

Fruit and vegetable intakes and the risk of colorectal cancer in the Breast Cancer Detection Demonstration Project follow-up cohort¹⁻³

Andrew Flood, Ellen M Velie, Nilanjan Chatterjee, Amy F Subar, Frances E Thompson, James V Lacey Jr, Catherine Schairer, Rebecca Troisi, and Arthur Schatzkin

ABSTRACT

Background: Recent findings have cast doubt on the hypothesis that high intakes of fruit and vegetables are associated with a reduced risk of colorectal cancer.

Objective: In a large prospective cohort of women, we examined the association between fruit and vegetable intakes and colorectal cancer.

Design: Between 1987 and 1989, 45490 women with no history of colorectal cancer satisfactorily completed a 62-item Block–National Cancer Institute food-frequency questionnaire. During 386 142 person-years of follow-up, 314 women reported incident colorectal cancer, searches of the National Death Index identified an additional 106 colorectal cancers, and a match with state registries identified another 65 colorectal cancers for a total of 485 cases. We used Cox proportional hazards regression analysis to estimate the relative risks (RRs) and 95% CIs in both energy-adjusted and fully adjusted models.

Results: In models using the multivariate nutrient-density model of energy adjustment, RRs for increasing quintile of fruit consumption indicated no significant association with colorectal cancer [RR (95% CI)]: 1.00 (reference), 0.94 (0.70, 1.26), 0.85 (0.63, 1.15), 1.07 (0.81, 1.42), and 1.09 (0.82, 1.44). For vegetable consumption, there was also no significant association in the multivariate nutrient-density model with increasing quintiles of consumption: 1.00 (reference), 0.77 (0.58, 1.02), 0.83 (0.63, 1.10), 0.90 (0.69, 1.19), and 0.92 (0.70, 1.22). Additionally, 3 alternative models of energy adjustment showed no significant association between increases in vegetable intake and the risk of colorectal cancer.

Conclusion: Although the limitations of our study design and data merit consideration, this investigation provides little evidence of an association between fruit and vegetable intakes and colorectal cancer. *Am J Clin Nutr* 2002;75:936–43.

KEY WORDS Fruit, vegetables, colorectal cancer, prospective study, women, energy adjustment, Breast Cancer Detection Demonstration Project

INTRODUCTION

Great geographic disparities exist in colorectal cancer rates around the world. Among women, age-standardized mortality rates differ 7.5-fold and age-standardized incidence rates differ

10.2-fold between regions with a high or low risk (1, 2). Studies of migrants showed striking differences in the rates of disease within ethnically homogeneous populations as they moved from region to region around the globe (3, 4). Time trends of disease also show the tendency of rates to change rapidly within countries (5). These ecologic data strongly suggest that lifestyle factors play an important role in the etiology of colorectal cancer.

The most recent comprehensive review of the literature on the association between diet and colorectal cancer concluded after an examination of results from 22 case-control and 4 prospective cohort studies that “convincing” evidence exists that vegetable, but not fruit, consumption decreases risk (5).

Four recent studies, however, have cast some doubt on these conclusions. Results from the Nurse’s Health Study and the Health Professionals Follow-up Study—both large, well-designed prospective cohort studies—showed no association between consumption of either fruit or vegetables and colorectal cancer (6). The Polyp Prevention Trial, an intervention study designed to test whether a diet low in fat and high in fruit and vegetables could reduce the recurrence of adenoma, showed no difference in recurrence rates between the intervention and control groups (7). The investigators in the Polyp Prevention Trial provided several possible explanations for this result—insufficient follow-up time, improper timing of the intervention, and no consideration of red meat as a potentially important dietary risk factor. However, these investigators could not rule out the possibility that these dietary factors simply do not influence colorectal neoplasia. Finally, the investigators in the Netherlands Cohort Study on Diet and Cancer (using traditional standards of statistical significance) failed to find any overall associations between fruit or vegetable intake and colon or rectal cancer (8). This study presents evidence from a

¹From the Divisions of Cancer Epidemiology and Genetics (AF, NC, JVL, CS, RT, and AS) and of Cancer Control and Population Sciences (AFS and FET), the National Cancer Institute, Bethesda, MD, and the Department of Epidemiology, Michigan State University, East Lansing (EMV).

²The views expressed are solely those of the authors and do not necessarily reflect the opinions of any state agency.

³Address reprint requests to A Flood, Division of Cancer Epidemiology and Genetics, the National Cancer Institute, 6120 Executive Boulevard, MSC 7232, Bethesda, MD 20892. E-mail: flooda@exchange.nih.gov.

Received January 4, 2001.

Accepted for publication May 29, 2001.

large prospective cohort of women that allows further evaluation of the relation between fruit and vegetable consumption and the incidence of colorectal cancer.

SUBJECTS AND METHODS

Breast Cancer Detection Demonstration Project

The Breast Cancer Detection Demonstration Project (BCDDP) was a breast cancer screening program conducted under the joint sponsorship of the National Cancer Institute (NCI) and the American Cancer Society. The project ran from 1973 through 1980 and enrolled 283 222 women at 29 screening centers in 27 cities across the United States.

Breast Cancer Detection Demonstration Project follow-up cohort

In 1979, the NCI established the BCDDP follow-up study cohort of 64 182 participants from a subset of the women enrolled in the original BCDDP screening study. All 4275 women in the screening study with a diagnosis of primary breast cancer, all 25 114 women who had undergone a breast biopsy that indicated a benign condition, and all 9628 women who had been recommended to have a biopsy or breast surgery performed but did not have a surgical procedure were included in the follow-up cohort. An additional 25 165 women with no history of breast disease were matched to the subjects with breast cancer and to the subjects with benign breast disease for age, time of entry in the BCDDP study, ethnicity, screening center, and duration of participation in the BCDDP. The exclusion of women with a history of breast cancer made no significant difference in the results of our analyses.

The follow-up study proceeded in several phases, beginning with baseline interviews between 1979 and 1981. Of the initial follow-up cohort, 61 433 women completed the baseline questionnaire and were therefore eligible for further participation in the study. Participants completed mailed questionnaires during 3 separate follow-up periods: 1987–1989, 1993–1995, and 1995–1998. Each follow-up questionnaire captured information about additional risk factors, updated existing information, and provided self-reports of any cancer diagnoses since the previous phase of the study.

Analytic cohort

We excluded from the study, in sequence, women who did not complete a 1987–1989 follow-up questionnaire (the time of dietary assessment) ($n = 9740$), women who reported a history of colorectal cancer on the 1987–1989 follow-up questionnaire or earlier ($n = 479$), women whose reported entry into the cohort occurred on or after their exit date (defined below) ($n = 6$), and women who did not complete >30 items on their food-frequency questionnaires (FFQs) or who had a reported energy intake >15 884 or <1672 kJ/d (>3800 and <400 kcal/d, respectively) ($n = 5647$). Of the 9740 women who did not complete the 1987–1989 questionnaire, 3066 had died, 505 did not complete the questionnaire because of illness, 1459 refused to complete the questionnaire, and 4710 were either nonresponsive or unable to be contacted. After these exclusions, the analytic cohort contained 45 561 women.

We also excluded an additional 71 women who either had missing information on fruit and vegetable intakes or reported an

unrealistically high consumption (ie, >16 times/d) on the FFQ. Thus, the final analytic cohort consisted of 45 490 individuals.

The maximum follow-up period for each subject extended until the date of completion of the 1995–1998 follow-up questionnaire, the last contact in the 1995–1998 follow-up period if no questionnaire was completed, or the phase 4 anniversary date for those not contacted in the 1995–1998 follow-up period. The phase 4 anniversary date is the estimated date on which subjects would have completed the 1995–1998 questionnaire, with use of mean time intervals from the rest of the cohort, if they had actually completed one.

In the final cohort analyzed, 90.8% (41 323) of the women had complete follow-up data through phase 4, meaning that their end-of-study date corresponded to either the date of their first colorectal cancer diagnosis, the date they filled out the phase 4 questionnaire, or their date of death from a cause other than colorectal cancer. The study was approved by the Institutional Review Board of the National Cancer Institute.

Dietary assessment

In the 1987–1989 questionnaire, respondents completed a 62-item Block-NCI FFQ to assess usual dietary intakes over the previous year. Detailed descriptions of this FFQ and its validity have appeared elsewhere (9–11). Software designed for this FFQ yielded estimates of daily intakes of total energy and micronutrients (11).

We expressed intakes of fruit and vegetables in terms of standardized, daily recommended servings based on dietary guidance from the US Department of Health and Human Services, US Department of Agriculture (USDA), as specified in *The Food Guide Pyramid* (12). A serving of fruit is defined as one medium-sized fresh fruit, 0.5 cup (119 mL) cut fruit, or 6 oz (178 mL) juice. A serving of vegetables is defined as 1 cup (237 mL) leafy vegetables, 0.5 cup (119 mL) other vegetables, or 6 oz (178 mL) juice. We calculated the servings of each fruit or vegetable item listed in the FFQ by converting a medium-sized serving as listed in the Block-NCI FFQ (eg, 0.5 cup, or 119 mL) into the equivalent number of servings as defined by the USDA pyramid. We computed servings for small and large portion sizes on the basis of the instructions for filling out the FFQ (ie, a small-sized serving is one-half as large as a medium-sized serving, and a large-sized serving is 1.5 times the medium-sized serving).

Foods that contributed to the vegetable and fruit food groups appear in **Table 1**. For mixtures on the vegetable list, we estimated from USDA recipe information (13) the proportion of the food that was vegetable and applied this value to calculate usual intakes of vegetables from that food for each individual. Intakes of red meat and grains were expressed in terms of the estimated daily frequency of consumption per 1000 kJ. Similarly, standard units of nutrients (eg, mg) per 1000 kJ were used for alcohol, folate, calcium, and vitamin D in all analyses.

Covariates

From the 1987–1989 questionnaire we ascertained usual ethanol intake, history of smoking behavior, adult height and current weight, and average weekday physical activity in metabolic equivalent time as defined by Ainsworth et al (14). We obtained information on the level of educational attainment from a form completed by the subjects at the beginning of the screening program. Information on the use of nonsteroidal antiinflammatory drugs (NSAIDs) came from the 1993–1995 questionnaire

TABLE 1
Individual food items in the fruit and vegetable groups in the Breast Cancer Detection Demonstration Project follow-up cohort

Fruit group	Vegetable group
Apples, applesauce, and pears	Beans
Cantaloupe	Broccoli
Grapefruit	Carrots
Orange juice and grapefruit juice	Cole slaw, cabbage, and sauerkraut
Oranges	Collards and other greens
	Green salad
	Potatoes, except French fries
	Spinach
	Sweet potatoes
	Tomatoes
	Vegetable soup
	Beef stew and pot pie with carrots or other vegetables ¹
	Chili with beans ²
	Spaghetti and other pasta with tomato sauce ³

¹The vegetable content was 42% by wt (13).

²The vegetable content was 78% by wt (13).

³The vegetable content was 35% by wt (13).

and was classified with respect to the subjects ever having been a regular user of aspirin or nonaspirin pain relievers or anti-inflammatory drugs (not including Tylenol; McNeil PPC, Inc, Ft Washington, PA) or not. We also examined NSAIDs modeled in terms of duration of use, frequency of use, and total pills consumed (duration \times frequency). In no case did these results differ significantly from those we obtained using the dichotomous classification of NSAIDs. The 1987–1989 questionnaire provided information on multivitamin use in the previous year.

Case ascertainment

We defined cases to be all-invasive carcinomas of the colon or rectum, International Classification of Diseases site codes 153.0–153.4, 153.6–153.9, and 154.0–154.1 (15). Case ascertainment came first through self-reports of colorectal cancer from the 1993–1995 and 1995–1998 questionnaires. Nonresponders to these questionnaires were vigorously followed up via phone calls and repeated mailings. Of 311 cases identified through questionnaires, we obtained 245 medical records; the diagnosis of colorectal cancer on the self-report was confirmed by 231 (94%) of these records. Given this high confirmation rate, we concluded that self-reports were sufficiently accurate to justify inclusion of all self-reported colorectal cancer cases without supporting medical records ($n = 66$). Removal of these 66 cases from the analysis did not significantly affect the results related to the main exposures of interest (data not shown).

Persons with pathology reports contradicting self-reported colorectal cancers were designated as noncases in these analyses. Pathology reports obtained for confirmation of other conditions reported in the questionnaire identified an additional 17 cases of colorectal cancer. In addition to the self-reported cases, we also included as cases subjects identified in reports from the National Death Index (through 1997) as having death certificates indicating colorectal cancer ($n = 106$). Finally, we matched all subjects residing in states with cancer registries (73.5% of the analytic cohort) against those registries. Subjects matched against state

registries did not differ significantly with respect to the distribution of risk factors from those who were not matched against state registries. This procedure resulted in the identification of an additional 65 cases of colorectal cancer. Thus, the final analytic cohort comprised 485 cases of invasive colorectal cancer.

Statistical analysis

We used Cox proportional hazards regression analysis (PROC PHREG, version 6.12; SAS Institute Inc, Cary, NC), with age as the underlying time metric to generate energy-adjusted and fully adjusted relative risks (RRs) and 95% CIs for fruit and vegetable intakes separately.

In analyzing continuous covariates (eg, fiber or physical activity), if a subject had an unrealistically extreme (always defined above the 99th percentile) or missing value, we imputed the median value from the whole sample for that variable. For categorical covariates (smoking status, education level, use of NSAIDs, and multivitamin use), we used a dichotomous classification system. The use of a broader classification system for these variables (ie, going from dichotomous to multiple categories) did not produce any significant change in the results. The assessment of use of NSAIDs in terms of duration of use, daily frequency of use, and the total quantity consumed (duration \times frequency) also did not significantly affect the results. For missing information about the categorical variables, we created a missing-value indicator variable for inclusion in all models.

We used 4 models to adjust for total energy intake. The primary model was the multivariate nutrient-density model, in which servings of fruit or vegetables divided by total energy entered the model along with total energy (as a separate covariate). The remaining 3 models were as follows: 1) the energy-partition model, in which servings of fruit or vegetables entered the model along with all other food groups contributing energy to the diet; 2) the residual model, in which the residuals of servings of fruit and vegetables regressed on total energy entered the model; and 3) the standard model, in which total energy entered the fruit or vegetable model as a covariate. A more detailed description of the energy-adjustment models is described elsewhere (16). Each of these energy-adjustment models generates different estimates of relative risk (RR) for fruit and vegetable intakes. Others have shown how the differences between these estimates can prove instructive in assessing associations between diet and disease (17–19).

To test the covariates as potential confounders, we examined fruit and vegetable intakes separately and compared the RRs in these models with those in the models with each of the other covariates added one at a time. Body mass index [wt (kg)/ht² (m)], height, physical activity, and intakes of grain, red meat, alcohol, folate, calcium, and vitamin D entered these models as continuous variables. To test for nonlinear associations between the covariates and colorectal cancer, we also tested models with each classified into quintiles based on the whole sample, but there were no significant differences between these models and the models using continuous terms. Multivitamin use (yes or no in the previous year), use of NSAIDs (ever or never a regular user), smoking status (ever or never a smoker), and education level (high school graduate or less or some college or more) entered the analyses as dichotomous variables. We also tested fruit as a potential confounder in the vegetable model and vegetables as a potential confounder in the fruit model. In no case, however, did the inclusion of any of the covariates result in a change of

TABLE 2

Baseline characteristics of the Breast Cancer Detection Demonstration Project follow-up cohort, by quintile of fruit and vegetable intakes¹

	Quintile of fruit intake					Quintile of vegetable intake				
	1 (lowest)	2	3	4	5 (highest)	1 (lowest)	2	3	4	5 (highest)
Fruit intake (servings/d)										
Median	0.05	0.14	0.22	0.32	0.50	—	—	—	—	—
Cutoff	<0.10	<0.18	<0.26	<0.38	≥0.38	—	—	—	—	—
Vegetable intake (servings/d)										
Median	—	—	—	—	—	0.25	0.40	0.52	0.68	0.98
Cutoff	—	—	—	—	—	<0.33	<0.46	<0.59	<0.79	≥0.79
Mean characteristic										
Age (y)	60.5	61.2	61.8	62.5	63.1 ²	61.8	61.6	61.7	62.0	62.2 ²
Energy intake (kJ/d)	5721	5895	5471	5046	4592 ²	6084	5718	5355	5063	4508 ²
BMI (kg/m ²)	24.9	25.0	24.7	24.5	24.3 ²	24.9	24.8	24.7	24.5	24.3 ²
Height										
(cm)	163	163	163	163	162 ²	162	163	163	163	162
(in)	64.0	64.0	64.0	64.0	63.8 ²	63.9	64.0	64.0	64.0	63.9
Physical activity ³	56.3	56.7	57.0	57.1	57.6 ²	56.1	56.6	57.1	57.4	57.5 ²
Alcohol (g/d)	4.7	4.6	4.2	3.5	2.8 ²	4.3	4.4	4.0	3.9	3.2 ²
Mean food intake										
Fruit (servings/d)	NA	NA	NA	NA	NA	0.20	0.23	0.25	0.28	0.33 ²
Vegetables (servings/d)	0.49	0.54	0.58	0.62	0.70 ²	NA	NA	NA	NA	NA
Grains (times eaten/d)	0.51	0.50	0.51	0.51	0.50	0.51	0.50	0.49	0.50	0.51
Red meat (times eaten/d)	0.17	0.16	0.15	0.15	0.13 ²	0.15	0.16	0.16	0.15	0.14 ²
Mean nutrient intake from dietary sources										
Folate (μg/d)	38.9	45.0	50.1	55.2	63.6 ²	42.4	46.3	49.5	53.6	61.0 ²
Calcium (mg/d)	119	125	130	134	130 ²	125	126	127	129.2	131.2 ²
Vitamin D (μg/d)	28.2	29.6	30.9	31.6	29.2 ²	30.5	30.2	30.1	30.2	28.5 ²
Fiber (g/d)	1.67	1.95	2.16	2.41	2.95 ²	1.65	1.92	2.13	2.43	3.02 ²
Percentage of cohort (%)										
Ever used multivitamin supplements in past year	64.9	69.3	72.2	72.3	72.0 ²	66.7	69.2	70.6	71.2	73.0 ²
Missing data on multivitamin supplement use	0.7	0.7	0.6	0.6	0.8	0.7	0.8	0.7	0.6	0.6
Ever used NSAIDs regularly	37.6	39.0	40.3	39.4	37.5	39.3	39.4	39.4	37.9	37.8 ²
Missing data on NSAIDs use	17.8	16.0	14.8	15.6	17.9	17.9	15.9	15.3	16.0	17.0
Ever smoked regularly	49.2	44.0	42.4	40.3	39.6 ²	43.2	42.3	42.4	43.4	44.4 ⁴
Missing data on smoking	0.9	0.9	1.1	0.6	0.8	1.0	0.6	0.9	0.9	0.8
More than a high school education	40.3	45.0	48.3	49.6	48.0 ²	49.3	44.0	47.7	48.8	51.4 ²
Missing data on education	0.8	0.9	1.0	0.7	0.8	0.7	1.0	0.9	0.8	0.8

¹n = 45 490. All intakes are per 1000 kJ. NSAIDs, nonsteroidal antiinflammatory drugs.²P for trend <0.01.³Expressed as mean metabolic equivalent time (MET-h/d).⁴P for trend <0.05.

≥10% in the RR for fruit or vegetable intake (data not shown), suggesting that none of the covariates were important confounders. We did, however, include all of these covariates in a single model for both fruit and vegetables to test the full effect of their combined inclusion.

We tested for interactions between fruit and vegetables and each of the covariates listed above by comparing the -2 log-likelihood statistic from models with and without interaction terms. We considered *P* values <0.05 as evidence of interaction.

To examine the data on a continuous scale rather than with a linear trend test, we used a spline-model approach for both fruit and vegetable intakes. This approach allowed for greater flexibility in the observation of associations on a continuous scale than would have been possible assuming a linear relation or by using a categorical method.

RESULTS

Between the 1987–1989 and the 1995–1998 questionnaires, the mean and median follow-up times for women in the cohort were 8.5 and 8.7 y, respectively. The interquartile range for follow-up time was 8.4–9.0 y.

The distribution of the sample by quintiles of daily fruit and vegetable consumption per 1000 kJ is shown in **Table 2**. The median daily intake for the quintiles of fruit ranged from 0.05 to 0.50 servings, a >10-fold difference across quintiles. For vegetables, the median for the high quintile (0.98 servings/d) was just under 4 times as great as that for the low quintile (0.25 servings/d).

The baseline characteristics of the women by quintile of fruit or vegetable intake are also shown in **Table 2**. Compared with the women in the lowest quintile of fruit intake, those in the highest quintile were slightly older; reported somewhat higher

TABLE 3

Energy-adjusted and fully adjusted relative risks (and 95% CIs) for colorectal cancer in the Breast Cancer Detection Demonstration Project follow-up cohort, by quintile (Q) of fruit and vegetable intakes¹

	Energy-adjusted model ²	Fully adjusted model ³
Fruit intake (servings/d)		
Q1, <0.09	1.00 (reference)	1.00
Q2, 0.10–0.17	0.94 (0.70, 1.26)	0.97 (0.72, 1.29)
Q3, 0.18–0.25	0.85 (0.63, 1.15)	0.91 (0.67, 1.23)
Q4, 0.26–0.37	1.07 (0.81, 1.42)	1.14 (0.86, 1.52)
Q5, 0.38	1.09 (0.82, 1.44)	1.15 (0.86, 1.53)
Vegetable intake (servings/d)		
Q1, <0.32	1.00 (reference)	1.00
Q2, 0.33–0.45	0.77 (0.58, 1.02)	0.78 (0.59, 1.04)
Q3, 0.46–0.58	0.83 (0.63, 1.10)	0.86 (0.65, 1.14)
Q4, 0.59–0.78	0.90 (0.69, 1.19)	0.93 (0.70, 1.22)
Q5, 0.79	0.92 (0.70, 1.22)	0.95 (0.71, 1.26)

¹*n* = 45 490. All intakes are per 1000 kJ.

²Used the nutrient-density method with energy in the model to adjust for total energy intake.

³Used the nutrient-density method with energy in the model and also adjusted for the following covariates: multivitamin supplement use, BMI, height, use of nonsteroidal antiinflammatory drugs, smoking status, education level, physical activity, and intakes of grains, red meat, calcium, vitamin D, and alcohol. The model for fruit also adjusted for vegetable intake, and the model for vegetables also adjusted for fruit intake.

consumptions of folate, calcium, and fiber; reported a noticeably lower consumption of total energy; reported somewhat lower intakes of red meat and alcohol; were more likely to have attended at least some college; and were less likely to have used tobacco. The baseline characteristics of the women by quintile of vegetable intake were similar to those for women by quintile of fruit intake, with few exceptions. Compared with the women in the lowest quintile of vegetable intake, those in the highest quintile were not older, consumed less vitamin D, and consumed similar amounts of red meat. In addition, we observed a modest positive correlation between the lowest and highest quintiles of fruit and vegetable intakes (Spearman's $r = 0.24$).

Results from the energy-adjusted and fully adjusted Cox proportional hazards regression analysis for both fruit and vegetable intakes (multivariate nutrient-density approach for energy adjustment) are shown in **Table 3**. For fruit intake, neither the energy-adjusted nor the fully adjusted model (accounting for all the potential confounders simultaneously) provided any indication of an association between servings of fruit and risk of colorectal cancer in this cohort. The RR for quintile 5 compared with quintile 1 was 1.09 (95% CI: 0.82, 1.44) in the energy-adjusted model and was 1.15 (95% CI: 0.86, 1.53) in the fully adjusted model. Similarly, for vegetable intake, the RR for quintile 5 compared with quintile 1 indicated no association between servings of vegetables and the risk of colorectal cancer in either the energy-adjusted (RR: 0.92; 95% CI: 0.70, 1.22) or the fully adjusted (RR: 0.95; 95% CI: 0.71, 1.26) model. We observed no evidence of a linear trend or of a dose-response relation for either fruit or vegetable intake in either the energy-adjusted or the fully adjusted model.

We investigated the risk of colorectal cancer by quintile of individual vegetable intake with the nutrient-density model of energy adjustment (**Table 4**). Only for broccoli, potatoes, sweet potatoes, and vegetables from chili did we observe any appreciable reduction

in the risk of colorectal cancer associated with increased consumption, and in no case was the reduction in risk for quintile 5 significant. Null associations were observed for all other individual vegetable intakes, except for vegetables from spaghetti and beef stew, which showed positive associations with colorectal cancer. Despite this positive association, removal of vegetables from spaghetti and beef stew from the vegetable group did not significantly change the estimated RR for total vegetable intake in any of the models.

We identified no significant interactions between use of NSAIDs, red meat intake, grain intake, alcohol intake, physical activity, body mass index, height, age group, or smoking status and either fruit or vegetable intake (data not shown). We observed significant interactions when we added a fruit-by-vegetable interaction term to the fruit model and a vegetable-by-education term to the vegetable model.

The results of the spline-model approach showed no nonlinear association between fruit or vegetable intake and colorectal cancer that differed in any qualitative sense from the results of the quintile-based analyses (data not shown). The energy-partition, standard, and residual models showed clear null associations with the risk of colorectal cancer for fruit and vegetable intakes in both the energy-adjusted and the fully adjusted models. Models with no energy adjustment also showed no associations between fruit or vegetable intake and the risk of colorectal cancer. The RRs for quintile 5 compared with quintile 1 for each of these models are shown in **Table 5**. In no case were the RRs significantly different from 1.0.

DISCUSSION

We observed no significant association between increasing quintiles of fruit intake and the risk of colorectal cancer, and this finding remained no matter which energy-adjustment model was used. This result is consistent with earlier reports from prospective studies of colorectal cancer (6, 8, 20–23). Thus, the evidence for a direct association between the risk of colorectal cancer and fruit intake continues to be weak if at all existent.

Our findings for vegetables were similar to those for fruit. We began the analyses by focusing on the multivariate nutrient-density model for energy adjustment to show the potential benefit associated with increasing the richness of a diet (servings per 1000 kJ) in fruit or vegetables rather than merely increasing the absolute intake. However, the highest quintile of vegetable intake was associated with no significant reduction in the risk of colorectal cancer compared with the lowest quintile. This result did not change when cases not confirmed by either a pathology report or a death certificate were removed from the analysis or when the covariates were added individually or as a group to the model. In addition, we identified no interactions between the covariates, except for the interaction between fruit and vegetable intake (negative interaction) and between vegetable intake and education level (negative interaction). These are potentially interesting findings (especially the interaction between fruit and vegetable intakes), but we must caution against placing too much weight on them because the *P* values determined from the interaction tests indicated only marginal significance. Thus, we cannot rule out the possibility of chance findings given the multiple-comparisons issues involved in performing a large number of interaction tests. The finding that our results did not change significantly after exclusion of cases identified in the first 2 y of follow-up (data not shown) suggests

TABLE 4Fully adjusted relative risks (RRs) and 95% CIs for colorectal cancer in the Breast Cancer Detection Demonstration Project follow-up cohort, by quintile of individual vegetable intakes¹

	Quintile of individual vegetable intakes (servings/d)				
	1	2	3	4	5
Beans					
Quintile median	<0.001	0.006	0.016	0.034	0.080
RR	1.00	1.36	0.87	1.07	1.03
95% CI	—	(1.04, 1.78)	(0.65, 1.18)	(0.80, 1.42)	(0.78, 1.37)
Broccoli					
Quintile median	0.002	0.014	0.026	0.047	0.097
RR	1.00	1.07	0.98	0.94	0.78
95% CI	—	(0.82, 1.40)	(0.75, 1.30)	(0.71, 1.24)	(0.58, 1.06)
Carrots					
Quintile median	0.004	0.018	0.033	0.059	0.124
RR	1.00	1.12	1.09	0.90	1.08
95% CI	—	(0.84, 1.48)	(0.82, 1.45)	(0.67, 1.21)	(0.81, 1.44)
Coleslaw					
Quintile median	<0.001	0.005	0.013	0.024	0.055
RR	1.00	1.23	1.45	1.27	1.11
95% CI	—	(0.92, 1.66)	(1.09, 1.93)	(0.95, 1.71)	(0.82, 1.49)
Potatoes					
Quintile median	0.009	0.029	0.054	0.084	0.142
RR	1.00	0.95	0.85	1.08	0.82
95% CI	—	(0.72, 1.25)	(0.63, 1.12)	(0.84, 1.44)	(0.65, 1.15)
Salad					
Quintile median	0.021	0.078	0.134	0.204	0.350
RR	1.00	0.69	0.84	0.82	1.03
95% CI	—	(0.51, 0.92)	(0.64, 1.11)	(0.62, 1.09)	(0.78, 1.35)
Spinach					
Quintile median	0.000	<0.001	0.006	0.015	0.038
RR	1.00	1.02	1.06	0.99	0.93
95% CI	—	(0.72, 1.45)	(0.82, 1.36)	(0.77, 1.28)	(0.72, 1.21)
Sweet potatoes					
Quintile median	0.000	0.001	0.002	0.006	0.020
RR	1.00	1.04	0.80	0.84	0.85
95% CI	—	(0.78, 1.38)	(0.61, 1.06)	(0.65, 1.10)	(0.65, 1.10)
Tomatoes					
Quintile median	<0.001	0.019	0.048	0.095	0.195
RR	1.00	0.84	1.07	0.95	0.98
95% CI	—	(0.63, 1.13)	(0.81, 1.40)	(0.72, 1.26)	(0.74, 1.30)
Vegetable soup					
Quintile median	<0.001	0.012	0.027	0.050	0.117
RR	1.00	1.20	1.20	1.22	1.08
95% CI	—	(0.89, 1.60)	(0.90, 1.61)	(0.91, 1.63)	(0.81, 1.45)
Beef stew²					
Quintile median	0.000	<0.001	0.006	0.013	0.030
RR	1.00	0.95	1.09	1.03	1.23
95% CI	—	(0.65, 1.39)	(0.83, 1.42)	(0.79, 1.35)	(0.95, 1.59)
Chili²					
Quintile median	0.000	<0.001	0.003	0.009	0.021
RR	1.00	1.03	0.91	0.87	0.87
95% CI	—	(0.67, 1.58)	(0.71, 1.18)	(0.67, 1.13)	(0.67, 1.13)
Spaghetti²					
Quintile median	<0.001	0.004	0.009	0.015	0.028
RR	1.00	1.08	1.13	0.96	1.25
95% CI	—	(0.82, 1.42)	(0.85, 1.49)	(0.72, 1.29)	(0.94, 1.64)

¹*n* = 45 490. All intakes are per 1000 kJ. All models used the nutrient-density method with energy in the model and also adjusted for the following covariates: multivitamin supplement use, BMI, height, use of nonsteroidal antiinflammatory drugs, smoking status, education level, physical activity, and intakes of fruit, grains, red meat, calcium, vitamin D, and alcohol.

²For these mixed foods, only that portion contributing vegetables was counted.

TABLE 5

Energy-adjusted and fully adjusted relative risks (and 95% CIs) for colorectal cancer (quintile 5 compared with quintile 1 of fruit or vegetable intake) in the Breast Cancer Detection Demonstration Project follow-up cohort, by different models of energy adjustment¹

Model	Energy-adjusted model ²	Fully adjusted model ³
Fruit intake (servings/d)		
Energy partition	1.01 (0.77, 1.34)	1.08 (0.81, 1.43)
Standard	1.06 (0.80, 1.40)	1.14 (0.86, 1.51)
Residual	1.05 (0.79, 1.39)	1.12 (0.84, 1.49)
No energy adjustment	1.05 (0.80, 1.37)	1.13 (0.86, 1.49)
Vegetable intake (servings/d)		
Energy partition	1.01 (0.76, 1.34)	1.06 (0.79, 1.41)
Standard	1.04 (0.78, 1.38)	1.10 (0.82, 1.48)
Residual	1.04 (0.80, 1.36)	1.08 (0.82, 1.43)
No energy adjustment	1.03 (0.79, 1.35)	1.09 (0.83, 1.43)

¹*n* = 45 490. All intakes are per 1000 kJ.

²Used the listed method of energy adjustment as described in Subjects and Methods and no other covariates.

³Used the listed method of energy adjustment as described in Subjects and Methods and also adjusted for the following covariates: multivitamin supplement use, BMI, height, use of nonsteroidal antiinflammatory drugs, smoking status, education level, physical activity, and intakes of grains, red meat, calcium, vitamin D, and alcohol. The model for fruit also adjusted for vegetable intake, and the model for vegetables also adjusted for fruit intake.

that the observed effects were not the result of dietary changes related to preclinical disease.

We observed no significant association between vegetable intake and colorectal cancer with the nutrient-density model or with the 3 alternative models of energy adjustment. Given the lack of association in the nutrient-density model and the decidedly null relations observed in the other models, we conclude that there was little overall association between vegetable intake and colorectal cancer in this data set.

The overall results for vegetable intake agree with those from the Nurse's Health Study, the Health Professionals Follow-up Study, and the Alpha-Tocopherol Beta-Carotene Cancer Prevention Study cohorts (6, 20), which also showed no evidence of an association between vegetable intake and colorectal cancer. Of the remaining prospective studies that did show an inverse association, the magnitude of risk reduction was always modest and in 3 of the 4 studies was not significant (8, 21–23). Our results fit with a growing body of evidence that fails to confirm the hypothesis of an inverse association between vegetable intake and colorectal cancer.

Furthermore, the results by quintiles of individual vegetable intakes did not provide substantial support for an inverse association between the intake of any single vegetable and colorectal cancer. The intake of only 4 vegetables showed any indication at all of a reduction in risk; of these 4 vegetables, none showed a risk substantially greater than that for total vegetable intake, and 2 foods (vegetables from spaghetti and beef stew) even showed an increased risk. Note, however, that the servings per day of vegetables from spaghetti and beef stew were very low in this cohort: the cutoffs for the highest quintile were only 0.020 and 0.030 servings per 1000 kJ, respectively. The servings per day of many individual vegetables were similarly low: the cutoff for the highest quintile was <0.035 servings per 1000 kJ for coleslaw, collards and other greens, spinach, sweet potatoes, beef stew,

chili, and spaghetti. However, the results did indicate that none of the vegetables individually and no single food or subset of foods appeared to be inversely associated with colorectal cancer.

However, there are several issues to consider when evaluating the association between fruit and vegetable intakes and colorectal cancer in this and other epidemiologic studies. First, the relative intake of fruit and vegetables in the women in the highest compared with the lowest quintiles of intake indicated a wide range of consumption. However, despite a 10-fold increase in intake from quintiles 1 to 5 for fruit, the median servings per day in the highest quintile was only 0.50 servings per 1000 kJ. The servings per day of vegetables in quintile 5 was somewhat higher, 0.98 servings per 1000 kJ; however, the range of intakes was lower—only 4 times that in quintile 1. Furthermore, the crude consumption (ie, not per 1000 kJ) of vegetables in quintile 5 of the BCDDP cohort was still only 4.9 servings/d, which is low compared with international ranges. According to 1996 data on national food supplies from the Food and Agriculture Organization, vegetable consumption in the United States (5.44 servings/d) was substantially less than that in, for example, China (7.03 servings/d) (24). Although ecologic comparisons of this type must be made with caution, it remains possible that we and other investigators (6, 8, 20–23, 25) did not observe an inverse association between vegetable intake and colorectal cancer because our study population did not consume these foods in sufficient quantity to yield a noticeable reduction in risk.

The possibility of measurement error introduces another obstacle to observing true associations in studies such as ours. FFQs must, by practical necessity, omit many foods that individuals actually consume. In the BCDDP cohort, the fruit group consisted of only 5 food items, and the vegetable group—although somewhat more comprehensive with 14 foods—was still far from exhaustive in its coverage. Furthermore, a single FFQ-based measurement in adulthood may not represent long-term intake without error and may not assess the diet accurately for times when exposure is most critical in determining disease outcome. It is possible that we misclassified people in terms of their total vegetable and fruit intakes, and we must consider seriously the possibility that the FFQ did not include a food or foods that make important contributions to colorectal carcinogenesis. Both the misclassification of intakes and the omission of important food items from the FFQ could lead to an attenuation of risk estimates.

Ultimately, this study failed to provide substantial evidence that the true relation between fruit and vegetable intakes and colorectal cancer is other than null. The limitations inherent to FFQ-based studies, however, make it difficult to rule out definitively the possibility of a reduction in risk of colorectal cancer with an increased intake of vegetables. Nonetheless, given the recent series of negative findings from studies by Michels et al (6), Schatzkin et al (7), and Voorrips et al (8), as well as the results of the present study, the case in favor of the hypothesized inverse association between fruit and vegetable intakes and risk of colorectal cancer has lost considerable strength. To resolve this uncertainty, studies using more robust and more direct tests of the hypothesis are needed. Extensions of the ongoing work to improve FFQ data (25) and the identification of study populations with wider ranges of exposure will make important contributions in this regard. We also must consider seriously, however, the possibility that the consumption of fruit and vegetables may not have a direct, independent role to play in the etiology of colorectal cancer. 

We thank the women who volunteered to participate in the BCDDP follow-up study, Leslie Carroll (IMS, Inc, Silver Spring, MD) for computer support, and Cathy Ann Grundmayer, Susan Englehart, and the BCDDP staff of Westat, Inc (Rockville, MD), for assistance in collecting and processing the data for the study. We acknowledge the California Department of Health Services, Cancer Surveillance Section; the Florida Cancer Data System (under contract to the state Department of Health); the Maryland Cancer Registry, Maryland Department of Health and Mental Hygiene; the Michigan Cancer Surveillance Program, Division for Vital Records and Health Statistics, Michigan Department of Community Health; the Division of Health Statistics, Pennsylvania Department of Health; the Tennessee Cancer Registry; the Texas Department of Health; and the states of Arizona, Georgia, Hawaii, Idaho, Iowa, New Jersey, New York, North Carolina, Ohio, Oregon, and Rhode Island for providing data from their cancer registries.

REFERENCES

- Pisani P, Parkin DM, Bray F, Ferlay J. Estimates of the worldwide mortality from 25 cancers in 1990. *Int J Cancer* 1999;83:18–29.
- Parkin DM, Pisani P, Ferlay J. Estimates of the worldwide incidence of 25 major cancers in 1990. *Int J Cancer* 1999;80:827–41.
- 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.
- Flood DM, Weiss NS, Cook LS, Emerson JC, Schwartz SM, Potter JD. Colorectal cancer incidence in Asian migrants to the United States and their descendants. *Cancer Causes Control* 2000;11:403–11.
- World Cancer Research Fund/American Institute for Cancer Research. Food, nutrition and the prevention of cancer: a global perspective. Washington, DC: American Institute for Cancer Research, 1997.
- Michels KB, Giovannucci E, Joshipura KJ, et al. A prospective study of fruit and vegetable consumption and incidence of colon and rectal cancers. *J Natl Cancer Inst* 2000;92:1740–52.
- Schatzkin A, Lanza E, Corle D, et al. Lack of effect of a low-fat, high-fiber diet on the recurrence of colorectal adenomas. *N Engl J Med* 2000;342:1149–55.
- Voorrips LE, Goldbohm RA, van Poppel G, Sturmans F, Hermus RJJ, van den Brandt PA. Vegetable and fruit consumption and risk of colon and rectal cancer in a prospective cohort study. *Am J Epidemiol* 2000;152:1081–92.
- Block G, Hartman AM, Dresser CM, Carroll MD, Gannon J, Gardner L. A data-based approach to diet questionnaire design and testing. *Am J Epidemiol* 1986;124:453–69.
- Block G, Hartman AM, Naughton D. A reduced dietary questionnaire: development and validation. *Epidemiology* 1990;1:58–64.
- National Cancer Institute, Information Management Services I. Block Dietary Data Systems. DIETSYS version 3.0 user's guide. Bethesda, MD: National Cancer Institute, 1994.
- US Department of Agriculture. The food guide pyramid. Hyattsville, MD: Human Nutrition Information Service, 1992.
- US Department of Agriculture. What we eat in America 1994–96, Continuing Survey of Food Intakes by Individuals (CSFII), 1994–1996. Beltsville, MD: Agricultural Research Service, 1998. (Public use CD-ROM.)
- Ainsworth BE, Haskell WL, Whitt MC, et al. Compendium of physical activities: an update of activity codes and MET intensities. *Med Sci Sports Exerc* 2000;32(suppl):S498–516.
- World Health Organization. International classification of diseases, ninth revision (ICD-9). Geneva: WHO, 1977.
- Willett W. Nutritional epidemiology. New York: Oxford University Press, 1990.
- Freedman LS, Kipnis V, Brown CC, Schatzkin A, Wacholder S, Hartman AM. Comments on "Adjustment for total energy intake in epidemiologic studies." *Am J Clin Nutr* 1997;65(suppl):1229S–31S.
- Wacholder S, Schatzkin A, Freedman LS, Kipnis V, Hartman A, Brown CC. Can energy adjustment separate the effects of energy from those of specific macronutrients? *Am J Epidemiol* 1994;140:848–55.
- Willett WC, Howe GR, Kushi LH. Adjustment for total energy intake in epidemiologic studies. *Am J Clin Nutr* 1997;65(suppl):1220S–8S.
- Pietinen P, Malila N, Virtanen M, et al. Diet and risk of colorectal cancer in a cohort of Finnish men. *Cancer Causes Control* 1999;10:387–96.
- Shibata A, Paganini-Hill A, Ross RK, Henderson BE. Intake of vegetables, fruits, beta-carotene, vitamin C and vitamin supplements and cancer incidence among the elderly: a prospective study. *Br J Cancer* 1992;66:673–9.
- Steinmetz KA, Kushi LH, Bostick RM, Folsom AR, Potter JD. Vegetables, fruit, and colon cancer in the Iowa Women's Health Study. *Am J Epidemiol* 1994;139:1–15.
- Thun MJ, Calle EE, Namboodiri MM, et al. Risk factors for fatal colon cancer in a large prospective study. *J Natl Cancer Inst* 1992;84:1491–500.
- Food and Agriculture Organization/United Nations. Food supply data. FAOSTAT nutrition database. 2000. Internet: <http://apps.fao.org/lim500/nph-wrap.pl?FS.CropsAndProducts&Domain=FS&Servlet=1> (accessed 26 February 2000).
- Phillips RL, Snowden DA. Dietary relationships with fatal colorectal cancer among Seventh-day Adventists. *J Natl Cancer Inst* 1985;74:307–17.
- Subar AF, Thompson FE, Smith AE, et al. Improving food frequency questionnaires: a qualitative approach using cognitive interviewing. *J Am Diet Assoc* 1995;95:781–90.