Sex differences in colonic function: a randomised trial

J W Lampe, S B Fredstrom, J L Slavin, J D Potter

Abstract

There are sex differences in large bowel cancer rates and a variety of other gastrointestinal disorders possibly because of differences in gut biology. To determine whether men and women have different gastrointestinal responses when consuming identical intakes of dietary fibre, 16 women and 18 men consumed liquid formula diets and 'quick breads' with 0 g, and 10 g, and 30 g of fibre as wheat bran and vegetable fibre. The five test diets were consumed in random order, each treatment lasting 23 days. Mean transit time was faster (p=0.02), and stool weights (g/day) were greater (p=0.0005) for men than women. Neutral detergent fibre (NDF) excretion was greater in men (p=0.01), and women tended to digest more NDF (p=0.06). Men and women seemed to respond differently to wheat bran and vegetable fibre with regard to NDF excretion and digestibility. There were no gender differences in the faecal pH or moisture content. Concentrations and daily excretion of the secondary bile acids, lithocholic and deoxycholic acid, were greater for men than women (p<0.05). Gender differences in bowel function and bile acid excretion, observed when men and women consumed the same amounts of dietary fibre, may be relevant for understanding colonic disease aetiology and for undertaking future dietary intervention trials.

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There is a male excess for most chronic diseases, and particularly cancer. Diseases of the biliary and intestinal systems, however, frequently show an excess in women. This is often even more noticeable before the age of menopause. Real sex differences in the physiological functioning of the biliary and intestinal organs may exist, differences that may be pertinent to the aetiology of colon cancer particularly, and are certainly pertinent to the gender differences in the age and subite distribution of that cancer.

In Western societies, rates of colon cancer in premenopausal women are often similar or exceed the male rates at all ages. These women tend to experience their colon cancers somewhat younger and more proximaly, while men present older with more distal cancers.

There are data from epidemiological, clinical, and animal studies to show that gender, hormonal status, and reproductive events may influence various bile, composition, transit time, faecal weight and faecal biochemistry. Furthermore, in ecological studies, an increased risk for colon cancer has been associated with reduced stool bulk.

Methods

SUBJECTS

Subjects were recruited from the University of Minnesota community. Healthy, non-smokers who had not used antibiotics within 6 months of the start of the study were screened on the basis of their ability to complete a rigorous schedule of defined diet ingestion and extensive biological sample collection. All subjects were healthy, had not been taking medication, and had no history of diabetes, heart disease, gastrointestinal malabsorption, or renal disease. The design of the study was approved by the Committee on Use of Human Subjects in Research at the University of Minnesota, and informed written consent was obtained from all subjects before the start of the study.

Forty-six subjects were initially randomised into the study, but because of commitment required, nine people dropped out during the first week on the defined diet and three more dropped out after two diet periods. Thirty-four subjects (16 women, 18 men) finished all aspects of the study. All the women were premenopausal and none were using oral contraceptives. The mean (SD) age, height, weight, and body mass index for the men and women were 25.9 (7.5) years, 1.79 (0.07) metres, 74.5 (9.1) kg, 23.3 (2.6) kg/m² and 26.7 (5.3) years, 1.69 (0.06) metres 63.4 (7.9) kg, 22.1 (1.9) kg/m², respectively.

STUDY DESIGN AND SAMPLE ANALYSIS

Before the start of the randomised fibre trial, baseline data were collected for 9 days while subjects ate their normal diet (self selected...
diet). Radiopaque pellets (Portex Ltd, Hythe, England) were swallowed on days 1 and 7 to measure transit time, and all stools were individually collected and frozen at −20°C over the 9 day period. Five day diet records were analysed for nutrient and dietary fibre content using a computerised nutrient analysis program (Nutritionist III, N-Squared Computing, Silverton, OR, USA).

Five test diets, varying in absolute amounts and type of fibre, were consumed by all subjects in assigned random order: (1) 0 g added fibre; (2) 10 g total dietary fibre (TDF) as white wheat bran (American Association of Cereal Chemists, St Paul, MN, USA); (3) 30 g TDF as white wheat bran; (4) 10 g TDF as mixed vegetable fibre (VF); (5) 30 g TDF as VF. The vegetable fibre in the 10 g VF and 30 g VF breads was a mixture of pea hull fibre (Fiberich Technologies Inc, Minneapolis, MN, USA), soy polysaccharide (Protein Technologies International, St Louis, MO, USA) and citrus pectin (Hercules, Wilmington, DE, USA), added at levels of 62, 33, and 5% by weight of total fibre, respectively. A ‘quick bread’, prepared in our laboratory, was the vehicle to deliver the fibres, and a quick bread without added fibre was provided during the 0 g fibre diet. The quick breads formulations were based on the TDF content of the products as reported by the companies. TDF content was also determined in our laboratory by a modification of the current Association of Official Analytical Chemists method.20

The subjects consumed a fibre free enteral supplement (Resource, Sandoz Nutrition, Minneapolis, MN, USA), deionised water, and one loaf of quick bread daily. Subjects were instructed to eat all of the quick bread and consume enough liquid supplement daily (in addition to the quick bread) to maintain their usual weight. The quick breads were consumed plain, without spreads. To limit formation of Maillard products in the breads, subjects were instructed not to heat the breads in a conventional oven and instead warm them in a microwave oven.

Each test diet was consumed for 23 days. No adjustment was made for the phase of menstrual cycle. There was a washout period of at least 10 days between each diet period during which subjects resumed their habitual diets. Subjects consumed the test diets for 1 week before any samples were collected. Radiopaque pellets were swallowed on days 7, 13, and 19 of each period for transit time determinations, and all stools were individually collected and frozen from days 7–23.

Subjects recorded all quick bread and nutrition supplement intake and daily exercise for each feeding period. Any bread that was not eaten was returned by the subjects and the uneaten portions were weighed and subtracted from the average bread weight. To ensure greatest compliance by this ‘outpatient’ group, subjects reported daily to pick up food and drop off faecal samples and diet records. The importance of total faecal collections and adherence to the diet were stressed continuously with the subjects. Daily nutrient and fibre intakes for 6 days during the last week of each feeding period were calculated using the nutrient content of the liquid supplement as reported by the company and the nutrient content of the quick breads analysed in our laboratory as previously described.21

All faecal samples were weighed and mean stool weight and mean daily faecal weight were determined. The samples were x rayed for pellet content and the time needed to pass each pellet was averaged to calculate mean transit time (MTT).21 The appearance of the first pellets swallowed on days 13 and 19 were used as the limit markers for faecal composites: starting with stools containing pellets swallowed on day 13, all stools up to the appearance of pellets swallowed on day 19 were included. Composites were homogenised with addition of deionized water and faecal pH was measured. Duplicate aliquots of the homogenates were freeze dried to determine faecal dry weight and faecal moisture content was calculated after correcting for the added water. Faecal acidic sterols were measured by gas chromatography as described previously.22 Minor bile acids detected in small amounts, were summed and presented as ‘miscellaneous bile acids’.

To determine the amount of fibre excreted and digested, the neutral detergent fibre (NDF) content of freeze dried faeces and food samples from the five test diets was analysed by the method of Robertson and Van Soest.24 Heat stable α amylase (Sigma, St Louis, MO, USA) and sodium sulphite (Aldrich Chemical, Milwaukee, WI, USA) were added to improve the removal of starch and protein. Fibre digestibility was calculated as: (g faecal fibre – g fibre ingested)/g fibre ingested.

STATISTICAL ANALYSIS

Bowel function parameters, bile acid excretion, and fibre digestibility in men and women were compared using repeated measures analysis of variance where gender was used as a group variable for subjects and the interaction of gender and diet was included in the model. Data are presented as means (SD) by gender.

Results

The effects of fibre type and dose on bowel function characteristics were published previously23 and are not discussed here.

Mean transit times were consistently faster (p=0.02) and faecal wet weights were consistently greater (p=0.0005) for men than women on all diets (Fig 1), despite the same fibre intakes by men and women (Table I). Faecal dry weights, 35 (2) and 26 (3) g/day for men and women, respectively, followed an identical pattern to that of wet weights (p<0.0001). The overall faecal moisture content (70·7 (1·8) and 70·5 (1·9)% for men and women, respectively) and the faecal pH (7·4 (0·1) and 7·4 (0·2) for men and women, respectively) were similar between the sexes.

The concentrations and daily excretion of faecal bile acids are presented in Figure 2 and Tables II and III. Both the concentrations and daily excretion of the secondary bile acids,
lithocholic and deoxycholic acid, were significantly greater (p<0.05) for men than women, as was daily excretion of chenodeoxycholic acid. As a result, the total bile acid concentration was greater for men than women on all diets (p=0.02) and, with the added effect of greater stool weights among men, daily total bile acid excretion was also greater for men (p<0.0001) (Fig 2). The only significant gender by diet interaction observed for the bile acid data was for daily lithocholic acid excretion (p=0.04), where men and women seemed to respond differently to the two doses of wheat bran and vegetable fibre. When the data were analysed for men and women separately, lithocholic acid excretion tended to decrease in men (350 (103) vs 311 (95) mmol/day, p=0.09) but not women (168 (50) vs 164 (49) mmol/day, p=0.5) with higher wheat bran (10 g vs 30 g); it tended to decrease in women (169 (71) vs 134 (89) mmol/day, p=0.08), but not men (256 (82) vs 253 (67) mmol/day, p=0.9), with higher vegetable fibre (10 g vs 30 g). There was no difference in the ratios of secondary to primary bile acids or of lithocholic acid to deoxycholic acid between the sexes.

Dietary fibre intakes during the test diet periods, calculated as TDF and NDF, are presented in Table IV. The amount of fibre as TDF and NDF were the same for the 0 g fibre bread and for the two wheat bran breads; NDF was 60% of the TDF value for the vegetable fibre breads. Faecal NDF excretion was greater in men than women (p=0.01) (Table IV) and the interaction of gender and diet was highly significant (p<0.0001). Men excreted more NDF than women with consumption of the 30 g fibre doses. Individual NDF digestibilities varied widely on all diets. However, digestibility tended to be greater in women than men (Table IV) (p=0.06). The interaction of gender and diet (p=0.015) seemed to be due primarily to greater digestion of the 10 g wheat bran and 30 g vegetable fibre diets in women.

Despite similar dietary fibre consumption by

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**Table I** Comparison of daily macronutrient and dietary fibre intakes for men and women during the self-selected diet period and the controlled feeding periods. (Values mean (SD))

<table>
<thead>
<tr>
<th></th>
<th>Self-selected</th>
<th>Controlled feeding</th>
<th>p value</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Energy (MJ)</td>
<td>10.54 (1.98)</td>
<td>8.34 (1.76)</td>
<td>0.003</td>
<td>0.003</td>
</tr>
<tr>
<td>Protein (g)</td>
<td>86 (19)</td>
<td>67 (18)</td>
<td>0.007</td>
<td>0.0001</td>
</tr>
<tr>
<td>Fat (g)</td>
<td>105 (29)</td>
<td>78 (21)</td>
<td>0.005</td>
<td>0.0001</td>
</tr>
<tr>
<td>Total dietary fibre (g)</td>
<td>12.1 (5.6)</td>
<td>13.8 (8.3)</td>
<td>0.5</td>
<td>0.4</td>
</tr>
</tbody>
</table>

* Data for individuals were averaged across all test diets prior to calculation of gender mean.

**Table II** Faecal bile acid concentrations (μmol/g dry faeces) for men (n=18) and women (n=16). (Values mean (SD))

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lithocholic acid</td>
<td>10.09 (1.15)</td>
<td>7.66 (1.13)</td>
<td>0.005</td>
</tr>
<tr>
<td>Deoxycholic acid</td>
<td>9.47 (1.21)</td>
<td>7.56 (1.48)</td>
<td>0.049</td>
</tr>
<tr>
<td>Chenodeoxycholic acid</td>
<td>0.87 (0.16)</td>
<td>0.81 (0.15)</td>
<td>0.7</td>
</tr>
<tr>
<td>Cholic acid</td>
<td>0.20 (0.15)</td>
<td>0.15 (0.08)</td>
<td>0.6</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>1.97 (0.28)</td>
<td>1.39 (0.26)</td>
<td>0.12</td>
</tr>
<tr>
<td>Total*</td>
<td>21.69 (2.39)</td>
<td>17.58 (2.63)</td>
<td>0.024</td>
</tr>
</tbody>
</table>

* Summation of the individual and miscellaneous bile acids.
we observed significant gender differences in bowel function parameters, faecal bile acid excretion, and faecal NDF excretion, even though men and women consumed the same absolute amount of fibre on each test diet.

Gastrointestinal transit times were shorter and faecal output greater for men than women. Similar results have been reported previously when men and women consumed their habitual diets\(^\text{26}\) and when fed controlled fibre diets.\(^\text{17}\) Using a single film technique for assessment of segmental colonic transit, Metcalf et al\(^\text{8}\) showed that the sex difference in transit time was most apparent in the right colon, with a smaller difference in the left colon, and no difference in the rectosigmoid. Ecological studies show higher stool weights in those populations with lower colon cancer risks,\(^\text{26,27}\) but to date no studies have shown an association between colon cancer risk and transit time. The findings of Metcalf et al\(^\text{8}\) provide additional detail on the sex difference we report here and are especially interesting in light of the epidemiological data that show that women have an excess of proximal cancers compared with men throughout life.\(^\text{1}\)

Faecal moisture content was the same for men and women. Thus, the significant sex difference in faecal wet weight was a function of difference in faecal dry matter. By administering drugs which change colonic motility, Stephen et al\(^\text{30}\) showed that changing transit time altered microbial growth. Greater faecal bulk as a function of faster transit time was due to an increase in faecal bacterial mass and in excretion of non-starch polysaccharides.\(^\text{30}\) Stephen et al attributed the efficiency of anaerobic microbial growth not only to substrate availability but also to the rate of passage of material through the lumen: somewhat counter intuitively, microbial growth is greater and a greater mass of bacteria is produced with faster transit.\(^\text{30}\) The pattern of faster gastrointestinal transit and greater faecal mass with faster transit was observed when the NDF fibre intake was increased in men compared with women in our study suggests that men have greater faecal bacterial mass than women despite a tendency to ferment less fibre. This suggests either that more non-fibre substrate is available in male colons (consistent with their higher energy intake and the possible influence of energy intake on stool weight) or that male and female colonic flora differ substantially. One possible explanation for the positive relationship between faster transit time and greater stool mass is that a more rapid transit time may reduce the likelihood of build up of 'toxic' antibiotic metabolites in the colonic microenvironment (for example compounds which may inhibit bacterial growth). It does suggest that, for whatever reason, there are male/female differences in the capacity to support the colonic microflora.

It has been reported previously that faecal output is positively correlated and gastrointestinal transit is negatively correlated with energy intake and total food consumption.\(^\text{31}\) Thus, reported sex differences in bowel function may be the result of energy intake differences between men and women. Unfortunately, in our study, the complete confounding of energy intake and gender made it difficult to resolve this issue. Men and women had similar fibre intakes.
Sex differences in colonic function

during the self selected diet period despite significant differences in intakes of other macro-

nutrients (Table I). Interestingly, no association between energy intake and faecal output was

observed when the subjects consumed the self

selected diet or 30 g fibre doses. The strongest

association was observed on the 0 g fibre diet.

This suggests that when fibre availability in the
colic lumen is low (that is, no or low fibre) the
volume of other macronutrients entering the
colic lumen may become more important in
determining faecal output. In our study, men
and women consumed the same amount of starch
and dietary fibre since both ate one loaf of quick
bread/day. The only difference in carbohydrate
intake between the sexes was male: dextrin and
sugar from the liquid formula. Refined sugars,30
in addition to starch,31 are known to influence gut
function and the composition of bowel contents.
Thus, these other aspects of diet must be
considered. Additional controlled studies are
needed to address this problem.

The colonic pH is largely determined by
fermentation and the production of short chain
fatty acids (SCFA).31 In humans, fibre fermenta-
tion occurs predominantly in the caecum and
proximal colon, and SCFA concentrations are
highest and the pH is lowest in these areas.32
SCFAs are rapidly absorbed and the pH rises as
the contents proceed distally.33 Stephen et al4 found
the faecal pH, corrected for stool weight,
to be indeed lower in men than women. In a
study in the US and China, faecal pH, not
corrected for fibre intake differences, was also
observed to be lower in men (6-4) than women
(6-9) when study subjects consumed their
habitual diets.1 In men, if less fibre is fermented
in the caecum and proximal colon, continued
fermentation and SCFA production length the
the colon and in the rectosigmoid may contribute
to the output of more acidic stools. In women,
slowing transit and greater fermentation in the
proximal colon with concomitant absorption of
SCFA may reduce the substrate available for
fermentation in the rectosigmoid and result in
more alkaline stools. In our study, however,
where fibre intakes were the same for men and
women, faecal pH was not significantly different
between the sexes. It is not clear what explains
the failure to observe the gender differences
in faecal pH that others have reported. One
important difference is that subjects in our study
consumed a highly controlled liquid diet, rather
than a diet of regular food.

Based on the epidemiological research which
suggests: (1) that female rates of colon cancer at
premenopausal ages may exceed male rates2 and
(2) that concentrations of faecal bile acids are
higher in populations at high risk for the
development of colon cancer,15 26 27 28 we
hypothesised that women would have higher bile
acid excretion than men. However, our results
indicate that secondary bile acid concentrations
and daily bile acid excretion were actually greater
in men than women.

There are few studies of faecal bile acid excretion in men and women with which to
compare our results, and the results of these
studies are conflicting. No significant sex difference in faecal bile acid excretion was detected in
a group of 25 subjects habitually consuming low
fibre diets,49 or in men and women with mean
daily fibre intakes of 15.4 and 11.9 g, respectively.50 Likewise, Reddy et al50 found no sex
difference in faecal bile acid excretion when men
and women ate their usual diets and diets
supplemented with wheat and rye flour. More
recently, Yeung et al51 reported significantly
higher concentrations of bile acids in women
than men consuming their habitual diets in Sha
Giao, People’s Republic of China and in San
Francisco County, United States. In a controlled
fibre feeding study, Stasse-Wolthuis et al52
observed that when men and women consumed
test diets containing various dietary fibres, men
and women seemed to respond differently to the
fibre containing diets. Bile acid excretion was
greater for male subjects consuming citrus pectin
or fruits and vegetables compared with women
on the same diets, while excretion was reduced
for men on the bran diet and was enhanced for
women consuming bran. None of the studies,
including ours, controlled for women’s
menstrual cycles. Despite this lack of control,
significant, albeit disparate, differences in bile
acid excretion have been observed. Since female
hormones are known to alter bile acid secretion,53
controlled, long-term studies taking into account
the subjects’ hormone status are warranted.

In conclusion, there were significant differences in transit time, faecal bulk, and bile acid
excretion between men and women consuming the same absolute amounts of fibre. Further-
more, faecal bile acid excretion was greater in men than women; correspondingly, women tended
to digest more fibre than men. The findings are
consistent with a lower degree of colonic fermenta-
tion in men than women and provide addi-
tional evidence for important sex differences
in bowel function between men and women.

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