ARTICLES

Fruit and Vegetable Intake and Risk of Major Chronic Disease

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Background: **Studies of fruit and vegetable consumption in relation to overall health are limited. We evaluated the relationship between fruit and vegetable intake and the incidence of cardiovascular disease and cancer and of deaths from other causes in two prospective cohorts.** ***Methods:*** **A total of 71 910 female participants in the Nurses' Health study and 37 725 male participants in the Health Professionals' Follow-up Study who were free of major chronic disease completed baseline semiquantitative food-frequency questionnaires in 1984 and 1986, respectively. Dietary information was updated in 1986, 1990, and 1994 for women and in 1990 and 1994 for men. Participants were followed up for incidence of cardiovascular disease, cancer, or death through May 1998 (women) and January 1998 (men). Multivariable-adjusted relative risks were calculated with Cox proportional hazards analysis.** ***Results:*** **We ascertained 9329 events (1964 cardiovascular, 6584 cancer, and 781 other deaths) in women and 4957 events (1670 cardiovascular diseases, 2500 cancers, and 787 other deaths) in men during follow-up. For men and women combined, participants in the highest quintile of total fruit and vegetable intake had a relative risk for major chronic disease of 0.95 (95% confidence interval [CI] = 0.89 to 1.01) times that of those in the lowest. Total fruit and vegetable intake was inversely associated with risk of cardiovascular disease but not with overall cancer incidence, with relative risk for an increment of five servings daily of 0.88 (95% CI = 0.81 to 0.95) for cardiovascular disease and 1.00 (95% CI = 0.95 to 1.05) for cancer. Of the food groups analyzed, green leafy vegetable intake showed the strongest inverse association with major chronic disease and cardiovascular disease. For an increment of one serving per day of green leafy vegetables, relative risks were 0.95 (95% CI = 0.92 to 0.99) for major chronic disease and 0.89 (95% CI = 0.83 to 0.96) for cardiovascular disease.** ***Conclusions:*** **Increased fruit and vegetable consumption was associated with a modest although not statistically significant reduction in the development of major chronic disease. The benefits appeared to be primarily for cardiovascular disease and not for cancer. [J Natl Cancer Inst 2004;96:1577–84]**

Cardiovascular disease and cancer are the leading causes of death in the United States *(1),* and eating at least five servings per day of fruits and vegetables is recommended to reduce risks for these diseases *(2–4).* Many studies have evaluated fruit and vegetable consumption in relation to the risk of cardiovascular disease and specific cancers *(5–24),* but the effect of fruits and vegetables on the overall incidence of these major chronic diseases has seldom been assessed in large cohort studies. We therefore examined the association between fruit and vegetable consumption and risk of major chronic diseases in two large cohorts of men and women followed up for more than a decade.

Methods

Study Populations

The Nurses' Health Study (NHS) was established in 1976, with the recruitment of 121 700 female registered nurses between the ages of 30 and 55 from 11 states. The Health Professionals' Follow-up Study was initiated in 1986 and consisted of 51 529 male dentists, optometrists, pharmacists, osteopathic physicians, podiatrists, and veterinarians who were between 40 and 75 years of age.

At baseline, participants completed mailed questionnaires on lifestyle practices and medical history. Every 2 years, questionnaires were sent to update individual characteristics and behaviors and new occurrences of cancers, cardiovascular diseases, and other outcomes. The study was approved by the Institutional Review Boards of Harvard School of Public Health and Brigham and Women's Hospital, Boston, MA, and return of the questionnaire(s) constituted written informed consent.

Assessment of Dietary Intake

A semiquantitative food-frequency questionnaire was included with the general health questionnaire in 1980, 1984, 1986, 1990, and 1994 for the NHS and in 1986, 1990, and 1994 for the Health Professionals' Follow-up Study. The 1980 food-frequency questionnaire for the NHS contained 61 items, including six questions on fruit consumption, 11 on vegetable consumption, and three on potato consumption. The subsequent

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food-frequency questionnaire, used in 1984, was expanded to include at least 15 questions about fruit consumption, 28 about vegetable consumption, and three about potato consumption. The baseline (1986) food-frequency questionnaire for Health Professionals' Follow-up Study had 15 questions about fruit consumption, 30 about vegetable consumption, and three about potato consumption. In these dietary questionnaires, a commonly used unit or portion of each food (such as one tomato or one glass of fruit juice) was specified, and participants indicated how often, on average, they had consumed that food over the past year. The frequencies were reported in nine categories, ranging from less than once a month to six or more times per day. The dietary data from both cohorts have been validated by comparisons with multiple weighted 1-week dietary records *(25–28)*.

The average daily intakes of all fruit and vegetable items (not including potatoes) reported by each participant were added to assess the consumption of total fruits and vegetables. Average daily intakes of foods in specific groups—citrus fruits, green leafy vegetables, cruciferous vegetables, vitamin C–rich fruits and vegetables (i.e., items with ≥30 mg of vitamin C per serving), legumes, and potatoes were also assessed. The definitions of these specific groups were modified from a report by Steinmetz et al. *(29)* to correspond with our questionnaires and hypotheses, as described previously *(9)*. For questionnaires that were missing values for an individual food but were otherwise substantially complete, we assumed no intake of that item when aggregating items to calculate the total and specific groups of fruits and vegetables.

Ascertainment of Outcomes

The primary endpoint was major chronic disease, defined as cardiovascular disease, cancer, or nontraumatic death, whichever came first *(30,31)*. Participants who reported cardiovascular disease or cancer on any biennial questionnaire were mailed letters to verify the reports and to request permission to review their medical records. Study investigators reviewed medical records without knowing the participants' risk factor status. Cardiovascular disease was defined as fatal or nonfatal myocardial infarction and fatal or nonfatal stroke. Myocardial infarction was confirmed based on World Health Organization criteria *(32)*. Stroke was confirmed if there was a typical neurologic defect of sudden or rapid onset lasting 24 hours or more that was attributable to a cerebrovascular event *(33)*.

We included all cancers except nonmelanoma skin cancer, *in situ* breast cancer in women, and organ-confined prostate cancer in men. Cardiovascular disease or cancers that were verified by letter or telephone interview but for which medical records or pathology reports were unavailable were defined as "probable" cases. The reported analyses used both confirmed cases (approximately 80% of total cardiovascular events and 90% of cancer events) and probable cases, but the analyses were also conducted separately for confirmed cases and showed similar results (data not shown).

Deaths were reported by next of kin, coworkers, or postal authorities or through the National Death Index *(34)*. The causes of deaths were confirmed by examining medical records or autopsy reports. All deaths except those from external causes, such as accidents and suicides, were included. Nonresponding participants were assumed to be alive if not listed in the National Death Index.

Statistical Methods

We excluded participants who reported daily energy intake outside the plausible range of 800 to 4200 kcal/day for men and 600 to 3500 kcal/day for women or who left 70 or more dietary questions blank at baseline. Participants who reported cancer, diabetes, myocardial infarction, angina, stroke, and other heart diseases before 1984 for women or 1986 for men were also excluded. We used 1984 as the starting year for the NHS in the analyses because the NHS questionnaires from 1984 onward and the Health Professionals' Follow-up Study questionnaires from 1986 onward were similar with respect to the questions on fruits and vegetables. The analyses thus included 71 910 women and 37 725 men.

Person-time of follow-up was contributed by each eligible participant from the date of return of the baseline food-frequency questionnaire (1984 for women and 1986 for men) to the diagnosis of cardiovascular disease or cancer, death, or May 31, 1998, for women or January 31, 1998, for men, whichever came first. Those who reported cardiovascular disease or cancer or who died were excluded from subsequent follow-up. Thus, each participant could contribute only one endpoint, and the cohort at risk included only those free of the outcome. We recorded 9329 major chronic disease endpoints—including 1964 cardiovascular diseases, 6584 cancers, and 781 non-traumatic deaths from causes other than cancer or cardiovascular disease—among women during 1984–1998 and 4957 endpoints—including 1670 cardiovascular events, 2500 cancers, and 787 nontraumatic deaths from other causes—among men during 1986–1998. To increase power, we conducted additional separate analyses for cancer that did not exclude participants with cardiovascular disease during follow-up and for cardiovascular disease that did not exclude participants with cancer during follow-up; the results were similar to those for cancer excluding the participants with cardiovascular diseases during follow-up and for cardiovascular disease excluding participants with reported cancer during follow-up (data not shown). The associations of fruit and vegetable intake with cancer and cardiovascular mortality were also evaluated separately, and the findings were similar to those for cancer and cardiovascular disease incidence (data not shown).

To reduce within-person variation and to best represent long-term diet, we used the cumulative average intake of fruits and vegetables from all available questionnaires up to the start of each 2-year follow-up interval *(35)*. If participants experienced angina, coronary artery bypass grafting, angioplasty, hypercholesterolemia, hypertension, or diabetes, we stopped updating diet at the beginning of the interval in which they developed the diagnosis. The nondietary variables were updated from the biennial questionnaires. We used Cox proportional hazards models with time-dependent variables to perform these analyses *(36)*. Proportionality of hazards was evaluated by visual examination of associations across intervals of time.

Participants were grouped into equal-sized quintiles of fruit and vegetable intake using the updated cumulative average *(35)*. For each outcome, the relative risks were calculated by dividing the incidence among participants in each quintile by that in the lowest quintile. Quintiles were used to avoid assumptions about

Table 1. Multivariable-adjusted relative risks for major chronic disease, by fruit and vegetable intake, in the Health Professionals' Follow-up Study, the Nurses' Health Study, and in the pooled data*

Food group	Cohort	RR (and 95% CI for pooled population)† by quintile 2	3	4	5	*P*, test for trend	Median servings per day	Median servings per day for quintiles 1 and 5
All fruits and vegetables	HPFS	1.05	0.96	0.92	0.97		5.21	2.61, 9.42
	NHS	0.95	0.96	0.97	0.94		5.32	2.65, 9.18
	Pooled	1.00 (0.90 to 1.10)	0.96 (0.91 to 1.01)	0.95 (0.90 to 1.00)	0.95 (0.89 to 1.01)	.07		
All fruits	HPFS	1.03	1.01	0.98	0.98		2.12	0.72, 4.41
	NHS	0.96	0.95	0.99	0.94		2.32	0.68, 4.47
	Pooled	0.99 (0.92 to 1.06)	0.97 (0.91 to 1.04)	0.99 (0.94 to 1.04)	0.95 (0.90 to 1.01)	.18		
All vegetables	HPFS	0.99	0.95	0.95	0.95		2.94	1.41, 5.58
	NHS	1.01	1.00	1.00	0.97		2.88	1.46, 5.25
	Pooled	1.00 (0.95 to 1.06)	0.98 (0.93 to 1.04)	0.98 (0.93 to 1.04)	0.96 (0.90 to 1.01)	.13		
Total citrus fruit	HPFS	0.99	1.03	1.02	1.05		0.86	0.08, 1.94
	NHS	0.92	0.98	0.96	0.94		0.80	0.14, 1.71
	Pooled	0.95 (0.89 to 1.02)	1.00 (0.95 to 1.05)	0.98 (0.93 to 1.04)	0.98 (0.88 to 1.10)‡	.91		
Citrus fruit juice	HPFS	0.97	1.03	1.05	1.05		0.43	0.00, 1.00
	NHS	1.02	1.00	1.04	1.01		0.43	0.00, 1.00
	Pooled	1.00 (0.95 to 1.06)	1.01 (0.96 to 1.06)	1.05 (0.99 to 1.11)	1.02 (0.97 to 1.08)	.38		
Cruciferous vegetables	HPFS	0.94	0.90	0.89	0.95		0.40	0.14, 1.02
	NHS	0.99	1.03	1.01	1.01		0.36	0.16, 0.94
	Pooled	0.97 (0.92 to 1.02)	0.97 (0.84 to 1.11)‡	0.96 (0.84 to 1.08)‡	0.98 (0.93 to 1.04)	.58		
Green leafy vegetables	HPFS	0.99	0.97	0.96	0.96		0.59	0.16, 1.42
	NHS	1.00	0.99	0.96	0.92		0.73	0.22, 1.57
	Pooled	1.00 (0.95 to 1.05)	0.99 (0.94 to 1.04)	0.96 (0.91 to 1.01)	0.94 (0.89 to 0.99)	.01		
Vitamin C–containing fruits and vegetables§	HPFS	1.05	0.99	1.04	1.01		1.43	0.46, 2.98
	NHS	0.98	0.97	0.99	0.97		1.57	0.44, 3.16
	Pooled	1.01 (0.95 to 1.08)	0.98 (0.92 to 1.03)	1.01 (0.95 to 1.06)	0.98 (0.93 to 1.04)	.44		
Legumes	HPFS	1.00	0.98	0.98	1.01		0.22	0.08, 0.57
	NHS	1.05	1.06	1.08	1.03		0.16	0.08, 0.51
	Pooled	1.03 (0.98 to 1.08)	1.02 (0.95 to 1.11)	1.03 (0.94 to 1.13)	1.02 (0.97 to 1.08)	.93		
Potatoes	HPFS	1.04	1.03	1.07	1.02		0.51	0.14, 1.02
	NHS	1.06	1.06	1.03	1.01		0.43	0.14, 1.00
	Pooled	1.05 (1.00 to 1.10)	1.05 (1.00 to 1.11)	1.04 (0.99 to 1.10)	1.01 (0.95 to 1.07)	.97		

*Data are based on 9329 major chronic disease events among 71 910 women followed up for 14 years (Nurses' Health Study; NHS) and 4957 major chronic disease events among 38 291 men followed up for 12 years (Health Professionals' Follow-up Study; HPFS). Quintiles were even-sized groups created according to the distributions. Relative risks were adjusted for total calorie intake, age, smoking status, alcohol use, body mass index, multivitamin and vitamin E supplement use, physical activity, family history of myocardial infarction, family history of colon cancer, personal history of hypertension, personal history of hypercholesterolemia, personal history of diabetes, and (for women only) family history of breast cancer, menopausal status, and use of hormone replacement therapy.

†RR = relative risk; CI = confidence interval.

‡*P* value for test for homogeneity by sex <.05.

§Items with >30 mg of vitamin C per serving.

the shape of the dose–response relationship. We also assessed linear relationships, using the median values of intake for deciles to minimize the influence of outliers. The relative risk for the continuous measure indicates the change in risk associated with an increment of five servings per day for total fruits and vegetables, an increment of three servings per day for all fruits and for all vegetables, and an increment of one serving per day for the specific food groups. We also compared groups with intakes of 1.5–2.99, 3.0–4.99, 5.0–5.99, 6.0–7.99, and 8 or more servings per day against participants with fewer than 1.5 servings of total fruit and vegetable intake per day as the referent group to evaluate the association of major chronic disease across the range of fruit and vegetable consumption and to assess the potential optimal intake.

We conducted the initial analyses adjusting for age (5-year categories) and smoking status (never, past, current, 1–14, 15–24, and ≥25 cigarettes/day) only. In the multivariable model, we also adjusted for total energy intake (continuous variable), alcohol (0, >0 to 5, >5 to 10, >10 to 30, and ≥30 g/day for women and 0, 0 to <5, 5 to <15, 15 to <30 and ≥30 g/day for men), body mass index (<21, 21 to <23, 23 to <25, 25 to <29 and ≥29 for women and <21, 21 to <23, 23 to <25, 25 to <30, and ≥30 for men), multivitamin supplement use (yes/no) and vitamin E supplement use (yes/no), physical activity (five categories), first-degree family history of myocardial infarction before age 60 (yes/no), first-degree family history of colon cancer (yes/no), personal history of hypertension, hypercholesterolemia, or diabetes (yes/no). In addition, for women, we adjusted for first-degree family history of breast cancer (yes/no), menopausal status (premenopausal/postmenopausal), and hormone replacement therapy use (current, past, and never).

We also carried out several subgroup analyses. In one subgroup analysis, we evaluated associations separately among users and nonusers of multivitamins. Nonusers of multivitamins who took other supplements such as vitamin E, B_6, B_{12}, and calcium were excluded from these subgroup analyses. We also conducted analyses separately for current, past, and never smokers to determine whether smoking modifies the association of fruit and vegetable intake with risk of major chronic disease. Interactions of fruit and vegetable consumption with smoking status and multivitamin use were tested separately in the two cohorts.

To increase the statistical power, we combined the results from both cohorts by using the random-effects model to pool the two relative risks. Tests for homogeneity between the two cohorts were conducted using the DerSimonian and Laird Q statistic *(37)*.

Results

The median intake of total fruits and vegetables was 5.3 servings/day for women and 5.2 servings/day for men, and the distributions of total fruits, total vegetables, and specific food groups were similar in the two cohorts (Table 1). Compared with participants in the lowest quintile of total fruit and vegetable consumption, participants in higher quintiles had slightly lower risks of major chronic diseases (Table 1). Pooled multivariable-adjusted relative risks for highest versus lowest quintiles were 0.95 (95% confidence interval [CI] = 0.89 to 1.01) for all fruits and vegetables (P_{trend} across quintiles = .07), 0.95 (95% CI = 0.90 to 1.01) for all fruits (P_{trend} across quintiles = .18), and 0.96 (95% CI = 0.90 to 1.01) for all vegetables (P_{trend} across quintiles = .13). Of the specific food groups, only green leafy vegetables showed a statistically significant association with lower risk among participants in the highest quintile compared with the lowest (relative risk [RR] = 0.94, 95% CI = 0.89 to 0.99; P_{trend} = .01).

The linear analyses also revealed no association between consumption of fruits and vegetables and cancer incidence (Table 2). Again, the intake of green leafy vegetables showed a statistically significant inverse association with the risk of major chronic disease (pooled RR = 0.95, 95% CI = 0.92 to 0.99 for one serving/day). For cardiovascular disease, the pooled relative risks in the continuous analysis were all statistically significant. Relative risks of cardiovascular disease were 0.88 (95% CI = 0.81 to 0.95) for an increment of five servings per day of total fruits and vegetables; 0.87 (95% CI = 0.80 to 0.94) and 0.93 (95% CI = 0.86 to 1.00) for increments of three servings per day of all fruits and of all vegetables, respectively; and 0.89 (95% CI = 0.83 to 0.96) and 0.94 (95% CI = 0.91 to 0.98) for increments of one serving per day of green leafy vegetables and of vitamin C–rich fruits and vegetables, respectively. The pooled relative risks for cancer were not statistically significant. Associations of total fruits and vegetables and specific groups of fruits and vegetables with cardiovascular disease and cancer separately were also evaluated using quintiles (data not shown), and the results were consistent with the continuous analysis.

We also calculated pooled multivariable-adjusted relative risks and 95% confidence intervals of major chronic disease, cancer, and cardiovascular disease for increasing servings per day of total intake of fruits and vegetables using those of fewer than 1.5 servings per day as referent group. (Fig. 1). Compared with people consuming fewer than 1.5 servings per day, those consuming increasing servings of total fruits and vegetables had a slightly lower risk of major chronic disease (relative risk for ≥8 versus <1.5 servings/day = 0.88, 95% CI = 0.75 to 1.05; P_{trend} = .05). Total fruit and vegetable consumption was not associated with cancer incidence (relative risk for ≥8 versus <1.5 servings/day = 1.05, 95% CI = 0.83 to 1.31; P_{trend} = .88), but higher fruit and vegetable intake showed a statistically significant inverse association with cardiovascular disease (relative risk for ≥8 versus <1.5 servings/day = 0.70, 95% CI = 0.55 to 0.89; P = .0003).

Table 2. Multivariable-adjusted relative risks for incidence of major chronic disease, cancer, and cardiovascular disease, by servings of fruit and vegetable categories from a linear model based on data from the Health Professionals' Follow-up Study, the Nurses' Health Study, and on pooled data*

	Major chronic disease (14 286 cases)			Cancer† (9261 cases)			Cardiovascular disease† (3864 cases)		
Food group	HPFS	NHS	Pooled‡	HPFS	NHS	Pooled‡	HPFS	NHS	Pooled‡
All fruits and vegetables	0.96	0.96	0.96 (0.92 to 1.00)	0.99	1.00	1.00 (0.95 to 1.05)	0.87	0.88	0.88 (0.81 to 0.95)
All fruit	0.97	0.97	0.97 (0.93 to 1.01)	0.98	1.02	1.01 (0.95 to 1.06)	0.85	0.88	0.87 (0.80 to 0.94)
All vegetable	0.97	0.97	0.97 (0.93 to 1.01)	0.99	0.99	0.99 (0.95 to 1.04)	0.92	0.93	0.93 (0.86 to 1.00)
Total citrus fruit	1.02	0.98	1.00 (0.96 to 1.04)	1.05	1.01	1.03 (0.99 to 1.07)	0.97	0.92	0.95 (0.90 to 1.00)
Citrus fruit juice	1.04	1.01	1.02 (0.98 to 1.06)	1.07	1.04	1.05 (1.00 to 1.10)	1.00	0.94	0.97 (0.91 to 1.04)
Cruciferous vegetables	0.96	1.00	0.98 (0.93 to 1.04)	0.95	1.01	0.99 (0.92 to 1.06)	0.93	0.88	0.91 (0.81 to 1.01)
Green leafy vegetables	0.97	0.94	0.95 (0.92 to 0.99)	1.02	0.97	0.98 (0.93 to 1.04)	0.89	0.90	0.89 (0.83 to 0.96)
Vitamin C–containing fruits and vegetables§	1.00	0.99	0.99 (0.97 to 1.01)	1.03	1.01	1.02 (0.99 to 1.04)	0.95	0.94	0.94 (0.91 to 0.98)
Legumes	0.99	1.02	1.00 (0.90 to 1.12)	0.99	1.03	1.00 (0.88 to 1.16)	0.84	1.32	1.04‖ (0.67 to 1.62)
Potatoes	1.03	0.98	1.00 (0.93 to 1.06)	1.04	0.97	0.99 (0.91 to 1.07)	1.14	1.05	1.10 (0.97 to 1.24)

*Relative risks were adjusted for total calorie intake, age, smoking status, alcohol use, body mass index, multivitamin and vitamin E supplement use, physical activity, family history of myocardial infarction, family history of colon cancer, personal history of hypertension, personal history of hypercholesterolemia, personal history of diabetes, and (for women only) family history of breast cancer, menopausal status, and use of hormone replacement therapy. Relative risks are based on a continuous measure for increments of five servings/day for all fruits and vegetables, three servings/day for all fruits and all vegetables, and one serving/day for other food groups, using median values of deciles of intake to represent the exposure of all participants in the same deciles.

†In separate analyses for cancer and cardiovascular disease, participants with both diseases were included in both analyses.

‡Relative risks and 95% confidence intervals for pooled data.

§Items with ≥30 mg of vitamin C per serving.

‖P value for test for homogeneity by sex <.05.

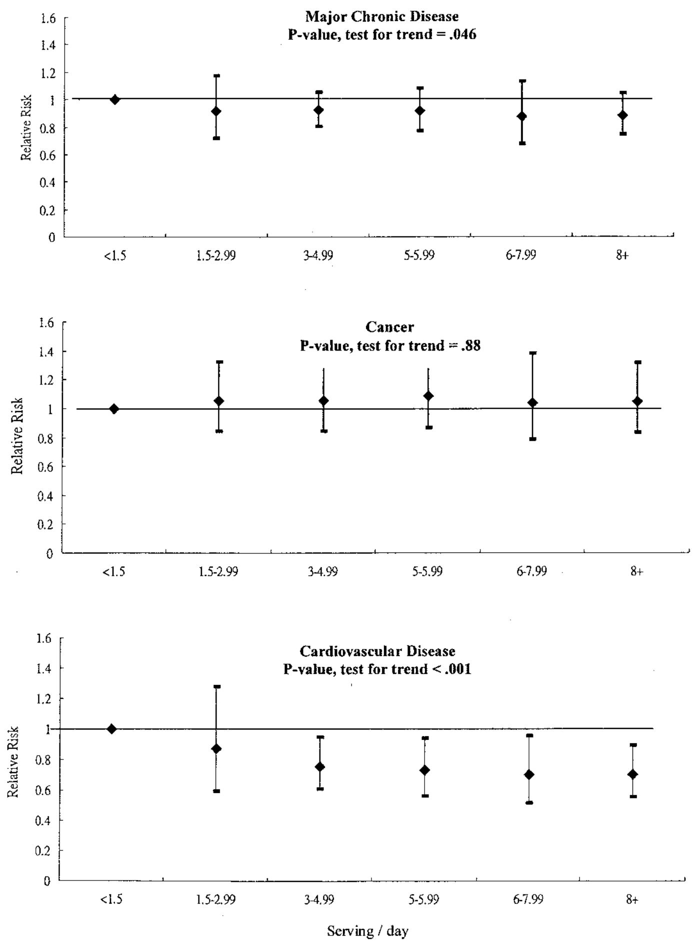

Fig. 1. Multivariable-adjusted relative risks and 95% confidence intervals of total fruit and vegetable consumption for major chronic diseases, cancer, and cardiovascular diseases using group with fewer than 1.5 servings per day as reference.

Similar associations with risk of cardiovascular disease were seen for fruits and for vegetables considered separately (data not shown).

We further examined the subgroups of non–vitamin supplement users and multivitamin users and of never smokers, past smokers, and current smokers (Table 3). There was no association between fruit and vegetable consumption and cancer risk among never smokers, past smokers, or current smokers except for cruciferous vegetable intake, for which linear analyses showed a relative risk for an increment of one serving per day of 0.55 (95% CI = 0.37 to 0.81) among male current smokers. There was a stronger inverse association of cancer with total fruit and vegetable, all fruit, all vegetable, and cruciferous vegetable intake among non–vitamin users than among multivitamin users (Table 3). In linear analyses, higher intake of cruciferous vegetables showed a statistically significant inverse association with cancer risk among male non–multivitamin supplement users (RR = 0.74, 95% CI = 0.60 to 0.91 for an increment of one serving/day). However, when pooled relative risks were examined, cruciferous vegetable intake was not statistically significantly associated with a reduced risk of cancer in either current smokers or non–multivitamin users because the results for men and women were heterogeneous. For cardiovascular disease, the inverse associations with fruit and vegetable intake were stronger among current smokers and among non–vitamin users than among past or never smokers and among multivitamin supplement users, respectively. The test for interaction of smoking with the association between total fruit and vegetable and cardiovascular diseases was statistically significant in women ($P = .04$), and the interaction of total fruit and vegetable consumption with multivitamin supplement use was statistically significant in men ($P = .03$) (data not shown).

Discussion

Our findings suggest that high consumption of fruits and vegetables, especially of green leafy vegetables, is associated with a small reduction in risk of major chronic disease. This risk reduction was due primarily to a lower incidence of cardiovascular disease. We found no association between fruit and vegetable intake (either total or of any particular group) and overall cancer incidence.

Consumption of five or more servings of fruits and vegetables per day has been recommended in the National 5 A Day for Better Health Program *(2,3)* for cancer prevention, but the protective effect of fruit and vegetable intake may have been overstated *(38)*. Indeed, most of the evidence supporting this recommendation is based on case–control studies, which are potentially affected by methodological biases such as recall bias and selection bias. Selective reporting and publication may also explain some of these statistically significant findings, because the authors of studies in which only one or a few items among many fruits and vegetables examined were statistically significantly related to cancer incidence may present their findings as positive, even though they may actually have been due to chance. Moreover, recent findings from Health Professionals' Follow-up Study, the NHS, and other cohort studies have reported weak or no associations between total fruit and vegetable intake and incidence of specific cancers *(12,14,16–21)*.

Our findings are consistent with results from a study of a cohort of 9608 adults, in which high frequency of fruit and vegetable intake was associated with lower risk of cardiovascular disease and all-cause mortality but not with non–cardiovascular disease mortality, which should consist mainly of cancer deaths *(39)*. To evaluate whether fruit and vegetable intake is associated with cancer mortality, we conducted further analyses using cancer mortality instead of cancer incidence as the outcome and also found no association between consumption of fruits and vegetables and death from cancer.

There are several possible explanations for why we did not observe an association between fruit and vegetable intake and cancer in this analysis, if one exists. One possibility is that cancer risk is elevated only in individuals with low intake of fruits and vegetables *(11)*. If an increased risk of cancer were associated only with a fruit and vegetable intake lower than that in our population, we would have been unable to detect a protective association with fruit and vegetable intake. In our population, the median fruit and vegetable intake in the lowest quintile was similar to the average intake of the U.S. population, i.e., approximately 0.7, 1.5, and 0.7 servings per day for fruits, vegetables including salad and potato, and vegetables excluding salad and potato, respectively *(40)*. However, even in analyses in which we used a referent group of intake below 1.5 servings per day (Fig. 1), we still did not observe a protective association with fruit and vegetable intake. Further exploration of associations with intake lower than 1.5 servings per day is not feasible

Table 3. Multivariable-adjusted relative risks with 95% confidence intervals for cancer and cardiovascular disease from linear models, by multivitamin use and smoking status*

Disease by food group	No. of cases by smoking status†			No. of cases by multivitamin supplement use†	
	Never	Past	Current	Non–vitamin use‡	Multivitamin use
Cancer	3577 cases	3945 cases	1694 cases	3128 cases	3948 cases
All fruit and vegetable	1.00 (0.92 to 1.08)	1.00 (0.93 to 1.09)	1.01 (0.89 to 1.14)	0.92 (0.84 to 1.00)	1.04 (0.96 to 1.12)
All fruit	1.03 (0.94 to 1.12)	0.97 (0.89 to 1.06)	1.07 (0.94 to 1.22)	0.94 (0.85 to 1.04)	1.06 (0.97 to 1.16)
All vegetable	1.02 (0.94 to 1.10)	1.01 (0.94 to 1.08)	0.94 (0.84 to 1.05)	0.93 (0.85 to 1.02)	1.01 (0.94 to 1.09)
Total citrus fruit	1.03 (0.96 to 1.10)	1.02 (0.96 to 1.08)	1.05 (0.96 to 1.14)	0.99 (0.93 to 1.06)	1.06 (1.00 to 1.12)
Citrus fruit juice	1.02 (0.95 to 1.10)	1.06 (0.98 to 1.14)	1.07 (0.95 to 1.19)	1.03 (0.95 to 1.12)	1.11 (1.03 to 1.19)
Cruciferous vegetables	1.09 (0.97 to 1.22)	0.98 (0.88 to 1.09)	0.73 (0.44 to 1.22)§‖	0.87 (0.64 to 1.20)§	1.03 (0.92 to 1.15)
Green leafy vegetables	1.01 (0.93 to 1.08)	0.97 (0.89 to 1.05)	0.98 (0.88 to 1.10)	0.95 (0.88 to 1.03)	0.99 (0.92 to 1.06)
Vitamin C–containing fruits and vegetables	1.02 (0.98 to 1.06)	1.01 (0.97 to 1.05)	1.03 (0.98 to 1.10)	0.99 (0.94 to 1.03)	1.04 (1.00 to 1.08)
Legumes	0.97 (0.76 to 1.23)	1.06 (0.86 to 1.30)	0.96 (0.68 to 1.34)	0.91 (0.72 to 1.15)	1.04 (0.70 to 1.55)§
Potatoes	1.03 (0.86 to 1.22)	0.98 (0.87 to 1.12)	0.92 (0.77 to 1.11)	1.03 (0.90 to 1.18)	0.95 (0.84 to 1.08)
Cardiovascular disease	1314 cases	1513 cases	988 cases	1625 cases	1444 cases
All fruit and vegetable	0.89 (0.76 to 1.03)	0.91 (0.80 to 1.03)	0.80 (0.67 to 0.94)	0.84 (0.74 to 0.95)	0.94 (0.78 to 1.13)
All fruit	0.94 (0.81 to 1.08)	0.86 (0.75 to 0.99)	0.78 (0.65 to 0.93)‖	0.88 (0.77 to 1.01)	0.89 (0.78 to 1.02)
All vegetable	0.90 (0.77 to 1.06)	0.97 (0.85 to 1.11)	0.87 (0.75 to 1.01)	0.86 (0.76 to 0.96)	1.00 (0.82 to 1.22)
Total citrus fruit	0.97 (0.89 to 1.07)	0.96 (0.88 to 1.05)	0.90 (0.80 to 1.01)	0.95 (0.87 to 1.04)	0.98 (0.90 to 1.08)
Citrus fruit juice	1.00 (0.88 to 1.13)	0.97 (0.83 to 1.12)	0.93 (0.80 to 1.08)	0.98 (0.87 to 1.09)	1.02 (0.91 to 1.15)
Cruciferous vegetables	0.89 (0.71 to 1.12)	0.96 (0.81 to 1.14)	0.87 (0.61 to 1.25)	0.84 (0.71 to 1.00)	1.07 (0.75 to 1.53)§
Green leafy vegetables	0.93 (0.82 to 1.05)	0.90 (0.80 to 1.01)	0.80 (0.60 to 1.06)	0.88 (0.78 to 0.98)	0.89 (0.79 to 1.00)
Vitamin C–containing fruits and vegetables	0.97 (0.91 to 1.04)	0.94 (0.89 to 1.01)	0.90 (0.83 to 0.98)	0.95 (0.89 to 1.01)	0.98 (0.90 to 1.05)
Legumes	1.00 (0.53 to 1.91)	1.29 (0.65 to 2.57)§	0.90 (0.59 to 1.39)	1.03 (0.40 to 2.64)§	1.02 (0.75 to 1.39)
Potatoes	1.02 (0.78 to 1.33)	1.09 (0.90 to 1.33)	1.12 (0.88 to 1.42)	0.97 (0.80 to 1.16)	1.18 (0.97 to 1.45)

*Relative risks were adjusted for total calorie intake, age, smoking status (not for never and past smokers in the analyses stratified by smoking status), alcohol use, body mass index, multivitamin and vitamin E supplement use (not in the analyses stratified by multivitamin use), physical activity, family history of myocardial infarction, family history of colon cancer, personal history of hypertension, personal history of hypercholesterolemia, personal history of diabetes, and (for women only) family history of breast cancer, menopausal status, and use of hormone replacement therapy. Relative risks are based on a continuous measure for increments of five servings/day for all fruits and vegetables, three servings/day for all fruits and all vegetables, and one serving/day for other food groups, using median values of deciles of intake as to represent the exposure of all participants in the same deciles.

†Excludes those with missing data on smoking.

‡Includes only participants not taking any vitamin or mineral supplements.

§P value for test for homogeneity by sex $<.05$.

‖P value for test for interaction (pooled across cohorts) with smoking or vitamin use $<.05$.

in this study population. The higher intake in our population is likely to reflect their being health professionals and having a higher socioeconomic status than the general U.S. population. It is also possible that the participants in our studies overestimated intake because of the relatively large number of questions for assessing intake of fruits and vegetables (approximately 15 questions for fruits and 30 questions for vegetables) on our questionnaires compared with national surveys, which contain seven such questions *(41,42)*. However, even if there was some overestimation of fruit and vegetable intake, such overestimation, which would alter the responses of all participants, is unlikely to bias the relative risk estimates.

Another possible explanation for the lack of an association of fruit and vegetable intake with cancer incidence in our study is that the induction period for some cancers may be longer than for cardiovascular disease and than the follow-up period in these cohorts. In other words, because the development of cancer is a multistage process that takes place over several decades, we might need a longer follow-up period than for cardiovascular disease to detect whether fruit and vegetable intake are associated with changes in the early stages of cancer development.

Although cancer risk may be directly related to intake of a specific dietary factor, such as folic acid or lycopene *(43–46)*, analyses based on overall fruit and vegetable intake may not be sufficiently specific to detect such associations. Also, the use of vitamin supplements and intake of fortified foods by the participants in our study might attenuate an effect of fruit and vegetable intake on the incidence of cancers if the nutrients in these supplements are associated with reduced cancer risk, because participants would have sufficient intake from sources other than fruits and vegetables. Indeed, in subgroup analyses, we did find a moderate benefit of fruit and vegetable intake among non–supplement users. Failure to find an expected association can also be due to low variation in the factors being studied or to an inability to measure the exposure well. The homogeneity of socioeconomic status among our populations might limit the variation in the amount of fruit and vegetable intake; on the other hand, it would reduce potential bias from unmeasured confounders. In addition, the nondifferential misclassification of information inherent in any dietary data would further attenuate a statistically significant association. However, the clear inverse relation between fruit and vegetable consumption and risk of cardiovascular disease indicates that exposure misclassification cannot account for the lack of an overall association with cancer incidence.

Finally, our findings do not preclude benefits of specific foods or food groups for prevention of specific cancers. We observed that intake of cruciferous vegetables was inversely associated with total cancer incidence among current smokers and non–multivitamin supplement users in men, although not in women, and we earlier reported an inverse association between cruciferous vegetable intake and bladder cancer incidence in men *(29)*.

The difference between men and women may reflect the fact that the major cancers are different for men and women, but chance is also a possible explanation.

In our analyses, we adjusted for confounding variables by using updated measurements collected in the followed-up questionnaire to better control for confounding compared with using only the baseline measurements. Some of these factors, such as obesity, hypertension, and hypercholesterolemia, may mediate the causal pathway between fruit and vegetable intake and cancer risk; overcontrolling for these factors could, therefore, mask a true association. However, the association was already attenuated to the null in the model adjusting for age and the amount of smoking. Comparing participants in the highest quintile with those in the lowest quintile, relative risk for total fruits and vegetables and cancer incidence was 0.92 (95% CI = 0.86 to 0.98) adjusted for age only and 0.97 (95% CI = 0.90 to 1.04) adjusted for age and smoking. Hence, overadjustment for potential mediators is unlikely to account for our null findings.

Our findings for cardiovascular disease still support the recommendations of the American Heart Association *(4)* of consuming at least five servings of fruits and vegetables per day, as in our earlier reports *(9,10)*. Participants in our study eating at least five servings of fruits and vegetables daily had a 28% lower risk of cardiovascular disease than participants eating fewer than 1.5 servings per day, probably due to higher intake of multiple nutrients, including folic acid, potassium, and possibly glucosinolates, diallyl sulfides, and flavonoids *(47–50)*. Fruits were associated with a greater reduction in risk of cardiovascular disease than vegetables. Among the specific groups of fruits and vegetables examined, green leafy vegetables were most strongly associated with a reduction in risk of cardiovascular disease; an increment of one serving was associated with an 11% lower risk of cardiovascular disease. In subgroup analyses, the association between fruit and vegetable intake and cardiovascular disease was stronger among current smokers and non–vitamin users than among nonsmokers and multivitamin users, respectively. Although a stronger association among smokers might be due to a need for higher intake of antioxidants among persons subjected to greater oxidative stress *(51,52)*, we cannot exclude the possibility of residual confounding of amount and type of cigarette use among smokers.

In conclusion, our results provide further evidence that high intake of fruits and vegetables is associated with a modest reduction in major chronic disease risk and support the recommendation of consuming five or more servings of fruits and vegetables daily. However, the benefit of increasing intake of fruits and vegetables appears to be due primarily to a lower risk of cardiovascular disease, not cancer.

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Notes

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