Title
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Effects of Dietary Wheat Bran Fiber on Rectal Epithelial Cell Proliferation in Patients With Resection for Colorectal Cancers


A preponderance of carcinogenesis studies in rodents and epidemiologic studies in humans suggests a potential role of dietary fiber in the prevention of colorectal cancer. Recently, wheat bran fiber used as a dietary supplement has been shown to decrease the growth of rectal adenomatous polyps in patients with familial polyposis; however, few studies of high-risk human populations have been attempted to determine the effects of dietary fiber supplementation on markers of carcinogenesis in the colon or rectum. We have designed a one-arm study to evaluate the effects of dietary supplementation with wheat bran fiber [i.e., 13.5 g/day for 8 wk; after 1 mo, 2 g/day (compliance evaluation period)] on \(^3\)H\]thymidine rectal mucosa cell labeling (i.e., percent of epithelial cells incorporating \(^3\)H\]thymidine into DNA in intact rectal crypt cells over a 90-min exposure as well as in minced rectal biopsy tissue over a 24-hr exposure) in rectal biopsy specimens. The biopsy specimens were obtained at sigmoidoscopy in 17 compliant patients with a history of resected colon or rectal cancer. We categorized patients as having initially low or initially high \(^3\)H\]thymidine-labeling indices (i.e., percent of mucosa cells that incorporate \(^3\)H\]thymidine into DNA during 1.5- or 24-hour in vitro incubations) by using the median baseline labeling index as a cutoff between high and low values. On the basis of a chi-square test used to identify patients with a statistically significant \((P < .001)\) change, six of the eight patients who initially had high 24-hour outgrowth labeling indices showed a significant decrease in the rectal mucosa biopsy specimens obtained after treatment. An overall 22% decrease was observed in rectal mucosa cell biopsy specimens obtained at study termination \((P < .001)\). Of the eight patients with initially high total \(^3\)H\]thymidine-labeling indices in crypt organ culture, four had a significant \((P < .001)\) decrease from baseline values, one had a significant increase, and three showed no change following the fiber intervention. The wheat bran fiber dietary supplement of 13.5 g/day was well tolerated by this group of older (54–70 yr) patients. Although the \(^3\)H\]thymidine labeling index data suggest that the wheat bran fiber supplement can inhibit DNA synthesis and rectal mucosa cell proliferation in high-risk patients, the results of this small pilot study should not be overinterpreted vis-à-vis the potential role of wheat bran fiber as a chemopreventive agent for colorectal cancer. Study results should be confirmed in the setting of a randomized double-blinded clinical trial in colorectal cancer patients. Intermediate markers of carcinogenesis should be used as end points. [J Natl Cancer Inst 82:1280–1285, 1990]

Considerable research in animals and humans has been performed to evaluate the potential role of dietary fiber in the prevention of colorectal cancer. In a recent review by Greenwald et al. (7), data from 55 epidemiologic reports involving 40 studies were analyzed for an association between dietary fiber intake and colon cancer incidence. This meta-analysis supported a direct relationship between colon cancer risk and diets low in fiber content. Of the 55 studies, 32 (58%) identified an inverse relationship between dietary fiber, fiber-rich diets, or other measures of fiber consumption and the risk of colon cancer. Twenty (37%) of these studies showed a statistically significant

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inverse association between fiber intake and colon cancer incidence (1).

Metabolic epidemiologic studies have focused on the difference in colon cancer incidence in Scandinavia, other western countries, and African countries (2-6). For example, rural Finns were observed to have dietary intakes of total calories and fat similar to intakes of urban New York residents, who have more than a threefold greater incidence of colon cancer. However, the daily dietary fiber intake in rural Finland has been shown to be two times that of New Yorkers (2). The New York subjects also had higher concentrations of fecal bile acids and lower quantities of dry feces.

In a recent double-blind, placebo-controlled study, DeCosse et al. (7) showed that a daily dietary supplement of 22.5 g of wheat bran fiber can significantly reduce the number of adenomatous polyps in the low sigmoid colon and rectum of patients with familial polyposis. As a follow-up study, we have designed a one-arm, compliance evaluation trial to evaluate the effects of short-term wheat bran fiber dietary supplementation. The effects are based on the degree of [3H]thymidine epithelial cell labeling (i.e., percent of epithelial cells incorporating [3H]thymidine into DNA) in superficial rectal biopsy specimens obtained at sigmoidoscopy in patients with a history of resected colon or rectal cancer. Several investigators have shown that the rectal mucosa of [3H]thymidine-labeling indices in these patients are significantly elevated above those observed in normal subjects.

Methods

Patient selection criteria. Criteria for entry in the study included an age of 40 years or older; history of colon or rectal cancer diagnosed and resected after 1980; no evidence of recurrent disease or history of other severe metabolic or life-threatening acute or chronic disease; and adequate dietary intakes of calories and protein, determined by 4 days of dietary records (>80% of the US recommended daily allowance), were required. Patients were excluded if their dietary fiber intake was 30 g/day or greater or if they were on special diets that precluded compliance with study requirements.

Patients were required to be completely ambulatory and capable of ordinary work efforts (performance status 0-1 by Southwest Oncology Group criteria) and to have normal renal and liver function (serum creatinine \( \leq \) 2.0 mg/dL and serum bilirubin \( \leq \) 2.5 mg/dL). This protocol was approved by the University of Arizona Institutional Review Board, and all patients signed informed consent forms prior to study entry.

Prestudy and on-study requirements. For each patient, we obtained a thorough medical history and performed a physical examination prior to study entry. The following tests were performed: complete blood cell and differential white blood cell counts and blood chemistries, including SMA-20 and determinations of levels of magnesium, zinc, copper, and lipids (cholesterol, triglycerides, and high- and low-density lipoproteins), as well as urinalysis. Prior to the 1-month placebo run-in period and at the end of the third month of the study, patients completed an expanded version of the National Cancer Institute Core Dietary Questionnaire (8), and we obtained 24-hour dietary intake records (on 3 randomly assigned week days and 1 weekend day at study entry over a 1-week period). This expanded version of the questionnaire better assesses fiber intake.

Records contained all foods consumed and their quantities, vitamin and mineral supplements taken, tobacco use, and use of over-the-counter medications and supplements, especially those that could modify stool characteristics or bowel function. A calendar for dietary fiber supplement intake, fiber supplement questionnaire, a compliance assessment record, and a toxicity review form were filled out and collected monthly at each clinic visit for the duration of the study. Additionally, a Health Behavior Questionnaire (9) was obtained at the beginning and end of the 3-month intervention period.

Wheat bran fiber supplement. All Bran, a shredded wheat bran cereal provided by the Kellogg Co. (Battle Creek, Mich), was the fiber supplement used in this clinical trial. One ounce (i.e., about one-third cup) of the fiber cereal supplement contains 70 calories, 3 g of protein, 22 g of carbohydrate, 8 g of starch and related carbohydrates, 5 g of sucrose and sugars, 1 g of fat, and 9 g of dietary fiber. Additionally, 1 oz of the supplement contains 1,250 IU of vitamin A, 15 mg of vitamin C, 25 mg of calcium, 50 IU of vitamin D, 0.1 mg of folic acid, 125 mg of magnesium, 3.75 mg of zinc, 0.35 mg of copper, 320 mg of sodium, and 300 mg of potassium.

A daily serving of 13.5 g of wheat bran fiber (1.5 oz of the cereal supplement) was used during the treatment phase of the present study. This serving size was based on results of an earlier intervention trial in a southern Arizona retirement community in which compliant subjects consumed approximately 13 g of All Bran cereal per day for up to 3 months with acceptable compliance and side effects (10).

Fiber intervention trial design. During an initial 1-month compliance evaluation, all patients were placed on a 2.0 g/day low-fiber cereal supplement provided by the Kellogg Co. The patients were unaware of the fiber content of this low-fiber cereal supplement. Following this 1-month compliance run-in period, all patients were given 13.5 g of wheat bran fiber supplement daily for 8 additional weeks. The All Bran was formulated to look similar to the low-fiber supplement used during the initial 1-month phase of the study. Both daily fiber supplements had similar volume, appearance, and taste. They were distributed in individual unmarked packages to all study participants monthly at each clinic visit. Instructions on building up tolerance to wheat bran fiber intake through small frequent intakes during the first week on low-fiber supplements and during the first week on high-fiber supplements were given to all patients.

Laboratory research procedures. At the end of the initial 1-month period on the low-fiber cereal supplement and at the end of the 2-month period on high-fiber daily cereal supplement, each patient underwent sigmoidoscopy for the purpose of obtaining multiple biopsy specimens of the rectal mucosa. Patients were prepared for these procedures without cathartics and received only a mild enema of normal saline (0.5 mol/L) prior to removal of up to eight superficial biopsy specimens taken from flat mucosa of the rectum, 8-12 cm above the level of the anal verge. Five of these biopsy specimens were processed for [3H]thymidine-labeling indices—three for crypt organ culture, to obtain at least 20 crypts, and two for 24-hour outgrowth culture, to obtain at least 11 outgrowth patches.
[3H]Thymidine-labeling of normal colonic epithelial cells in culture. The sigmoid biopsy specimens were finely minced to pieces smaller than 1 mm and placed into 3 mL of antibiotic-containing wash medium that contained M199 medium plus N- (2-hydroxyethyl)piperazine-N'-2-ethanesulfonylic acid (25 mmol/L), amikacin (100 μg/mL), tetracycline (10 μg/mL), amphotericin B (5 μg/mL), penicillin (250 μg/mL), streptomycin (100 μg/mL), chloramphenicol (150 μg/mL), gentamicin (100 μg/mL), and bovine serum albumin (1.4 mg/mL) (Sigma Chemical Co., St. Louis, Mo) plus 1 mL each of hyaluronidase (300 U/mL), neuraminidase (4 U/mL), and collagenase (600 U/mL). Digestion was carried out at room temperature on a blood rotor for 1 hour. The digest was then washed three times and cell pellets were resuspended in an appropriate volume of growth medium (NCTC 168; Hazelton; Lenexa, Kan) plus 0.1 units of insulin, 1 μg/mL of hydrocortisone, 50 μg/mL of epidermal growth factor, 1 × 10⁻⁷ M of selenious acid, 8 × 10⁻⁵ M of sodium deoxycholate, 5 μg/mL of pentagastrin, 1 × 10⁻⁴ M of ethanalamine, 1 × 10⁻⁴ M of phosphoethanolamine, 50 μg/mL of gentamicin (Sigma Chemical Co.), and 15% fetal bovine serum. Aliquots of cell suspension were then placed onto 0.1% gelatin-coated, 35-mm tissue-culture dishes and allowed to adhere for 45 minutes at 37 °C in 5% CO₂ as described previously by Buset et al. (11). One milliliter of growth medium containing [3H]thymidine (5 μCi/mL; 20 Ci/mmol) was added, and the tissue cultures were incubated an additional 24 hours at 37 °C in 5% CO₂. The cell cultures were then fixed and processed for autoradiography at the Arizona Cancer Center.

[3H]Thymidine-labeling of crypt cells from rectal mucosa biopsy specimens. All biopsy specimens were incubated with 5 μCi/mL of [3H]thymidine (20 Ci/mmol) for 90 minutes and then processed for microautoradiography at the Arizona Cancer Center according to the methods of Lipkin et al. (12,13). Proliferation of epithelial cells lining colonic crypts was measured by microautoradiographic observation of cells labeled through incorporation of [3H]thymidine into cellular DNA. Crypts longitudinally sectioned from base to lumen were analyzed according to the criteria of Lipkin et al. (14).

Statistical analysis. The data from this trial were analyzed on an IBM System 2, model 80 computer, using the statistical analysis system SAS version 6.03 (15). The effect of wheat bran fiber supplementation on the baseline [3H]thymidine labeling index was tested with a paired t-test. A chi-square test was used to identify individual patients with a statistically significant (P < .001) change in the prelabeling versus postlabeling index as shown in table 1. Since an a priori definition of a biologically important percent change in the [3H]thymidine-labeling index does not currently exist, we used a significance level of 1 in 1,000 to define a biologically important change in this cellular proliferation marker.

A kappa statistic was used to assess the degree of agreement in the classification of significant difference between the [3H]thymidine-labeling index for crypt organ culture and that for outgrowth culture (16). A series of quality-control studies were completed to determine the reproducibility of the [3H]thymidine-labeling index procedures (17). The results of these studies, which involved more than 100 subjects, revealed that (a) counting at least 20 crypts per rectal mucosa biopsy specimen yields a 95% confidence limit around the calculated labeling index within 1.5% of the estimated mean, (b) intraobserver variability between two labeling index determinations was 0.5% (P = .35, paired t-test), and (c) interobserver site variability between labeling index determinations was 0.6% (P = .4, paired t-test).

Results

Patient characteristics. Between January and November 1988, 17 patients (11 females and six males) with a history of colon or rectal cancer were registered in this trial. The median age of the patients was 70 years (range, 54–78). All patients were white and 65% were college educated.

Of the 17 patients, 15 had resection for colon cancer and two had resection for rectal cancer. The cancer diagnosis had been made between 12 and 48 months prior to trial registration in 14 patients and between 5 and 8 years before registration in three patients. Five patients had Astler-Coller-Duke's stage C cancers (C1, two patients; C2, three patients); seven patients had stage B cancers (B1, four patients; B2, three patients); and five patients had stage A cancers (A1, one patient; A2, four patients).

Dietary data. For the 11 females and six males, the average daily intakes of fiber from all dietary sources, based on food records from 4 random days at the start of the study, were 19 ± 7.7 and 20.6 ± 7.7 g, respectively. Mean elemental calcium intake was slightly greater than 1 g/day in females (1,037 ± 299 mg) and somewhat lower in males (887 ± 362 mg). Three of the 11 females and none of the males consumed high-fiber breakfast cereals before entry in the study.

The cumulative average compliance level for supplemental fiber intake was 97.6% in 16 of the 17 subjects. One subject consumed 50%–75% of the predicted daily fiber supplement for approximately 10 days during the study and then achieved good compliance for the majority of the 8-week high-fiber supplementation.

Shown in table 2 are daily intakes of selected nutrients for the trial subjects estimated from the Food-Frequency Questionnaire during treatment with the high-fiber supplement. Baseline values were recorded prior to the 1-month compliance evaluation for the 11 females and 6 males in the study. In most cases, absolute increases were observed between study entry and study completion in the daily intakes of total calories, protein, carbohydrate, fat, and calcium; however, percents of calories for the macronutrients were not increased over baseline values. The total dietary fiber intake in grams per day, including the supplemental cereal fiber, increased significantly (P = .02 in males and P = .04 in

Table 1. [3H]Thymidine-labeling indices for crypt organ and 24-hr outgrowth culture in patients with resection for colorectal cancer

<table>
<thead>
<tr>
<th>Type of culture</th>
<th>Decrease*</th>
<th>Increase*</th>
<th>No change</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crypt organ</td>
<td>5</td>
<td>3</td>
<td>9</td>
<td>17</td>
</tr>
<tr>
<td>24-hr outgrowth</td>
<td>9</td>
<td>1</td>
<td>6</td>
<td>16</td>
</tr>
</tbody>
</table>

*P < .001. Significant response required. [3H]Thymidine-labeling indices after 2 mo of wheat bran fiber supplementation compared with baseline control values for each patient.
females according to a one-tailed $t$-test) between study entry and completion. The absolute intake of fiber from grains was somewhat less than the 13.5 g/day provided by the wheat bran fiber supplement because three female study subjects substituted store-bought high-fiber cereals for the wheat bran supplement.

**Toxicity evaluation.** The frequency and severity of gastrointestinal, constitutional, and clinically evident toxic effects of the wheat bran fiber dietary supplement were rated on a scale of 0–3 (0 = none, 1 = mild, 2 = moderate, and 3 = severe). Patients who experienced moderate or severe toxic effects of any type were evaluated for removal from the study. Toxicity monitoring was carried out at the monthly clinic visit and data are shown in figure 1. There were 55 assessments of possible toxic effects in the 17 patients; no toxicity was found in more than 90% of the assessments, and no patient was removed from the study. Mild diarrhea was noted in less than 10% of assessments. No significant change of the assessments, and no patient was removed from the study. Mild diarrhea was noted in less than 10% of assessments. No significant change of the assessments, and no patient was removed from the study.

**24-Hour outgrowth culture data.** After 2 months of wheat bran fiber supplementation in the 16 patients who had 24-hour outgrowth cultures taken at entry to the study, the mean number of outgrowths per biopsy specimen was 11.6 ± 7.8 SD. Calculations using this value yielded an average of 2,695 ± 1,272 SD cells per specimen and an average of 431 ± 351 SD cells per outgrowth. The cellular response to the 13.5-g/day wheat bran fiber supplement was evaluated statistically in each patient by comparing the baseline $[^3]$Hthymidine-labeling indices to values for rectal biopsy specimens obtained 2 months after treatment. To be considered a significant response, the on-treatment labeling index had to be decreased or increased by sufficient magnitude, compared with the baseline value, to permit computation of a $P$ value ($<.001$). The labeling index was significantly decreased in nine of the 16 patients who could be evaluated, increased significantly in one patient, and unchanged in six patients. One patient could not be evaluated because of a malfunction of the incubator following the second rectal biopsy (table 1).

The data from the $[^3]$Hthymidine-labeling index of the 24-hour outgrowth were categorized further according to initially low versus initially high baseline values. The median baseline labeling index (9.9%) was used as a cutoff between high and low values. Six of the eight patients who had initially high baseline labeling indices showed a significant decrease ($P < .001$) in the rectal mucosa biopsy specimens obtained during the second month of fiber treatment. Of the eight patients with initially low baseline labeling indices, three showed a significant decrease, one showed a significant increase, and the four remaining patients showed no significant change.

As shown in table 3, there was an overall 22% decrease in the 24-hour outgrowth $[^3]$Hthymidine-labeling index following 2 months of dietary supplementation with 13.5 g/day of wheat bran fiber in the rectal mucosa biopsy specimens obtained from the 16 patients who could be evaluated. This change was highly significant ($P < .001$).

**Crypt organ culture data.** Thirty-four biopsy specimens from the 17 patients were evaluated. There was an average of 32 crypts per biopsy specimen. The average crypt column had 44.8 cells (average, 89.6 cells per crypt) and an average of 2,867 cells were counted per biopsy specimen. Again, the cellular response to the 13.5-g/day wheat bran fiber supplement was evaluated statistically in each patient by comparing the baseline to 3-month $[^3]$Hthymidine-labeling indices in the rectal biopsy specimens.

### Table 2. Selected nutrient intakes of patients with resection for colorectal cancer estimated from Arizona Food-Frequency Questionnaire data*

<table>
<thead>
<tr>
<th>Nutrients</th>
<th>Females at baseline†</th>
<th>Females (last month of study)</th>
<th>Males at baseline†</th>
<th>Males (last month of study)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy (kcal)</td>
<td>1,671 ± 274</td>
<td>1,779 ± 455</td>
<td>1,761 ± 668</td>
<td>2,173 ± 690</td>
</tr>
<tr>
<td>Protein (g)</td>
<td>70.5 ± 10.3</td>
<td>73.2 ± 13.5</td>
<td>75.2 ± 32.0</td>
<td>94.6 ± 31.0</td>
</tr>
<tr>
<td>% kcal</td>
<td>17.1 ± 2.2</td>
<td>16.7 ± 19</td>
<td>16.8 ± 2.3</td>
<td>17.4 ± 0.9</td>
</tr>
<tr>
<td>Carbohydrate (g)</td>
<td>202.2 ± 47.2</td>
<td>224.8 ± 64.0</td>
<td>215.5 ± 74.3</td>
<td>264.0 ± 75.5</td>
</tr>
<tr>
<td>% kcal</td>
<td>48.5 ± 8.5</td>
<td>50.5 ± 7.0</td>
<td>49.6 ± 5.7</td>
<td>49.0 ± 3.4</td>
</tr>
<tr>
<td>Fat (g)</td>
<td>65.3 ± 20.2</td>
<td>64.6 ± 22.3</td>
<td>62.0 ± 22.9</td>
<td>77.5 ± 31.2</td>
</tr>
<tr>
<td>% kcal</td>
<td>35.1 ± 8.3</td>
<td>32.9 ± 7.2</td>
<td>32.1 ± 3.7</td>
<td>32.1 ± 4.9</td>
</tr>
<tr>
<td>Calcium (mg)</td>
<td>1,090 ± 321</td>
<td>1,037 ± 285</td>
<td>938 ± 402</td>
<td>1,011 ± 355</td>
</tr>
<tr>
<td>Dietary fiber (g)</td>
<td>100</td>
<td>90</td>
<td>80</td>
<td>70</td>
</tr>
<tr>
<td>Total</td>
<td>18.8 ± 7.5</td>
<td>27.3 ± 6.8</td>
<td>23.5 ± 7.7</td>
<td>34.5 ± 8.7</td>
</tr>
<tr>
<td>From grains</td>
<td>7.5 ± 3.5</td>
<td>13.6 ± 2.3</td>
<td>8.4 ± 5.9</td>
<td>20.8 ± 7.6</td>
</tr>
</tbody>
</table>

*Values = mean ± SD. % kcal = % of total energy from nutrients per day.
†Baseline values were recorded prior to initial 1-mo compliance evaluation of the 11 females and six males in the study.

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**Figure 1.** Percent of anticipated toxic effects graded on a scale of none, mild, moderate, or severe.

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The rectal mucosa biopsy specimens from five patients showed a labeling index after 24-hour outgrowth culture. LI = labeling index at baseline; LI2 = labeling index after 24-hour wheat bran fiber supplementation. Three patients whose rectal mucosa biopsy specimens showed a significant increase, and six showed no change following the 2-month wheat bran fiber intervention. Of the nine patients who had an initially low labeling index, one showed a significant decrease, two showed a significant increase, and six showed no change.

Shown in table 4 are the individual [3H]thymidine-labeling indices for rectal mucosa crypt compartments 1–5 in the eight patients who had initially high values. Because of the small numbers of patients, subset analysis was inappropriate; nevertheless, there appears to be a trend toward lower on-treatment labeling indices in compartments 3, 4, and 5 with LI2/LI1 values of 0.60, 0.74 and 0.62, respectively.

Correlation between the two labeling index data sets. An excellent correlation was found between [3H]thymidine-labeling indices in crypt organ cultures and in 24-hour outgrowth cultures. The rectal mucosa biopsy specimens from five patients showed a significant decrease from baseline in response to the fiber supplementation in both culture systems. There was no change in either crypt organ culture or 24-hour outgrowth culture labeling indices in six patients. Three patients whose rectal mucosa biopsy specimens had a significant decrease in 24-hour outgrowth culture labeling indices showed no change in crypt organ culture labeling indices. Thus, a significant correlation (P < .001) was found in the crypt organ and 24-hour outgrowth culture [3H]thymidine-labeling indices data.

Discussion

The results of this study suggest that a wheat bran fiber dietary supplement of 13.5 g/day for 2 months can inhibit DNA synthesis and epithelial cell proliferation within the rectal mucosa crypts of patients at high risk for recurrence of colorectal cancer. We used stringent statistical criteria for determining whether the [3H]thymidine-labeling index in rectal epithelial cells was significantly changed from the baseline (i.e., before any wheat bran fiber supplement was taken) value (P < .001) in any one study subject. A combination of [3H]thymidine-labeling index data obtained from 24-hour outgrowth and crypt organ culture studies suggests an inhibitory effect of wheat bran fiber on DNA synthesis within rectal mucosa cells. Buset et al. (11) have previously shown a positive correlation between crypt organ culture and 24-hour outgrowth culture labeling index data.

The wheat bran fiber dietary supplement of 13.5 g/day was well tolerated by this group of older patients with previous resection for colorectal cancer. The major toxic effect was flatulence, which was mild in more than 90% of patient assessments. The only other significant fiber-related toxic effect was mild diarrhea, noted in 1%-2% of assessments. No evidence that fiber supplementation caused hypocalcemia or other significant blood chemistry changes was found. Whether this level of fiber supplementation will be tolerated for an extended period must be tested in a more prolonged study. In such a trial, the monitoring of loss of minor nutrients and loss of bone density will be important, since wheat bran fiber can chelate and subsequently enhance excretion of calcium and other cations (18,19).

For our study, we selected a group of patients at high risk for colorectal cancer recurrence. As previously demonstrated by Lipkin et al. (20) and Terpstra et al. (21), there appears to be a hierarchy of risk for colon cancer in relation to proliferation rates of epithelial cells lining colorectal mucosa crypts. These investigators have shown the [3H]thymidine-labeling index in crypt organ culture of uninvolved rectal mucosa cells obtained from patients with resected colon cancer to be significantly elevated compared with values for cultures from patients with small adenomas or no prior history of gastrointestinal disease. In the patients with colorectal cancer involved in our study, the mean baseline [3H]thymidine-labeling indices in rectal crypt organ cultures and 24-hour outgrowth cultures (8.6% ± 2% and 10.0% ± 2%),

Table 3. [3H]Thymidine-labeling indices for 24-hr outgrowth and crypt organ culture in patients with resection for colorectal cancer

<table>
<thead>
<tr>
<th>Labeling index type</th>
<th>No. of patients</th>
<th>LI1 ± SD</th>
<th>LI2 ± SD</th>
<th>LI2/LI1</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crypt organ culture</td>
<td>17</td>
<td>0.086 ± 0.02</td>
<td>0.088 ± 0.03</td>
<td>1.02</td>
<td>.83</td>
</tr>
<tr>
<td>24-hour outgrowth</td>
<td>16</td>
<td>0.100 ± 0.03</td>
<td>0.078 ± 0.03</td>
<td>0.78</td>
<td>.02</td>
</tr>
</tbody>
</table>

*Values = mean ± SD. Wheat bran fiber supplementation (13.5 g/day) was given for 8 wk. LI1 = labeling index at baseline; LI2 = labeling index after 8 wk of wheat bran fiber supplementation.

†Paired t-test.

Table 4. [3H]Thymidine-labeling indices for crypt organ culture by compartment in patients with resection for colorectal cancer

<table>
<thead>
<tr>
<th>Compartment</th>
<th>Initial high labeling index</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LI1</td>
</tr>
<tr>
<td>1</td>
<td>0.150</td>
</tr>
<tr>
<td>2</td>
<td>0.171</td>
</tr>
<tr>
<td>3</td>
<td>0.128</td>
</tr>
<tr>
<td>4</td>
<td>0.058</td>
</tr>
<tr>
<td>5</td>
<td>0.013</td>
</tr>
<tr>
<td>Entire crypt</td>
<td>0.104</td>
</tr>
</tbody>
</table>

*Median labeling index was used as cutoff between high and low labeling indices. LI1 = labeling index at baseline; LI2 = labeling index after 8 wk of wheat bran fiber supplementation. There were eight patients.
± 3%, respectively, are comparable to the average [3H]thymidine-labeling index observed by Lipkin et al. (22) in patients with a history of familial colon cancer or familial polyposis (9.9%). Obviously, if the baseline labeling index in rectal mucosa cells in the high-risk population is comparable to that measured in normal subjects, this intermediate marker will not prove useful in evaluating the effects of a new chemopreventive agent.

Recently, DeCosse et al. (7) completed a double-blind, placebo-controlled phase III trial of dietary wheat bran fiber supplementation in 72 patients with familial polyposis. The results of that trial documented a decreased growth of adenomatous polyps in the rectum of those patients whose intake of bran fiber was in excess of 11 g/day for up to 4 years. The results of the present pilot study appear to provide a confirmatory mechanism (i.e., reduction in mucosa cell DNA synthesis rates induced by wheat bran fiber) by which wheat bran fiber may decrease rectal polyp growth in patients at high risk for developing colorectal cancer. However, the ability of supplemental dietary fiber to inhibit DNA synthesis in rectal mucosa cells must be confirmed in the setting of a randomized, double-blind clinical trial in high-risk subjects. A study of this type, sponsored by the Division of Cancer Prevention and Control of the National Cancer Institute and the Arizona Cancer Center, is ongoing in Sun City, Ariz, and involves patients with resected colorectal adenomas.

Ultimate confirmation of the chemopreventive effects of fiber, as well as the validity of [3H]thymidine-labeling index as a marker of carcinogenic potential, will require additional randomized phase III trials. These trials must take place in high risk patient populations such as those with familial polyposis, familial colon cancer, or colorectal adenomas.

References


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1Colon Cancer Prevention Program. Project Grant PO-1, CA-41108. Bethesda, Md: Division of Extramural Activities, National Cancer Institute.