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VIA FACSIMILE AND U.S. MAIL

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RE: Health Claim: Fiber and Colorectal Cancer (Docket No. 91N-0098)

Dear Mr. Emord:

This letter is in reference to the court decision directing the Food and Drug Administration (FDA) to reconsider the health claim "Consumption of fiber may reduce the risk of colorectal cancer" in dietary supplement labeling (*Pearson v. Shalala*, 164 F.3d 650 (D.C. Cir. 1999)). The other three health claims that FDA was directed to reconsider will be addressed in separate letters.

I. PROCEDURE AND STANDARD FOR EVALUATING THE CLAIM

In reconsidering this claim and the three other health claims that were the subject of *Pearson*, FDA proceeded as described in the October 6, 2000, Federal Register notice entitled "Food Labeling; Health Claims and Label Statements for Dietary Supplements; Update to Strategy for Implementation of *Pearson* Court Decision." 65 Fed. Reg. 59,855 (2000). As noted below in section III, FDA first gathered new scientific evidence on the claims by contracting for a literature search and publishing two notices in the Federal Register soliciting comments and data. After reviewing the updated body of evidence on the claims, FDA applied the "significant scientific agreement" standard by which the health claim regulations require the agency to evaluate the scientific validity of claims. Under this standard, FDA may issue a regulation authorizing a health claim only "when it determines, based on the totality of publicly available scientific evidence (including evidence from well-designed studies conducted in a manner which is consistent with generally recognized scientific procedures and principles), that there is significant scientific agreement, among experts qualified by scientific training and experience to evaluate such claims, that the claim is supported by such evidence." 21 C.F.R. § 101.14.

For claims that did not meet the significant scientific agreement standard, FDA next considered whether to exercise enforcement discretion for qualified claims about the substance-disease relationship. Consistent with the *Pearson* decision, the agency

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considered whether consumer health and safety would be threatened by the claim, and, if not, whether the evidence in support of the claim was outweighed by evidence against the claim, either quantitatively or qualitatively. See 164 F.3d at 650, 659 & n.10. If the evidence for the claim outweighed the evidence against the claim and there was no health or safety threat, the agency went on to consider whether a qualified claim could meet the general health claim requirements of 21 C.F.R. § 101.14, other than the requirement to meet the significant scientific agreement standard and the requirement that the claim be made in accordance with an authorizing regulation. These requirements were not challenged in *Pearson* and therefore still apply.

In the October 6 notice, FDA explained that it would consider exercising enforcement discretion for a dietary supplement health claim that did not meet the significant scientific agreement standard if the scientific evidence for the claim outweighed the scientific evidence against the claim, if the claim included appropriate qualifying language, and if the other criteria listed in the notice were met. In that event, the agency explained, FDA would send a letter to the petitioner outlining the agency's rationale for its determination that the evidence did not meet the significant scientific agreement standard and stating the conditions under which the agency would ordinarily expect to exercise enforcement discretion for the claim. See 65 Fed. Reg. at 59,856. The agency also stated that, conversely, if the scientific evidence for the claim did not outweigh the scientific evidence against the claim, or the substance posed a threat to health, or the other criteria for the exercise of enforcement discretion were not met, FDA would issue a letter denying the claim and explaining its reasons for doing so. See 65 Fed. Reg. at 59,856.

Although the deadlines for FDA action in 21 C.F.R. § 101.70(j) apply to health claims that are submitted by petition, they do not apply to the four claims that were the subject of *Pearson*. FDA is reconsidering those claims under a court order that sets no specific deadlines but clearly contemplates prompt action because of First Amendment concerns and the agency's obligation to comply with court orders as soon as possible. Accordingly, even though the deadlines in § 101.70(j) do not apply, FDA is using them as a guideline. Section 101.70(j)(2) requires the agency to issue a denial or a proposed regulation to authorize the health claim within 190 days of submission of the petition summarizing the scientific evidence relevant to the claim. FDA is issuing this decision letter on October 10, 2000, 190 days after the close of the second comment period for the submission of scientific evidence relevant to the claim.

II. SUMMARY OF REVIEW

In 1993, FDA authorized a health claim for fiber-containing grain products, fruits, and vegetables and reduced risk of cancer. 58 Fed. Reg. 2537 (1993) (codified at 21 C.F.R. § 101.76). FDA had concluded that the evidence available at the time did not support an association of reduced risk of cancer and dietary fiber *per se*, but did support an association of reduced risk of cancer and diets high in fiber-containing grain products, fruits, and vegetables and low in total fat. The available evidence did not resolve whether this association is due to the dietary fiber component of the foods in question, to other

components in these foods, to displacement of other foods in the diet (e.g., fats and meats), or to other combinations of factors. Thus, while the available evidence established that dietary fiber is a marker of the types of foods associated with reduced cancer risk, the evidence was not sufficient to support a finding of significant scientific agreement that dietary fiber itself helps to protect against the development of cancer. Because of this limitation in the evidence, the authorized health claim for fiber-containing grain products, fruits, and vegetables and cancer in § 101.76 characterizes the association between reduced risk of cancer and consumption of certain types of foods, not fiber or any other individual component of those foods.

The agency's decision was also based in part on other limitations in the scientific evidence. See 56 Fed. Reg. 60566, 60575-60576 (1991); 58 Fed. Reg. at 2541, 2543-44. Fiber-rich foods differ significantly in the amounts and types of fiber they contain, and different types of fiber vary considerably in chemical composition, physical characteristics, and biological effects. The commonly used analytical methodologies often do not detect many of the characteristics that vary among fibers and that may be related to biological function (e.g., particle size, chemical composition, or water holding capacity). In the animal studies the agency reviewed, different types of fiber produced widely varying results; in fact, some types of fiber appeared to promote the development of cancer. Fiber in general showed no consistent protective effect, and even results for a single type of fiber were not consistent. Human studies were limited by problems in identifying and measuring the type and amount of fiber consumed. Thus, the agency concluded that the evidence for a health claim about dietary fiber and reduced risk of colorectal cancer was inconclusive and did not meet the significant scientific agreement standard.

In response to *Pearson*, FDA has reconsidered the scientific evidence on the putative relationship between dietary fiber and the risk of developing colorectal cancer, focusing on human study evidence that has become available since the original fiber - cancer health claim rulemaking that concluded in 1993. Both the agency's original 1991-93 scientific evaluation and its evaluation of the evidence that has become available since that time were conducted consistent with the principles and procedures articulated in FDA's *Guidance for Industry: Significant Scientific Agreement in the Review of Health Claims for Conventional Foods and Dietary Supplements* (December 1999).

Based on its review of the scientific evidence, FDA finds that (1) the most directly relevant, scientifically probative, and therefore most persuasive evidence (i.e., randomized, controlled clinical trials with fiber as a test substance) consistently finds that dietary fiber has no effect on incidence of adenomatous polyps, a precursor of and surrogate marker for colorectal cancer; and (2) other available human evidence does not adequately differentiate dietary fiber from other components of diets rich in foods of plant origin, and thus is inconclusive as to whether diet-disease associations can be directly attributed to dietary fiber. FDA has concluded from this review that the totality of the publicly available scientific evidence not only demonstrates lack of significant scientific agreement as to the validity of a relationship between dietary fiber and

colorectal cancer, but also provides strong evidence that such a relationship does not exist.

III. REVIEW OF THE SCIENTIFIC EVIDENCE

A. 1991 - 1993 SCIENTIFIC REVIEW

Congress enacted the health claims provisions of the Nutrition Labeling and Education Act of 1990 (the NLEA) to help consumers maintain good health through appropriate dietary patterns and to protect consumers from unfounded health claims. The NLEA specifically required the agency to determine whether claims respecting 10 nutrient/disease relationships met the statutory requirements for health claims. Pub. L. No. 101-535, § 3(b)(1)(A), 104 Stat. 2353, 2361. The relationship between dietary fiber and cancer was one of these 10 claims the agency was required to evaluate.

Early in 1991, FDA began its review of these 10 claims by publishing a notice in the Federal Register requesting scientific data and information relevant to the claims. 56 Fed. Reg. 12,932 (1991). The agency also contracted with the Life Sciences Research Office for a review of recent evidence on dietary fiber and cancer. In November 1991, FDA published a proposed rule setting forth its review of available scientific evidence and tentative conclusions with respect to authorization of a health claim for the relationship between dietary fiber and cancer. 56 Fed. Reg. 60,566. In the 1991 proposed rule, the agency proposed not to authorize such a health claim for either dietary supplements or conventional foods, tentatively concluding that the evidence supporting an association between dietary fiber and reduced risk of colorectal cancer was inconclusive and therefore did not meet the significant scientific agreement standard. FDA also tentatively concluded, however, that the scientific evidence was sufficient to establish an association between consumption of fiber-rich plant foods and reduced cancer risk. Accordingly, the agency asked for comment on whether it should authorize a health claim for such foods.

While the proposed rule was pending, Congress passed the Dietary Supplement Act of 1992 (the DSA). Pub. L. No. 102-571, 106 Stat. 4500. The DSA imposed a moratorium on FDA's implementation of the NLEA with respect to dietary supplements until December 15, 1993. The DSA also directed FDA to repropose implementing regulations for dietary supplements by June 15, 1993, and provided that the proposed regulations would become final by operation of law if final rules were not issued by December 31, 1993.

In a final rule published in January 1993, FDA concluded that there was significant scientific agreement that diets high in fiber-containing grain products, fruits, and vegetables reduce the risk of some types of cancer, including colorectal cancer. 58 Fed. Reg. 2537. However, such diets also differ from the typical U.S. diet in levels of many nutrients other than dietary fiber, making it difficult to attribute observed diet-disease relationships to any single nutrient. Overall, FDA concluded that the available evidence

was not sufficient to demonstrate that it is total dietary fiber, specific dietary fiber components, specific vitamins or minerals, or interactions of nutrients that are related to lower cancer risk among population groups consuming diets high in dietary fiber-rich foods. 58 Fed. Reg. at 2538. Therefore, FDA did not authorize a health claim for a relationship between dietary fiber intake and the risk of cancer.

Because of the DSA's moratorium on implementation of the NLEA with respect to dietary supplements, the January 1993 final rule applied only to health claims for conventional foods, not dietary supplements. In response to the DSA's directive to issue proposed regulations specific to dietary supplements, FDA proposed in October 1993 not to authorize a health claim for fiber and cancer in the labeling of dietary supplements. 58 Fed. Reg. 53,296 (1993). The October 1993 proposal relied on the scientific review conducted as part of the fiber-cancer health claim rulemaking that concluded in January 1993. FDA did not issue a final rule by December 31, 1993, and therefore the October 1993 proposal became final on that date. See 59 Fed. Reg. 436 (1994).

B. CURRENT SCIENTIFIC REVIEW

FDA's first step in reconsidering the dietary fiber-colorectal cancer health claim was to gather the relevant scientific evidence that had become available since the previous rulemaking on this topic. To update its earlier review, the agency reviewed comments¹ and data submitted in response to two Federal Register notices requesting scientific data and information, as well as data identified by a literature search. See 64 Fed. Reg. 48,841 (1999); 65 Fed. Reg. 4252 (2000). The literature search covered publications that were issued after 1991.

During its 1991-93 review, FDA considered preclinical studies because the number of relevant human studies was limited. Preclinical studies (studies not performed in humans), such as those with experimental animal cancer models or *in vitro* techniques, are useful for developing hypotheses or investigating mechanisms of putative relationships between food substances and disease risk. However, the usefulness of data from preclinical studies is limited in that such studies cannot fully simulate human disease and physiology. Additionally, they cannot accurately estimate appropriate intake levels or the size of effects in humans. Since FDA's 1991-93 review, a number of well-designed new studies have been performed in humans, including several intervention trials specifically designed to test the fiber-colorectal cancer hypothesis. In the current review, therefore, FDA focused its attention on these more relevant human studies.

The threshold criteria for selection of human studies to review were the same as those used in the 1991-93 FDA review of this health claim topic: that they be publicly available

¹FDA received three comments after the close of the comment period. The agency was not obligated to and did not consider the late comments. All other comments were considered.

in English, provide a description of study design and results adequate to permit an evaluation of the study, include either direct measurements or quantitative estimates of intake of dietary fiber as a supplement or component of food, and include a direct measure of colorectal cancer risk (e.g., incidence, mortality, prognostic indicators such as pre-malignant tumors). See 56 Fed. Reg. at 60570.

1. INTERVENTION STUDIES

In an intervention study, the investigator controls whether the subjects receive an exposure (the intervention), whereas in an observational study, the investigator does not have control over the exposure. Therefore, intervention studies generally provide the strongest evidence for an effect. Unlike observational studies, which provide evidence of an association--but not necessarily a cause and effect relationship--between the substance and disease of interest, intervention studies can provide evidence of causal relationships or the lack thereof. Randomized controlled clinical trials are considered the most persuasive studies. When the results of such studies are available, they will be given the most weight in the evaluation of the totality of the evidence. See *Guidance for Industry: Significant Scientific Agreement in the Review of Health Claims for Conventional Foods and Dietary Supplements*, at 5.

Several randomized controlled clinical intervention trials of dietary fiber have been published since 1992. Four of these studies were well designed and well conducted large-scale studies in which incidence of recurrent colorectal adenomatous polyps was used as a surrogate marker (measure) of colorectal cancer risk (Alberts et al., 2000; Schatzkin et al., 2000; MacLennan et al., 1995; and McKeown-Eyssen et al., 1994). Other dietary fiber randomized controlled clinical trials addressed as endpoints epithelial cell proliferation rate (Alberts et al., 1997; Rooney et al., 1994), fecal bile acid excretion (Alberts et al., 1996; Reddy et al., 1992), and bowel transit time, fecal bulk and colonic pH (Lewis and Heaton, 1997).

Validation of an experimental endpoint as a surrogate marker of cancer requires that there be evidence that altering the surrogate marker affects the risk of developing cancer. Development of colorectal adenocarcinomas is a multi-step process, beginning with adenomatous polyps. Most colorectal adenomatous polyps remain as small tubular polyps, but a small proportion grow into larger, advanced villous polyps, which in turn evolve into malignant adenocarcinomas. Because all colorectal cancers develop from adenomatous polyps, polyp appearance is considered a surrogate marker for a cancer endpoint (Einspahr et al., 1997). Furthermore, it has been established that the removal of adenomatous polyps prevents the development of colorectal cancer (Winawer et al., 1993); i.e., colorectal cancer does not develop in the absence of adenomatous polyps. Thus, the link between adenomatous polyps and subsequent colorectal cancer risk in humans is established.

Because the recurrence rate of colorectal adenomatous polyps among individuals who have had a previous colorectal polyp is relatively high, approximately 10 percent

annually, intervention studies with recurrent adenomas as an endpoint provide much greater statistical power to detect effects than do intervention studies with malignant disease endpoints (Schatzkin et al., 1994). The incidence of colorectal adenomatous polyps correlates with dietary factors shown to influence risk of colorectal cancer, e.g., total fat, fruit, vegetable, and cereal grain consumption (Platz et al., 1997; Giovannucci et al., 1992).

There are some limitations in the use of adenomatous polyps as surrogate markers for colorectal cancer. These include: (1) factors influencing formation of polyps may differ from factors influencing the progression of a polyp to malignant lesion; and (2) the time period required for a significant number of adenomatous polyps to progress to advanced polyps is greater than the duration of most polyp intervention studies. Despite these limitations, adenomatous polyp incidence is generally accepted by qualified experts as the best available surrogate marker for colorectal cancer in humans (Earnest et al., 1999).

The intervention treatment for two of the adenomatous polyp studies was wheat bran fiber dietary supplements (Alberts et al., 2000; MacLennan et al., 1995); the other two studies used low-fat, high-dietary fiber diet modification to reach a targeted fiber intake (Schatzkin et al., 2000; McKeown-Eyssen et al., 1994). One study (McKeown-Eyssen et al., 1994) added wheat bran-fortified snacks to increase dietary fiber consumption. None of these four intervention studies found any effect of dietary fiber consumption on the incidence of recurrent adenomatous polyps. Thus, there has become available in recent years a persuasive body of scientific evidence from randomized controlled intervention studies that are consistent in showing no effect of dietary fiber consumption on a surrogate marker of colorectal cancer risk.

FDA discussed possible risk factors that might serve as surrogate markers for colorectal cancer in its 1991 proposal and 1993 final rule on dietary fiber and cancer. See 56 Fed. Reg. at 60573-74, 60575; 58 Fed. Reg. at 2539, 2543-44. FDA noted that studies on such possible risk factors are difficult to interpret because actual risk factors are not completely understood, and it is not known how valid certain markers are for colon cancer. See 58 Fed. Reg. at 2539. When such uncertainties are present, the significance of favorable effects is unclear. See 56 Fed. Reg. at 60575. As discussed above, adenomatous polyps are now accepted by qualified experts as surrogate markers for colorectal cancer. However, the usefulness of other surrogate markers potentially relevant to colorectal cancer risk in humans is still unclear (Earnest et al., 1999). Because four well-done clinical intervention studies using adenomatous polyps were available, FDA focused its efforts in the current literature review on the polyp intervention trials, and did not focus on studies with less useful endpoints.

In the interest of a comprehensive review, however, FDA did consider five new studies that addressed putative surrogate markers other than adenomatous polyps, although it gave such studies little weight. These were studies on epithelial cell proliferation rate (Alberts et al., 1997; Rooney et al., 1994); fecal bile acid excretion (Alberts et al., 1996; Reddy et al., 1992); and bowel transit time, fecal bulk and colonic pH (Lewis and Heaton,

1997). One cell proliferation study reported a reduction in cell proliferation rate (Rooney et al., 1994), while the other reported no effect (Alberts et al., 1997). The two bile acid studies reported decreased stool concentrations of secondary bile acids, and the Lewis and Heaton study reported decreased bowel transit time and colonic pH and increased fecal bulk. However, none of these five studies provided evidence that altering any of these factors alters the risk of colorectal cancer in humans. Because of the uncertainty about the validity of the endpoints of these studies as surrogate markers, FDA considered them to be of limited usefulness in its scientific evaluation.

2. OBSERVATIONAL STUDIES

Several types of observational, or epidemiological, studies can provide information on the association between dietary fiber and colorectal cancer; however, these studies often do not provide a sufficient basis for determining whether a substance-disease association reflects a causal, rather than a coincidental, relationship. Population, or correlational, studies use grouped data to examine the relationship between dietary exposure and health outcome among populations. Such studies do not examine relationships for individuals and have traditionally been regarded as useful for generating, rather than testing, hypotheses regarding diet-disease relationships. As such, population studies were not given much weight in the current evaluation. In case-control studies, subjects with existing diagnosed disease (the cases) are enrolled in a study. These subjects are matched by identifiable characteristics (i.e., age, race, gender) to disease-free subjects (the controls). The diets of the two groups are then compared to discern dietary habits associated with risk for the disease. In prospective, or cohort, studies, disease-free subjects are recruited within a specified group of people, such as female nurses (the cohort), and the dietary habits of the subjects are determined. The study tracks the subjects over an extended period of time to see whether they develop the disease being investigated. At the end of the follow-up period, the dietary patterns of subjects who developed the disease during the follow-up period are compared to those of the subjects who did not develop the disease to discern dietary patterns that are associated with risk of the disease.

An inherent limitation of dietary observational studies is the extent to which dietary fiber intake can be assessed. There is considerable uncertainty in the quantitative measurement of habitual food intake over long periods of time. Some studies typically use a retrospective food frequency questionnaire in which the study subjects are asked to recall their typical diets (in terms of foods eaten, frequency of eating, and serving sizes) over several previous years. Such techniques are subject to recall bias, particularly for dietary factors thought possibly related to the disease. Further, there is more uncertainty in the translation of food intake data into fiber intake data by calculation from food composition tables. The natural variability of foods, the effects of processing on fiber content, the complexity of dietary fiber, the lack of a universally accepted definition of dietary fiber, and the consequential inconsistencies in analytical methods together make it impossible to accurately calculate dietary fiber intake from food intake data. Moreover, diets containing fiber-rich foods differ from low-fiber diets in many respects. This makes it

difficult to establish whether dietary fiber or some other component of the diet is responsible for any observed benefit. Therefore, there are significant limitations to assessing dietary fiber intake data from observational studies and relating intake to the disease. Since the primary variable assessed in these studies is food consumption, and there is uncertainty involved in the computation of dietary fiber intake from such data, the usefulness of these types of studies to differentiate effects of the dietary fiber component of the food from effects of other components of the food is limited.

As a consequence of their inherent shortcomings, observational studies are of limited use in resolving the key issue from the 1993 evaluation. That is, one cannot determine from such studies whether fiber was in fact the agent that provided any benefit that might have been observed. Of far greater usefulness are the intervention studies that have recently become available, and which, unlike observational studies, were not available in 1993. Nonetheless, FDA considered recent observational studies from among the available evidence, although the agency gave these studies little weight.

The recently available observational evidence includes results from six large-scale prospective cohort studies, a review of 13 pre-1992 case-control studies (Howe et al., 1992), and 16 more recent case-control studies. (See Summary Tables - Dietary Fiber/Colorectal Cancer Studies.) Among observational studies, prospective cohort studies are, in general, the most persuasive because they are less vulnerable to recall bias and to measurement errors than other observational studies, such as case-control studies. See *Guidance for Industry: Significant Scientific Agreement in the Review of Health Claims for Conventional Foods and Dietary Supplements*, at 6.

The results of the prospective cohort studies that FDA considered were consistent with the polyp intervention studies in finding no association between colorectal cancer incidence and total dietary fiber consumption. While the analysis of the pre-1992 case-control studies predominantly showed an inverse association between dietary fiber intake and colorectal cancer, the newer case-control studies yielded no consistent pattern. Thus, the case-control studies published since 1992 do not advance our understanding of the putative relationship between dietary fiber consumption and the risk of developing colorectal cancer.

The results of the more powerful intervention studies outweigh the results of the less definitive observational studies. Furthermore, the cohort studies, which are more persuasive among observational studies than are case-control studies, provide evidence consistent with the intervention study results.

IV. AGENCY'S CONSIDERATION OF SIGNIFICANT SCIENTIFIC AGREEMENT

As discussed in section II, a major factor in FDA's 1993 decision not to authorize a health claim for dietary fiber and colorectal cancer was the absence of human evidence directly linking fiber to reduction of colorectal cancer risk. The evidence available at that time only supported significant scientific agreement for a link between fiber-containing grain

products, fruits, and vegetables and reduced colorectal cancer risk. See 21 C.F.R. 101.76. Hence, FDA's current review focused primarily on evaluating whether the newer studies resolved previous uncertainties. The studies most relevant to this analysis were four recent well-designed intervention trials that studied the effect of dietary fiber on adenomatous polyps in humans.

The data from these recent intervention studies consistently fail to show any protective effect from consumption of dietary fiber alone. Because the intervention studies specifically administered dietary fiber as a test substance, the results of these studies are much more persuasive than the results of observational studies. As in the 1991-93 rulemaking, the varying results from recent observational studies are inconclusive, although the results of the prospective (cohort) studies, generally the most persuasive type of observational study, also showed no relationship. As previously discussed, observational studies of intake of fiber from food cannot distinguish the action of fiber from that of other substances in fiber-rich foods. By contrast, the four recent intervention studies administered carefully controlled amounts of dietary fiber. These studies provide strong and consistent evidence that dietary fiber provides no risk reduction benefit.

Therefore, based on its evaluation of the publicly available scientific evidence, the agency concludes that there is not significant scientific agreement among qualified experts that a relationship exists between dietary fiber intake and risk of colorectal cancer.

V. AGENCY'S CONSIDERATION OF A QUALIFIED CLAIM

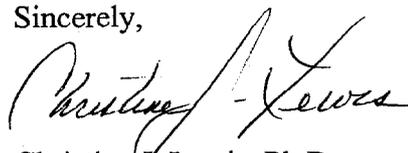
It is well recognized that diets high in certain fiber-rich plant foods and low in fat are associated with lower incidences of certain types of cancers, including colorectal cancer. See 21 C.F.R. § 101.76(a)(2); 58 Fed. Reg. at 2538. Since dietary fiber is a dietary component unique to foods of plant origin and has known physiological effects in the colon, it has been a popular hypothesis that dietary fiber is the component of such diets that influences the development of colorectal cancer. Evidence to support the hypothesis was initially based on observational studies and other data that suggested but did not demonstrate a causal relationship between dietary fiber and reduction of the risk of colorectal cancer.

The most persuasive scientific evidence on this topic comes from randomized, controlled clinical intervention studies with fiber as the test substance. At the time of FDA's initial 1991-93 review, no such studies had been conducted. Since then, the results of four major clinical intervention studies designed to test the fiber-cancer hypothesis have been published, including two studies that used fiber supplements. FDA considers the results of these studies to be the most scientifically probative evidence in evaluating a possible role of dietary fiber in risk reduction for colorectal cancer. These studies consistently showed that dietary fiber had no effect on the incidence of adenomatous polyps, the best available surrogate marker for colorectal cancer. Thus, the evidence against a relationship for dietary fiber and colorectal cancer is more compelling than the evidence for a relationship.

Based on its scientific review, FDA concludes that the evidence is strong that there is not a relationship between dietary fiber and colorectal cancer. The best-done studies have found no such relationship. The findings are consistently seen across four intervention trials and the prospective cohort studies available since 1992. Given this evidence, a claim for a relationship between fiber and colorectal cancer cannot be qualified in such a way as not to mislead consumers. The *Pearson* court noted that FDA had deemed the fiber - cancer claim and two other claims for dietary supplements to lack significant scientific agreement because existing research had examined only the relationship between consumption of foods containing these components and the risk of these diseases, and that FDA had therefore concluded that the specific effect of the food component constituting the dietary supplement could not be determined with certainty. The court added that this concern could be accommodated by adding a prominent disclaimer to the label along the following lines: "The evidence is inconclusive because existing studies have been performed with *foods* containing [dietary fiber], and the effect of those foods on reducing the risk of cancer may result from other components in those foods." 164 F.3d at 658 (emphasis in original).

Now there are indeed results from studies performed with dietary fiber supplements in addition to studies performed with foods. The evidence is no longer inconclusive; results of four randomized, controlled intervention studies in humans consistently show a lack of relationship between dietary fiber and risk of colorectal cancer. In light of this new evidence, the disclaimer suggested by the *Pearson* court would now be misleading. The weight of the evidence for a health claim about dietary fiber and colorectal cancer is outweighed by the evidence against such a claim. Therefore, FDA has determined that health claims relating dietary fiber and reduced risk of colorectal cancer are inherently misleading and cannot be made non-misleading with a disclaimer or other qualifying language. See *Pearson*, 164 F.3d at 659. The use of such health claims is therefore prohibited by the Federal Food, Drug, and Cosmetic Act. A dietary supplement that bears a claim about dietary fiber and reduced risk of colorectal cancer will be subject to regulatory action as a misbranded food under 21 U.S.C. § 343(a)(1) and (r)(1)(B); as a misbranded drug under 21 U.S.C. § 352(a) and (f)(1); and as an unapproved new drug under 21 U.S.C. § 355(a).

Sincerely,



Christine J. Lewis, Ph.D.

Director

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Center for Food Safety

and Applied Nutrition

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SUMMARY TABLES - Dietary Fiber/Colorectal Cancer Studies

This table summarizes studies discussed in FDA's October 10, 2000, letter evaluating the evidence for a health claim for dietary fiber and colorectal cancer.

Intervention Studies

ADENOMATOUS POLYP RECURRENCE

STUDY	DESCRIPTION	RESULTS	CONCLUSIONS																								
<p><i>Arizona Wheat Bran Fiber Study</i></p> <p>Alberts et al. (2000)</p>	<p>3-yr randomized, placebo-controlled RCT of wheat bran fiber (13.5 or 2 g/day) to study effect of DF supplementation in reducing the rate of recurrent colorectal adenomas.</p> <p>SUBJECTS- 1429 males and females, age 40 to 80, with colorectal adenomatous polyp removed within 3-mo. prior to enrollment.</p> <p>ENDPOINT- adenomatous polyp incidence at 3 yr.</p>	<table border="1"> <thead> <tr> <th>Incidence</th> <th>Intervn</th> <th>Ctrl</th> <th>RR</th> </tr> </thead> <tbody> <tr> <td>Overall</td> <td>47.0%</td> <td>51.2%</td> <td>0.88</td> </tr> <tr> <td>≥ 3</td> <td>18.5%</td> <td>15.1%</td> <td>(p=0.03)</td> </tr> <tr> <td>Large</td> <td>15.4%</td> <td>16.1%</td> <td></td> </tr> <tr> <td>Advanced</td> <td>3.9%</td> <td>4.3%</td> <td></td> </tr> <tr> <td>n</td> <td>719</td> <td>584</td> <td></td> </tr> </tbody> </table>	Incidence	Intervn	Ctrl	RR	Overall	47.0%	51.2%	0.88	≥ 3	18.5%	15.1%	(p=0.03)	Large	15.4%	16.1%		Advanced	3.9%	4.3%		n	719	584		<p>(1) NO EFFECT of wheat bran fiber dietary supplement on risk of recurrent colorectal adenoma.</p>
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<p><i>Polyp Prevention Trial.</i></p> <p>Schatzkin et al. (2000)</p>	<p>4-yr double-blinded RCT comparing usual diet to a diet low in fat (20% of total calories), high in fiber (18 g DF/1000 kcal) and high in fruits and vegetables (3.5 servings/1000 kcal)</p> <p>SUBJECTS- 2079 males and females, over 35 yrs of age, with colorectal adenomatous polyp removed within 6-mo prior to enrollment.</p> <p>ENDPOINT- incidence of colorectal adenomas after 4-yr.</p>	<table border="1"> <thead> <tr> <th>Incidence</th> <th>Intervn</th> <th>Ctrl</th> <th>RR</th> </tr> </thead> <tbody> <tr> <td>Overall</td> <td>39.7%</td> <td>39.5%</td> <td>1.00</td> </tr> <tr> <td>≥ 3</td> <td>7.6%</td> <td>7.9%</td> <td>0.96</td> </tr> <tr> <td>Large</td> <td>4.9%</td> <td>5.6%</td> <td>0.88</td> </tr> <tr> <td>Advanced</td> <td>6.3%</td> <td>7.0%</td> <td>0.90</td> </tr> <tr> <td>n</td> <td>958</td> <td>947</td> <td></td> </tr> </tbody> </table>	Incidence	Intervn	Ctrl	RR	Overall	39.7%	39.5%	1.00	≥ 3	7.6%	7.9%	0.96	Large	4.9%	5.6%	0.88	Advanced	6.3%	7.0%	0.90	n	958	947		<p>(1) NO EFFECT of low-fat, high-fiber diet on risk of recurrent colorectal adenomas.</p>
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SUMMARY TABLES - Dietary Fiber/Colorectal Cancer Studies Page 2

<p><i>Australian Polyp Prevention Trial</i></p> <p>MacLennan et al. (1995)</p>	<p>2-yr (extended to 4-yr) RCT of 3 dietary variables: low fat diet (25% of calories), beta-carotene supplement (20 mg/d) and dietary fiber supplement (11 g DF/day finely milled raw wheat bran) in a 2x2x2 factorial design, to study dietary effects on recurrent colorectal adenomas.</p> <p>SUBJECTS- 411 males and females, age 30 to 75, with recent colorectal adenomatous polyp removal</p> <p>ENDPOINT- adenomatous polyp incidence at 2 and 4 yr.</p>	<p>2-yr analysis</p> <table border="1"> <thead> <tr> <th>Incidence</th> <th>Fiber</th> <th>Ctrl</th> <th>OR</th> </tr> </thead> <tbody> <tr> <td>Overall</td> <td>23.3%</td> <td>20.8%</td> <td>1.2</td> </tr> <tr> <td>Large</td> <td>3.6%</td> <td>5.6%</td> <td>0.6</td> </tr> <tr> <td>Advanced</td> <td>3.6%</td> <td>6.6%</td> <td>0.5</td> </tr> <tr> <td>n</td> <td>193</td> <td>197</td> <td></td> </tr> </tbody> </table> <p>4-yr analysis</p> <table border="1"> <thead> <tr> <th>Incidence</th> <th>Fiber</th> <th>Ctrl</th> <th>OR</th> </tr> </thead> <tbody> <tr> <td>Overall</td> <td>32.7%</td> <td>29.5%</td> <td>1.2</td> </tr> <tr> <td>Large</td> <td>4.7%</td> <td>6.4%</td> <td>0.7</td> </tr> <tr> <td>Advanced</td> <td>4.0%</td> <td>6.4%</td> <td>0.6</td> </tr> <tr> <td>n</td> <td>150</td> <td>156</td> <td></td> </tr> </tbody> </table>	Incidence	Fiber	Ctrl	OR	Overall	23.3%	20.8%	1.2	Large	3.6%	5.6%	0.6	Advanced	3.6%	6.6%	0.5	n	193	197		Incidence	Fiber	Ctrl	OR	Overall	32.7%	29.5%	1.2	Large	4.7%	6.4%	0.7	Advanced	4.0%	6.4%	0.6	n	150	156		<p>(1) DF alone not protective;</p> <p>(2) non-significant reduction of no. large adenomas with either low fat or DF supplement;</p> <p>(3) DF + low fat protective against <u>large</u> adenomas.</p>
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<p><i>Toronto Polyp Prevention Trial</i></p> <p>McKeown-Eyssen et al. (1994)</p>	<p>2-yr randomized trial of low fat, high fiber diet counseling vs normal diet on recurrent colorectal adenomas. Included wheat bran snack product (20 g DF/snack)</p> <p>SUBJECTS- 201 males and females, under 85 yr of age, with recent colorectal adenomatous polyp removal.</p> <p>ENDPOINT- incidence of colorectal adenomas after 2-yr.</p>	<table border="1"> <thead> <tr> <th>Incidence</th> <th>Intervn</th> <th>Ctrl</th> <th>RR</th> </tr> </thead> <tbody> <tr> <td>Overall</td> <td>21.8%</td> <td>18.4%</td> <td></td> </tr> <tr> <td>n</td> <td>78</td> <td>87</td> <td></td> </tr> <tr> <td>Men</td> <td>30.8</td> <td>15.9</td> <td>2.1</td> </tr> <tr> <td>Women</td> <td>11.5</td> <td>21.2</td> <td>0.5</td> </tr> </tbody> </table>	Incidence	Intervn	Ctrl	RR	Overall	21.8%	18.4%		n	78	87		Men	30.8	15.9	2.1	Women	11.5	21.2	0.5	<p>(1) NO EFFECT of low-fat, high-fiber diet on overall recurrent colorectal adenoma incidence.</p> <p>(2) Low-fat, high-fiber diet INCREASED adenoma incidence in men, DECREASED adenoma incidence in women.</p>																				
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Intervention Studies**ENDPOINTS OTHER THAN POLYP RECURRENCE**

STUDY	DESCRIPTION	RESULTS	CONCLUSIONS
Alberts et al. (1997)	<p>9-mo double-blinded, placebo-controlled RCT of calcium supplements and wheat bran fiber (13.5 or 2 g DF/d) to study effect of DF supplementation on rectal mucosal proliferation rate.</p> <p>SUBJECTS- 100 males and female, ages 50-75, with recent colonic polyp removal.</p> <p>ENDPOINT- [³H]thymidine labeling index in crypt organ culture and 24-hr outgrowth culture, from rectal mucosal biopsies.</p>	<p>Labeling index of crypt cultures- 1.94% (-Ca/-DF), 2.16% (-Ca/+DF), 1.98% (+Ca/-DF), 2.67% (+Ca/+DF)</p> <p>Labeling index of outgrowth cultures- 2.85% (-Ca/-DF), 1.91% (-Ca/+DF), 2.65% (+Ca/-DF), 2.50% (+Ca/+DF)</p>	(1) NO EFFECT of calcium supplements, wheat bran fiber, or their combination on rectal epithelial cell labeling index.
Lewis and Heaton (1997)	<p>Sequential cross-over design of three 9-d treatment periods interspaced with 2-4 wk washout periods. Treatments in sequence were- wheat bran (28.3 ± 8.7 g/d), senna tablets, and loperamide.</p> <p>SUBJECTS- 13 healthy adults</p> <p>ENPOINTS- gut transit time, defecation frequency, stool form, fecal β-glucuronidase activity, fecal pH, fecal short chain fatty acid concentration, intracolonic pH.</p>	<p>During the wheat bran ingestion period- gut transit time decr by 43%; stool output incr by 40%; interdefaecatory interval decr by 25%; distal colon pH decr from 7.1 to 6.9; fecal pH was unaffected.</p> <p>Fecal short chain fatty acid concentrations (acetic, propionic, butyric acids) were unaffected by wheat bran fiber ingestion.</p>	(1) Wheat bran fiber increases stool output and decreases gastrointestinal transit time.

SUMMARY TABLES - Dietary Fiber/Colorectal Cancer Studies Page 4

<p>Alberts et al. (1996)</p>	<p>9-mo double-blinded, placebo-controlled RCT of calcium supplements and wheat bran fiber (13.5 or 2 g DF/d) to study effect of DF supplementation on fecal bile acid excretion.</p> <p>SUBJECTS- 100 males and female, ages 50-75, with recent colonic polyp removal.</p> <p>ENDPOINT- primary and secondary bile acid concentrations in 72-h stool samples.</p>	<p>At 9-mo concentrations of fecal bile acids (total, chenodeoxycholic, cholic, deoxycholic, lithocholic bile acids) were appx 25-50% of baseline values in high fiber groups.</p> <p>At 9-mo fecal bile acid excretion rates were appx 25-75% of baseline values in high fiber groups.</p>	<p>(1) Wheat bran fiber reduced both total and secondary fecal bile acid concentrations and excretion rates.</p>
<p>Rooney et al. (1994)</p>	<p>Single-blinded, 12-wk study with dietary treatment of 10.5 g/d wheat fiber or 60 ml/d lactulose.</p> <p>SUBJECTS- 38 individuals at increased CRC risk due to family history of the disease.</p> <p>ENDPOINTS- in vitro crypt cell production rate in rectal biopsy tissue</p>	<p>Rectal crypt epithelial cell proliferation decreased following 12-wk of wheat fiber ingestion from 10.2 ± 5.1 cells/crypt/hr (baseline) to 7.2 ± 3.4 cells/crypt/hr.</p>	<p>(1) Wheat fiber has an anti-proliferative effect in rectal mucosa of people with family history of CRC.</p>
<p>Reddy et al. (1992)</p>	<p>8-wk treatment period, subjects randomly assigned to 13-15 g/d wheat bran, oat bran or corn bran baked in muffins. 24-h stool collections at baseline and end of 8-wk.</p> <p>SUBJECTS- 78 premenopausal women, age 20-50 yr.</p> <p>ENDPOINTS- fecal bacterial enzyme activity; fecal bile acids and neutral sterols.</p>	<p>Wheat bran decreased fecal concentrations of deoxycholic acid, lithocholic acid, 12-ketolithocholic acid, and neutral sterols. Oat bran had no effect on secondary bile acids. Corn bran increased some secondary bile acids, decreased others.</p> <p>Wheat bran decreased the activities of all fecal bacterial enzymes measured. Oat bran decreased activities of some bacterial enzymes. Corn bran increased fecal activities of some bacterial enzymes, decreased others.</p>	<p>(1) Modifying effect of dietary fiber on fecal secondary bile acids and on fecal bacterial enzymes depends on the source of fiber consumed.</p>

Prospective Cohort Studies

STUDY	DESCRIPTION	CONCLUSIONS
<p><i>Nurses' Health Study.</i> Fuchs et al. (1999)</p>	<p>Cohort of 88,757 women nurses; 16 year follow-up; to determine if DF intake is associated w/ colorectal cancer. Dietary intake determined from FFQ; fiber intake calculations based on Southgate et al, 1976. 31% of cohort underwent a sigmoidoscopy exam. Disease endpoints- CRC diagnosis or death; distal colorectal adenomas. 787 CRC cases, 1012 patients with distal colon or rectal adenomas.</p> <p>Energy-adjusted total DF intake- 9.8 g DF/d (lowest quintile), 24.9 g DF/d (highest quintile).</p> <p>CRC incidence- 0.55 cases/1000 person-year adenoma incidence- 2.30 cases/1000 person-year</p>	<p>In women-</p> <p>(1) NO ASSOCIATION of CRC incidence with total DF intake.</p> <p>(2) NO ASSOCIATION of colorectal adenoma incidence with total DF intake</p> <p>(3) NO ASSOCIATIONS when analyses adjusted for CRC site, food sources of fiber (cereal, fruit or vegetable), cohort subgroupings, fiber intake deciles, etc.</p>
<p><i>Iowa Women's Health Study.</i> Sellers et al. (1998)</p>	<p>Cohort of 35,216 postmenopausal women, stratified by family history (FHx) of colon cancer; 10-yr follow-up. Self-reported, semi-quantitative FFQ at baseline; analyzed for intake of fruit and vegetable groups and dietary fiber. Disease endpoint- colon cancer incidence (documented by State Health Registry of Iowa - SEER); 212 cases.</p> <p>Total DF intake (mean \pm SD) - 20.4 \pm 8.5 g DF/d (neg FHx) and 20.9 \pm 8.7 g DF/d (pos FHx)</p> <p>Colon cancer incidence- 0.6 cases/1000 person-year</p>	<p>In postmenopausal women-</p> <p>(1) NO ASSOCIATION of colon cancer incidence in women without FHx of colon cancer with fruit and vegetable intake</p> <p>(2) INCREASED colon cancer incidence in women with FHx of colon cancer associated with fruit and vegetable intake.</p> <p>(2) NO ASSOCIATION of colon cancer incidence both in women with and without FHx of colon cancer with total DF intake.</p>
<p><i>NYU Women's Health Study.</i> Kato et al. (1997)</p>	<p>Cohort of 14,727 women; 7-yr follow-up. Self-reported, 70 item, semiquantitative FFQ. Disease endpoint - diagnosed colorectal cancer, confirmed by medical records, state cancer registries; 100 cases.</p> <p>CRC incidence- 0.95 cases/1000 person-year</p>	<p>In women-</p> <p>(1) NO ASSOCIATION of CRC incidence with total DF, or with total carbohydrate, total fat, saturated fat, or cholesterol.</p> <p>(2) NO ASSOCIATION of CRC incidence with meats, poultry, egg, fruits, vegetables or potatoes, or cereals/bread.</p>

SUMMARY TABLES - Dietary Fiber/Colorectal Cancer Studies Page 6

<p><i>Health Professionals Follow-up Study.</i> Platz et al. (1997)</p>	<p>Cohort of 16,448 U.S. male health professionals who had endoscopy exams during an 8-yr follow-up. Self-reported, semi-quantitative FFQ; compute total DF intake based on FFQ. Disease endpoint - distal colon and rectal adenomatous polyps (690 cases).</p> <p>Total DF intake- 11.6 to 32.3 g DF/d (means of lowest and highest quintiles)</p> <p>adenoma incidence- 5.24 cases/1000 person-year</p>	<p>In males-</p> <p>(1) REDUCED distal colon adenoma incidence associated with fruit DF.</p> <p>(2) NO ASSOCIATIONS of distal colon adenoma incidence with total DF, cereal DF, or vegetable DF.</p> <p>(3) REDUCED distal colon adenoma incidence associated with soluble DF intake.</p> <p>(4) NO ASSOCIATIONS of distal colon adenoma incidence with insoluble DF or with cellulose or lignin.</p>
<p><i>Health Professionals Follow-up Study.</i> Giovannucci et al. (1994)</p>	<p>Cohort of 47,949 U.S. male health professionals; 6-yr follow-up. Self-administered, semi-quantitative, 12 month-recall FFQ at entry, and every 2 yr. Disease endpoint- diagnosed colon cancer (205 cases).</p> <p>Total DF intake- 18.3 to 32.8 g DF/d (means of 1st and 5th quintiles) Crude fiber intake- 4.6 to 8.6 g DF/d (means of 1st and 5th quintiles)</p> <p>Colon cancer incidence- 0.71 cases/1000 person-year</p>	<p>In males-</p> <p>(1) NO ASSOCIATION of colon cancer incidence with total DF (or crude fiber).</p> <p>(2) NO ASSOCIATIONS of colon cancer incidence with fruit, vegetable, or cereal sources of DF.</p> <p>(3) NO ASSOCIATIONS of colon cancer incidence with fruit or vegetable intake (no analysis for grains).</p>
<p><i>Health Professionals Follow-up Study.</i> Giovannucci et al. (1992)</p>	<p>Cohort of 7,284 U.S. male health professionals who had endoscopy exams during an 2-yr follow-up. Self-reported, semi-quantitative FFQ; compute total DF intake based on FFQ. Disease endpoint - distal colon and rectal adenomatous polyps (170 cases).</p> <p>Total DF intake- 11.6 to 32.3 g DF/d (means of lowest and highest quintiles)</p> <p>adenoma incidence- 5.24 cases/1000 person-year</p>	<p>In males-</p> <p>(1) REDUCED colorectal adenoma incidence associated with total DF and with all sources (vegetables, fruits, and grains) of DF.</p>

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<p><i>Iowa Women's Health Study.</i> Steinmetz et al. (1994)</p>	<p>Cohort of 41,837 postmenopausal women (licenced Iowa drivers); 5 yr follow-up. Self-reported, semi-quantitative FFQ at baseline; analyzed for intake of fruit and vegetable groups and dietary fiber. Disease endpoint- colon cancer incidence (documented by State Health Registry of Iowa - SEER); 212 cases.</p> <p>Total DF intake (means)- 19.3 g DF/d (cases) and 20.4 g DF/d (non-cases) <14.5 g DF/d (1st quartile) and >24.7 g DF/d (4th quartile)</p> <p>colon cancer incidence- 1.01 cases/1000 person-year</p>	<p>In postmenopausal women-</p> <p>(1) NO ASSOCIATIONS of colon cancer incidence with total fruit and/or vegetable intake, nor with any of 15 fruit and vegetable groups.</p> <p>(2) NO ASSOCIATION of colon cancer incidence with total DF intake (age & energy adjusted).</p> <p>(3) REDUCED colon cancer incidence weakly associated with unadjusted DF intake (relative risk Q4/Q1 of 0.72, p < 0.10).</p>
<p><i>Cancer Prevention Study II</i> Thun et al. (1992)</p>	<p>Cohort of 764,343 North American men and women; 6 yr follow-up. Dietary habits assessed by 32 food item FFQ, assumed medium portion sizes. Data analyzed by food groups (vegetables, citrus, grains etc), not by computed DF intake. Disease endpoint- death due to colon cancer; 1,150 deaths.</p> <p>Total DF intake- not determined</p> <p>Colon cancer mortality- 0.25 deaths/1000 person-year</p>	<p>(1) REDUCED colon cancer mortality associated with more frequent consumption of "plants" (vegetables, citrus and high-fiber grains).</p> <p>(2) REDUCED colon cancer mortality in women associated with vegetable, but not grain, consumption.</p> <p>(3) REDUCED colon cancer mortality in men associated with grain, but not vegetable, consumption.</p>

Case-Control Studies

STUDY	DESCRIPTION	CONCLUSIONS
Franceschi et al. (1998)	Cases- 1,953 histologically confirmed CRC in Italy. 2 yr dietary history assessed by 79 item FFQ. Dietary fiber intake not computed.	(1) INCREASED CRC risk associated with intake of bread and cereal grain foods. (2) INCREASED CRC risk associated with refined flour bread; no association with wholemeal bread. (3) REDUCED CRC risk associated with fish and vegetable intake.
Negri et al. (1998)	same data as reported in Franceschi, et al., 1998. DF intake computed as non-starch polysaccharides (Englyst method)	(1) REDUCED CRC risk associated with total DF, soluble DF, insoluble DF, cellulose, insoluble non-cellulose polysaccharide; NO ASSOCIATION with lignin. (2) REDUCED CRC risk associated with vegetable fiber, and fruit fiber. (3) NO ASSOCIATION with grain fiber.
Ghadirian et al. (1997)	Cases- 402 colon cancer cases in French-speaking Montreal, identified by hospital records. Usual diet 1-2 yr prior to diagnosis assessed by Nat'l Cancer Inst of Canada FFQ. Total DF intake (mean \pm SD) 28.7 \pm 13.1 g DF/d (cases) and 29.5 \pm 13.7 g DF/d (controls)	(1) REDUCED colon cancer risk associated with DF intake in females, NO ASSOCIATION in males. (2) REDUCED colon cancer risk associated with DF from vegetable sources. (3) NO ASSOCIATION with DF from fruit or cereal sources.

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<p>Le Marchand et al. (1997)</p>	<p>Cases- 1,192 CRC cases in Oahu, Hawaii; identified through Hawaii Tumor Registry. Usual diet over previous 3 yr assessed by 282 item quantitative FFQ. DF intake computed based on USDA nutrient composition tables.</p> <p>Total DF intake (25th - 75th percentile range)- 16 - 26 (σ) and 15 - 22 (φ) g DF/d</p>	<p>(1) REDUCED CRC risk associated with vegetable and DF intake (as crude fiber, dietary fiber, or non-starch polysaccharide).</p> <p>(2) NO ASSOCIATION with DF from cereal or fruit sources.</p>
<p>Lubin et al. (1997)</p>	<p>Cases- 196 asymptomatic colorectal adenoma patients identified in screening program of the Tel Aviv Medical Center, Israel; and had at least 3yr follow-up with repeat colonoscopic exam. 15 yr dietary history assessed with 180 item quantitative FFQ.</p> <p>DF intake: low tertile- < 24 g DF/d; high tertile- > 34 g DF/d</p>	<p>(1) NO ASSOCIATION of DF intake with colorectal adenoma risk; whereas inverse association was reported for calories, total carbohydrate and sugar.</p> <p>(2) REDUCED colorectal adenoma risk associated with beverage intake; and significant synergistic interaction between water and fiber.</p> <p>(3) REDUCED colorectal adenoma risk associated with bread and cereal intake; NO ASSOCIATION with fruit and vegetable intake</p>
<p>Slattery et al. (1997)</p>	<p>Cases- 1,993 colon cancer cases from Kaiser Permanente Program of Northern Calif., Utah and Minneapolis, St Paul. Usual diet over previous month assessed by adapted CARDIA diet history; nutrient intake computed using the Nutrition Coordinating Center nutrient database.</p> <p>Total DF intake (mean \pm SD)- 26.5 \pm 12.7 (σ) and 22.8 \pm 10.4 (φ) g DF/d</p>	<p>(1) REDUCED colon cancer risk associated with vegetable consumption.</p> <p>(2) REDUCED colon cancer risk associated with whole grain consumption.</p> <p>(3) NO ASSOCIATION of colon cancer risk with Total DF.</p>
<p>Slattery et al. (1994)</p>	<p>Cases- 321 colon cancer cases, white men & women in Utah, age 40-79.; stratified by age and sex [<65 yr - 56σ, 63φ; \geq65 yr - 56σ, 56φ] 2 yr diet history assessed with FFQ; computed <u>crude</u> fiber intake</p> <p>NOTE: paper reports 2 case-control studies (Utah & Adelaide); however, only the Utah study has dietary fiber data.</p>	<p>(1) REDUCED colon cancer risk associated with crude fiber in men under 65 years.</p> <p>(2) NO ASSOCIATION of colon cancer risk associated with crude fiber in women nor in men > 65 yrs.</p> <p>(3) NO ASSOCIATION of colon cancer risk associated with crude fiber in overall study population.</p>

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Benito et al. (1993)	<p>Cases- 101 male and female residents of island of Majorca with diagnosed colorectal adenomatous polyps. Dietary patterns assessed by a 99 food item semi-quantitative FFQ.</p>	<p>(1) REDUCED colorectal adenoma risk associated with vegetable consumption.</p> <p>(2) REDUCED colorectal adenoma risk associated with total DF, and fiber from fruit and vegetable sources (but not fiber from cereal or beans).</p>
Little et al. (1993)	<p>Cases- 147 asymptomatic colorectal adenomatous polyp cases identified in subjects participating in fecal occult blood screening in Nottingham, England. Diet of previous 1 yr assessed by diet recall; nutrient intake computed from McCance and Widdowson food composition tables.</p> <p>Total DF intake (mean) 24 -27 g DF/d (m/f, cases/controls)</p>	<p>(1) NO ASSOCIATION between adjusted total DF intake and colorectal adenoma risk.</p> <p>(2) REDUCED colorectal adenoma risk associated with cereal fiber intake.</p>
Meyer and White (1993)	<p>Cases- 424 incident cases of colon cancer; white, 30-62 yr old western Washington state, identified from the SEER registry. 7 yr dietary history assessed by 71 item semi-quantitative FFQ.</p> <p>Total DF intake (means)- 23.7 g DF/d (male) 22.8 g DF/d (female)</p>	<p>(1) Alcohol consumption strongly related to colon cancer risk.</p> <p>(2) REDUCED alcohol-adjusted colon cancer risk associated with total DF; marginally in men.</p> <p>(3) Strongest associations (among 4 sources of DF- cereal, fruits, vegetables, & legumes) with cereal in men, with fruits and vegetables in women.</p>
Neugut et al. (1993)	<p>Cases- 286 histologically confirmed <u>incident</u> colorectal adenomatous polyps; 186 <u>recurrent</u> adenomatous polyps; from NYC university-based colonoscopy practices. 3-5 year dietary history assessed with Block FFQ; nutrient composition database used for computing dietary fiber intake was not reported.</p> <p>Total DF intake- men (1st quartile) <11.4 g DF/d; (4th quartile) >20.6 g DF/d women (1st quartile) <10.3 g DF/d; (4th quartile) >18.0g DF/d</p>	<p>(1) REDUCED <u>recurrent</u> colorectal adenoma risk associated with DF only in women, NO ASSOCIATION in men</p> <p>(2) NO ASSOCIATION of <u>incident</u> colorectal adenoma risk and DF in men or women.</p>

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<p>Sandler et al. (1993)</p>	<p>Cases- 236 asymptomatic patients with one or more colorectal adenomatous polyp or cancer found during colonoscopy at Univ. North Carolina Hospital 1 yr dietary history assessed by NCI quantitative FFQ.</p> <p>Total DF intake- men (1st quartile) <10.7 g DF/d; (4th quartile) >18.6 g DF/d women (1st quartile) <9.1 g DF/d; (4th quartile) >15.6 g DF/d</p>	<p>(1) NO ASSOCIATIONS of total DF, fiber from beans, or fiber from grains with colorectal adenoma risk.</p> <p>(2) REDUCED colorectal adenoma risk in women associated with DF from fruits & vegetables; NO ASSOCIATION in men.</p> <p>(3) REDUCED colorectal adenoma risk in women associated with frequency of fruit consumption (but not consumption of vegetable or of high-fiber bread and cereals); NO ASSOCIATION in men.</p>
<p>Arbman et al. (1992)</p>	<p>Cases- 41 male and female surgical CRC patients in Sweden. 10-15 yr dietary history assessed by interview.</p> <p>Total DF intake (mean ± SD) 21.2 ± 1.3 g DF/d (cases) and 21.2 ± 1.2 g DF/d (control)</p>	<p>(1) NO ASSOCIATION of CRC risk with total DF intake.</p> <p>(2) REDUCED CRC risk associated with cereal fiber (No analyses for other food sources of DF)</p>
<p>Bidoli et al. (1992)</p>	<p>Cases- 248 CRC patients admitted to hospitals in Pordenone province, Italy. 10 yr dietary history assessed by FFQ. DF intake not computed.</p>	<p>(1) INCREASED CRC risk associated with intake of refined starchy foods, bread and polenta.</p> <p>(2) DECREASED CRC risk associated with intake of tomatoes, whole grain bread and pasta.</p>
<p>Peters et al. (1992)</p>	<p>Cases- 746 colon cancer cases; Caucasian males and females in Los Angeles County, CA. 15 yr dietary history assessed by semi-quantitative FFQ.</p> <p>Total DF intake (mean ± SD) 25.8 ± 14.1 g DF/d (cases) and 24.8 ± 11.5 g DF/d (control)</p>	<p>(1) NO ASSOCIATION of colon cancer risk with DF intake.</p> <p>(2) NO ASSOCIATION of colon cancer risk with fruit, vegetable, or whole grain consumption.</p> <p>(3) slight INCREASED colon cancer risk associated with bread (including sweet rolls and doughnuts) consumption.</p>

Randall et al. (1992)	Cases- 428 colon cancer cases among men and women in Western New York state, identified by hospital records. 1 yr dietary history assessed by 128 item FFQ. Data analyzed by 7 gender-specific dietary patterns and by nutrients.	(1) Colon cancer risk more strongly associated with dietary patterns than any single nutrient. (2) NO ASSOCIATION of colon cancer risk in either gender with DF intake.
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Abbreviations

CRC-- colorectal cancer
 Ctrl-- control group
 RR-- relative risk

g DF/d-- grams of dietary fiber per day
 FFQ-- food frequency questionnaire
 RCT-- randomized clinical trial

DF-- dietary fiber
 Intervn--dietary fiber intervention group
 OR-- odds ratio