Vegetable and fruit intakes and risk of Barrett's esophagus in men and women[1–3]

Olivia M Thompson, Shirley AA Beresford, Elizabeth A Kirk, and Thomas L Vaughan

ABSTRACT

Background: Barrett's esophagus (BE) is a risk factor for esophageal adenocarcinoma. Modifiable risk factors for BE are largely unknown.

Objective: The purpose of this study was to determine whether vegetable and fruit intakes are associated with BE risk.

Design: In a case-control study based in western Washington State, we compared the vegetable and fruit intakes of 170 patients with newly diagnosed BE with those of 182 controls from the general population. Relations between vegetable and fruit intakes and BE were examined by using unconditional logistic regression to compute odds ratios (ORs) and corresponding 95% CIs.

Results: Participants in the second (adjusted OR: 0.40; 95% CI: 0.23, 0.71) and third (adjusted OR: 0.33; 95% CI: 0.17, 0.63) tertiles of vegetable intake appeared to have a lower risk of BE (P for trend = 0.048) than did participants in the first tertile of vegetable intake. Similarly, participants in the second (adjusted OR: 0.49; 95% CI: 0.28, 0.86) and third (adjusted OR: 0.39; 95% CI: 0.21, 0.75) tertiles of combined vegetable and fruit intakes had a lower risk of BE (P for trend = 0.047) than did participants in the first tertile of vegetable and fruit intakes. Similar results were obtained in subanalyses limited to patients with visible and with long-segment BE.

Conclusions: The results support previous findings that increased intakes of vegetables and of vegetables and fruit are associated with a lower risk of BE in men and women. Prospective data that examine relations between diet and BE are needed. *Am J Clin Nutr* 2009;89:890–6.

INTRODUCTION

Esophageal adenocarcinoma (EA), the most rapidly increasing cancer in the United States (1), develops from a premalignant metaplastic condition termed Barrett's esophagus (BE) (2). Many of the identified risk factors for EA and BE, such as male sex, white race, advanced age, and gastroesophageal reflux disease (GERD), are difficult or impossible to modify, whereas others, including obesity, cigarette use, and possibly decreased intakes of vegetables and fruit (3–6) are more amenable to intervention. Efforts to modify such factors should be focused not only on the neoplastic process from BE to invasive cancer, but also on the early stages of disease progression, such as during the development of GERD and BE.

Prevention strategies designed to improve diet might be particularly important to consider given that circulating concentrations of chemopreventive nutrients such as vitamin C (7) and selenium (8) are low in patients with BE (9–11). Moreover, several recent reports have indicated that healthful diets characterized by increased intakes of vegetables and fruit, which are rich sources of phytochemicals, including vitamin C and selenium, are associated with a lower risk of BE (4–6). In a population-based case-control study set in Ireland, a significant inverse association between intake of vegetables and fruit and BE was shown (4). In a community-based case-control study set in northern California, a significant inverse association was observed between BE and a "health-conscious" diet of fruit, vegetables, and nonfried fish (5). In an additional report from the US-based study, significant inverse associations were observed between BE and dietary intakes of vegetables and fruit, vitamin C, vitamin E, β-carotene, and selenium; however, long-term use of dietary supplements (ie, vitamin C, vitamin E, β-carotene, selenium, or a multivitamin) was not associated with BE risk (6). To evaluate further the relation between dietary intake of vegetables and fruit and risk of BE, we compared the number of vegetable and fruit servings consumed per day (standardized by energy intake) by patients with newly diagnosed BE with those of controls from the general population who participated in our community-based case-control study (12). We hypothesized that increased intakes of vegetables and fruit would be associated with a lower risk of BE.

SUBJECTS AND METHODS

Study participants

Case participants were defined as men and women aged 20–80 y of western Washington State with newly diagnosed BE by biopsy of the tubular esophagus, after upper endoscopy for re-

[1] From the Nutritional Sciences Program (OMT and EAK) and the Departments of Epidemiology (SAAB and TLV) and Pathobiology (EAK), University of Washington, Seattle, WA, and the Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA (OMT, SAAB, and TLV).

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[3] Reprints not available. Address correspondence to OM Thompson, Division of Cancer Control and Population Sciences, National Cancer Institute, 6130 Executive Boulevard, Room 4074A, MSC 7332, Bethesda, MD 20892-7335. E-mail: thompsonom@mail.nih.gov.

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fractory GERD symptoms between 1 October 1997 and 30 September 2000 as previously described (12). Cases were recruited through 1 of 5 participating gastroenterology clinics, where they underwent an esophageal endoscopy, and, for the purposes of the study, had 4 quadrant biopsy samples taken from columnar epithelium distal to the squamocolumnar junction within the tubular esophagus. The endoscopists documented the presence or absence of any columnar epithelium observed during esophageal endoscopy. Columnar epithelium length was later calculated by subtracting the distance between the incisors and squamocolumnar junction from the distance between the incisors and the lower esophageal sphincter or top of the gastric folds. Experienced pathologists prepared biopsy slides and documented the presence or absence of specialized metaplastic epithelium. Approximately 7.2% of eligible cases did not elect to participate.

Vegetable and fruit intakes were estimated by using a food-frequency questionnaire (FFQ). Participants whose estimated total daily energy intakes were between 500 and 4000 kcal (for women) and between 800 and 5000 kcal (for men) were considered to have valid FFQs. Of the 193 case participants who participated in the main study (12), 170 (88%) completed a valid FFQ and were therefore included in this report. Consistent with the concept of "ultra-short segment BE" (13–15), cases were defined by the presence of specialized metaplastic epithelium, termed specialized intestinal metaplasia (SIM). A subset, 87 in all, of the SIM cases also had endoscopically visible columnar epithelium, termed visible BE (VBE); 48 of these 87 participants had endoscopically visible columnar epithelium extending >2 cm above the squamocolumnar junction, termed long-segment BE (LSBE). Those in the latter 2 subgroups meet the American College of Gastroenterology criteria for defining BE (16).

Controls were selected from geographic areas in close proximity to those of case participants with the use of a modified version of the Waksberg random-digit dialing method (17, 18), where the first 5 digits of a case participant's residential telephone number were used to identify potential control participants (19, 20). Controls were matched to cases by age (±3 y) and sex. Of the 211 population controls who completed the main study (12), 182 (86%) completed a valid FFQ and were therefore included in these analyses. In the main study, participants who underwent an upper endoscopy for refractory GERD symptoms but were not diagnosed with BE were included as a second control group. We did not include GERD control participants in the current analyses, but they were included with the population controls in defining quantiles for continuous exposure or confounding variables to be consistent with other study reports. Approximately 31.3% of eligible population controls did not elect to participate in the main study. The Institutional Review Board of the Fred Hutchinson Cancer Research Center located in Seattle, WA, approved this study.

Vegetable and fruit intakes

Vegetable and fruit intakes were measured by using a self-administered, validated, 131-item FFQ designed to measure past-year dietary consumption (21) (to view a sample FFQ, *see* http://www.fhcrc.org/science/shared_resources/nutrition/ffq/gsel.pdf). Intakes were quantified by using the following method: participants were asked to choose from 9 categories that ranged from "less than one per week" to "5 or more per day" *1*) how frequently they ate a serving of vegetables (excluding salad, potatoes, or dried beans or peas) and *2*) how frequently they ate a serving of fruit (excluding juices). The number of vegetable servings reported was added to the sum of vegetable servings for lettuce, mixed lettuce, sweet potatoes and yams, and other potatoes. The total sum of vegetable servings was then divided by 365. To determine the total sum of vegetable servings for lettuce, mixed lettuce, sweet potatoes and yams, and other potatoes, participants were asked to choose how frequently they consumed specific vegetables from 9 categories that ranged from "never, or less than once per month" to "2 or more per day." Standard serving sizes were listed next to each vegetable item, and participants were asked to indicate whether their serving size was smaller, larger, or the same as the serving size listed.

The number of fruit servings reported was added to the sum of fruit servings for orange and grapefruit juice and other fruit juices. The total sum of fruit servings was then divided by 365. To determine the total sum of fruit juice servings, participants were asked to choose how frequently they consumed specific fruit juices from 9 categories that ranged from "never, or less than once per month" to "2 or more per day." Standard serving sizes were listed next to each fruit juice item, and participants were asked to indicate whether their serving size was smaller, larger, or the same as the serving size listed.

Vegetable intake, fruit intake, and vegetable and fruit intakes were examined in their continuous (natural and transformed) forms and were later categorized according to tertile distributions among GERD and population controls who completed a valid FFQ. Using the nutrient density method to correct for measurement error in the record of frequency of foods (22), vegetable intake was categorized (in servings per 1000 kcal/d) as <0.67, 0.67–1.23, and ≥1.24; fruit intake was categorized (in servings per 1000 kcal/d) as <0.44, 0.44–0.99, and ≥1.00; and vegetable and fruit intake was categorized (in servings per 1000 kcal/d) as <1.24, 1.24–2.30, and ≥2.31. Participants in the lowest category of vegetable intake, fruit intake, and vegetable and fruit intake served as the referent group.

Additional exposure information

Study participants provided additional medical and lifestyle data through in-person, structured interviews with trained interviewers, who also took anthropometric measurements. We considered factors with a known association with vegetable and fruit intake and/or BE as potential confounders. Selected variables were sex, age (as a continuous variable in years and grouped by the following age categories: 20–39, 40–59, or 60–80 y), race or ethnicity (non-Hispanic whites, Hispanics, or other), educational attainment (grouped by the following education categories: grade/high/technical school graduate/1–2 y of college education, 3–4 y of college education, or ≥5 y of college education), annual income (grouped by the following income categories, in US dollars: <$45,000, $45,000–$74,999, or ≥$75,000), past 12-mo health insurance coverage (yes or no), past 12-mo medical-care attainment difficulty (yes or no), cigarette use (as a continuous variable in pack-years; and ever or never smoked greater than one cigarette per day for ≥6 mo), heartburn (grouped by the following frequency categories: less than once per week or once per week or more), regurgitation (grouped by the following frequency categories: less than once per week or once per week or more), body mass index [BMI; in weight (kg)/height^2 (m), as a continuous variable], waist-to-hip ratio (WHR; in inches, as a continuous variable), and estimated daily energy intake (as a continuous variable in kcal).

Statistical methods

We examined participant characteristics using proportions and mean values with corresponding SDs and SEs. Pearson correlations, the Student's *t* test, and the Mantel-Haenszel chi-square test were used to explore univariate relations between participants' characteristics and both vegetable and fruit intakes and BE.

To explore the relation between vegetable and fruit intakes and BE, we computed odds ratios (ORs) and corresponding 95% CIs using unconditional logistic regression in a series of regression models. We regressed BE first on vegetable intake, second on fruit intake, and third on vegetable and fruit intake in models that included cases with SIM, VBE, and LSBE. Models were shown as adjusted for sex and continuous age; and sex, continuous age, categorical cigarette use, BMI, WHR, and total daily energy intake. We decided a priori to adjust for sex, age, race or ethnicity, cigarette use, BMI, WHR, and total daily energy intake; participant race or ethnicity was not included in adjusted models because of the small number of nonwhite participants, but we ran all models both with and without nonwhite participants. Additionally, we examined models both with and without adjustment for GERD symptoms (ie, heartburn and regurgitation) and both with and without adjustment for past 12-mo health insurance coverage and past 12-mo medical care attainment difficulty. We reported ORs and 95% CIs for point estimates that were altered by $\geq$10%.

Educational attainment and annual income were evaluated as possible confounding variables, but were not included in adjusted models because they were not independently associated with both vegetable and fruit intake and BE, and they did not alter the ORs for BE risk by $\geq$10%. In addition, in preliminary analyses of our data, we evaluated the relation between use of dietary supplements (ie, a multivitamin/mineral supplement) and risk of BE. We did not observe an interaction of use of dietary supplements on the relation of vegetable and fruit intakes and risk of BE, and thus we did not control for use of dietary supplements in our regression analyses.

In summary, final analyses adjusted for sex, age, cigarette use, BMI, WHR, and total daily energy intake. Tests for linear trends were performed by modeling vegetable intake, fruit intake, and vegetable and fruit intake in their natural continuous forms. *P* values reported were those that corresponded to linear trends in multivariate-adjusted models. For all analytic tests, a 2-sided probability of $P \leq 0.05$ was considered statistically significant. All analyses were conducted using SAS version 9.1 (SAS Institute, Cary, NC).

RESULTS

Participant characteristics are presented in **Table 1**. Included in this study were 170 BE cases with SIM, 87 of whom also had VBE and 48 of whom also had LSBE, and 182 controls from the general population. The vast majority of participants were non-Hispanic whites, with males representing 62% of the controls and from 58% to 75% of the cases. In each study group, the mean age was ≈55 y. Most of the participants reported earning $\geq$\$45,000 annually and having some college-level education. Moreover, most participants (cases and controls) reported having health insurance coverage within the past 12 mo and not having difficulty getting medical care when needed. From 60% to 69% of cases and 48% of controls reported smoking at least one cigarette per day for $\geq$6 mo. Additionally, from 77% to 79% of cases and 28% of controls reported heartburn at a frequency of once per week or more; from 31% to 41% of cases and 11% of controls reported regurgitation at a frequency of once per week or more. Across study groups, the mean BMI ranged from 28.0 $\pm$ 5.3 to 30.1 $\pm$ 5.2, and the mean WHR ranged from 0.89 $\pm$ 0.12 to 0.94 $\pm$ 0.07. Moreover, the mean energy intake ranged from 1679.7 $\pm$ 703 to 1869.1 $\pm$ 698 kcal/d, and the mean vegetable and fruit intake ranged from 2.6 $\pm$ 2.1 to 3.3 $\pm$ 1.8 servings/d.

Adjusted ORs and 95% CIs for vegetable and fruit intake and BE risk for SIM case participants (n = 170) and controls are presented in **Table 2**. In all models, participants in the second (multivariate-adjusted OR: 0.40; 95% CI: 0.23, 0.71) and third (multivariate-adjusted OR: 0.33; 95% CI: 0.17, 0.63) tertiles of vegetable intake had a lower BE risk (*P* for trend = 0.048) than did participants in the first tertile of vegetable intake. Furthermore, whereas fruit intake alone was not associated with BE risk, participants in the second (multivariate-adjusted OR: 0.49; 95% CI: 0.28, 0.86) and third (multivariate-adjusted OR: 0.39; 95% CI: 0.21, 0.75) tertiles of vegetable and fruit intake had a lower BE risk (*P* for trend = 0.047) than did participants in the first tertile of vegetable and fruit intake.

Adjusted ORs and 95% CIs for vegetable and fruit intake and BE risk in the VBE case participants (n = 87) and controls are presented in **Table 3**. In all models, participants in the second (multivariate-adjusted OR: 0.45; 95% CI: 0.24, 0.87) and third (multivariate-adjusted OR: 0.24; 95% CI: 0.11, 0.55) tertiles of vegetable intake had a lower BE risk (*P* for trend = 0.030) than did participants in the first tertile of vegetable intake. Furthermore, whereas fruit intake alone was not associated with BE risk, participants in the second (multivariate-adjusted OR: 0.50; 95% CI: 0.26, 0.97) and third (multivariate-adjusted OR: 0.31; 95% CI: 0.14, 0.68) tertiles of vegetable and fruit intake had a lower BE risk (*P* for trend = 0.036) than did participants in the first tertile of vegetable and fruit intake.

Adjusted ORs and 95% CIs for vegetable and fruit intake and BE risk in the LSBE case participants (n = 48) and controls are presented in **Table 4**. In all models, participants in the second (multivariate-adjusted OR: 0.32; 95% CI: 0.14, 0.75) and third (multivariate-adjusted OR: 0.24; 95% CI: 0.09, 0.65) tertiles of vegetable intake had a lower BE risk (*P* for trend = 0.003) than did participants in the first tertile of vegetable intake. Furthermore, whereas fruit intake alone was not associated with BE risk, participants in the second (multivariate-adjusted OR: 0.41; 95% CI: 0.18, 0.96) and third (multivariate-adjusted OR: 0.25; 95% CI: 0.09, 0.70) tertiles of vegetable and fruit intake had a lower BE risk (*P* for trend = 0.004) than did participants in the first tertile of vegetable and fruit intake.

To investigate whether the association between vegetable and/or fruit intakes and BE risk might be mediated through GERD symptoms, we carried out additional analyses controlling for frequency of heartburn and regurgitation. ORs were similar to the

TABLE 1
Characteristics of controls and case participants with specialized intestinal metaplasia (SIM), visible Barrett's esophagus (VBE), and long-segment Barrett's esophagus (LSBE)

Characteristic	Controls (n = 182)	SIM cases (n = 170)	VBE cases (n = 87)	LSBE cases (n = 48)
Sex [n (%)]				
Male	113 (62)	98 (58)	62 (71)	36 (75)
Female	69 (38)	72 (42)	25 (29)	12 (25)
Race and ethnicity [n (%)]				
Non–Hispanic white	162 (89)	142 (83)	78 (90)	47 (98)
Hispanic	4 (2)	8 (5)	3 (3)	0 (0)
Other	16 (9)	20 (12)	6 (7)	1 (2)
Educational attainment [n (%)]				
<3 y of college	76 (42)	91 (54)	44 (50)	34 (71)
3–4 y of college	58 (32)	45 (26)	25 (29)	11 (23)
≥5 y of college	48 (26)	34 (20)	18 (21)	3 (6)
Annual income [n (%)][1]				
<$45,000	54 (31)	50 (32)	25 (32)	16 (36)
$45,000–$74,999	51 (29)	48 (31)	22 (28)	14 (32)
≥$75,000	70 (40)	57 (37)	32 (40)	14 (32)
Health insurance coverage, past 12 mo [n (%)]				
Yes	173 (95)	162 (95)	82 (94)	43 (90)
No	9 (5)	8 (5)	5 (6)	5 (10)
Medical care attainment difficulty, past 12 mo [n (%)]				
Yes	178 (98)	165 (97)	85 (98)	46 (96)
No	4 (2)	5 (3)	2 (2)	2 (4)
Cigarette use [n (%)]				
Ever used	88 (48)	108 (64)	52 (60)	33 (69)
Never used	94 (52)	62 (36)	35 (40)	15 (31)
Heartburn [n (%)][2]				
Up to once per week	131 (72)	39 (23)	22 (25)	10 (21)
Once per week or more	50 (28)	131 (77)	65 (75)	38 (79)
Regurgitation [n (%)][3]				
Up to once per week	159 (89)	100 (59)	60 (69)	32 (67)
Once per week or more	20 (11)	70 (41)	27 (31)	16 (33)
Age (y)	53.3 ± 12.3[4]	54.4 ± 12.9	54.1 ± 12.1	56.1 ± 13.3
BMI (kg/m^2)[5]	28.0 ± 5.3	29.6 ± 5.4	29.4 ± 5.3	30.1 ± 5.2
Waist-to-hip ratio[6]	0.89 ± 0.12	0.90 ± 0.11	0.92 ± 0.08	0.94 ± 0.07
Energy intake (kcal/d)	1679.7 ± 703	1724.5 ± 703	1813.6 ± 729	1869.1 ± 698
Vegetable intake (servings/d)	1.8 ± 1.1	1.6 ± 1.1	1.5 ± 1.1	1.4 ± 0.91
Fruit intake (servings/d)	1.4 ± 1.2	1.2 ± 1.2	1.3 ± 1.4	1.2 ± 1.4
Vegetable and fruit intake (servings/d)	3.3 ± 1.8	2.8 ± 1.9	2.7 ± 2.1	2.6 ± 2.1

[1] Control: n = 175; SIM cases: n = 155; VBE cases: n = 79; LSBE cases: n = 44.
[2] Control: n = 181.
[3] Control: n = 179.
[4] Arithmetic mean ± SD (all such values).
[5] Control: n = 180.
[6] Control: n = 177; SIM cases: n = 168.

estimates without adjustment for GERD symptoms. For example, the ORs comparing extreme tertiles of vegetable and fruit intakes for cases with SIM and controls changed from 0.39 (95% CI: 0.21, 0.75) to 0.43 (95% CI: 0.21, 0.91) when adjusted for heartburn and to 0.47 (95% CI: 0.24, 0.93) when adjusted for regurgitation. Additionally, to investigate whether the association between vegetable and/or fruit intakes and BE risk was confounded by factors related to medical care access, we carried out additional analyses controlling for past 12-mo health insurance coverage and past 12-mo medical-care attainment difficulty. ORs were not altered by the inclusion of either variable (entered separately or combined) into models.

DISCUSSION

The primary purpose of this study was to determine whether standardized measures of vegetable and fruit intakes were associated with BE risk. Using multivariate models adjusted for sex, age, cigarette use, BMI, WHR, and total daily energy intake, we found a reduction in BE risk associated with *1*) a vegetable intake above the lower tertile of daily intake and *2*) a total vegetable and fruit intake above the lower tertile of daily intake. Our finding that increased vegetable and fruit intake is associated with a lower BE risk is consistent with recently published reports by Kubo et al (6) and Anderson et al (4). Kubo et al published data from a community-based case-control study of

TABLE 2
Odds ratios and 95% CIs for vegetable and fruit intake and risk of Barrett's esophagus in cases with specialized intestinal metaplasia and controls ($n = 352$)

Intake	Cases:controls	Model A[1]	Model B[2]	P for trend[3]
Vegetables (servings/1000 kcal/d)				0.048
<0.67	69:44	1.0	1.0	
0.67–1.23	54:69	0.43 (0.25, 0.73)	0.40 (0.23, 0.71)	
≥1.24	47:69	0.30 (0.16, 0.55)	0.33 (0.17, 0.63)	
Fruit (servings/1000 kcal/d)				0.191
<0.44	63:55	1.0	1.0	
0.44–0.99	56:65	0.67 (0.40, 1.13)	0.73 (0.42, 1.26)	
≥1.00	51:62	0.61 (0.36, 1.06)	0.76 (0.42, 1.36)	
Vegetables and fruit (servings/1000 kcal/d)				0.047
<1.24	71:48	1.0	1.0	
1.24–2.30	53:65	0.49 (0.29, 0.84)	0.49 (0.28, 0.86)	
≥2.31	46:69	0.34 (0.19, 0.60)	0.39 (0.21, 0.75)	

[1] Adjusted for sex and continuous age.
[2] Adjusted for sex, categorical cigarette use, continuous age, BMI, waist-to-hip ratio, and total daily energy intake (kcal). Control: $n = 174$; cases: $n = 168$.
[3] P values derived from tests for linear trends when vegetable, fruit, and vegetable and fruit servings were modeled in their continuous forms in models adjusted for age, sex, cigarette use, BMI, waist-to-hip ratio, and total daily energy intake (kcal).

BE conducted in northern California between 2002 and 2005. In that study, vegetable and fruit intakes were determined by using an FFQ designed to measure past-year dietary consumption and were quantified in median servings per day. Compared with a vegetable and fruit intake of 2.0 median servings per day, an intake of 8.3 median servings per day was associated with the greatest reduction in BE risk (OR: 0.27; 95% CI: 0.15, 0.50) in the multivariate-adjusted model of BE patients and population controls. Importantly, consideration of long-term dietary supplement use did not substantially alter the observed association. Anderson et al published data from a population-based case-control study of BE and EA conducted in Ireland between 2002 and 2004. In that study, vegetable and fruit intakes were determined by using an FFQ designed to measure dietary consumption 5 y before the study's initiation and were quantified in weekly frequencies. Compared with a vegetable and fruit intake frequency of <20 times/wk, a frequency of 20–34 times per week was associated with a lower BE risk (OR: 0.50; 95% CI: 0.30, 0.84) in the multivariate-, GERD-adjusted model). A similar, but smaller effect size was shown for a like association between vegetable and fruit intake and EA risk, which, although expected (23), could suggest that the protective effect of an increased intake of vegetables and fruit against EA is more limited once the disease process has advanced.

This suggestion is difficult to evaluate, however, because few other studies have examined this possibility. Most of the

TABLE 3
Odds ratios and 95% CIs for vegetable and fruit intake and risk of Barrett's esophagus (BE) in cases with visible BE and controls ($n = 269$)

Intake	Cases:controls	Model A[1]	Model B[2]	P for trend[3]
Vegetables (servings/1000 kcal/d)				0.030
<0.67	39:44	1.0	1.0	
0.67–1.23	31:69	0.47 (0.25, 0.87)	0.45 (0.24, 0.87)	
≥1.24	17:69	0.23 (0.11, 0.50)	0.24 (0.11, 0.55)	
Fruit (servings/1000 kcal/d)				0.208
<0.44	39:55	1.0	1.0	
0.44–0.99	23:65	0.49 (0.26, 0.92)	0.55 (0.28, 1.06)	
≥1.00	25:62	0.59 (0.31, 1.13)	0.70 (0.35, 1.39)	
Vegetables and fruit (servings/1000 kcal/d)				0.036
<1.24	41:48	1.0		
1.24–2.30	28:65	0.47 (0.25, 0.88)	0.50 (0.26, 0.97)	
≥2.31	18:69	0.28 (0.13, 0.58)	0.31 (0.14, 0.68)	

[1] Adjusted for sex and continuous age.
[2] Adjusted for sex, categorical cigarette use, continuous age, BMI, waist-to-hip ratio, and total daily energy intake (kcal). Control: $n = 174$.
[3] P values derived from tests for linear trends when vegetable, fruit, and vegetable and fruit servings were modeled in their continuous forms in models adjusted for age, sex, cigarette use, BMI, waist-to-hip ratio, and total daily energy intake (kcal).

TABLE 4
Odds ratios and 95% CIs for vegetable and fruit intake and risk of Barrett's esophagus (BE) in cases with long-segment BE and controls ($n = 230$)

Intake	Cases:controls	Model A[1]	Model B[2]	*P* for trend[3]
Vegetables (servings/1000 kcal/d)				0.003
<0.67	24:44	1.0	1.0	
0.67–1.23	14:69	0.32 (0.15, 0.71)	0.32 (0.14, 0.75)	
≥1.24	10:69	0.21 (0.08, 0.53)	0.24 (0.09, 0.65)	
Fruit (servings/1000 kcal/d)				0.081
<0.44	23:55	1.0	1.0	
0.44–0.99	14:65	0.47 (0.22, 1.04)	0.55 (0.24, 1.23)	
≥1.00	11:62	0.40 (0.17, 0.95)	0.49 (0.20, 1.24)	
Vegetables and fruit (servings/1000 kcal/d)				0.004
<1.24	25:48	1.0	1.0	
1.24–2.30	14:65	0.35 (0.16, 0.78)	0.41 (0.18, 0.96)	
≥2.31	9:69	0.20 (0.08, 0.51)	0.25 (0.09, 0.70)	

[1] Model A was adjusted for sex and continuous age.

[2] Adjusted for sex, categorical cigarette use, continuous age, BMI, waist-to-hip ratio, and total daily energy intake (kcal). Control: $n = 174$.

[3] *P* values derived from tests for linear trends when vegetable, fruit, and vegetable and fruit servings were modeled in their continuous forms in models adjusted for age, sex, cigarette use, BMI, waist-to-hip ratio, and total daily energy intake (kcal).

published data come from case-control studies (4, 24–30) and cohort studies (31, 32) of vegetable and/or fruit intakes and EA. Data from case-control studies show that the population attributable risk of EA is ≈15% for consuming <2 servings of vegetables and fruits per day (24) and that increased intakes of vegetables and/or fruits are associated with a lower risk of EA (4, 25–30). However, these findings are not supported by results from 2 cohort studies (31, 32). Whereas it is possible that vegetable and fruit intakes were not measured at the most relevant time period for EA development, prospectively designed studies are not subject to recall or selection biases, both of which affect retrospective studies and could bias the true association between intake of vegetables and/or fruit and EA away from the null.

Our study of vegetable and fruit intakes and BE had several limitations. As for participants in the retrospective case-control studies of vegetable and fruit intakes and EA, participants in our study were selected on the basis of the study's outcome and therefore may have recalled typical diet and other exposure histories differently depending on case status, which may have resulted in recall biases in directions difficult to predict. However, the psychological impact of a diagnosis of BE is likely to be less than that of a cancer diagnosis, and the potential for bias may be correspondingly less. In addition, because persons who experience GERD-related symptoms (ie, heartburn and regurgitation) are counseled to make dietary changes that include reducing their intake of citrus fruit and juices and tomatoes and tomato-based products (33), it is possible that the BE patients changed their diet in response to GERD-related symptoms and before their diagnosis of BE. However, the evidence published to date suggests that, with regard to vegetable and fruit intake, this is not the case (34). We note that adjustment for frequency of GERD symptoms did not materially change the relative risk estimates for vegetables and fruit, which suggests that the associations we observed cannot be explained by the avoidance of certain fruit or vegetables by persons with more frequent GERD.

Selection bias remains a concern, despite the use of population controls. We did not have covariate data for the cases and controls who did not elect to participate in the main study; it is possible that those who did participate differed from those who did not participate. Of particular relevance, our case participants might not be representative of individuals with BE from the general population because they were required to undergo an upper endoscopy to be diagnosed with BE. We attempted to control for possible selection biases in a number of ways, however, including selecting a matched control from the same phone exchange as a case and adjusting statistically (as needed) for the possible confounding effects of demographic, biobehavioral, and medical-care access factors related to both vegetable and/or fruit intake and the likelihood of undergoing an endoscopy. Of note, we did not have information for physical activity, a behavior that is positively associated with vegetable and fruit intake (35); therefore, we were unable to control for differences in energy expenditure between cases and controls. Another limitation is that, because of the small number of nonwhite participants, we were unable to consider the effect of participant race or ethnicity on BE risk. However, the ORs in models that excluded nonwhite participants were not appreciably different from models that included nonwhite participants.

In summary, data from our study show that, in line with the national recommendation for Americans to increase their consumption of fruit and vegetables to improve health (36), vegetable intakes of ≈2.5 servings per 2000 kcal/d and vegetable and fruit intakes of ≈4.6 servings per 2000 kcal/d are associated with the greatest reduction in BE risk among men and women. These findings add to the limited number of published epidemiologic studies of diet and BE, several of which support adoption of a plant-based diet that includes a variety of fruit and vegetables to protect against EA early in its development, before the onset of either GERD or BE. Prospective data that examine relations between fruit and vegetable intakes (as well as other dietary patterns) and occurrence of BE are needed.

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