Hypothesis

Fiber from Fruit and Colorectal Neoplasia

Mia A. Papas,[1] Edward Giovannucci,[3,4] and Elizabeth A. Platz[1,2]

[1]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, and [2]Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins Medical Institutions, Baltimore, Maryland and [3]Departments of Nutrition and Epidemiology, Harvard School of Public Health, and [4]Channing Laboratory, Department of Medicine, Harvard Medical School and Brigham & Women's Hospital, Boston, Massachusetts

The role of fiber intake in the etiology of colorectal cancer and precursor adenomatous polyps has been controversial. Although a clear inverse association was observed in several case-control studies (reviewed in refs. 1, 2), large prospective studies subsequently found inconsistent associations between intake of dietary fiber and colorectal cancer (3-8). The lack of an influence was further supported by the findings from intervention studies of dietary modifications designed to increase total fiber intake (9) and of wheat bran (10) and ispaghula husk (11) fiber supplements on risk of recurrent colorectal adenomas. Taken together, the findings from the prospective studies and clinical trials cast doubt on the protective effect of dietary fiber. With the findings of two studies reported in *Lancet* in 2003, the controversy continues (12, 13).

The latest observational findings come from two large studies conducted in the United States and Europe. Data from the Prostate, Lung, Colorectal, and Ovarian Screening Trial and the European Prospective Investigation into Cancer and Nutrition cohort were used to examine the association between dietary fiber and colorectal adenoma or cancer, respectively. Both studies observed statistically significant inverse associations of dietary fiber intake with colorectal neoplasia.

Several hypotheses have been put forth addressing the question of why results from the fiber studies have been so inconsistent. Some of the reasons given include differences in study design, end points, study population characteristics, distribution of fiber intake, and the array of confounders that were controlled for (14). The role of confounding may be of particular importance. Fiber intake is associated with many healthy lifestyle choices, making it difficult to disentangle the effect of fiber from several modifiable factors. For example, people who eat diets rich in fiber also tend to eat less red meat, smoke less, drink less alcohol, and exercise regularly (15). Careful adjustment for these factors is essential in investigations of fiber and colorectal cancer.

Different sources of dietary fiber preferentially consumed within cohorts of people may also contribute to the conflicting results found in investigations of overall dietary fiber (16). Dietary fiber primarily consists of plant cell walls. These plant cell walls vary tremendously in structure and composition (17). In experimental studies, fibers derived from different plant cell wall types have been found to have diverse effects on the potential for carcinogenesis (18, 19). The type or source of fiber consumed also may be important in conferring protection against human colorectal cancer. Therefore, we briefly examined the associations of different sources of fiber among several recent prospective cohort studies and clinical trials.

Table 1 provides the estimates of association of dietary fiber with colorectal neoplasia by source of fiber. Relative risk estimates for total dietary fiber or fiber supplements have ranged from inverse associations to no association with the exception of an intervention study that reported a statistically significant elevated odds ratio (OR) of 1.67 (11). When investigating source of fiber within the prospective studies and the two recent large observational studies, modest inverse associations are found for fruit fiber in some of the studies (see Table 1). The relative risk estimates for fruit fiber range from 0.78 to 1.10, with all but two of the eight point estimates <1.00. Given the differences among the various studies in designs, populations, and assessment tools, these modest yet suggestive associations for fruit fiber may provide some insight into the etiologic role of fiber source and composition in colorectal carcinogenesis.

A moderate to high proportion of fruit fiber from commonly consumed fruits is soluble fiber (largely pectin). Oats (largely gums), legumes (largely gums), and some vegetables (largely pectin), including carrots, cabbage, Brussels sprouts, squash, and broccoli, also contain higher proportions of soluble fiber, whereas wheat bran fiber primarily consists of insoluble fiber. For example, 58% of the fiber content of an orange and 44% of the fiber content of an apple are soluble fiber (20). Soluble fiber estimates for beans, oats, and vegetables range from 15% to 20% of total fiber (20). On the other hand, only 7% of the total dietary fiber in all-bran cereals are soluble fiber (21); the insoluble component is primarily cellulose.

Potential mechanisms of action for soluble fiber that might be hypothesized to reduce the risk of colorectal neoplasia may be through its influence on insulin and glucose control or on the production of short-chain fatty acids. Soluble fiber slows the absorption of glucose from the small intestines, which may reduce hyperinsulinemia

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Table 1. Relative risks comparing the top quantile versus the bottom quantile and 95% CIs from cohort studies and clinical trials examining the role of dietary fiber and colorectal neoplasia by type of fiber and disease type

Study author	Fiber source (Relative risk comparing the top quantile vs the bottom quantile and 95% CI)						
	Total fiber	Cereal fiber	Vegetable fiber	Fruit fiber	Legume fiber	Soluble fiber	Insoluble fiber
Bingham et al. (12)							
Colorectal cancer	0.75 (0.59-0.95)	0.78 (0.62-0.98)	0.88 (0.70-1.11)	0.78 (0.64-0.97)	1.04 (0.84-1.30)		
Peters et al. (13)							
Distal colorectal adenomas	0.91 (0.86-0.97)	0.88 (0.79-0.97)	1.00 (0.89-1.15)	0.80 (0.71-0.93)	0.99 (0.78-1.20)		
Mai et al. (8)							
Colorectal cancer	0.94 (0.70-1.26)	1.02 (0.76-1.37)	0.92 (0.69-1.21)	1.10 (0.83-1.46)	0.84 (0.63-1.10)		
Jacobs et al. (7)							
Recurrent colorectal adenomas	0.83 (0.57-1.19)	0.84 (0.59-1.19)	1.34 (0.94-1.91)	0.92 (0.64-1.32)			
Terry et al. (5)							
Colorectal cancer	0.96 (0.70-1.33)	0.91 (0.69-1.20)	1.17 (0.85-1.61)	0.97 (0.69-1.38)			
Colon cancer		0.84 (0.59-1.20)					
Proximal colon cancer		0.77 (0.45-1.32)					
Distal colon cancer		0.86 (0.47-1.60)					
Rectal cancer		1.10 (0.69-1.76)					
Fuchs et al. (4)							
Colorectal cancer	0.95 (0.73-1.25)	1.00 (0.79-1.27)	1.35 (1.05-1.72)	0.86 (0.67-1.10)			
Distal colorectal adenomas	0.91 (0.71-1.16)	0.92 (0.75-1.14)	0.89 (0.71-1.12)	0.85 (0.68-1.06)			
Pietinen et al. (6)							
Colorectal cancer	1.00 (0.6-1.5)	1.00 (0.7-1.6)	1.2 (0.8-1.9)	1.10 (0.8-1.7)		1.1 (0.7-1.6)	1.0 (0.6-1.5)
Platz et al. (3)							
Distal colon adenomas	0.88 (0.59-1.31)	1.20 (0.86-1.66)	0.93 (0.67-1.30)	0.81 (0.59-1.11)	0.82 (0.60-1.11)	0.69 (0.46-1.03)	1.14 (0.77-1.69)

(22). Insulin is a growth factor that influences proliferation and apoptosis, and there is increasing evidence that high levels of insulin and poor glucose control (23) are associated with increased risk of colon cancer (24, 25). Soluble fiber is also converted to short-chain fatty acids by bacteria (26). *In vitro* studies have demonstrated the ability of short-chain fatty acids to inhibit growth and induce differentiation of cancer cell lines (27). Lower concentrations of butyrate, one of the short-chain fatty acids, have been found in the stool samples of patients with colorectal tumors (28).

Two of the epidemiologic studies reported in Table 1 examined the association between soluble fiber and risk of distal colorectal adenomas (3) and colorectal cancer (6). In the first study (3), an inverse association (*P* for trend = 0.007) was found for soluble fiber and adenomatous polyps of the distal colon. An inverse association was not evident for insoluble fiber. However, the second study (6) found a null association for both soluble and insoluble fiber and colorectal cancer. The results of the latter study, though, should be interpreted with caution. The findings may not be broadly generalizable because the analyses were conducted solely among smokers. In

addition, when compared with the study investigating soluble fiber intake and adenomas, this population had a narrower range of soluble fiber intake (3.7 to 7.3 versus 3.4 to 9.4 g/d). A third study that investigated the association between soluble fiber and colorectal neoplasia was a randomized trial of an ispaghula husk supplement in the prevention of recurrent adenomas (11). This husk is higher in mucilaginous soluble fiber. A statistically significant positive association was observed for this supplement [OR 1.67, 95% confidence interval (95% CI) 1.01 to 2.76]. Explanations for these findings were unclear but may include that ingesting fiber as a processed supplement gives very different results from consuming a diet high in fiber-rich foods.

Some may question the quality of data on fiber subtypes and thus the ability to distinguish effects among the different sources of fiber. Recent investigations of the association between sources of fiber and diverticular disease (29) as well as duodenal ulcer (30) were conducted using the Health Professionals Followup Study cohort. As hypothesized, insoluble fiber consumption was inversely related to risk of diverticular disease (OR comparing extreme quantiles 0.63, 95% CI

0.44 to 0.91), whereas, as hypothesized, soluble fiber intake was more strongly inversely related to risk of duodenal ulcer (OR comparing extreme quantiles 0.40, 95% CI 0.22 to 0.74). These studies suggest that the mechanism of action for insoluble fiber on diverticular disease may be due to the bulking and softening properties of insoluble fiber on stool, whereas the mechanism of action for soluble fiber on duodenal ulcer may be due to the ability of soluble fiber to delay gastric emptying of meals. Taken together, these findings support the ability to distinguish effects of various sources of fiber on disease.

In addition to the particular importance of the source and chemical composition of dietary fiber in colorectal neoplasia, there may also be differences of effect by the location of the tumor in the large bowel or by sex. There is some evidence that total dietary fiber intake may have different effects on colon and rectal neoplasia. Within studies that examined adenomas separately for the colon and rectum, the nonsignificant, protective effect of fiber seems to be more evident for the colon and not the rectum (5). In an analysis of data from two large prospective cohort studies in the United States, associations with commonly identified risk factors for colorectal cancer were compared between colon and rectal cancer (31). Although the investigators did not investigate fiber per se, they did find other risk factor differences by location, supporting the possibility of etiologic differences in rectal and colon cancer (31). Etiologic distinctions may also exist between the proximal and distal colon. However, few studies have examined the association between sources of dietary fiber and colorectal neoplasia separately for the proximal and distal colon (Table 1). Interestingly, some of the studies that found inverse associations for fruit and colorectal neoplasia and that have examined differences by gender seem to find an association for females but less so for males (32-34). Future studies should also address whether the associations of fiber source or composition with colorectal neoplasia vary by sex.

The possibility remains that fruit fiber or soluble fiber may merely be acting as a marker for other components of the diet that may protect against colorectal carcinogenesis. Fruits contain a vast array of potentially beneficial substances that may provide protection against carcinogenesis. For example, fruits contain several phenolic compounds that are strong antioxidants. In addition, folate intake is high in people who consume diets rich in fruits and vegetables. Low dietary folate intakes have been associated with increased risk of colorectal adenomas and cancer. In the United States, folate intake may not be as highly correlated with fiber intake as in European countries. The frequent consumption of folate-containing dietary supplements and multivitamins along with the fortification of breakfast cereals and flours gives Americans the ability to consume folate irrespective of their fiber consumption. In the study of adenomas in the Health Professionals Follow-up Study cohort, independent effects of fruit fiber or soluble fiber and folate-rich vegetables were supported in models containing terms for both (3). Investigations in Europe may be more prone to confounding by folate intake, because European countries have not adopted a policy of folate fortification. Possible evidence for confounding by folate comes from examining the two European studies in

Table 1. Bingham et al. (12) did not adjust for folate intake and found a statistically significant inverse association of fiber (OR 0.75, 95% CI 0.59 to 0.95) and colorectal cancer. On the other hand, Terry et al. (5) did adjust for folate intake and found no association (OR 0.96, 95% CI 0.70 to 1.33). This discrepancy in the findings from these two European studies possibly supports confounding by folate consumption on the association between fiber and colorectal cancer in European populations.

The importance of source and composition of fiber should be investigated further within large prospective studies with detailed measures of dietary fiber. More focus should be given to the consumption of fiber from fruit and soluble fiber. In addition, studies should investigate these associations separately by cancers of the proximal colon, distal colon, and rectum because of possible differences of effect by location in the large bowel. Finally, these associations should be evaluated separately in men and women. Until the results of further investigations have been produced or the trial evidence has been accumulated, eating a diet rich in a wide array of plant foods, including fruits, along with maintenance of weight, being physically active, not smoking, and not drinking excessive alcohol, may be a sound recommendation to avoid colorectal cancer and precursor adenomatous polyps.

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