Fruit and vegetable intake and risk of cancer: a prospective cohort study[1–3]

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ABSTRACT

Background: There is probable evidence that some types of fruit and vegetables provide protection against many cancers.

Objective: We hypothesized that fruit and vegetable intakes are inversely related to the incidence of total cancers among women and men aged >50 y.

Design: We performed a prospective study among the cohort of the National Institutes of Health–AARP Diet and Health Study. We merged the MyPyramid Equivalents Database (version 1.0) with food-frequency-questionnaire data to calculate cup equivalents for fruit and vegetables. From 1995 to 2003, we identified 15,792 and 35,071 cancer cases in 195,229 women and 288,109 men, respectively. We used Cox proportional hazards models to estimate multivariate relative risks (RRs) and 95% CIs associated with the highest compared with the lowest quintile (Q) of fruit and vegetable intakes.

Results: Fruit intake was not associated with the risk of total cancer among women ($RR_{Q5\ vs\ Q1} = 0.99$; 95% CI: 0.94, 1.05; P trend = 0.059) or men ($RR_{Q5\ vs\ Q1} = 0.98$; 95% CI: 0.95, 1.02; P for trend = 0.17). Vegetable intake was not associated with risk of total cancer among women ($RR_{Q5\ vs\ Q1} = 1.04$; 95% CI: 0.98, 1.09; P for trend = 0.084), but was associated with a significant decrease in risk in men ($RR_{Q5\ vs\ Q1} = 0.94$; 95% CI: 0.91, 0.97; P trend = 0.004). This significant finding among men was no longer evident when we limited the analysis to men who never smoked ($RR_{Q5\ vs\ Q1} = 0.97$; 95% CI: 0.91, 1.04; P for trend = 0.474).

Conclusions: Intake of fruit and vegetables was generally unrelated to total cancer incidence in this cohort. Residual confounding by smoking is a likely explanation for the observed inverse association with vegetable intake among men. *Am J Clin Nutr* 2009;89:347–53.

INTRODUCTION

The 20-fold variation in risk of many cancers across geographic regions suggests that environmental factors, such as diet, might be important in the respective etiologies of cancers (1). On the basis of international variation, time trends, and epidemiologic research, it has been estimated that 30% of cancer could be explained by diet (2) and that fruit and vegetable intake could potentially prevent 5–12% of cancers (3).

Fruit and vegetables are rich sources of nutrients (eg, fiber, vitamins, carotenoids, and phytochemicals) that have anticarcinogenic properties. These nutrients and bioactive compounds have antioxidant and antiproliferative activities, modulate steroid hormone concentrations and metabolism, and stimulate the immune system and synthesis and methylation of DNA (4).

The 2007 report *Food, Nutrition, Physical Activity and the Prevention of Cancer: A Global Perspective* by the World Cancer Research Fund and American Institute for Cancer Research indicated a probable protective role for fruit, vegetables, and their constituents against cancers of the esophagus, head and neck, stomach, lung, colorectum, pancreas, and prostate (5). However, no associations with specific cancer sites were found to be "convincing," which indicated the need for further research (5). We sought to investigate the association of fruit and vegetable intake and cancer incidence in a very large prospective cohort of men and women aged >50 y with a wide range of intakes. Given the probable evidence for many of the leading sites of cancer incidence, we hypothesized that fruit, vegetable, and fruit and vegetable intakes are inversely related to the incidence of total cancers.

SUBJECTS AND METHODS

Subjects

The National Institutes of Health (NIH)–AARP Diet and Health Study was initiated in 1995–1996 with the mailing of a self-administered questionnaire to 3.5 million AARP members aged 50–71 y from 6 US states (California, Florida, Louisiana, New Jersey, North Carolina, and Pennsylvania) and 2 metropolitan areas (Atlanta, GA, and Detroit, MI). The design was reported previously (6), but a brief description follows.

Of the 566,402 respondents (339,669 men and 226,733 women) who filled out the survey in satisfactory detail and consented to be in the study, we excluded those who indicated that they were proxies for the intended respondents ($n = 15,760$), had a prevalent cancer other than nonmelanoma skin cancer at baseline ($n = 51,193$), had self-reported end-stage renal disease at baseline ($n = 997$), and had a cancer cause of death record and no cancer registry record ($n = 3,876$). We further excluded individuals who reported ex-

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treme intakes (>2 times the interquartile range of sex-specific Box-Cox log-transformed intakes) of total energy ($n = 4382$) and of fruit and vegetables (continuous and nutrient densities) ($n = 6,856$) to account for erroneous overreporting and underreporting of foods. After these primary exclusions, the analytic cohort consisted of 288,109 men and 195,229 women. For the analyses of cancers of the ovary and uterus, we excluded women who had self-reported bilateral oophorectomy ($n = 52,499$) or hysterectomy ($n = 95,857$) at baseline, respectively.

Cancer ascertainment

Cases were identified through probabilistic linkage with 8 states and 3 additional state cancer registry databases, certified by the North American Association of Central Cancer Registries as being ≥90% complete within 2 y of cancer occurrence (6). We recently expanded our cancer registry ascertainment area by 3 states (Texas, Arizona, and Nevada) to capture cancer cases occurring among participants who moved to those states during follow-up. The case ascertainment method used in the study detected 90% of all cancer cases in our cohort (7).

We counted as incident cancer cases only those who were both invasive and the first malignancy diagnosed during the follow-up period (through 31 December 2003). Cancers were defined on the basis of criteria from the Surveillance Epidemiology and End Results Program and the International Classification of Diseases for Oncology (8). For reasons of statistical power, only cancers with >50 cases in a sex-combined cohort were considered in site-specific analyses.

Dietary assessment

At baseline, dietary intakes were assessed with a self-administered 124-item food-frequency questionnaire (FFQ), which was an earlier grid-based version of the diet history questionnaire developed at the National Cancer Institute. Participants reported their usual frequency of intake and portion size over the past 12 mo according to 3 predefined categories of portion size and 10 predefined frequency categories ranging from "never" to "≥6 times/d" for beverages and from "never" to "≥2 times/d" for foods. The food items, portion sizes, and nutrient database for this FFQ were constructed by using Subar et al's (9) method from the US Department of Agriculture 1994–1996 Continuing Survey of Food Intake by Individuals. We merged the MyPyramid Equivalents Database (MPED) version 1.0 (10) with the FFQ data to calculate cup equivalents for fruit and vegetables (1 cup = 237 mL). We excluded white potatoes from the vegetable group. In general, a cup equivalent is 1 cup of raw or cooked fruit or vegetable, 1 cup of 100% juice, 2 cups of raw leafy greens, or 0.5 cup of dried fruit.

The FFQ used in the study was evaluated in a calibration study by using 2 nonconsecutive 24-h dietary recalls in 2053 participants (11). When the 26 nutrient constituents examined in the FFQ were adjusted for reported energy intake, estimated correlations with intake in the reference method ranged from 0.36 to 0.70 for women and from 0.40 to 0.76 for men (11). Estimated correlations of fruit and vegetable intake between the FFQ and the reference method were 0.61 for women and 0.72 for men (11). We also collected information on demographic characteristics, medical history, and lifestyle characteristics at baseline.

Statistical analysis

Multivariate relative risks (RRs) and 2-sided 95% CIs were estimated with Cox proportional hazards models using the SAS PROC PHREG procedure (version 9.1.3; SAS Institute, Cary, NC). Person-years of follow-up time were calculated from the date of the baseline questionnaire until the date of a cancer diagnosis, death, move out of the registry areas, or end of follow-up, whichever came first. The proportional hazards assumption was evaluated by modeling an interaction term of time with total fruit and vegetable intake, and no significant deviations were found. The relative risks of all and site-specific cancers were estimated according to sex-specific quintiles of intake of fruit or vegetable cup equivalents/1000 kcal. The test for linear trend across categories of fruit and vegetable intakes was performed by assigning participants the median value of their categories, creating a continuous variable from those values, and entering that variable in a regression model.

Multivariate models were adjusted for age, race-ethnicity (non-Hispanic white, non-Hispanic black, and others), education (less than high school, high school graduate, some college, and college graduate or post graduate), marital status (married or unmarried), body mass index (in kg/m^2; <18.5, 18.5 to <25, 25 to <30, 30 to <35, or ≥35), family history of any cancer (yes or no), physical activity (never or rarely, 1–3 times/mo, or 1–2, 3–4, or ≥5 times/wk), smoking (never, ≤20 cigarettes/d in the past, >20 cigarettes/d in the past, currently ≤20 cigarettes/d, and currently >20 cigarettes/d), alcohol consumption (0, <5, 5 to <15, 15 to <30, or ≥30 g/d), menopausal hormone therapy (never, past, or current) (MHT), and total energy intake. To adjust for energy intake, we used the nutrient density method. We divided fruit and vegetable intake by total energy intake (per 1000 kcal) and also included total energy from all dietary sources in the models. Models for fruit intake also were adjusted for vegetable intake, and models for vegetable intake were adjusted for fruit intake. For categorical variables, an indicator variable for missing responses in each covariate was created, if applicable.

In multivariate models for bladder, esophageal, head and neck, pancreatic, lung, and total cancer, we used a more detailed cigarette smoking variable that incorporated smoking status (never, former, or current), time since quitting smoking (≥10 y ago, 5–9 y ago, 1–4 y ago, within the past year, or current smoker), and smoking dose (1–10 cigarettes/d, 11–20 cigarettes/d, 21–30 cigarettes/d, 31–40 cigarettes/d, 41–60 cigarettes/d, ≥60 cigarettes/d, or missing) to better control for smoking. In the lung and total cancer analyses, because of the potential for residual confounding by smoking, we chose to additionally exclude cases with missing smoking information (12). For all statistically significant associations found, we ran additional analyses that were restricted to never smokers. The proportion of never-smokers was 29% for men and 44% for women.

RESULTS

Descriptive characteristics of the study population by sex and quintiles of fruit and vegetable intakes are provided in **Table 1**. All comparisons were statistically significant at $P < 0.001$. For both fruit intake and vegetable intake, as compared with the lowest quintile (Q1), women and men in the highest quintile (Q5) of intake were older, more educated, more likely to exercise ≥5 times/wk, and less likely to be current smokers or have

TABLE 1
Descriptive statistics for the study population by quintile (Q) of fruit and vegetable intake[1]

	Fruit				Vegetable			
	Women (n = 195,229)		Men (n = 288,109)		Women (n = 195,229)		Men (n = 288,109)	
	Q1	Q5	Q1	Q5	Q1	Q5	Q1	Q5
Fruit (cup equivalents/1000 kcal)[2]	0.4	2.4	0.3	1.4	0.9	1.4	0.7	1.2
Vegetable (cup equivalents/1000 kcal)[2]	0.7	1.1	0.5	0.8	0.4	1.4	0.8	1.3
Mean age (y)[3]	60.9 ± 0.03	62.4 ± 0.03	61.1 ± 0.02	62.7 ± 0.02	61.7 ± 0.03	61.9 ± 0.03	61.9 ± 0.02	62.4 ± 0.02
White, non-Hispanic (%)	92.6	83.6	94.3	89.2	87.4	89.3	91.1	91.8
College or postcollege (%)	48.7	56.1	60.4	68.9	45.4	62	57.7	72.3
Married (%)	44.9	41.1	83.9	83.4	38.9	44.7	81.8	85.1
BMI $<$ 25[4] (%)	40.1	46.7	27.4	31.6	14.4	45.5	29.2	29.8
Family history of any cancer (%)	51.7	49.8	47.2	45.4	50.9	50.7	46.7	46.1
Current smoker (%)	26.6	7.8	21.8	4.12	20.6	10.3	16.9	6.2
Physical activity ≥5 times/wk (%)	10.5	21.7	15.4	27.9	11.5	22.4	16.8	27.2
Alcohol intake ≥15g/d (%)	17.2	5.3	38.3	16.7	12.6	9.4	32.1	22.7
Current MHT (%)	42.5	42.7	≈≈	≈≈	41.1	45.2	≈≈	≈≈
Total energy intake (kcal/d)[3]	1647 ± 3.7	1412.1 ± 2.8	2251.3 ± 4.2	1738 ± 2.8	1647.1 ± 3.7	1421.7 ± 2.9	2188.2 ± 4.1	1801.5 ± 2.9

[1] MHT, menopausal hormone therapy. All difference between Q5 and Q1 were statistically significant for men and women, $P < 0.0001$ (chi-square test for categorical variables; t test for continuous variables).
[2] All values are medians.
[3] All values are means ± SDs.
[4] BMI in kg/m^2.

a BMI $>$ 25. For both exposures, compared with those in Q1, women in Q5 were more likely to be receiving MHT and to have a family history of cancer and were less likely to be married and white. However, men in Q5 were less likely to have family history of cancer and were more likely to be married and white.

The adjusted RRs from a comparison of Q5 with Q1 ($RR_{Q5\ vs\ Q1}$) and 95% CIs for fruit and vegetable intakes and cancer are shown

TABLE 2
Total fruit intake in relation to cancer incidence among US women in the National Institutes of Health (NIH)–AARP Diet and Health Study by quintile (Q) of fruit intake

		Multivariate relative risk (95% CI)[1]					
Type of cancer	No. of events	Q1 (reference) (0–0.60)[2]	Q2 (0.60–0.97)[2]	Q3 (0.97–1.35)[2]	Q4 (1.35–1.90)[2]	Q5 (1.90–5.58)[2]	P value for quintile median trend
All cancers[3,4]	15,792	1.00	1.01 (0.96, 1.06)	0.98 (0.93, 1.03)	0.99 (0.94, 1.05)	0.99 (0.94, 1.05)	0.059
Breast	5815	1.00	1.02 (0.94, 1.11)	0.99 (0.91, 1.07)	0.96 (0.88, 1.04)	0.91 (0.84, 1.00)	0.010
Lung[3,4]	2347	1.00	0.91 (0.81, 1.02)	0.94 (0.83, 1.07)	0.94 (0.83, 1.07)	0.89 (0.77, 1.02)	0.163
Colorectal	1618	1.00	0.93 (0.80, 1.09)	0.81 (0.69, 0.95)	0.96 (0.82, 1.13)	0.93 (0.79, 1.09)	0.656
Endometrial	1158	1.00	1.22 (1.01, 1.47)	1.14 (0.93, 1.38)	1.33 (1.09, 1.61)	1.25 (1.02, 1.52)	0.044
Non-Hodgkin lymphoma	657	1.00	0.82 (0.63, 1.09)	0.82 (0.62, 1.09)	0.93 (0.71, 1.23)	1.15 (0.87, 1.53)	0.063
Ovarian	514	1.00	1.42 (1.07, 1.89)	1.19 (0.88, 1.60)	1.3 (0.96, 1.74)	1.02 (0.74, 1.40)	0.509
Skin	577	1.00	1.08 (0.82, 1.42)	1.21 (0.93, 1.58)	1.00 (0.76, 1.33)	1.06 (0.80, 1.41)	0.986
Kidney	363	1.00	0.90 (0.64, 1.24)	0.97 (0.70, 1.35)	0.99 (0.71, 1.37)	0.74 (0.52, 1.05)	0.154
Pancreas[3]	377	1.00	0.94 (0.67, 1.31)	1.10 (0.80, 1.53)	1.08 (0.77, 1.50)	1.21 (0.87, 1.70)	0.173
Head and neck[3]	318	1.00	0.81 (0.60, 1.11)	0.68 (0.48, 0.96)	0.77 (0.54, 1.10)	0.70 (0.48, 1.02)	0.057
Bladder[3]	258	1.00	1.56 (1.06, 2.30)	1.24 (0.81, 1.88)	1.40 (0.92, 2.13)	1.52 (1.00, 2.33)	0.147
Thyroid	197	1.00	0.91 (0.58, 1.44)	0.94 (0.59, 1.49)	1.00 (0.63, 1.59)	1.18 (0.75, 1.86)	0.338
Brain	159	1.00	0.98 (0.60, 1.60)	0.97 (0.59, 1.59)	0.82 (0.49, 1.38)	0.83 (0.49, 1.42)	0.389
Myeloma	169	1.00	1.57 (0.91, 2.71)	1.56 (0.90, 2.70)	1.49 (0.85, 2.61)	1.60 (0.92, 2.80)	0.255
Myeloid leukemia	127	1.00	1.03 (0.57, 1.88)	1.58 (0.90, 2.77)	1.44 (0.80, 2.59)	1.60 (0.88, 2.91)	0.089
Stomach	137	1.00	0.66 (0.38, 1.14)	0.91 (0.54, 1.51)	0.72 (0.42, 1.24)	0.75 (0.43, 1.31)	0.463
Esophagus[3]	78	1.00	0.71 (0.35, 1.41)	0.85 (0.42, 1.69)	0.78 (0.37, 1.63)	1.09 (0.54, 2.2)	0.706
Liver	84	1.00	0.95 (0.50, 1.82)	0.69 (0.34, 1.41)	0.73 (0.36, 1.49)	0.93 (0.47, 1.84)	0.788

[1] Adjusted for age, smoking, energy intake (log-transformed kcal), BMI, alcohol, physical activity, education, race, marital status, family history, menopausal hormone therapy, and vegetable intake.
[2] Range of intake (cup equivalents/1000 kcal).
[3] Adjusted for smoking by using smoking status, time since quitting smoking, and smoking dose.
[4] Excluding individuals with missing smoking information, consistent with Wright et al (12).

TABLE 3
Total vegetable (no potato) intake in relation to cancer incidence among US women in the National Institutes of Health (NIH)–AARP Diet and Health Study by quintile (Q) of vegetable intake

Type of cancer	No. of events	Multivariate relative risk (95% CI)[1]					*P* value for quintile median trend
		Q1 (reference) (0–0.56)[2]	Q2 (0.56–0.79)[2]	Q3 (0.79–1.04)[2]	Q4 (1.04–1.43)[2]	Q5 (1.43–4.38)[2]	
All cancers[3,4]	15,792	1.00	1.01 (0.96, 1.06)	1.02 (0.97, 1.07)	1.03 (0.98, 1.09)	1.04 (0.98, 1.09)	0.084
Breast	5815	1.00	0.98 (0.90, 1.06)	1.01 (0.92, 1.09)	1.04 (0.96, 1.13)	1.08 (1.00, 1.18)	0.009
Lung[3,4]	2347	1.00	0.93 (0.82, 1.05)	1.03 (0.91, 1.17)	1.04 (0.92, 1.18)	1.08 (0.94, 1.23)	0.219
Colorectal	1618	1.00	0.85 (0.73, 0.99)	0.98 (0.85, 1.14)	0.88 (0.76, 1.03)	0.87 (0.74, 1.02)	0.390
Endometrial	1158	1.00	1.23 (1.02, 1.48)	1.04 (0.86, 1.26)	1.17 (0.97, 1.42)	1.04 (0.86, 1.27)	0.939
Non-Hodgkin lymphoma	657	1.00	0.80 (0.61, 1.05)	0.97 (0.74, 1.28)	0.90 (0.69, 1.17)	0.80 (0.61, 1.05)	0.303
Ovarian	514	1.00	1.07 (0.80, 1.42)	1.13 (0.85, 1.50)	1.01 (0.75, 1.35)	1.19 (0.90, 1.59)	0.454
Skin	577	1.00	0.97 (0.74, 1.28)	1.12 (0.86, 1.46)	1.09 (0.83, 1.43)	1.04 (0.79, 1.37)	0.600
Kidney	363	1.00	0.96 (0.70, 1.33)	1.06 (0.77, 1.47)	1.13 (0.82, 1.56)	0.80 (0.56, 1.15)	0.372
Pancreas[3]	377	1.00	0.90 (0.66, 1.22)	0.72 (0.53, 0.99)	0.75 (0.54, 1.04)	0.82 (0.59, 1.13)	0.159
Head and neck[3]	318	1.00	1.21 (0.88, 1.66)	0.93 (0.65, 1.32)	1.13 (0.80, 1.59)	0.79 (0.53, 1.16)	0.158
Bladder[3]	258	1.00	0.95 (0.64, 1.41)	1.06 (0.72, 1.56)	1.13 (0.77, 1.67)	1.07 (0.71, 1.60)	0.610
Thyroid	197	1.00	0.88 (0.58, 1.34)	0.69 (0.44, 1.09)	0.88 (0.57, 1.35)	0.76 (0.48, 1.19)	0.353
Brain	159	1.00	1.53 (0.87, 2.70)	2.02 (1.17, 3.49)	1.88 (1.07, 3.28)	1.59 (0.89, 2.85)	0.245
Myeloma	169	1.00	1.39 (0.84, 2.31)	1.51 (0.92, 2.48)	0.98 (0.57, 1.70)	1.36 (0.81, 2.28)	0.555
Myeloid leukemia	127	1.00	0.67 (0.39, 1.14)	0.57 (0.33, 1.00)	0.69 (0.40, 1.18)	0.76 (0.44, 1.30)	0.653
Stomach	137	1.00	1.42 (0.85, 2.37)	1.32 (0.78, 2.25)	1.12 (0.64, 1.95)	0.86 (0.47, 1.58)	0.365
Esophagus[3]	78	1.00	1.52 (0.74, 3.12)	1.25 (0.58, 2.71)	2.20 (1.10, 4.43)	1.21 (0.54, 2.71)	0.576
Liver	84	1.00	0.51 (0.24, 1.09)	0.99 (0.53, 1.86)	0.84 (0.43, 1.63)	0.86 (0.44, 1.67)	0.643

[1] Adjusted for age, smoking, energy intake (log-transformed kcal), BMI, alcohol, physical activity, education, race, marital status, family history, menopausal hormone therapy, and fruit intake.
[2] Range of intake (cup equivalents/1000 kcal).
[3] Adjusted for smoking by using smoking status, time since quitting smoking, and smoking dose.
[4] Excluding individuals with missing smoking information, consistent with Wright et al (12).

in **Tables 2–5**. Fruit intake was not associated with risk of total cancer among women ($RR_{Q5\ vs\ Q1} = 0.99$; 95% CI: 0.94, 1.05) or men ($RR_{Q5\ vs\ Q1} = 0.98$; 95% CI: 0.95, 1.02). Vegetable intake was not associated with the risk of total cancer among women ($RR_{Q5\ vs\ Q1} = 1.04$; 95% CI: 0.98, 1.09) but was associated with significant decreased risk among men ($RR_{Q5\ vs\ Q1} = 0.94$; 95% CI: 0.91, 0.97). When we looked at the combined cancer sites for which evidence was termed ''probable'' by the World Cancer Research Fund/American Institute for Cancer Research (esophagus, head and neck, stomach, lung, colorectum, pancreas, and prostate) (5), the risk estimates were similar to those from the total cancer analysis (data not shown).

When we examined specific cancer sites, fruit intake was associated with a significantly increased risk of endometrial cancer ($RR_{Q5\ vs\ Q1} = 1.25$; 95% CI: 1.02, 1.52), but when we restricted this analysis to never-users of MHT, this association did not remain. Fruit intake was associated with a decreased risk of breast cancer ($RR_{Q5\ vs\ Q1}$: 0.91; 95% CI: 0.84, 1.00), and vegetable intake was associated with an increased risk of breast cancer ($RR_{Q5\ vs\ Q1}$: 1.08; 95% CI: 1.00, 1.18).

Among men, fruit intake was associated with a significantly lower risk of pancreatic cancer ($RR_{Q5\ vs\ Q1} = 0.73$; 95% CI: 0.57, 0.95). Also among men, vegetable intake was associated with a significantly decreased risk of colorectal cancer ($RR_{Q5\ vs\ Q1} = 0.84$; 95% CI: 0.75, 0.93) and lung cancer ($RR_{Q5\ vs.\ Q1} = 0.87$; 95% CI: 0.78, 0.98) and a significantly increased risk of advanced prostate cancer ($RR_{Q5\ vs\ Q1} = 1.10$; 95% CI: 1.01, 1.38) and thyroid cancer ($RR_{Q5\ vs\ Q1} = 1.95$; 95% CI: 1.16, 3.28).

When we restricted the analysis to never-smokers, the inverse relation between vegetable intake and total cancer among men was attenuated and no longer statistically significant ($RR_{Q5\ vs\ Q1} = 0.97$; 95% CI: 0.91, 1.04; *P* for trend = 0.474), as were all of the aforementioned significant findings, except for the association between vegetable intake and thyroid cancer in men (data not shown).

DISCUSSION

Our results do not support an association between the intake of fruit and vegetables and the incidence of total cancer in men or women. When we restricted the analyses of significant findings to those who had never smoked, the only association we found was between vegetable intake and thyroid cancer in men. Our restricted results may have partly changed because of the small number of cancer cases in nonsmokers, but residual confounding by cigarette smoking is a likely explanation for these associations. It is also possible that the biological effects of fruit and vegetable intake are different among smokers, given their exposure to tobacco carcinogens (13). With regard to endometrial cancer, the association was also not present in women who had never received MHT, which suggests that the positive association may be explained by residual confounding by smoking and MHT.

The association between vegetable intake and thyroid cancer among men may have been a chance finding. A well-cited animal study showed a positive relation between administered goitrogens and thyroid tumor promotion. A recent review of evidence from case-control and cohort studies on vegetables and thyroid cancer

TABLE 4
Total fruit intake in relation to cancer incidence among US men in the National Institutes of Health (NIH)–AARP Diet and Health Study by quintile (Q) of fruit intake

Type of cancer	No. of events	Multivariate relative risk (95% CI)[1]					*P* value for quintile median trend
		Q1 (reference) (0–0.44)[2]	Q2 (0.44–0.75)[2]	Q3 (0.75–1.09)[2]	Q4 (1.09–1.59)[2]	Q5 (1.59–5.13)[2]	
All cancers[3,4]	35,071	1.00	1.01 (0.98, 1.04)	0.98 (0.95, 1.01)	0.98 (0.95, 1.02)	0.98 (0.95, 1.02)	0.17
Prostate	17,034	1.00	1.03 (0.98, 1.09)	1.02 (0.97, 1.07)	1.03 (0.97, 1.08)	1.01 (0.95, 1.06)	0.766
Lung[3,4]	4092	1.00	0.99 (0.91, 1.08)	0.91 (0.83, 1.01)	0.95 (0.86, 1.05)	0.91 (0.81, 1.01)	0.05
Colorectal	3421	1.00	0.96 (0.86, 1.06)	0.91 (0.82, 1.02)	0.86 (0.77, 0.97)	0.94 (0.84, 1.05)	0.211
Advanced prostate	1778	1.00	1.00 (0.86, 1.16)	0.97 (0.74, 1.01)	1.04 (0.89, 1.21)	0.98 (0.83, 1.15)	0.91
Skin	1634	1.00	1.10 (0.93, 1.29)	1.04 (0.88, 1.23)	1.01 (0.86, 1.20)	1.16 (0.98, 1.37)	0.169
Bladder[3]	1406	1.00	0.95 (0.81, 1.12)	1.10 (0.94, 1.30)	0.97 (0.82, 1.16)	0.90 (0.75, 1.08)	0.244
Non-Hodgkin lymphoma	1261	1.00	1.06 (0.87, 1.29)	1.08 (0.90, 1.31)	1.10 (0.92, 1.33)	1.14 (0.94, 1.39)	0.196
Head and neck[3]	1029	1.00	0.98 (0.82, 1.17)	0.86 (0.71, 1.04)	0.85 (0.69, 1.04)	0.84 (0.68, 1.04)	0.064
Kidney	973	1.00	0.95 (0.78, 1.15)	0.96 (0.78, 1.17)	0.91 (0.74, 1.12)	0.94 (0.76, 1.16)	0.553
Pancreatic[3]	713	1.00	0.90 (0.72, 1.13)	0.93 (0.74, 1.18)	0.80 (0.63, 1.02)	0.73 (0.57, 0.95)	0.012
Stomach	507	1.00	1.29 (0.99, 1.69)	0.89 (0.66, 1.20)	1.10 (0.82, 1.47)	1.15 (0.85, 1.55)	0.674
Esophagus[3]	463	1.00	0.88 (0.67, 1.15)	0.96 (0.73, 1.27)	0.88 (0.65, 1.18)	0.74 (0.53, 1.02)	0.084
Brain	385	1.00	0.74 (0.52, 1.04)	0.86 (0.61, 1.20)	0.95 (0.69, 1.33)	1.08 (0.78, 1.51)	0.146
Myeloma	365	1.00	1.21 (0.86, 1.70)	1.02 (0.72, 1.46)	1.23 (0.86, 1.74)	1.10 (0.76, 1.59)	0.746
Myeloid leukemia	323	1.00	1.23 (0.86, 1.75)	1.16 (0.80, 1.67)	1.37 (0.95, 1.96)	1.02 (0.69, 1.52)	0.986
Liver	310	1.00	0.86 (0.60, 1.23)	1.02 (0.72, 1.46)	1.08 (0.76, 1.54)	0.90 (0.62, 1.32)	0.886
Thyroid	165	1.00	0.87 (0.50, 1.49)	0.95 (0.55, 1.62)	1.16 (0.69, 1.95)	1.24 (0.74, 2.09)	0.174

[1] Adjusted for age, smoking, energy intake (log-transformed kcal), BMI, alcohol, physical activity, education, race, marital status, family history, and vegetable intake.
[2] Range of intake (cup equivalents/1000 kcal).
[3] Adjusted for smoking by using smoking status, time since quitting smoking, and smoking dose.
[4] Excluding individuals with missing smoking information, consistent with Wright et al (12).

indicated a slightly inverse (although nonsignificant) relation (14). Future research is warranted.

We found some associations for only one sex. It is possible that the biology of how fruit or vegetable intakes affect cancer incidence may differ by sex because of hormonal, genetic, and metabolic factors. Alternatively, there may have been exposure misclassification differences between women and men because of differential reporting. Power was also low for several cancer sites in women.

Our study strengths include having 500,000 participants, >50,000 cancer cases, 3,320,418 person-years of follow up (mean = 6.9 y), and a wide range of fruit and vegetable intakes. Additionally, this is the first prospective cohort study to report results consistent with the most current US Department of Agriculture classification of fruit and vegetable cup equivalents. We used the MPED to calculate cup equivalents for fruit and vegetables rather than servings. These cup equivalents align with the 2005 *Dietary Guidelines for Americans* (15), which include recommendations based on common household measures rather than servings. The MPED replaced the Pyramid Servings Database in October 2006. The results per servings per day were similar (data not shown).

To our knowledge only 3 other cohorts have examined the relation between fruit and vegetable intake and total cancer incidence. A pooled analysis of the Health Professionals Follow-Up Study and the Nurses' Health Study (16) as well as the Japanese Public Health Center Based Prospective Study (17) found no evidence of an association. The Greek European Prospective Investigation into Cancer Cohort Study (18) found an inverse association between total fruit and vegetable intake and total cancer incidence, but the sample size (10,582 men; 15,031 women) and total number of cancer cases (men: 421 cases; women: 430 cases) were much smaller than in other cohorts reporting null results.

Similar to other cohorts, the participants in our study who ate more fruit and vegetables also exercised more, drank less alcohol, and had lower BMIs (19). Also, in general, nonsmokers had higher average median intakes of fruit and vegetables than did nonsmokers. When multiple dietary variables were measured with error (and potentially correlated with one another), the effect on the risk estimate of main dietary exposure is unclear (20). Therefore, it is also possible that measurement error obscured associations between fruit, vegetables, and cancer in this study.

Fruit and vegetables are among the most widely studied dietary risk factors for cancer. On the basis of previous research and reviews conducted in the 1980s, the National Cancer Institute began an intensive campaign in 1991 known as the 5 A Day for Better Health Program (now known as Fruits & Veggies–More Matters and run by the Centers for Disease Control and Prevention), the purpose of which is to increase fruit and vegetable consumption with the goal of preventing cancer and other chronic diseases (21). Although fruit and vegetable intake should be encouraged for many reasons related to overall health, energy balance, and nutritional requirements, our data do not provide support regarding the cancer preventative properties of fruit and vegetables as a group.

In this large US prospective cohort study, we observed no association between fruit and vegetable intake and total cancer incidence. However, on the basis of animal studies, human case control and cohort studies, and randomized controlled trials, there is likely no harm associated with the consumption of fruit and vegetables (22) and their consumption may prevent cardiovascular disease (16). Additionally, the consumption of

TABLE 5
Total vegetable (no potato) intake in relation to cancer incidence among US men in the National Institutes of Health (NIH)–AARP Diet and Health Study by quintile (Q) of vegetable intake

Type of cancer	No. of events	Multivariate relative risk (95% CI)[1]					*P* value for quintile median trend
		Q1 (reference) (0–06-0.44)[2]	Q2 (0.44–0.61)[2]	Q3 (0.61–0.81)[2]	Q4 (0.81–1.10)[2]	Q5 (1.10–3.25)[2]	
All cancers[3,4]	35,071	1.00	0.97 (0.94, 1.00)	0.96 (0.93, 0.99)	0.98 (0.94, 1.01)	0.94 (0.91, 0.97)	0.004
Prostate	17,034	1.00	1.03 (0.98, 1.08)	1.03 (0.98, 1.08)	1.01 (0.96, 1.06)	0.97 (0.93, 1.02)	0.106
Lung[3,4]	4092	1.00	0.89 (0.81, 0.97)	0.94 (0.85, 1.03)	0.93 (0.84, 1.02)	0.87 (0.78, 0.96)	0.024
Colorectal	3421	1.00	0.81 (0.73, 0.90)	0.79 (0.71, 0.88)	0.87 (0.79, 0.97)	0.84 (0.75, 0.93)	0.041
Advanced prostate	1778	1.00	1.07 (0.92, 1.25)	1.13 (0.97, 1.32)	1.14 (0.98, 1.34)	1.18 (1.01, 1.38)	0.04
Skin	1634	1.00	0.89 (0.76, 1.04)	0.88 (0.75, 1.03)	0.88 (0.75, 1.03)	0.90 (0.76, 1.05)	0.332
Bladder[3]	1406	1.00	0.97 (0.82, 1.13)	0.82 (0.69, 0.97)	0.95 (0.81, 1.13)	0.92 (0.77, 1.09)	0.424
Non-Hodgkin lymphoma	1261	1.00	1.09 (0.91, 1.30)	1.02 (0.84, 1.23)	1.14 (0.95, 1.38)	1.04 (0.86, 1.27)	0.681
Head and neck[3]	1029	1.00	0.90 (0.75, 1.08)	0.96 (0.80, 1.16)	0.90 (0.74, 1.10)	0.98 (0.80, 1.19)	0.897
Kidney	973	1.00	0.89 (0.73, 1.09)	0.93 (0.76, 1.13)	0.86 (0.70, 1.05)	0.95 (0.78, 1.17)	0.719
Pancreatic[3]	713	1.00	0.86 (0.68, 1.10)	0.99 (0.78, 1.25)	1.21 (0.96, 1.52)	1.03 (0.81, 1.32)	0.243
Stomach	507	1.00	1.17 (0.90, 1.54)	1.01 (0.76, 1.34)	1.21 (0.92, 1.60)	0.93 (0.69, 1.25)	0.536
Esophagus[3]	463	1.00	0.94 (0.72, 1.24)	0.87 (0.65, 1.16)	0.85 (0.63, 1.14)	1.04 (0.78, 1.39)	0.85
Brain	385	1.00	1.15 (0.81, 1.64)	1.30 (0.92, 1.83)	1.59 (1.13, 2.22)	1.34 (0.94, 1.90)	0.065
Myeloma	365	1.00	0.82 (0.59, 1.14)	0.81 (0.58, 1.14)	0.94 (0.68, 1.30)	0.93 (0.67, 1.29)	0.929
Myeloid leukemia	323	1.00	1.04 (0.73, 1.46)	1.01 (0.71, 1.44)	1.06 (0.75, 1.51)	0.91 (0.63, 1.32)	0.616
Liver	310	1.00	0.99 (0.72, 1.38)	0.76 (0.53, 1.09)	0.98 (0.70, 1.38)	0.67 (0.46, 0.98)	0.052
Thyroid	165	1.00	1.08 (0.61, 1.91)	1.20 (0.68, 2.09)	1.31 (0.76, 2.27)	1.95 (1.16, 3.28)	0.002

[1] Adjusted for age, smoking, energy intake (log-transformed kcal), BMI, alcohol, physical activity, education, race, marital status, family history, and vegetable intake.
[2] Range of intake (cup equivalents/1000 kcal).
[3] Adjusted for smoking by using smoking status, time since quitting smoking, and smoking dose.
[4] Excluding individuals with missing smoking information, consistent with Wright et al (12).

nutrient-dense, high-fiber foods is important for meeting nutrient requirements, in weight-loss programs, and in maintaining energy balance. Future studies of dietary patterns may complement single food group analyses of fruit and vegetables in understanding the role that diet plays in cancer prevention (23). Indeed, analyses in this cohort and in others that have investigated dietary patterns rich in fruit and vegetables have found reduced risks of colorectal cancer (24–26) and mortality, including death from cardiovascular disease and all cancers (27).

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The authors' responsibilities were as follows—SAM: analyzed and interpreted the data; drafted, reviewed, and revised the manuscript; and approved the final version of the manuscript. YP, MFL, JR, and NDF: analyzed and interpreted the data, reviewed and revised the manuscript, and approved the final version of the manuscript. ECD: reviewed and revised the manuscript, assisted with the tables, and approved the final version of the manuscript; and AS, AH, and AFS: helped with the conception and design of the study, acquired the data, analyzed and interpreted the data, reviewed and revised the manuscript, and approved the final version of the manuscript. No conflicts of interest were declared.

REFERENCES

1. Terry P, Terry JB, Wolk A. Fruit and vegetable consumption in the prevention of cancer: an update. J Intern Med 2001;250:280–90.
2. Doll R, Peto R. The causes of cancer: quantitative estimates of avoidable risks of cancer in the United States today. J Natl Cancer Inst 1981;66: 1191–308.
3. Vainio H, Weiderpass E. Fruit and vegetables in cancer prevention. Nutr Cancer 2006;54:111–42.
4. Barta I, Smerak P, Polivkova Z, et al. Current trends and perspectives in nutrition and cancer prevention. Neoplasma 2006;53:19–25.
5. World Cancer Research Fund, American Institute for Cancer Research. Food, nutrition, physical activity, and the prevention of cancer: a global perspective Second Expert Report. Washington, DC: AICR, 2007.
6. Schatzkin A, Subar AF, Thompson FE, et al. Design and serendipity in establishing a large cohort with wide dietary intake distributions: the National Institutes of Health-American Association of Retired Persons Diet and Health Study. Am J Epidemiol 2001;154:1119–25.
7. Michaud DS, Midthune D, Hermansen S, et al. Comparison of cancer registry case ascertainment with SEER estimates and self-reporting in a subset of the NIH-AARP Diet and Health Study. J Registry Manage 2005;32:70–5.
8. Fritz A, Percy C, Tack A. International classification of diseases for oncology: ICD-O. 3rd ed. Geneva, Switzerland: World Health Organization, 2000.

9. Subar AF, Midthune D, Kulldorff M, et al. Evaluation of alternative approaches to assign nutrient values to food groups in food frequency questionnaires. Am J Epidemiol 2000;152:279–86.
10. Friday JE, Bowman SA. MyPyramid Equivalents Database for USDA Survey Food Codes, 1994–2002 Version 1.0. [Online]. USDA, ARS, Community Nutrition Research Group, 2006. Available from: http://www.ars.usda.gov/ba/bhnrc/fsrg/ (cited 29 November 2007).
11. Thompson FE, Kipnis V, Midthune D, et al. Performance of a food frequency questionnaire in the US National Institutes of Health-AARP Diet and Health Study. Public Health Nutr 2008;11:183–95.
12. Wright ME, Park Y, Subar AF, et al. Intakes of fruit, vegetables, and specific botanical groups in relation to lung cancer risk in the NIH-AARP Diet and Health Study. Am J Epidemiol 2008;168:1024–34.
13. Hininger I, Chopra M, Thurnham DI, et al. Effect of increased fruit and vegetable intake on the susceptibility of lipoprotein to oxidation in smokers. Eur J Clin Nutr 1997;51:601–6.
14. Dal Maso L, Bosetti C, La Vecchia C, Franceschi S. Risk factors for thyroid cancer: an epidemiological review focused on nutritional factors Cancer Causes and Control. (Epub ahead of print 3 September 2008).
15. US Department of Health and Human Services, US Department of Agriculture. Dietary guidelines for Americans. Washington, DC: US Department of Health and Human Services, 2005.
16. Hung HC, Joshipura KJ, Jiang R, et al. Fruit and vegetable intake and risk of major chronic disease. J Natl Cancer Inst 2004;96:1577–84.
17. Takachi R, Inoue M, Ishihara J, et al. Fruit and vegetable intake and risk of total cancer and cardiovascular disease: Japan Public Health Center-based Prospective Study. Am J Epidemiol 2008;167:59–70.
18. Benetou V, Orfanos P, Lagiou P, Trichopoulos D, Boffetta P, Trichopoulou A. Vegetables and fruits in relation to cancer risk: evidence from the Greek EPIC Cohort Study. Cancer Epidemiol Biomarkers Prev 2008;17:387–92.
19. Anonymous. What if it were fruits or vegetables? Harv Health Lett 2006;31:6.
20. Schatzkin A, Kipnis V. Could exposure assessment problems give us wrong answers to nutrition and cancer questions? J Natl Cancer Inst 2004;96:1564–5.
21. CDC. Fruit and Veggies More Matters: About the National Fruit & Vegetable Program 2008.
22. Mayne ST. Women's Health Initiative: complex answers to simple questions on dietary fat and breast cancer. Nat Clin Pract Oncol 2006;3:285.
23. Slattery ML. Defining dietary consumption: is the sum greater than its parts? Am J Clin Nutr 2008;88:14–5.
24. Flood A, Rastogi T, Wirfalt E, et al. Dietary patterns as identified by factor analysis and colorectal cancer among middle-aged Americans. Am J Clin Nutr 2008;88:176–84.
25. Reedy J, Mitrou PN, Krebs-Smith SM, et al. Index-based dietary patterns and risk of colorectal cancer: the NIH-AARP Diet and Health Study. Am J Epidemiol 2008;168:38–48.
26. Wirfalt E, Midthune D, Reedy J, et al. Associations between food patterns defined by cluster analysis and colorectal cancer incidence in the NIH-AARP Diet and Health Study. Eur J Clin Nutr 2008.
27. Mitrou PN, Kipnis V, Thiebaut AC, et al. Mediterranean dietary pattern and prediction of all-cause mortality in a US population: results from the NIH-AARP Diet and Health Study. Arch Intern Med 2007;167:2461–8.