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Fruit and Vegetable Consumption, *Helicobacter pylori* Antibodies, and Gastric Cancer Risk: a Pooled Analysis of Prospective Studies in China, Japan and Korea

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Abstract

Epidemiological findings on the association between fruit and vegetable consumption and gastric cancer risk remain inconsistent. The present analysis included 810 prospectively ascertained non-cardia gastric cancer cases and 1,160 matched controls from the *Helicobacter pylori* Biomarker Cohort Consortium, which collected blood samples, demographic, lifestyle, and dietary data at baseline. Conditional logistic regression adjusting for total energy intake, smoking, and *H. pylori* status, was applied to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for gastric cancer risk across cohort- and sex-specific quartiles of fruit and vegetable intake. Increasing fruit intake was associated with decreasing risk of non-cardia gastric cancer (OR=0.71, 95% CI: 0.52–0.95, *p*-trend =0.02). Compared to low-fruit consumers infected with CagA-positive *H. pylori*, high-fruit consumers without evidence of *H. pylori* antibodies had the lowest odds for gastric cancer incidence (OR=0.12, 95% CI: 0.06–0.25), whereby the inverse association with high-fruit consumption was attenuated among individuals infected with CagA-positive *H. pylori* (OR=0.82, 95% CI: 0.66–1.03). To note, the small number of *H. pylori* negative individuals does influence this finding. We observed a weaker, non-dose-response suggestion of an inverse association of

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vegetable intake with non-cardia gastric cancer risk. High fruit intake may play a role in decreasing risk of non-cardia gastric cancer in Asia.

Keywords

diet; fruit; vegetables; *Helicobacter pylori*; stomach neoplasms

Gastric cancer is a major public health concern worldwide due to its frequency, limited therapies, and poor prognosis. Half of all the incident gastric cancers in the world occur in East Asia, where non-cardia gastric cancer is predominant [1].

While infection with *Helicobacter pylori* (*H. pylori*) is the leading causal factor for gastric cancer, it is generally believed that risk also is associated with other environmental factors, including diet [2]. Fruit and vegetables are rich sources of many vitamins and minerals, such as vitamin C, vitamin A, vitamin E, carotenoids, folate and flavonoids, which have been suggested to prevent the formation of nitrosamines, neutralize the action of preformed nitrosamines, modulate DNA methylation, induce detoxifying phase II enzymes, and promote apoptosis [3, 4]. With antioxidant properties, those vitamins can scavenge reactive radical species formed in the gastric mucosa, leading to reduced radical-mediated DNA damage [5]. Moreover, vitamin C may inhibit the growth of gastric cancer cells and alter *H. pylori* induced cell cycle events [6]. Currently, no clear conclusions on the association between diet and gastric cancer have been drawn from previous epidemiology research [7–9]. Some cohort studies and the majority of case-control studies have suggested that high intake of fruit and vegetables is inversely associated with gastric cancer risk, especially in non-cardia gastric cancers, while others have found no evidence of an association [8, 10–15].

Thus, this research aims to better understand the association between fruit and vegetable intake and non-cardia gastric cancer incidence in a large consortium of prospective cohort studies in East Asia, with the consideration of *H. pylori* infection as a potential confounder or effect modifier.

Material and Methods

Study subjects

The current analyses comprise 5 prospective cohort studies from the *Helicobacter pylori* Biomarker Cohort Consortium (HpBCC) in the highest gastric cancer risk countries in East Asia - China, Japan, and Korea. Incident non-cardia gastric cancer, the outcome in this study, was defined using the International Classification of Diseases for Oncology (including C16.1–C16.6, C16.8, and C16.9) and was ascertained through a combination of registry linkage and active follow-ups. For all cohorts except for Shanghai Men's Health Study (SMHS) and Shanghai Women's Health Study (SWHS), incidence density sampling was used, with one control matched on sex, age and date of biological collection chosen at random within each cohort for each non-cardia gastric cancer case from the appropriate risk sets consisting of all cohort members alive, free of cancer (except non-melanoma skin cancer), and with no history of a gastrectomy at the time of diagnosis of the index case. For

SMHS and SWHS, the same sampling scheme was used, except that two controls for every case were selected.

Since this study focused on nutrition, some of Korean Cancer Prevention Study-II (KCPS) were excluded because of missing dietary data (n=178). We also excluded those with implausible total energy data, defined as an average daily energy intake of <500 or >4,000 kcal (n=7). To keep the matched sets in the analyses, the entire set was excluded if there was not at least one case and one control in each set (n=63). Our final analysis included 810 prospectively ascertained non-cardia gastric cancer cases with 1,160 matched controls from 5 cohorts: SMHS, SWHS, Japan Public Health Center-based Prospective Study I & II (JPHC I & II), and KCPS [16–19]. Written informed consent was provided by all participants in the study. This study was approved by the Institutional Review Boards of Vanderbilt University (Nashville, TN, USA); German Cancer Research Center (Heidelberg, Germany); Shanghai Cancer Institute (Shanghai, China); National Cancer Center (Tokyo, Japan); Yonsei University (Seoul, Korea).

Diet assessment

At baseline, a comprehensive food frequency questionnaire (FFQ) was administered for members of these cohorts. The FFQs for the SWHS and SMHS contained 77 and 81 items, respectively [20, 21]. The FFQs applied in these two studies were virtually identical with the exception of four additional items in the SMHS. For each food item or food group, subjects were asked how frequently they consumed the food or food group (daily, weekly, monthly, annually, or never) over the past 12 months and then reported the amount of consumption per unit of time in liangs (1 liang=50 grams).

In JPHC I, the FFQ had 44 items and the consumption frequency of fruit and vegetables was asked using 4 categories: less than 1 day/week, 1–2 days/week, 3–4 days/week, and almost daily (5 days or more/week). For the amount of fruit and vegetable consumption, the portion size and the content of each food item were determined based on the observed median values on diet data recorded over 14–28 days by participants [22]. In JPHC II, a revised version of the FFQ was applied. The intake frequency was changed to include five categories: never, occasionally, 1–2 days/week, 3–4 days/week, almost every day (5 days or more/week) [14, 18].

In KCPS, the FFQ contained 17 items for seven food groups: (1) fish, meat, eggs, and soy bean products; (2) milk and dairy products; (3) vegetables; (4) fruits; (5) cereals and potatoes; (6) sugars and candies; and (7) fats and oil [23]. The amount of each item typically consumed per day was investigated by trained dietitians using food models. While the number of each fruit consumed everyday was asked, the vegetable intake was measured using 3 categories: none, moderate (estimated at 70 g/day), or sufficient intake (estimated at 140 g/day). Finally, the portion size was evaluated according to the list of Korean food exchanges [24].

H. pylori multiplex serology

H. pylori multiplex serology is based on a glutathione *S*-transferase capture immunosorbent assay combined with fluorescent bead technology (Luminex, Austin, Texas) to

simultaneously detect human IgA, IgM, and IgG antibodies to 15 *H. pylori* recombinantly expressed fusion proteins (UreA, Catalase, GroEL, NapA, CagA, CagM, Cagδ, HP 0231, VacA, HpaA, Cad, HyuA, Omp, HcpC, and HP 0305) [25]. Overall sero-positivity for *H. pylori* was defined as four or more sero-positive results to the 15 *H. pylori* antigens assessed, in accordance with previous validation utilizing commercial serological assay classification [25].

Statistical methods

The present analysis includes 1,970 participants (810 prospectively ascertained gastric cancer cases with 1,160 matched controls). Since the measured intake levels of fruit and vegetables varied substantially in different cohorts in this study, cut points of dietary variable sex-specific quartiles were calculated based on the distribution of intake among controls in each cohort at baseline (Supporting Information Table 7). Notably, in SMHS and SWHS, watermelon was excluded from the all fruit variable. This is because in these cohorts watermelon is eaten in great quantities, albeit seasonally, and accounts for almost half of all fruit intake [13]. Thus the contribution of watermelon to the all fruit variable, which is not on its own associated with gastric cancer risk, is large, and yet prone to measurement error. Furthermore, the watermelon intake alone was not associated with gastric cancer risk.

A series of conditional logistic regression models were constructed to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for gastric cancer risk across cohort- and sex-specific quartiles of fruit and vegetable intake. Model 1 evaluated the odds of gastric cancer incidence by fruit or vegetable intake conditioned on matched case-control sets only, without adjusting for other variables. Then, in model 2 the potential confounders of smoking (never smoker, former smoker, and current smoker) and total energy intake (kcal/day) were added. These confounders were chosen as they were associated with both the exposure (fruit and vegetable intake) and the outcome (gastric cancer incidence) but not in the causal pathway, and their inclusion significantly increased the model's fit. Model 3 adjusted for all variables in model 2 together with *H. pylori* status based on 3 categories of sero-positivity to *H. pylori* and CagA (*H. pylori* negative, *H. pylori* positive and CagA negative, *H. pylori* and CagA positive). Model 4 then adjusted for *H. pylori* using combined Omp and HP 0305 status (Omp and/or HP 0305 negative, Omp and HP 0305 positive), as these *H. pylori* proteins were previously found to be better markers than CagA of gastric cancer risk in our population [26]. With the same analysis strategy used in model 3, as an alternative, the data were calculated separately by study and then the results were pooled by meta-analysis. Education was evaluated as a potential confounder but not included in the final models, because it did not substantially alter the risk estimates (Supporting Information Table 5 and 6). Combined effect between fruit intake, and *H. pylori* and CagA status, or Omp and HP 0305 status, was calculated with adjustment of total energy intake, vegetable intake and smoking. We calculated Spearman's correlation coefficients (r) to assess colinearity between categorical variables. Tests for linear trend were performed by entering the categorical variables as continuous parameters in the models. Effect modification by either *H. pylori* and CagA status, or Omp and HP 0305 status was calculated using a likelihood ratio test to compare models with and without interaction terms. We also examined effect modification by sex and follow-up time (<5 vs. ≥5 years). Sensitivity analyses were performed excluding

cases diagnosed within one year of biological collection and their matched controls. All statistical analyses were conducted with SAS statistical software version 9.4 (SAS Institute Inc., Cary, North Carolina). *p* value of <0.05 was considered significant and all statistical tests were two-sided.

Results

Among the 1,970 participants, 54.4% (n=1,072) were from China, 40.1% (n=790) were from Japan, and 5.5% (n=108) were from Korea (Table 1). The median age at study entry was 59.5 years and the median follow-up time was 6.2 years. The median intakes for fruit and vegetables were 88.2 and 209.8 grams/day, respectively. The majority of study participants were female (58.5%), non-smokers (67.1%), sero-positive to both *H. pylori* and CagA (83.7%), and sero-positive to both Omp and HP 0305 (56.0%). Almost half of the population did not have a high school education (47.6%).

Among quartiles of fruit and vegetable consumption, the higher intake groups of both were more likely to be better educated (p <0.01 for fruit and p =0.03 for vegetables, Table 2). Higher fruit consumption quartiles included more never smokers (p <0.01). The differences among quartiles for fruit and vegetables in age, sex, and *H. pylori* status were not statistically significant.

Total fruit intake was inversely associated with non-cardia gastric cancer risk in all 4 models in this study (p <0.05, Table 3). In model 1, increasing consumption of fruit led to decreasing risks of non-cardia gastric cancer with a 31% (95% CI: 0.53–0.90) reduction observed in the fourth quartile compared to the first (p-trend <0.01). Similar trend (p-trend =0.01) and reduction (OR=0.67, 95% CI: 0.50–0.90) were shown in model 2, which additionally adjusted for smoking status and total energy intake. After adding *H. pylori* and CagA status in model 3, the descending risk was still significant (p-trend =0.02), as well as the reduction of risk (OR=0.71, 95% CI: 0.52–0.95). In model 4 adjusting for *H. pylori* using combined Omp and HP 0305 status instead of *H. pylori* and CagA, the association remained significant (OR=0.65, 95% CI: 0.48–0.88, p-trend <0.01).

Despite a suggestion of an inverse trend with increasing vegetable intake, no significant linear association was found (Table 3). We did observe a significant decrease in the second quartile in models 1 and 2 and in the third quartile in the first three models, but not in the fourth quartile.

If the data were calculated separately by study with the same variables adjusted in model 3, and then pooled by meta-analysis with fixed effect model, similar trend and reduction in both fruit and vegetable intake could be found (for fruit, Quartile 4 vs. 1, OR=0.65, 95% CI: 0.47–0.90, p-trend <0.01, p for heterogeneity 0.16; for vegetables, Quartile 4 vs. 1, OR=0.92, 95% CI: 0.67–1.26, p-trend =0.43, p for heterogeneity 0.19).

Compared to CagA-positive *H. pylori* low-fruit consumers, the strongest inverse association of gastric cancer risk was amongst those high fruit consumers without evidence of *H. pylori* antibodies (OR=0.12, 95% CI: 0.06–0.25), whereby the inverse association by increasing fruit consumption was attenuated among individuals infected with CagA-positive *H. pylori*

(OR=0.82, 95% CI: 0.66–1.03) (Table 4). For the combination of fruit intake, and Omp and HP 0305, the lowest risk group appeared in Omp negative and/or HP 0305 negative high fruit consumers with 66% reduction in risk compared to dual sero-positive Omp and HP 0305 low fruit consumers (OR=0.34, 95% CI: 0.26–0.46). Similarly, the inverse association by elevating fruit intake was not statistically significant for both Omp and HP 0305 positive group (OR=0.79, 95% CI: 0.61–1.02).

No effect modification was found by sex, time from blood draw to diagnosis, or *H. pylori* strain (data not shown). Secondary analyses that examined the fruit and vegetable association with gastric cancer excluding those cases and their matched controls diagnosed with cancer within one year of blood draw did not find differing results.

Discussion

The present study found that increasing fruit intake was associated with decreasing risk of non-cardia gastric cancer with adjustment for *H. pylori*. The most recent summary estimate from a meta-analysis of 22 cohort studies was 0.90 (95% CI: 0.83–0.98), comparing the highest to the lowest fruit consumption categories [8]. Though weaker, it is consistent with our finding (OR=0.71, 95% CI: 0.52–0.95). Our stronger findings may be due to the fact that we used a validated FFQ and adjusted for both smoking and dietary energy intake, all factors related to stronger associations in the meta-analysis cited above [20, 21, 27–29]. Among previously published prospective studies of fruit intake and non-cardia gastric cancer, two observed significant 32 to 33% decreases of risk in higher fruit consumers in all populations, somewhat stronger than the current study at a 29% reduction [14, 30]. One study found this association (50% reduction) only in men while another study with all male smokers also observed similar findings (49% reduction) [13, 15]. In our study, the association of fruit and gastric cancer was stronger for men than for women, but it was not significantly different (Quartile 4 vs. 1: OR=0.70 for men, OR=0.75 for women). In four European studies and one Japanese study, a non-significant suggestion of an inverse association was observed, with OR ranging from 0.75 to 0.90 [9, 31–34]. One American study found no association with fruit intake, although more than half of all cases were diagnosed as cardia tumors, rather than only non-cardia gastric cancer [10].

Notably, *H. pylori* status was not considered in these studies. As the strongest known risk factor for gastric cancer and its precursors, it is estimated that about 80–90% of gastric cancer cases could be attributed to *H. pylori* infection [2, 35]. Compared with *H. pylori* negative subjects, the amount of antioxidants in plasma, such as beta-carotene, vitamin C, and vitamin E, has been found to be lower among *H. pylori* positive subjects [36]. It has been suggested that with antioxidant properties, fruit and vegetables potentially ameliorate the effects of *H. pylori* by protecting the gastric epithelium from inflammatory response and preventing endogenous nitrosation [37]. In our study, the inverse association between fruit intake and non-cardia gastric cancer was most evident among high-fruit consumers not infected with a high-risk *H. pylori* (dual positivity to *H. pylori* and CagA, or dual positivity to Omp and HP 0305). Similar results were seen in the two case-control studies that examined the combined effect of fruit intake and *H. pylori* status [4, 38]. Specifically, compared to the *H. pylori*-negative high-fruit group, the *H. pylori*-positive low-fruit group

showed an increased risk in gastric cancer (OR=2.0, 95% CI: 1.2–6.7 in China; OR=10.6, 95% CI: 3.3–33.9 in Japan). The wide confidence interval in the Japanese study may be due to the small number of *H. pylori* negative cases (n=10) included in the study. Additionally, the high OR in the Japanese study could be associated with the selection of controls based on participation in a health check-up program, resulting in a particularly healthy comparison group with an unusually low prevalence of *H. pylori* for this population. If we attempt a similar categorization in the present study, we also find a strong increased risk of gastric cancer among *H. pylori*-positive low-fruit individuals, as compared to *H. pylori*-negative high-fruit group (OR=7.93, 95% CI: 3.93–16.01).

Vegetable consumption, in the present study, showed a weaker, non-dose-response suggestion of an inverse association for non-cardia gastric cancer. This finding is consistent with other comparable prospective cohort studies, except one Swedish study, which found a significant inverse association [9, 10, 13–15, 30–34]. A suggestion of a non-linear association with vegetable intake was also found in the most recent meta-analysis [8]. Some studies suggested a threshold effect where the protective effect may not increase in a stepwise manner as the consumption increases [13, 14]. This hypothesis was supported by our study, whereby only individuals in the third quartile of vegetable intake had a significant reduction in gastric cancer risk. While findings for the other quartiles suggested a similar decrease in risk, it was not statistically significant. Moreover, in Asia vegetables are typically consumed after cooking, which may change the availability of some nutrients, destruction of digestive enzymes, and the structure and digestibility of food [39].

Beyond gastric cancer, fruit and vegetable intake has also been found to be associated with other cancers. For example, the most recent summary estimate of lung cancer risk from two meta-analyses found that increasing fruit and vegetable consumption was inversely associated with lung cancer risk (for fruit intake, relative risk (RR)=0.80 (95% CI: 0.74–0.88) and 0.84 (95% CI: 0.79–0.90), respectively; for vegetable intake, RR=0.74 (95% CI: 0.67–0.82) and 0.90 (0.84–0.96), respectively) [40, 41]. Another meta-analysis found the relative risk of bladder cancer to be decreased both for fruit intake (RR=0.81; 95% CI: 0.73–0.89) and for vegetable intake (RR=0.84; 95% CI: 0.72–0.96) [42]. Citrus intake, specifically, has been found to be associated with reduced risk of esophageal cancer (OR=0.63, 95% CI: 0.52–0.75) [43]. However, the association between fruit and vegetable consumption and colon or rectal cancer was not found in an European study with more than 10-year follow-up [44].

There are a number of limitations to the present analyses. The follow-up time in this study was relatively short (median follow-up time, 6.2 years). One meta-analysis found that longer follow-up time may lead to a stronger association in fruit intake (RR=0.82 for all participants; RR=0.66 for those with follow-up period ≥10 years) [11]. In our study, when stratifying by follow-up time (≥5 years and <5 years), we observed similar trends, as the longer follow-up group obtained a lower OR for high fruit intake (Quartile 4 vs. 1: OR=0.63 and 0.78, separately). And in our study, we did not have the data for the specific types of fruit and vegetables from each cohort study. Previously a paper from our group discussed the association between the types of fruit and vegetable consumption and risk of gastric cancer in SMHS and SWHS, and no significantly differing results could be observed by specific fruit or vegetable type [13]. A similar conclusion was found in another paper from our

Japanese coauthors [31]. Additionally, socioeconomic status (SES) and alcohol intake have been regarded as potential risk factors for gastric cancer [45]. When we focused on participants without missing values in education variables (n=1,555), the most common SES variable in relevant studies, current trends were maintained (p-trend =0.04 for fruit and p =0.22 for vegetables; Supporting Information Table 5). Unfortunately, we have limited information on alcohol consumption, which has been hypothesized to play a role by some epidemiology studies [46, 47]. However, only a small proportion of Asian women drink alcohol, thus potential confounding by this variable in women is likely to be small [16, 19, 48]. Also, we only evaluated dietary intakes and did not include vitamin or mineral supplements. In Asia, the rate of vitamin supplement intake is 7.1–15.3% for different regions [49–51]. Most previous intervention studies for vitamin supplementation did not observe significant results for decreased gastric cancer risk [52]. We also did not have soy food intake for all cohorts, which has been previously found to be associated with gastric cancer risk in Asian populations [53, 54]. However, when soy food intake was added into the model among those for whom we had soy data (the SWHS and SMHS), the fruit and vegetable associations with gastric cancer did not change. Finally, because the two exposures, diet and *H. pylori* status, were assessed at the same time point, we are not able to assess causality between these two factors, a separate but also interesting question.

Our study had several strengths, including its prospective design, large study size, wide range of fruit and vegetable intake, and adjustment for most gastric cancer risk factors, especially the infection of *H. pylori*. To our knowledge, it comprises the largest number of prospectively ascertained non-cardia gastric cancer cases to examine the association of fruit and vegetable consumption with gastric cancer risk with adjustment of *H. pylori* in the high-risk region of East Asia. Additionally, we focused our analyses on non-cardia gastric cancer, which is the dominant type of gastric cancer in Asia and has a potentially different etiology compared to cardia gastric cancer [55].

In conclusion, this large prospective study in East Asia confirms the previous research and provides additional evidence that, even after adjusting for *H. pylori*, the major causal factor for gastric cancer, increased fruit consumption is inversely associated with non-cardia gastric cancer. Our study also suggests that increasing fruit intake may gain more benefits in gastric cancer etiology among individuals in East Asia not infected with the more virulent, CagA-positive strains of *H. pylori*, a finding that warrants replication.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

CagA Cytotoxin-associated antigen

CI	confidence interval
FFQ	food frequency questionnaire
H. pylori	*Helicobacter pylori*

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What's new?

This large prospective study in East Asia confirms the previous research and provides additional evidence that, even after adjusting for H. pylori, the major causal factor for gastric cancer, increased fruit consumption is inversely associated with non-cardia gastric cancer. Our study also suggests that increasing fruit intake may gain more benefits in gastric cancer etiology among individuals not infected with the more virulent, CagA-positive strains of H. pylori, a finding that warrants replication.

Table 1

Distribution of Selected Demographic Characteristics of Gastric Cancer and Matched Controls at Baseline in the *H. pylori* Biomarker Cohort Consortium

	Cases (n=810)	Controls (n=1160)	All (n=1970)
Country, n (%)			
China	361 (44.5)	711 (61.3)	1072 (54.4)
Japan	395 (48.8)	395 (34.0)	790 (40.1)
Korea	54 (6.7)	54 (4.7)	108 (5.5)
Age, years, median (IQR)	59.1 (52.3–65.3)	59.7 (52.2–65.6)	59.5 (52.2–65.4)
Follow-up time, median (IQR)	6.0 (3.1–8.8)	6.4 (3.4–9.2)	6.2 (3.3–9.1)
Fruit intake, grams/day, median (IQR)	83.4 (33.9–150.0)	94.0 (42.1–162.6)	88.2 (39.1–151.0)
Vegetable intake, grams/day, median (IQR)	188.9 (92.9–286.7)	220.0 (125.5–334.8)	209.8 (110.8–316.3)
Sex, n (%)			
Female	434 (53.6)	718 (61.9)	1152 (58.5)
Male	376 (46.4)	442 (38.1)	818 (41.5)
Smoking, n (%)			
Never smoker	496 (61.2)	826 (71.2)	1322 (67.1)
Former smoker	107 (13.2)	123 (10.6)	230 (11.7)
Current smoker	207 (25.6)	211 (18.2)	418 (21.2)
Education, n (%)			
Elementary school or less	138 (17.0)	252 (21.7)	390 (19.8)
Junior high school	216 (26.7)	331 (28.5)	547 (27.8)
High school	174 (21.5)	231 (19.9)	405 (20.6)
Professional education or above	81 (10.0)	146 (12.6)	227 (11.5)
Missing	201 (24.8)	200 (17.3)	401 (20.3)
H. pylori infection status, n (%)			
Negative	29 (3.6)	187 (16.1)	216 (11.0)
Positive	781 (96.4)	973 (83.9)	1754 (89.0)
H. pylori and CagA status, n (%)			
H. pylori−	29 (3.6)	187 (16.1)	216 (11.0)
H. pylori+ and CagA-	33 (4.1)	71 (6.1)	104 (5.3)
H. pylori+ and CagA+	748 (92.3)	902 (77.8)	1650 (83.7)
Combined Omp and HP 0305 status, n (%)			
Low risk (Omp− and/or HP 0305−)	257 (31.7)	610 (52.6)	867 (44.0)
High risk (Omp+ and HP 0305+)	553 (68.3)	550 (47.4)	1103 (56.0)

Abbreviations: IQR, interquartile range.

Table 2

Distribution of Selected Demographic Characteristics Across Quartiles of All Fruit and Vegetable Consumption at Baseline in the *H. pylori* Biomarker Cohort Consortium

	All Fruit Intake				All Vegetable Intake			
	Q1	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**
Age, years, median (IQR)	59.5 (53.1–66.3)	58.9 (51.5–65.3)	60.1 (53.3–65.3)	59.5 (52.0–64.6)	60.4 (51.9–66.2)	58.2 (51.7–65.4)	59.3 (52.9–64.9)	60.0 (53.1–65.4)
Sex, n (%)								
Female	324 (54.3)	313 (60.8)	251 (59.5)	264 (60.6)	316 (58.2)	290 (59.1)	266 (59.2)	280 (57.5)
Male	273 (45.7)	202 (39.2)	171 (40.5)	172 (39.4)	227 (41.8)	201 (40.9)	183 (40.8)	207 (42.5)
Smoking, n (%) [1]								
Never smoker	366 (61.3)	351 (68.1)	288 (68.3)	317 (72.7)	357 (65.8)	333 (67.8)	315 (70.2)	317 (65.1)
Former smoker	69 (11.6)	58 (11.3)	43 (10.1)	60 (13.8)	63 (11.5)	55 (11.2)	50 (11.1)	62 (12.7)
Current smoker	162 (27.1)	106 (20.6)	91 (21.6)	59 (13.5)	123 (22.7)	103 (21.0)	84 (18.7)	108 (22.2)
Education, n (%) [12,3]								
Elementary school or less	154 (25.8)	94 (18.3)	79 (18.7)	63 (14.5)	137 (25.2)	93 (18.9)	79 (17.5)	81 (16.6)
Junior high school	171 (28.6)	137 (26.6)	111 (26.3)	128 (29.4)	142 (26.2)	139 (28.3)	133 (29.6)	133 (27.3)
High school	115 (19.3)	108 (21.0)	86 (20.4)	96 (22.0)	97 (17.9)	109 (22.2)	95 (21.2)	104 (21.4)
Professional education or above	45 (7.5)	61 (11.8)	52 (12.3)	69 (15.8)	55 (10.1)	61 (12.4)	47 (10.5)	64 (13.1)
Missing	112 (18.8)	115 (22.3)	94 (22.3)	80 (18.3)	112 (20.6)	89 (18.2)	95 (21.2)	105 (21.6)
H. pylori infection status, n (%)								
Negative	53 (8.9)	55 (10.7)	56 (13.3)	52 (11.9)	64 (11.8)	57 (11.6)	45 (10.0)	50 (10.3)
Positive	544 (91.1)	460 (89.3)	366 (86.7)	384 (88.1)	479 (88.2)	434 (88.4)	404 (90.0)	437 (89.7)
H. pylori and CagA status, n (%)								
H. pylori−	53 (8.9)	55 (10.7)	56 (13.3)	52 (11.9)	64 (11.8)	57 (11.6)	45 (10.0)	50 (10.3)
H. pylori+ and CagA−	28 (4.7)	26 (5.0)	28 (6.6)	22 (5.1)	25 (4.6)	25 (5.1)	28 (6.3)	26 (5.3)
H. pylori+ and CagA+	516 (86.4)	434 (84.3)	338 (80.1)	362 (83.0)	454 (83.6)	409 (83.3)	376 (83.7)	411 (84.4)
Combined Omp and HP 0305 status, n (%)								
Low risk (Omp− and/or HP 0305−)	243 (40.7)	222 (43.1)	205 (48.6)	197 (45.2)	223 (41.1)	229 (46.6)	203 (45.2)	212 (43.5)
High risk (Omp+ and HP 0305+)	354 (59.3)	293 (56.9)	217 (51.4)	239 (54.8)	320 (58.9)	262 (53.4)	246 (54.8)	275 (56.5)

Abbreviations: IQR, interquartile range; Q, quartile.

[1] $p < 0.05$ among quartiles of all fruit intake.

[2] $p < 0.05$ among quartiles of all vegetable intake.

[3] Chi-square test was done within those non-missing subjects.

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Table 3

Risk of Non-cardia Gastric Cancer by All Fruit and Vegetable Intakes in the *H. pylori* Biomarker Cohort Consortium

	n, cases/controls	Model 1 [1]	Model 2 [2]	Model 3 [3]	Model 4 [4]
		OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
All fruit intake					
Q1	273/324	1	1	1	1
Q2	218/297	0.88 (0.69–1.13)	0.86 (0.67–1.11)	0.88 (0.68–1.14)	0.85 (0.66–1.10)
Q3	162/260	0.79 (0.61–1.02)	0.77 (0.59–1.01)	0.79 (0.59–1.04)	0.78 (0.59–1.03)
Q4	157/279	0.69 (0.53–0.90)	0.67 (0.50–0.90)	0.71 (0.52–0.95)	0.65 (0.48–0.88)
p-trend		<0.01	0.01	0.02	<0.01
All vegetable intake					
Q1	247/296	1	1	1	1
Q2	191/300	0.76 (0.59–0.98)	0.77 (0.60–1.00)	0.77 (0.59–1.01)	0.83 (0.64–1.09)
Q3	168/281	0.73 (0.56–0.94)	0.72 (0.55–0.95)	0.72 (0.54–0.96)	0.76 (0.57–1.01)
Q4	204/283	0.87 (0.67–1.13)	0.89 (0.66–1.18)	0.88 (0.65–1.19)	0.94 (0.70–1.26)
p-trend		0.24	0.30	0.30	0.50

Abbreviations: CI, confidence interval; OR, odds ratio; Q, quartile.

[1]Conditional logistic regression with cases and controls matched on sex, age, and date of biological collection.

[2]Conditional logistic regression with cases and controls matched on sex, age, and date of biological collection, adjusted for smoking, total energy intake, and fruit intake or vegetable intake (whichever one is not the main exposure).

[3]Conditional logistic regression with cases and controls matched on sex, age, and date of biological collection, adjusted for smoking, total energy intake, *H. pylori* and CagA status (*H. pylori* negative, *H. pylori* positive and CagA negative, *H. pylori* and CagA positive), and fruit intake or vegetable intake (whichever one is not the main exposure).

[4]Conditional logistic regression with cases and controls matched on sex, age, and date of biological collection, adjusted for smoking, total energy intake, Omp and HP 0305 status (Omp and/or HP 0305 negative, Omp and HP 0305 positive), and fruit intake or vegetable intake (whichever one is not the main exposure).

Table 4

Risk of Non-cardia Gastric Cancer by Fruit Intake and *H. pylori* and CagA Status, or Combined Omp and HP 0305 Status in the *H. pylori* Biomarker Cohort Consortium

***H. pylori* status**	**Fruit Intake**	**n, cases/controls**	**OR (95% CI)**
H. pylori positive and CagA positive	≤50th percentile	454/496	1
	>50th percentile	294/406	0.82 (0.66–1.03)
H. pylori positive and CagA negative	≤50th percentile	19/35	0.56 (0.30–1.03)
	>50th percentile	14/36	0.44 (0.23–0.85)
H. pylori negative	≤50th percentile	18/90	0.22 (0.13–0.38)
	>50th percentile	11/97	0.12 (0.06–0.25)
Omp positive and HP 0305 positive	≤50th percentile	340/307	1
	>50th percentile	213/243	0.79 (0.61–1.02)
Omp negative and/or HP 0305 negative	≤50th percentile	151/314	0.45 (0.34–0.58)
	>50th percentile	106/296	0.34 (0.26–0.46)

Abbreviations: CI, confidence interval; OR, odds ratio.

Conditional logistic regression with cases and controls matched on sex, age, and date of biological collection, adjusted for total energy intake, vegetable intake, and smoking status.