

Dietary intakes of fruit, vegetables, and fiber, and risk of colorectal cancer in a prospective cohort of women (United States)

Jennifer Lin^{1,*}, Shumin M. Zhang^{1,2}, Nancy R. Cook¹, Kathryn M. Rexrode¹, Simin Liu^{1,2}, JoAnn E. Manson^{1,2,3}, I-Min Lee^{1,2} & Julie E. Buring^{1,2,4}

¹*Division of Preventive Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA;* ²*Department of Epidemiology, Harvard School of Public Health, Boston, MA, USA;* ³*Channing Laboratory, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA;* ⁴*Department of Ambulatory Care and Prevention, Harvard Medical School, Boston, MA, USA*

Received 17 June 2004; accepted in revised form 30 September 2004

Key words: colorectal cancer, dietary fiber, fruit, legume fiber, vegetables.

Abstract

Objective: Although animal studies suggest an inverse association between consumption of plant foods and risk of colorectal cancer, many observational data have failed to support such an association. We prospectively examined the association between dietary intakes of fruit, vegetables, and fiber and colorectal cancer risk in a large female cohort from the Women's Health Study.

Methods: Among 39,876 healthy women aged ≥ 45 years at baseline, 36,976 with baseline self-reported information on dietary intakes and other risk factors for colorectal cancer were included in the analyses. During an average follow-up of 10 years, 223 women were diagnosed with colorectal cancer. Intakes of fruit, vegetables, and fiber were assessed by a baseline food-frequency questionnaire. The analyses were carried out using the Cox proportional hazards regression and all tests were two-sided.

Results: Intakes of fruit, vegetables, and the specific subgroups were not found to be associated with colorectal cancer risk. Multivariate relative risks (RRs) comparing the highest with lowest quintile were 0.79 (95% CI = 0.49–1.27, p for trend = 0.30) for fruit intake, and 0.88 (95% CI = 0.56–1.38, p for trend = 0.30) for vegetables intake. Similarly, intake of total fiber was not associated with colorectal cancer risk; the RR for the highest relative to lowest quintile was 0.75 (95% CI = 0.48–1.17, p for trend = 0.12). However, higher intake of legume fiber was associated with a lower risk of colorectal cancer; the RR for the highest *versus* lowest quintile was 0.60 (95% CI = 0.40–0.91, p for trend = 0.02).

Conclusions: Our data offer little support for associations between intakes of fruit, vegetables, and fiber, and colorectal cancer risk. However, our data suggest that legume fiber and/or other related sources may reduce risk of colorectal cancer.

Introduction

Numerous animal studies suggest that fruit and vegetables inhibit the development of colorectal cancer [1–5]. Fruit and vegetables contain several anticarcinogenic components, such as antioxidant vitamins, folate, phy-

toestrogens, and protease inhibitors, that protect against DNA damage and mutations [6]. In addition, a diet high in fiber may prevent gastrointestinal cancer by increasing stool weight, reducing transit time and stimulating anaerobic bacterial fermentation [7, 8].

Epidemiologic data supporting an inverse association between dietary intakes of fruit and vegetables derive mostly from case-control studies [9], while data from prospective cohort studies have been inconsistent. Some found no association between intakes of fruit and vegetables and risk of colorectal cancer [10–13]; others

*Address correspondence to: Jennifer Lin, Division of Preventive Medicine, Brigham and Women's Hospital, Harvard Medical School, 900 Commonwealth Ave. East, Boston, MA 02215, USA. E-mail: jhlin@rics.bwh.harvard.edu

found an inverse association confined to fruit or vegetables alone [14–18]. Intake of fiber in relation to colorectal cancer risk has also been inconclusive in most cohort studies. Although two recent cohort studies found an inverse association between fiber intake and colorectal cancer or recurrence of colorectal adenomas [19, 20], several other prospective studies [15, 17, 21–24] as well as three interventional trials with fiber supplements [25–27] found no such an association. The role of fruit, vegetables, and fiber in prevention of colorectal cancer remains unclear.

To further address this issue, we prospectively examined dietary intakes of fruit, vegetables, and fiber in relation to risk of colorectal cancer as well as specific tumor location (*e.g.*, proximal and distal colon) in a large cohort of female health professionals. We also investigated the risk associated with specific subgroups of fruit, vegetables, and fiber.

Materials and methods

Study cohort

The Women's Health Study (WHS) is a randomized, double-blind, placebo-controlled 2×2 factorial trial evaluating low-dose aspirin and vitamin E for the primary prevention of cardiovascular disease and cancer [28]. In 1993, 39,876 female professionals aged ≥ 45 years and free of cardiovascular disease and cancer (except non-melanoma skin cancer) were randomized into the trial. The participants in the WHS are mainly nurses (75% registered nurses and 14.6% licensed practical nurses or vocational/visiting nurses) followed by 11% physicians and other health professionals. They reside in the 50 states of the United States; 28% of them are from the Midwest, 23% are from the Northeast, 22% are from the South, 15% are from the far west, 9% are from the Southwest, and 3% are from the Mountain area. For the current analysis, we excluded women who did not provide sufficient dietary information at baseline, had implausible total energy intake (< 600 or ≥ 3500 kcal/day), or failed to provide information on potential risk factors at baseline, resulting in 36,976 women in the present study.

Dietary assessment

On the 131-item food-frequency questionnaire, participants were asked to report the average use of foods and beverages during the past year. There were nine possible responses, ranging from 'never or less than once per month' to 'six or more times per day.' We also

asked about the brand of breakfast cereal and multivitamin use. Responses regarding individual food items were converted to average daily intake of each fruit and vegetable item in servings per day. The average daily intake of individual food items was then combined to obtain intakes of total fruit and vegetables, as well as their subgroups, which were defined based on those used by Michels and colleagues [10]. The composite items of fruit, vegetables as well as their subgroups are provided in Appendix 1. Sweet potatoes were considered vegetables, but regular potatoes were not. Nutrient intake was computed by multiplying the frequency of responses by the nutrient content of specified portion size based on USDA food-composition data [29] and supplemented with information from manufacturers. Values for total dietary fiber and its subgroups were first derived from food composition data tables based on the AOAC method [30, 31] and were then adjusted for total energy using the residuals method [32].

The reproducibility and validity of individual fruit and vegetable items have been assessed in the Nurses' Health Study (NHS), which enrolled a cohort of female nurses sharing similar profiles with the participants in our study. In the NHS, the average Pearson correlation coefficient between specific intake of fruit and vegetables from the food-frequency questionnaire and from four 1-week dietary records was 0.54, ranging from 0.17 for spinach to 0.84 for orange juice [33]. The Pearson correlation coefficient for crude intake of total fiber was 0.61 [34]. With respect to individual food contributors to dietary fiber, the energy-adjusted correlation coefficients between intake from the food-frequency questionnaire and from the dietary records were 0.69 for broccoli, 0.80 for apples, 0.79 for cold cereal, 0.50 for peas, and 0.63 for string beans [33].

Ascertainment of colorectal cancer cases

Every six months during the first year and annually thereafter, participants were asked on the follow-up questionnaires whether they had been diagnosed with colorectal cancer. When a case of colorectal cancer was reported, we sought permission to obtain hospital records and pathology reports. An endpoints committee of physicians then reviewed the records. During an average follow-up of ten years, we documented 240 colorectal cancer cases in the entire cohort; 223 among those with self-reported information on dietary intake and other risk factors for colorectal cancer were included in the current analysis. Ninety-one cases were further identified as cancer of the proximal colon, 81 cases were cancer of the distal colon, and 46 were cancer

of the rectum. Five cases had tumors that could not be designated as either proximal or distal colon.

Statistical analysis

Intakes of fruit, vegetables, fiber as well as their subgroups were divided into quintiles on the basis of the distribution of dietary intake in all women. The baseline distribution of risk factors for colorectal cancer was compared according to the quintiles of dietary intake. We tested difference in proportions with stratified Cochran–Mantel–Haenszel test [35], and in means with multiple linear regression [36].

We used Cox proportional hazards regression to estimate relative risks (RRs) and 95% confidence interval (CI) for colorectal cancer, comparing the incidence rate for a given quintile of intake with the rate for the lowest quintile. Multivariate models were simultaneously adjusted for risk factors for colorectal cancer assessed at baseline, including age (in years), body mass index (<23, 23–24.9, 25–26.9, 27–29.9, ≥30 kg/m²), family history of colorectal cancer in a first-degree relative (yes, no), self-reported colon or rectal polyps (yes, no), cigarette smoking (never, past, current), physical activity (quartiles of total calories spent per week, which was calculated based on the MET score of reported activities, time spent on these activities, and body weight), alcohol consumption (never, <15, ≥15 ethanol gram/day), red meat consumption

(serving/day, in tertiles), aspirin use before the trial (yes, no), menopausal status (pre-, post-menopausal, uncertain/unknown), use of post-menopausal hormone therapy (HT) (never, past, current), total energy intake (kcal/day, in quintiles), and randomized treatment assignment (aspirin *versus* placebo, vitamin E *versus* placebo). We additionally adjusted for total folate intake (mcg/day, in tertiles) and multivitamin use (never, past, current use for <5 years, current use for five to nine years, and current use for ≥10 years) at baseline in the multivariate models. Tests for trend were performed by treating dietary intakes of fruit, vegetables, and fiber, as continuous variables. All *p* values were two-sided.

In our cohort, glycemic load has been shown to be associated with colorectal cancer risk [37]. However, inclusion of glycemic load in the multivariate model was not found to change the overall results, and therefore, glycemic load was not added to the final models.

Results

The baseline distribution of risk factors for colorectal cancer according to intakes of fruit, vegetables, and total fiber is presented in Table 1. Women who consumed greater amounts of fruit, vegetables, and fiber appeared to be older, less likely to have a history of colon polyps, and less likely to smoke currently. They were more likely to be physically active, take multivitamins, and have

Table 1. Age-adjusted baseline characteristics according to intakes of fruit vegetable and fiber in the Women's Health Study

| Characteristics | Fruit ^a | | | | Vegetable ^a | | | | Fiber ^{a,b} | | | |
|---|--------------------|------|------|---------------------------|------------------------|------|------|---------------------------|----------------------|------|------|---------------------------|
| | Q ^c 1 | Q3 | Q5 | <i>p</i> _{trend} | Q1 | Q3 | Q5 | <i>p</i> _{trend} | Q1 | Q3 | Q5 | <i>p</i> _{trend} |
| Participants | 7394 | 7369 | 7381 | | 7396 | 7389 | 7387 | | 7403 | 7410 | 7388 | |
| Age (years) | 52.2 | 54.0 | 55.4 | <0.001 | 53.0 | 54.1 | 54.6 | <0.001 | 52.2 | 53.9 | 55.7 | <0.001 |
| BMI (kg/m ²) | 26.4 | 26.0 | 25.6 | <0.001 | 26.1 | 25.9 | 26.1 | <0.001 | 26.5 | 26.1 | 25.3 | <0.001 |
| Family history of colorectal cancer (%) | 10.2 | 10.7 | 10.6 | 0.95 | 10.7 | 10.4 | 10.0 | 0.22 | 10.5 | 10.2 | 10.1 | 0.50 |
| Colon polyps (%) | 2.8 | 2.6 | 2.2 | <0.01 | 2.9 | 2.6 | 2.1 | <0.01 | 2.9 | 2.3 | 2.5 | 0.20 |
| Post-menopausal HT ^d (% current use) | 39.4 | 43.3 | 42.7 | <0.001 | 41.0 | 42.6 | 42.5 | <0.01 | 38.0 | 42.5 | 44.8 | <0.001 |
| Physical activity (kcal/week) | 675 | 944 | 1323 | <0.001 | 698 | 931 | 1331 | <0.001 | 639 | 933 | 1360 | <0.001 |
| Current cigarette smoking (%) | 24.2 | 10.9 | 6.9 | <0.001 | 17.2 | 12.3 | 9.8 | <0.001 | 23.9 | 11.2 | 6.5 | <0.001 |
| Alcohol consumption (g/day) | 4.9 | 4.1 | 3.5 | <0.001 | 3.6 | 4.2 | 4.5 | <0.001 | 5.8 | 3.9 | 2.9 | <0.001 |
| Total calories intake (kcal/day) | 1424 | 1708 | 2097 | <0.001 | 1377 | 1704 | 2110 | <0.001 | 1707 | 1753 | 1701 | 0.003 |
| Redmeat (serving/day) | 0.77 | 0.72 | 0.68 | <0.001 | 0.64 | 0.73 | 0.75 | <0.001 | 0.98 | 0.74 | 0.42 | <0.001 |
| Aspirin (% current use) | 11.6 | 10.8 | 12.2 | 0.24 | 11.6 | 11.5 | 11.6 | 0.84 | 12.2 | 11.4 | 10.7 | 0.04 |
| Multivitamin use (% current use) | 24.7 | 29.4 | 32.6 | <0.001 | 28.5 | 29.5 | 30.2 | 0.03 | 26.0 | 29.0 | 33.1 | <0.001 |
| Total folate (mcg/day) | 304 | 415 | 549 | <0.001 | 319 | 410 | 553 | <0.001 | 331 | 419 | 513 | <0.001 |
| Total calcium (mg/day) | 768 | 1006 | 1214 | <0.001 | 807 | 998 | 1198 | <0.001 | 899 | 1008 | 1069 | <0.001 |
| Total vitamin D (IU/day) | 269 | 344 | 408 | <0.001 | 292 | 342 | 396 | <0.001 | 316 | 346 | 364 | <0.001 |

^a Intake ranges by quintile were <1, 1–<2, 2–<2.3, 2.3–<3.1, ≥3.1 for fruit (serving/day), <2.1, 2.1–<3.0, 3.0–<4.0, 4.0–<5.4, ≥5.4 for vegetables (serving/day), and <12.5, 12.5–<17.0, 17.0–<20.0, 20.0–<23.1, ≥23.1 for fiber (g/day).

^b Intake values of fiber was energy-adjusted.

^c Q = quintile.

^d HT = hormone therapy.

higher intakes of folate, vitamin D, and calcium. Women with higher intakes of fruit and fiber tended to consume less alcohol and red meat. Intakes of fruit and vegetables were positively associated with consumption of total calories. Intakes of fruit, vegetables and fiber in relation to baseline uses of post-menopausal HT and aspirin were less clear. Family history of colorectal cancer in a first-degree relative did not appear related to intakes of fruit, vegetables, and fiber.

In both analyses adjusted for age and random treatment assignment (Model 1 in Table 2), and additionally for multiple risk factors for colorectal cancer (Model 2 in Table 2), we found no association between intakes of fruit and vegetables and risk of colorectal cancer. The multivariate-adjusted RRs comparing the highest with lowest quintile were 0.79 for fruit intake (95% CI = 0.49–1.27, p for trend = 0.30), and 0.88 for vegetable intake (95% CI = 0.56–1.38, p for trend = 0.30). However, we observed a non-linear relationship with intakes of fruit and legumes; the lowest RR was shown in the second quintile of intakes relative to those in the higher quintiles of intake (Table 2). When examining intakes of specific fruit or vegetable subgroups, we found no decreased risk with intakes of citrus fruit, cruciferous vegetables, legumes, green leafy vegetables, and potatoes (Table 2). Additional adjustment for folate intake and multivitamin use in the multivariate model did not appreciably change the results (Model 3 in Table 2). Similarly, results were not changed with further adjustment for intakes of calcium and vitamin D (data not shown). Intakes of individual fruit and vegetable items were also found not appreciably to be associated with colorectal cancer risk (data not shown).

A non-significantly inverse association was observed between energy-adjusted intake of dietary fiber and risk of colorectal cancer; the multivariate RR for the highest compared with lowest quintile was 0.75 (95% CI = 0.48–1.17, p for trend = 0.12) (Table 3). When examining fiber from specific food sources, intakes of fiber from fruit, vegetables, cruciferous vegetables, and cereals, were not associated with risk of colorectal cancer (Table 3). However, a significantly inverse association with intake of fiber from legumes was noted; the RR for the highest intake of quintile relative to the lowest was 0.60 (95% CI = 0.40–0.91, p for trend = 0.02). The RRs for intakes of total fiber and subgroups of fiber did not change when we added folate intake and multivitamin use to the multivariate model (Table 3), or when we further adjusted for intakes of calcium and vitamin D (data not shown).

Since cancers of the proximal and distal colon are believed to have distinct etiologies [38–40], we examined whether the risk associated with intakes of fruit,

vegetables, and fiber pertained specifically to either tumor site. Intakes of fruit, vegetables, fiber as well as their subgroups were not associated with risk of proximal colon. However, a decrease in risk of distal colon cancer was found with increasing intake of legumes; the multivariate RRs comparing the higher four quintiles with the lowest one were 0.68 (95% CI = 0.35–1.34), 1.15 (95% CI = 0.61–2.16), 0.62 (95% CI = 0.32–1.20), and 0.56 (95% CI = 0.26–1.19), respectively (p for trend = 0.05). Intake of legume fiber was also inversely associated with risk of distal colon cancer; the multivariate RRs for the higher four quintiles were 0.79 (95% CI = 0.42–1.50), 0.62 (95% CI = 0.33–1.15), 0.70 (95% CI = 0.33–1.50), 0.52 (95% CI = 0.26–1.06), respectively (p for trend = 0.03). We did not assess the associations related to risk of rectal cancer due to the small number of cases.

Since women might have changed their dietary habit in response to clinical symptoms of colorectal cancer before they were diagnosed, we reexamined the association between intakes of fruit, vegetables, and fiber, and colorectal cancer risk using cases identified after the first two years of follow-up (new n cases = 186). We also adjusted for screening test of colonoscopy/sigmoidoscopy acquired during this time period in the multivariate model. The results were not appreciably changed (data not shown).

Discussion

In this prospective study, we observed no overall association between consumption of fruit and vegetables and colorectal cancer incidence. Intakes of specific subgroups of fruit and vegetables, including citrus fruit, cruciferous vegetables, legumes, green leafy vegetables, and potatoes, also had similar null associations. Intake of total fiber was also not significantly associated with colorectal cancer. However, we observed an inverse association between legume fiber intake and colorectal cancer risk.

Consistent with several other cohort studies [10–13], we found no association in our cohort between consumption of fruit and vegetables and colorectal cancer risk. In a recent report of two prospective cohorts from the NHS and the Health Professionals Follow-up Study, higher intakes of fruit and vegetables were not related to colon and rectal cancer incidence [10]. In addition, the Iowa Women's Health Study found that the non-significant RRs were greatly attenuated when additional adjustment for energy was carried out [13]. Similarly, in a cohort of Seventh-day Adventists, consumption of green salad was not associated with colorectal cancer

Table 2. Relative risks (RRs) and 95% confidence intervals (CIs) of colorectal cancer according to quintile intakes of fruit and vegetables, and their subgroups in the Women Health's Study

| | Quintile intake | | | | | <i>P</i> _{trend} |
|---|-----------------|------------------|------------------|------------------|------------------|---------------------------|
| | 1 | 2 | 3 | 4 | 5 | |
| Fruit and vegetables (serving/day) | | | | | | |
| Median intake | 2.6 | 4.1 | 5.5 | 7.0 | 10.0 | |
| No. of cases | 42 | 43 | 44 | 42 | 52 | |
| Model 1 ^a | 1.00 | 0.96 (0.63–1.47) | 0.91 (0.59–1.38) | 0.82 (0.54–1.26) | 0.98 (0.65–1.47) | 0.28 |
| Model 2 ^b | 1.00 | 0.98 (0.64–1.51) | 0.92 (0.59–1.45) | 0.81 (0.51–1.30) | 0.96 (0.59–1.57) | 0.18 |
| Model 3 ^c | 1.00 | 0.99 (0.64–1.53) | 0.95 (0.60–1.50) | 0.84 (0.51–1.37) | 0.96 (0.58–1.62) | 0.14 |
| Fruit (serving/day) | | | | | | |
| Median intake | 0.6 | 1.3 | 1.9 | 2.6 | 3.8 | |
| No. of cases ^d | 43 | 32 | 51 | 48 | 48 | |
| Model 1 ^a | 1.00 | 0.67 (0.43–1.08) | 1.01 (0.66–1.56) | 0.84 (0.53–1.31) | 0.82 (0.54–1.24) | 0.38 |
| Model 2 ^b | 1.00 | 0.66 (0.42–1.05) | 0.98 (0.62–1.55) | 0.81 (0.50–1.32) | 0.79 (0.49–1.27) | 0.30 |
| Model 3 ^c | 1.00 | 0.67 (0.42–1.06) | 1.00 (0.65–1.55) | 0.88 (0.55–1.39) | 0.79 (0.48–1.30) | 0.27 |
| Vegetables (serving/day) | | | | | | |
| Median intake | 1.5 | 2.5 | 3.4 | 4.5 | 6.8 | |
| No. of cases | 48 | 41 | 44 | 40 | 50 | |
| Model 1 ^a | 1.00 | 0.82 (0.54–1.25) | 0.84 (0.56–1.26) | 0.74 (0.49–1.13) | 0.90 (0.61–1.34) | 0.38 |
| Model 2 ^b | 1.00 | 0.83 (0.54–1.27) | 0.85 (0.55–1.30) | 0.74 (0.47–1.16) | 0.88 (0.56–1.38) | 0.30 |
| Model 3 ^c | 1.00 | 0.84 (0.55–1.28) | 0.86 (0.56–1.32) | 0.76 (0.48–1.21) | 0.89 (0.56–1.41) | 0.27 |
| Citrus fruit (serving/day) | | | | | | |
| Median intake | 0.1 | 0.3 | 0.6 | 1.0 | 1.6 | |
| No. of cases ^d | 41 | 53 | 38 | 36 | 54 | |
| Model 1 ^a | 1.00 | 1.08 (0.72–1.62) | 1.02 (0.65–1.58) | 0.75 (0.48–1.17) | 1.07 (0.71–1.62) | 0.60 |
| Model 2 ^b | 1.00 | 1.08 (0.71–1.62) | 1.04 (0.66–1.63) | 0.76 (0.48–1.21) | 1.10 (0.71–1.70) | 0.64 |
| Model 3 ^c | 1.00 | 1.09 (0.72–1.65) | 1.06 (0.67–1.66) | 0.78 (0.49–1.24) | 1.11 (0.71–1.74) | 0.61 |
| Cruciferous vegetables (serving/day) | | | | | | |
| Median intake | 0.1 | 0.3 | 0.4 | 0.6 | 1.1 | |
| No. of cases | 56 | 38 | 41 | 41 | 47 | |
| Model 1 ^a | 1.00 | 0.90 (0.60–1.36) | 0.83 (0.55–1.24) | 0.89 (0.60–1.34) | 0.91 (0.61–1.34) | 0.86 |
| Model 2 ^b | 1.00 | 0.91 (0.61–1.38) | 0.83 (0.55–1.24) | 0.88 (0.58–1.33) | 0.86 (0.57–1.30) | 0.65 |
| Model 3 ^c | 1.00 | 0.92 (0.61–1.39) | 0.84 (0.56–1.26) | 0.89 (0.59–1.35) | 0.87 (0.57–1.31) | 0.63 |
| Legumes (serving/day) | | | | | | |
| Median intake | 0.1 | 0.2 | 0.4 | 0.5 | 0.9 | |
| No. of cases | 65 | 31 | 33 | 56 | 38 | |
| Model 1 ^a | 1.00 | 0.64 (0.41–0.97) | 0.88 (0.58–1.33) | 0.93 (0.65–1.34) | 0.82 (0.55–1.22) | 0.23 |
| Model 2 ^b | 1.00 | 0.65 (0.42–1.00) | 0.88 (0.58–1.37) | 0.94 (0.65–1.36) | 0.83 (0.54–1.27) | 0.20 |
| Model 3 ^c | 1.00 | 0.66 (0.43–1.01) | 0.90 (0.59–1.38) | 0.95 (0.66–1.38) | 0.83 (0.54–1.28) | 0.19 |
| Green leafy vegetables (serving/day) | | | | | | |
| Median intake | 0.1 | 0.4 | 0.6 | 0.9 | 1.4 | |
| No. of cases | 43 | 62 | 22 | 46 | 50 | |
| Model 1 ^a | 1.00 | 1.22 (0.83–1.80) | 0.73 (0.44–1.23) | 1.02 (0.67–1.55) | 1.23 (0.82–1.85) | 0.93 |
| Model 2 ^b | 1.00 | 1.23 (0.88–1.90) | 0.80 (0.47–1.34) | 1.09 (0.73–1.67) | 1.30 (0.85–2.01) | 0.87 |
| Model 3 ^c | 1.00 | 1.30 (0.87–1.93) | 0.82 (0.48–1.38) | 1.12 (0.73–1.72) | 1.33 (0.85–2.08) | 0.90 |
| Potatoes (serving/day) | | | | | | |
| Median intake | 0.1 | 0.3 | 0.4 | 0.6 | 1.0 | |
| No. of cases | 47 | 44 | 58 | 33 | 41 | |
| Model 1 ^a | 1.00 | 1.21 (0.84–1.83) | 1.27 (0.87–1.87) | 0.94 (0.60–1.47) | 1.08 (0.71–1.64) | 0.81 |
| Model 2 ^b | 1.00 | 1.29 (0.85–1.96) | 1.33 (0.90–1.99) | 1.06 (0.66–1.70) | 1.19 (0.75–1.99) | 0.84 |
| Model 3 ^c | 1.00 | 1.30 (0.85–1.97) | 1.34 (0.90–2.00) | 1.07 (0.66–1.72) | 1.21 (0.76–1.92) | 0.80 |

^a Models were adjusted for age and randomized treatment assignment.

^b Multivariate models were adjusted for age, randomized treatment assignment, body mass index, family history of colorectal cancer in a first-degree relative, history of colon polyps, physical activity, smoking status, baseline aspirin use, red meat intake, alcohol consumption, total energy intake, menopausal status and baseline post-menopausal HT use.

^c Multivariate models were adjusted for variables denoted in b, as well as folate intake and multivitamin use.

^d The number of cases did not add up to the total because one woman had missing value for the intake.

Table 3. Relative risks (RRs) and 95% confidence intervals (CIs) of colorectal cancer according to quintile intake of energy-adjusted total dietary fiber and fiber from different sources in the Women Health's Study

| | Energy-adjusted quintile intake | | | | | <i>P</i> _{trend} |
|----------------------------------|---------------------------------|------------------|------------------|------------------|------------------|---------------------------|
| | 1 | 2 | 3 | 4 | 5 | |
| Total fiber (g/day) | | | | | | |
| Median intake | 12 | 16 | 18 | 21 | 26 | |
| No. cases | 43 | 44 | 33 | 50 | 53 | |
| Model 1 ^a | 1.00 | 0.92 (0.61–1.40) | 0.65 (0.41–1.02) | 0.91 (0.61–1.38) | 0.87 (0.58–1.32) | 0.36 |
| Model 2 ^b | 1.00 | 0.89 (0.58–1.37) | 0.61 (0.38–0.97) | 0.84 (0.55–1.29) | 0.75 (0.48–1.17) | 0.12 |
| Model 3 ^c | 1.00 | 0.90 (0.59–1.38) | 0.62 (0.39–0.98) | 0.84 (0.54–1.31) | 0.75 (0.47–1.18) | 0.11 |
| Fruit fiber (g/day) | | | | | | |
| Median intake | 2.5 | 3.5 | 4.2 | 4.9 | 6.0 | |
| No. cases ^d | 46 | 39 | 48 | 36 | 53 | |
| Model 1 ^a | 1.00 | 0.88 (0.51–1.19) | 1.19 (0.74–1.74) | 0.70 (0.45–1.08) | 1.07 (0.72–1.58) | 0.59 |
| Model 2 ^b | 1.00 | 0.89 (0.51–1.19) | 1.15 (0.75–1.76) | 0.68 (0.44–1.05) | 1.00 (0.67–1.49) | 0.67 |
| Model 3 ^c | 1.00 | 0.78 (0.51–1.19) | 0.95 (0.63–1.43) | 0.67 (0.44–1.04) | 1.00 (0.67–1.49) | 0.65 |
| Vegetable fiber (g/day) | | | | | | |
| Median intake | 5.9 | 6.4 | 6.8 | 7.3 | 8.0 | |
| No. cases | 39 | 36 | 46 | 59 | 43 | |
| Model 1 ^a | 1.00 | 0.88 (0.56–1.39) | 1.19 (0.74–1.74) | 1.44 (0.96–2.15) | 1.02 (0.66–1.57) | 0.59 |
| Model 2 ^b | 1.00 | 0.89 (0.57–1.40) | 1.15 (0.75–1.76) | 1.45 (0.97–2.18) | 1.00 (0.64–1.55) | 0.67 |
| Model 3 ^c | 1.00 | 0.90 (0.57–1.41) | 1.16 (0.75–1.78) | 1.46 (0.97–2.20) | 1.00 (0.65–1.56) | 0.66 |
| Cereal fiber (g/day) | | | | | | |
| Median intake | 3.1 | 3.9 | 4.4 | 5.0 | 6.1 | |
| No. cases | 51 | 46 | 26 | 45 | 55 | |
| Model 1 ^a | 1.00 | 0.98 (0.66–1.49) | 0.56 (0.35–0.90) | 0.97 (0.66–1.44) | 1.02 (0.69–1.49) | 0.93 |
| Model 2 ^b | 1.00 | 1.00 (0.67–1.49) | 0.56 (0.35–0.90) | 0.94 (0.63–1.41) | 0.97 (0.66–1.43) | 0.72 |
| Model 3 ^c | 1.00 | 1.00 (0.67–1.49) | 0.56 (0.35–0.90) | 0.95 (0.63–1.42) | 0.97 (0.66–1.42) | 0.69 |
| Cruciferous fiber (g/day) | | | | | | |
| Median intake | 0.7 | 0.9 | 1.1 | 1.3 | 1.6 | |
| No. cases | 57 | 35 | 58 | 45 | 28 | |
| Model 1 ^a | 1.00 | 1.00 (0.65–1.52) | 1.19 (0.83–1.72) | 1.14 (0.77–1.69) | 0.76 (0.49–1.20) | 0.50 |
| Model 2 ^b | 1.00 | 0.99 (0.65–1.51) | 1.18 (0.82–1.70) | 1.12 (0.78–1.67) | 0.74 (0.47–1.17) | 0.40 |
| Model 3 ^c | 1.00 | 0.99 (0.65–1.52) | 1.18 (0.82–1.71) | 1.13 (0.76–1.68) | 0.74 (0.47–1.17) | 0.40 |
| Legume fiber (g/day) | | | | | | |
| Median intake | 0.4 | 0.8 | 1.1 | 1.4 | 1.8 | |
| No. cases | 62 | 47 | 51 | 26 | 37 | |
| Model 1 ^a | 1.00 | 0.74 (0.51–1.08) | 0.61 (0.42–0.88) | 0.69 (0.43–1.08) | 0.62 (0.41–0.93) | 0.03 |
| Model 2 ^b | 1.00 | 0.75 (0.51–1.11) | 0.62 (0.42–0.90) | 0.67 (0.43–1.07) | 0.60 (0.40–0.91) | 0.02 |
| Model 3 ^c | 1.00 | 0.76 (0.51–1.11) | 0.63 (0.43–0.91) | 0.67 (0.42–1.08) | 0.60 (0.40–0.91) | 0.02 |

^a Models were adjusted for the same variables denoted in Model 1 in table 2.

^b Multivariate models were adjusted for the same risk factors denoted in Model 2 in table 2.

^c Multivariate models were adjusted for variables denoted in Model 3 in table 2.

^d The number of cases did not add up to the total because one woman had missing value for the intake.

mortality [11]. In the same cohort, a later analysis continued to observe a null association between higher consumption of cooked green vegetables or of salad and colon cancer risk [12]. Other cohort studies found that the reduced risk was confined to consumption of fruit or vegetables alone [14–18]. Among these studies, three found an inverse association between fruit intake and incident colon or colorectal cancer in women (the RRs for the highest *versus* lowest intake category in the range of 0.50–0.73, *p* values in the range of 0.01–0.10), but a null association between consumption of vegetables and

colon cancer risk in either sex [16–18]. Conversely, the other two studies found that intake of vegetables, but not fruit, was inversely associated with colon cancer incidence in men (RR for the highest *versus* lowest quintile of vegetable intake = 0.69, *p* = 0.10) (15), or in men and women (RR for the highest *versus* lowest quintile = 0.76, 95% CI = 0.57–1.02 in men, and 0.62, 95% CI = 0.45–0.86 in women) [14]. Moreover, we found a non-linear relationship in our cohort between intakes of fruit and legumes, and colorectal cancer; the lowest RR was shown in the second quintile of intakes

(a median intake of 1.3 and 0.2 serving/day for fruit and legumes, respectively) as compared with those in the higher quintiles of intake. Similar pattern of relative risks were also observed in other cohort studies [13, 17, 18]; the risk reduction for fruit (and/or legumes) consumption was most noticeable in the lower intake categories but no greater reduction in risk could be observed when further increasing the intake.

Most retrospective case-control studies showed an inverse association between intake of vegetables, and possibly fruit, and colon cancer risk [9]. A meta-analysis of six case-control studies found that higher intake of vegetables was associated with nearly half the risk of colon cancer (OR = 0.48, 95% CI = 0.41–0.57) [41]. The differences in findings between case-control and cohort studies remain to be elucidated. In general, case-control studies are more prone to bias because dietary information is collected retrospectively and controls may not represent the underlying population from which cases were drawn [42]. Given the null association observed from most cohort studies and in a recent randomized trial for recurrence of colorectal adenomas [25], fruit and vegetables may play a smaller role in risk reduction of colorectal cancer than had previously been thought.

Findings of an association between total fiber intake and colorectal cancer risk have been inconclusive. Our study, like most other cohort [15, 17, 21–24, 43] and intervention [25–27] studies found no evidence that fiber consumption contributes to the prevention of colorectal cancer or colorectal adenoma recurrence. Conversely, a meta-analysis pooling 13 case-control studies obtained an odds ratio of 0.53 for colon cancer comparing the highest with the lowest quintile of fiber intake (95% CI = 0.47–0.61) [44]. Two very recent prospective cohort studies also reported a lower risk of colorectal cancer and adenoma recurrence with higher intake of total fiber [19, 20]. The higher consumption of fiber in those two cohorts relative to most other cohorts may have explained their significant findings. In those two cohorts, the median intake of total fiber in the highest intake group was 33–36 g/day, approximately 30–40% higher than that in our cohort (26 g/day). In addition, different food sources preferentially consumed by different population groups are likely to be responsible, since different food sources may have different implications for cancer. The significant association in one of those two cohorts was attributable to higher intake of cereal/grain fiber [20], consistent with a recent cohort study suggesting that higher intake of cereal fiber over a long period may prevent development of advanced colonic neoplasia [45]. If intake of cereal fiber truly prevents development of colorectal cancer, then our cohort may not have benefited since cereal intake in our cohort was low.

However, we observed a lower risk of colorectal cancer with higher intake of legume fiber. The dietary fiber in legumes is a good source of insoluble dietary fiber that has been shown to be readily converted to short-chain fatty acids, such as butyrate, in the colon [46], resulting in reduction of colonic pH and altering bile acid metabolism [47]. Short-chain fatty acids including butyrate have also been shown to regulate the APC and β -catenin genes, believed to be responsible for initiation of colorectal tumors [48]. Alternatively, the lower risk associated with intake of legume fiber may be attributed to other components in the legume that are highly correlated with fiber. Our finding of legume fiber intake warrants more examination.

At least three limitations are present in this study. First, intakes of fruit, vegetables and fiber were measured only once at baseline without further update, which could be a potential source of bias. However, the NHS has found that results from baseline diet questionnaire were consistent with those from updated data [10]. Second, changes in diet intake after enrollment are likely, especially among individuals who had clinical symptoms of colorectal cancer before they were diagnosed. When we repeated the analyses by excluding cases with a diagnosis of colorectal cancer in the first two years of follow-up, we found no appreciable change in the results. Finally, we have limited statistical power for subgroup analyses by colon subsite due to limited number of cases.

In conclusion, our data could not confirm an inverse association of intakes of fruit, vegetables, and fiber with colorectal cancer risk. However, our data suggest that higher intake of legume fiber and/or other sources related to this intake may reduce risk of colorectal cancer.

Acknowledgements

This work was supported by Public Health Service grants CA-47988 from the National Cancer Institute, and HL-43851 from the National Heart, Lung, and Blood Institute. We acknowledge the contributions of the entire staff of the WHS under the leadership of David Gordon, as well as Mary Breen, Susan Burt, Marilyn Chown, Georgina Friedenberg, Inge Judge, Jean Mac-Fadyean, Geneva McNair, David Potter, Claire Ridge, and Harriet Samuelson. We also acknowledge the Endpoints Committee of the WHS (Dr Wendy Y Chen) and Rimma Dushkes for their assistance with the manuscript, and the 39,876 dedicated participants of the WHS.

Appendix A. Definition of fruit and vegetable groups in the Women's Health Study

| | |
|-------------------------|---|
| Fruits: | apples, apple juice, avocado, banana, blue berries, cantaloupe, grape fruit juice, grape fruit, orange juice, oranges, other juice, peaches, prunes, raisins, and strawberries. |
| Citrus fruit: | grapefruit, oranges, grapefruit juice, orange juice. |
| Vegetables: | beans, beets, broccoli, Brussels sprouts, cabbage, cooked carrots, raw carrots, cauliflower, celery, red chili sauce, corn, eggplant, green pepper, iceberg lettuce, kale, mixed vegetables, cooked onions, raw onions, orange squash, peas, romaine lettuce, cooked spinach, raw spinach, string beans, soybeans, tofu, tomatoes, tomato juice, tomato sauce, yams/sweet potatoes. |
| Cruciferous vegetables: | broccoli, kale, cauliflower, cabbage, and Brussels sprouts. |
| Green leafy vegetables: | Head lettuce, iceberg lettuce, kale, mustard greens, chard greens, leaf lettuce, romaine lettuce, spinach. |
| Legumes: | beans, lentils, lima beans, peas, string beans, soybeans, tofu. |
| Potatoes: | potatoes, french fries, potato chips. |

References

- Kim DJ, Shin DH, Ahn B, *et al.* (2003) Chemoprevention of colon cancer by Korean food plant components. *Mutat Res* **523–524**: 99–107.
- Sengupta A, Ghosh S, Das S (2003) Tomato and garlic can modulate azoxymethane-induced colon carcinogenesis in rats. *Eur J Cancer Prev* **12**(3): 195–200.
- Wargovich MJ (1997) Experimental evidence for cancer preventive elements in foods. *Cancer Lett* **114**(1–2): 11–17.
- Huang MT, Deschner EE, Newmark HL, Wang ZY, Ferraro TA, Conney AH (1992) Effect of dietary curcumin and ascorbyl palmitate on azoxymethanol-induced colonic epithelial cell proliferation and focal areas of dysplasia. *Cancer Lett* **64**(2): 117–121.
- Rijken PJ, Timmer WG, van de Kooij AJ, *et al.* (1999) Effect of vegetable and carotenoid consumption on aberrant crypt multiplicity, a surrogate end-point marker for colorectal cancer in azoxymethane-induced rats. *Carcinogenesis* **20**(12): 2267–2272.
- Frei B, Higdon JV (2003) Antioxidant activity of tea polyphenols *in vivo*: evidence from animal studies. *J Nutr* **133**(10): 3275S–3284S.
- Kritchevsky D (1995) Epidemiology of fibre, resistant starch and colorectal cancer. *Eur J Cancer Prev* **4**(5): 345–352.
- Giovannucci E, Willett WC (1994) Dietary factors and risk of colon cancer. *Ann Med* **26**(6): 443–452.
- Steinmetz KA, Potter JD (1996) Vegetables, fruit, and cancer prevention: a review. *J Am Diet Assoc* **96**(10): 1027–1039.
- Michels KB, Edward G, Josphipura KJ, *et al.* (2000) Prospective study of fruit and vegetable consumption and incidence of colon and rectal cancers. *J Natl Cancer Inst* **92**(21): 1740–1752.
- Phillips RL, Snowdon DA (1998) Dietary relationships with fatal colorectal cancer among Seventh-Day Adventists. *J Natl Cancer Inst* **74**(2): 307–317.
- Singh PN, Fraser GE (1998) Dietary risk factors for colon cancer in a low-risk population. *Am J Epidemiol* **148**(8): 761–774.
- Steinmetz KA, Kushi LH, Bostick RM, Folsom AR, Potter JD (1994) Vegetables, fruit, and colon cancer in the Iowa Women's Health Study. *Am J Epidemiol* **139**(1): 1–15.
- Thun MJ, Calle EE, Namboodiri MM, *et al.* (1992) Risk factors for fatal colon cancer in a large prospective study. *J Natl Cancer Inst* **84**(19): 1491–1500.
- McCullough ML, Robertson AS, Chao A, *et al.* (2003) A prospective study of whole grains, fruits, vegetables and colon cancer risk. *Cancer Causes Control* **14**(10): 959–970.
- Shibata A, Paganini-Hill A, Ross RK, Henderson BE (1992) Intake of vegetables, fruits, beta-carotene, vitamin C and vitamin supplements and cancer incidence among the elderly: a prospective study. *Br J Cancer* **66**(4): 673–679.
- Terry P, Giovannucci E, Michels KB, *et al.* (2001) Fruit, vegetables, dietary fiber, and risk of colorectal cancer. *J Natl Cancer Inst* **93**(7): 525–533.
- Voorrips LE, Goldbohm RA, van Poppel G, Sturmans F, Hermus RJ, van den Brandt PA (2000) Vegetable and fruit consumption and risks of colon and rectal cancer in a prospective cohort study: The Netherlands Cohort Study on Diet and Cancer. *Am J Epidemiol* **152**(11): 1081–1092.
- Bingham SA, Day NE, Luben R, *et al.* (2003) Dietary fibre in food and protection against colorectal cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC): an observational study. *Lancet* **361**(9368): 1496–1501.
- Peters U, Sinha R, Chatterjee N, *et al.* (2003) Dietary fibre and colorectal adenoma in a colorectal cancer early detection programme. *Lancet* **361**(9368): 1491–1495.
- Fuchs CS, Giovannucci EL, Colditz GA, *et al.* (1999) Dietary fiber and the risk of colorectal cancer and adenoma in women. *N Engl J Med* **340**(3): 169–176.
- Steinmetz KA, Potter JD (1993) Food-group consumption and colon cancer in the Adelaide Case-control Study. II. Meat, poultry, seafood, dairy foods and eggs. *Int J Cancer* **53**(5): 720–727.
- Giovannucci E, Rimm EB, Stampfer MJ, Colditz GA, Ascherio A, Willett WC (1994) Intake of fat, meat, and fiber in relation to risk of colon cancer in men. *Cancer Res* **54**(9): 2390–2397.
- Mai V, Flood A, Peters U, Lacey JV, Jr., Schairer C, Schatzkin A (2003) Dietary fibre and risk of colorectal cancer in the Breast Cancer Detection Demonstration Project (BCDDP) follow-up cohort. *Int J Epidemiol* **32**(2): 234–239.
- Schatzkin A, Lanza E, Corle D, *et al.* (2000) Lack of effect of a low-fat, high-fiber diet on the recurrence of colorectal adenomas. Polyp Prevention Trial Study Group. *N Engl J Med* **342**(16): 1149–1155.
- Bonithon-Kopp C, Kronborg O, Giacosa A, Rath U, Faivre J (2000) Calcium and fibre supplementation in prevention of colorectal adenoma recurrence: a randomised intervention trial.

- European Cancer Prevention Organisation Study Group. *Lancet* **356**(9238): 1300–1306.
27. Alberts DS, Martinez ME, Roe DJ, *et al.* (2000) Lack of effect of a high-fiber cereal supplement on the recurrence of colorectal adenomas. Phoenix Colon Cancer Prevention Physicians' Network. *N Engl J Med* **342**(16): 1156–1162.
 28. Rexrode KM, Lee IM, Cook NR, Hennekens CH, Buring JE (2000) Baseline characteristics of participants in the Women's Health Study. *J Womens Health Gen Based Med* **9**(1): 19–27.
 29. U.S. Department of Agriculture ARS. USDA Nutrient DataBase for Standard Reference, Release 10: Nutrient Data Laboratory Home Page, <http://www.nal.usda.gov/fnic/foodcomp>, (1993).
 30. Prosky L, Asp NG, Furda I, DeVries JW, Schweizer TF, Harland BF (1985) Determination of total dietary fiber in foods and food products: collaborative study. *J Assoc Off Anal Chem* **68**(4): 677–679.
 31. Prosky L, Asp NG, Schweizer TF, DeVries JW, Furda I (1988) Determination of insoluble, soluble, and total dietary fiber in foods and food products: interlaboratory study. *J Assoc Off Anal Chem* **71**(5): 1017–1023.
 32. Willett W (1998) *Nutritional Epidemiology*. 2nd edn. New York: Oxford University Press.
 33. Salvini S, Hunter DJ, Sampson L, *et al.* (1989) Food-based validation of a dietary questionnaire: the effects of week-to-week variation in food consumption. *Int J Epidemiol* **18**(4): 858–867.
 34. Willett W, Stampfer M, Chu NF, Spiegelman D, Holmes M, Rimm E (2001) Assessment of questionnaire validity for measuring total fat intake using plasma lipid levels as criteria. *Am J Epidemiol* **154**(12): 1107–1112.
 35. Landis RJ, Heyman, ER, Koch, G.G (1978) Average partial association in three-way contingency tables: a review and discussion of alternative tests. *In Stat Rev* **46**: 237–254.
 36. Bock RD. (1975) *Multivariate Statistical Methods in Behavioral Research*. New York: McGraw-Hill.
 37. Higginbotham S, Zhang ZF, Lee IM, *et al.* (2004) Dietary glycemic load and risk of colorectal cancer in the Women's Health Study. *J Natl Cancer Inst* **96**(3): 229–233.
 38. Sato M, Ahnen DJ (1992) Regional variability of colonocyte growth and differentiation in the rat. *Anat Rec* **233**(3): 409–414.
 39. Brackett KA, Townsend SF (1980) Organogenesis of the colon in rats. *J Morphol* **163**(2): 191–201.
 40. Iacopetta B (2002) Are there two sides to colorectal cancer? *Int J Cancer* **101**(5): 403–408.
 41. Trock B, Lanza E, Greenwald P (1990) Dietary fiber, vegetables, and colon cancer: critical review and meta-analyses of the epidemiologic evidence. *J Natl Cancer Inst* **82**(8): 650–661.
 42. Giovannucci E (2002) Modifiable risk factors for colon cancer. *Gastroenterol Clin North Am* **31**(4): 925–943.
 43. Pietinen P, Malila N, Virtanen M, *et al.* (1999) Diet and risk of colorectal cancer in a cohort of Finnish men. *Cancer Causes Control* **10**(5): 387–396.
 44. Howe GR, Benito E, Castelletto R, *et al.* (1992) Dietary intake of fiber and decreased risk of cancers of the colon and rectum: evidence from the combined analysis of 13 case-control studies. *J Natl Cancer Inst* **84**(24): 1887–1896.
 45. Lieberman DA, Prindiville S, Weiss DG, Willett W (2003) Risk factors for advanced colonic neoplasia and hyperplastic polyps in asymptomatic individuals. *Jama* **290**(22): 2959–2967.
 46. Fleming SE, O'Donnell AU, Perman JA (1985) Influence of frequent and long-term bean consumption on colonic function and fermentation. *Am J Clin Nutr* **41**(5): 909–918.
 47. Bingham SA (1990) Mechanisms and experimental and epidemiological evidence relating dietary fibre (non-starch polysaccharides) and starch to protection against large bowel cancer. *Proc Nutr Soc* **49**(2): 153–171.
 48. Augenlicht LH, Mariadason JM, Wilson A, *et al.* (2002) Short chain fatty acids and colon cancer. *J Nutr* **132**(12): 3804S–3808S.