: 0.28, 1.07; P-trend: 0.09) and 0.58 (95% CI: 0.21, 1.59; P-trend: 0.23), respectively. We found that the associations between total combined fruit and vegetable intake and total cancer incidence or mortality did not vary by these characteristics.

In the site-specific analysis of common cancers in Korea (stomach, colorectal, liver and bile duct, and lung cancers), we did not observe a statistically significant inverse association of total combined fruit and vegetable intake with any specific cancer incidence or mortality (Supplemental Table 3).

**Discussion**

In this prospective study of Korean middle-aged men, we observed that vegetable intake was linearly associated with a decrease in total cancer incidence or mortality and that this association was independent of other dietary factors, lifestyle factors, and other potential confounders. This finding is consistent with previous studies that have shown a protective effect of dietary vegetables on cancer incidence and mortality, even after adjusting for other factors.

(Supplemental Table 2) varied by BMI, smoking habits, or history of diabetes and cardiovascular disease at baseline. We found an apparent inverse association between total vegetable intake and total cancer incidence and mortality among ever-smokers, whereas no association was found among never-smokers (P-interactions were 0.04 and 0.01, respectively). Among ever-smokers, the multivariable-adjusted RR of total cancer incidence and mortality that compared ≥500 g/d with <100 g/d of total vegetable intake was 0.73 (95% CI: 0.57, 0.93; P-trend: 0.08) and 0.68 (95% CI: 0.46, 0.99; P-trend: 0.18), respectively. Among never-smokers, the corresponding RRs were 0.55 (95% CI: 0.28, 1.07; P-trend: 0.09) and 0.58 (95% CI: 0.21, 1.59; P-trend: 0.23), respectively. We found that the associations between total combined fruit and vegetable intake and total cancer incidence or mortality did not vary by these characteristics.

In the site-specific analysis of common cancers in Korea (stomach, colorectal, liver and bile duct, and lung cancers), we did not observe a statistically significant inverse association of total combined fruit and vegetable intake with any specific cancer incidence or mortality (Supplemental Table 3).
lower risk of total cancer incidence but was nonlinearly associated with a lower risk of total cancer mortality. However, our results did not support a possible benefit of fruit intake in preventing total cancer. We evaluated the total combined fruit and vegetable intake and the association with subtypes of major cancers and found no significant inverse associations. However, because of the small number of deaths, our study might lack sufficient statistical power to detect a true association. The results of the present study should be interpreted with caution, and further studies with larger sample sizes and that include women are needed to confirm these results.

Fruit and vegetable intake is considered to be a likely protective factor against cancer because of the large number of beneficial bioactive compounds in fruits and vegetables, including carotenoids, vitamins C and E, selenium, folic acid, β-carotene, lycopene, dithiolthione, indoles, isothiocyanates, flavonoids, allium compounds, isoflavones, protease inhibitors, and dietary fiber. These components may protect cells against carcinogenesis through antioxidant activity, modulating the detoxification enzymes, stimulating the immune system, transferring the methyl groups in the DNA methylation, modulating steroid hormone metabolism, and antiproliferative effects (25, 26).

A few prospective studies have examined the association between total fruit and vegetable intake and total cancer risk (5–8, 27). The European Prospective Investigation into Cancer and Nutrition study showed a significant linear association but with a small reduction in the risk of total cancer incidence associated with total vegetable intake [RR for Q5 (≥307 g/d) vs. Q1 (<97 g/d): 0.93; P-trend: <0.001] (5). A similar association was observed for the association between fruit intake and total cancer incidence [RR for top quintile (≥367 g/d) vs. bottom quintile (<90 g/d): 0.94; P-trend: 0.006] in the NIH-AARP Diet and Health Study, elderly men who consumed large quantities of vegetables had a slightly lower risk of total cancer incidence than elderly men who consumed low quantities [RR for top quintile (1.10–3.25 cup equivalents/1000 kcal) vs. bottom quintile (<0.44 cup equivalent/1000 kcal): 0.94; P-trend: 0.004] (27). In this study, fruit intake was not associated with total cancer risk among men. However, other cohort studies conducted in Japan, Sweden, and the United States did not find any significant associations between total fruit and vegetable intake and total cancer risk, regardless of whether the intakes were evaluated separately or combined (6–8). We found that total vegetable intake was linearly associated with total cancer risk. Several characteristics of our population may differ from Western populations, such as low BMI, high rate of smoking, and low red meat intake, which could yield a clear inverse association with total vegetable intake, as we observed here. This finding warrants further studies. In addition, the differences in the types and number of food items included in the FFQs, ethnicity, the proportion of supplement use, measurement error, and the potential presence of residual or unmeasured confounding factors could be considered.

A few prospective studies reported the association between total fruit or total vegetable intake with the risk of cancer mortality. Two prospective studies have shown that higher vegetable intake conferred an 8% (12) to 70% (11) lower risk of total cancer mortality (B).
and vegetable consumption measured in our study was similar to average dietary intake (33). However, the average total fruit intake may not be as accurate as the cumulative dietary intake was assessed only at baseline, any changes in dietary intake was investigated with a validated FFQ. Second, because random measurement errors inherent in dietary assessment could have attenuated the association, although fruit and vegetable intake in our study was similar to that consumed in middle-aged men in the Korea Health and Nutrition Examination Survey (34), a nationwide dietary survey conducted among a representative sample of Korean adults. Third, although we attempted to adjust for important confounders, we could not rule out the possibility that residual or unmeasured confounding factors may exist. However, a more pronounced inverse association among nonsmokers, albeit not statistically significant possibly due to small sample size, compared with past or current smokers may suggest the possibility of minimal residual confounding variables that may explain the observed inverse association between total fruit intake and vegetable intake and total cancer risk. Although red meat intake was not a confounding factor in the association between total fruit and vegetable intake and the risks of total cancer incidence and mortality, we cannot rule out the possibility that the weak association observed for >800 g/d could be partially explained by the residual effect of risk factors correlated with fruit and vegetable intake. Finally, this study consisted of middle-aged men; therefore, the results may not be generalized to women.

In conclusion, our findings suggest that vegetable intake was linearly associated with a lower risk of total cancer incidence but was nonlinearly associated with a lower risk of total cancer mortality. However, our results did not support the association between fruit intake and total cancer mortality. Although the antimutagenic and anticarcinogenic effects of kimchi were reported in both in vitro and in vivo studies (28–31), the effect of kimchi on cancer prevention remains equivocal because of limited evidence from clinical trials or epidemiologic studies.

The strengths of this study include the use of a prospective cohort design and the long follow-up period. The consistent results between the main analysis and the secondary analysis, excluding diagnosed cancer cases within the first 2 y of follow-up, suggest that reverse causality is unlikely. We included a Korean population that consumes many vegetables (32), allowing a large contrast between total fruit and vegetable intake. To the best of our knowledge, this investigation is the first prospective study to examine the association of fruit and vegetable intake and total cancer risk and mortality in Korean middle-aged men. This study has several limitations. First, we cannot rule out the possibility that random measurement errors inherent in dietary assessment could have attenuated the association, although fruit and vegetable intake was investigated with a validated FFQ. Second, because dietary intake was assessed only at baseline, any changes in dietary intake during the follow-up period were unknown, and measuring long-term usual intake may not be as accurate as the cumulative average dietary intake (33). However, the average total fruit and vegetable consumption measured in our study was similar to consumption in middle-aged men in the Korea Health and Nutrition Examination Survey (34), a nationwide dietary survey conducted among a representative sample of Korean adults. Third, although we attempted to adjust for important confounders, we could not rule out the possibility that residual or unmeasured confounding factors may exist. However, a more pronounced inverse association among nonsmokers, albeit not statistically significant possibly due to small sample size, compared with past or current smokers may suggest the possibility of minimal residual confounding variables that may explain the observed inverse association between total fruit intake and vegetable intake and total cancer risk. Although red meat intake was not a confounding factor in the association between total fruit and vegetable intake and the risks of total cancer incidence and mortality, we cannot rule out the possibility that the weak association observed for >800 g/d could be partially explained by the residual effect of risk factors correlated with fruit and vegetable intake. Finally, this study consisted of middle-aged men; therefore, the results may not be generalized to women.

In conclusion, our findings suggest that vegetable intake was linearly associated with a lower risk of total cancer incidence but was nonlinearly associated with a lower risk of total cancer mortality. However, our results did not support the association between fruit intake and total cancer incidence and mortality. The findings from our study need to be corroborated in large prospective studies and in the Korean female population.

Acknowledgments

YC, JEL, and M-HS designed the research; J-MB, Z-ML, D-HK, M-SL, Y-OA, and M-HS conducted the research; YC, JEL, and M-HS analyzed the data; and YC and JEL wrote the paper. M-HS assumed primary responsibility for the final content. All authors read and approved the final manuscript.

### Table 4

Multivariable RRs and 95% CIs for total cancer incidence and mortality risk by total vegetable intake (in g/d), stratified by selected subgroups in Korean middle-aged men

<table>
<thead>
<tr>
<th>Total cancer incidence</th>
<th>BMI, kg/m²</th>
<th>Smoking habit</th>
<th>History of diabetes or CVD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;25</td>
<td>≥25</td>
<td>Never</td>
</tr>
<tr>
<td>n</td>
<td>987</td>
<td>342</td>
<td>228</td>
</tr>
<tr>
<td>&lt;100</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>100 to &lt;200</td>
<td>0.77 (0.64, 0.93)</td>
<td>0.92 (0.67, 1.27)</td>
<td>1.11 (0.76, 1.61)</td>
</tr>
<tr>
<td>200 to &lt;300</td>
<td>0.78 (0.64, 0.95)</td>
<td>0.97 (0.68, 1.38)</td>
<td>0.74 (0.47, 1.17)</td>
</tr>
<tr>
<td>300 to &lt;500</td>
<td>0.82 (0.66, 1.00)</td>
<td>0.92 (0.64, 1.31)</td>
<td>1.05 (0.68, 1.62)</td>
</tr>
<tr>
<td>≥500</td>
<td>0.73 (0.56, 0.94)</td>
<td>0.76 (0.48, 1.19)</td>
<td>0.55 (0.28, 1.07)</td>
</tr>
<tr>
<td>Trend</td>
<td>0.08</td>
<td>0.26</td>
<td>0.09</td>
</tr>
<tr>
<td>Interaction</td>
<td>0.89</td>
<td>0.04</td>
<td>0.38</td>
</tr>
</tbody>
</table>

| Total cancer mortality | n          | 372          | 126                      | 74                        | 422                      | 476                      | 31                       |
|                       | <100       | 1.00         | 1.00                     | 1.00                      | 1.00                     | 1.00                     |                          |
|                       | 100 to <200| 0.74 (0.55, 0.99) | 0.54 (0.32, 0.90) | 0.69 (0.36, 1.31) | 0.68 (0.52, 0.90) | 0.67 (0.52, 0.86) | 1.18 (0.42, 3.31) |
|                       | 200 to <300| 0.77 (0.56, 1.06) | 0.74 (0.44, 1.26) | 0.88 (0.40, 1.78) | 0.71 (0.44, 1.15) | 0.77 (0.58, 1.02) | 0.49 (0.14, 1.75) |
|                       | 300 to <500| 0.73 (0.52, 1.03) | 0.73 (0.42, 1.25) | 0.59 (0.23, 1.13) | 0.75 (0.55, 1.03) | 0.74 (0.55, 0.99) | 0.53 (0.14, 1.93) |
|                       | ≥500       | 0.72 (0.46, 1.18) | 0.82 (0.31, 1.27) | 0.59 (0.21, 1.59) | 0.69 (0.46, 0.99) | 0.69 (0.48, 0.98) | 0.42 (0.07, 2.50) |
| Trend                  | 0.21      | 0.52         | 0.23                      | 0.18                      | 0.18                      | 0.15                     |
| Interaction            | 0.85      | 0.01          | 0.79                      |                           |                           |                          |

1 Values are RRs (95% CIs) unless otherwise indicated. CVD, cardiovascular disease.

2 Adjusted for age at baseline (years, continuous), vigorous physical activity (≤1, 1 to <3, or ≥3 h/wk), total energy intake (kcal/d, continuous), red meat intake (g/d, continuous or missing indicator), alcohol drinking (none, 1–6 times/wk, daily, 2–3 times/d, or missing), pack-years of smoking (<0.1, 0.1 to <15, 15 to <30, or ≥30 pack-years), BMI (<18.5, 18.5 to <23, 23 to <25, ≥25, or missing), educational level (<high school, ≥high school, or missing), family history of cancer (yes or no), and fruit and vegetable intake (g/d, continuous).
References


