Protein Degradation in the Large Intestine: Relevance to Colorectal Cancer

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Abstract

Colorectal cancer is the second most common form of cancer death in Western countries. Diet has been implicated in the aetiology of this disease. Epidemiological evidence suggests that diets high in meat and fat and low in fermentable carbohydrate increase colorectal cancer risk. One mechanism that could explain the association with meat is increased colonic protein metabolism due to increased protein intake from high meat diets. Products of colonic protein degradation and metabolism include ammonia, phenols, indoles and amines which have been shown to exert toxic effects in vitro and in animal models. These compounds are present in faecal samples suggesting that they may exert gut mucosal effects. Human studies have shown that colonic protein metabolism via the gut microflora is responsive to dietary protein as faecal ammonia and urinary phenolic compound concentrations increase in response to increased intake of protein rich foods. Other toxic metabolites from dietary protein precursors such as N-nitroso compounds and sulphides are also formed. Recent work has shown that diets high in meat, fat and low in fibre increase human faecal water genotoxicity. It is likely that metabolites from colonic protein metabolism contribute to this increase in genotoxicity during high meat intakes.

Introduction

Colorectal cancer is the second most common cause of death from cancer in Western countries (Potter, 1996). In high incidence populations, the majority of colorectal cancer cases tend to be sporadic hence implying a role for environmental factors. Most specifically, diet is thought to be an important factor as 80% of colorectal cancer cases have been attributed to dietary factors (Willett, 1995). Evidence from epidemiological studies show high rates of colorectal cancer in populations consuming diets high in meat and fat and low in starch, NSP (non-starch polysaccharides, fibre) and vegetables. In general, prospective studies tend to support these findings although estimates of relative risk are not high (Bingham, 2000). In 1995, Potter reported that approximately 30 case-control and cohort studies had been carried out to explore the association between cancer risk and meat, fat or protein consumption. Two thirds of these studies had shown a positive risk for intake of all three dietary factors with very few studies showing an inverse association. Prospective studies showing a positive association with protein refer to protein from red meat sources (Table 1). Following review of the epidemiological literature, two recent reports stated

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Population</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stemmermen et al, 1984</td>
<td>7074 men of Japanese ancestry aged 45-68 years</td>
<td>Protein (%calories) (↓)*</td>
</tr>
<tr>
<td>Phillips and Snowdon, 1985</td>
<td>25,493 Seventh Day Adventists</td>
<td>Meat (0)</td>
</tr>
<tr>
<td>Willett et al, 1990</td>
<td>88,751 women aged 34-59 years</td>
<td>Eggs (↑)</td>
</tr>
<tr>
<td>Thun et al, 1992</td>
<td>764,343 adults</td>
<td>Fresh red meat (↑)*</td>
</tr>
<tr>
<td>Goldbohm et al, 1994</td>
<td>120,852 aged 55-69</td>
<td>Processed meat (↑)*</td>
</tr>
<tr>
<td>Giovannucci et al, 1994</td>
<td>47,949 male health professionals aged 40-75</td>
<td>Red meat (0)</td>
</tr>
<tr>
<td>Gaard et al, 1996</td>
<td>50,635 aged 20-24</td>
<td>Fresh red meat (↑)*</td>
</tr>
<tr>
<td>Heing et al, 1998</td>
<td>17, 633 males aged &gt;35</td>
<td>Processed meat (↑)*</td>
</tr>
<tr>
<td>Fraser, 1999</td>
<td>34,192 Seventh day Adventists</td>
<td>Non red meat protein(↓)*</td>
</tr>
</tbody>
</table>

(↑) = positive association; (↓) = negative association; (0) = no association
* statistically significant association.
that red meat probably increases colorectal cancer risk. No association with white meat or fish was apparent due to insufficient evidence (WCRF, 1997; Department of Health, 1998).

Mechanisms whereby red meat may be involved in colorectal carcinogenesis are unknown. Evidence from animal work so far does not suggest a role for promotion by meat (Parnaud et al., 1998). There are animal studies however which suggest a role for cooked meat containing high levels of heterocyclic amines (HAA) (Layton et al., 1995; Pence et al., 1998). Some of these compounds have been shown to be carcinogenic in the large gut and are formed from amino acids during cooking at a high temperature (Skog et al., 1995). Formation of HAA upon cooking meat may be one mechanism to explain the epidemiological association between colorectal cancer risk and meat intake. Other hypotheses involve saturated fat and undigested protein which is metabolised in the colon forming a number of compounds which are known to exert toxic effects. The following review discusses the contribution of the gut flora to this metabolism and possible toxic effects to the host.

### Protein Degradation and Metabolism in the Large Intestine

The human large intestine is host to a diverse range of bacteria with total numbers reaching $10^{11}$ to $10^{12}$ CFU per ml of faecal material (Parodi, 1999). The composition of the gut microflora varies between individuals (Drasar, 1976). So far, diet is known to exert only a modest influence on the flora composition (Hill, 1981) although future advances in identification methodology may provide more information. The principal role of the gut microflora is to salvage energy from non-digestible dietary substrates and endogenous mucus during fermentation. Carbohydrates and protein are the main fermentative substrates in the large intestine (MacFarlane and Cummings, 1991). The main products of this metabolism include gases, hydrogen, carbon-dioxide, short-chain fatty acids (SCFA), branched chain fatty acids, lactic acid, ethanol, ammonia, amines, phenols and indoles (Roberfroid et al., 1995). SCFA especially butyrate are important sources of energy for colonocytes (MacFarlane and Cummings, 1991) and the cancer protective effects of butyrate have been reviewed.

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**Figure 1. Colonic protein metabolism.**
elsewhere (Smith et al., 1998). The nature and extent of fermentation depends upon the characteristics of the bacterial microflora, colonic transit time and the availability of nutrients. The products of carbohydrate metabolism are thought to benefit the host as compared to the toxic end products of protein metabolism. The beneficial effects of high fibre diets in the colon have been previously reviewed (Bingham, 1990 and 1996; Slavin et al., 1997).

The large intestine has been described as a site of intense protein turnover (Macfarlane et al., 1986). Numerically important proteolytic species identified in the large bowel include species belonging to the genera Bacteroides, Propionibacterium, Clostridium, Fusobacterium, Streptococcus and Lactobacillus (MacFarlane and Cummings, 1991). Protease enzymes of bacterial origin may be extracellular or cell bound and those detected in human faecal samples include trypsin, chymotrypsin, elastase, serine, cysteine and metalloproteases (MacFarlane et al., 1988; Gibson et al., 1989). On average, 12g of proteinaceous material or 0.5 - 4g total nitrogen, enters the large intestine each day mainly in the form of protein (48 - 51%) and peptides (20 - 30%). Dietary sources make up at least 50% of this protein material, however the amount may vary due to protein intake and the physical form of the food (Chacko and Cummings, 1988; Silvester and Cummings, 1995). In humans, dietary nitrogen is positively associated with nitrogen detected in ileal effluent (p = 0.005) (Silvester and Cummings, 1995). This finding shows that it is the amount of protein in the diet rather than its source that determines the amount reaching the colon. The remaining proteinaceous material arriving at the colon is made up of endogenous material, namely pancreatic enzymes, mucus and exfoliated epithelial cells (Chacko and Cummings, 1988). In the large intestine, nitrogenous residues are initially depolymerized by a mixture of residual pancreatic endopeptidases and bacterial proteases and peptidases (MacFarlane et al., 1988) forming short peptides and amino acids available for fermentation. Carbohydrate fermentation products are also formed during protein fermentation i.e. SCFA, hydrogen, CO₂ and biomass, in addition to branched chain fatty acids such as isobutyrate, isovalerate and 2-methylbutyrate, together with other organic acids. Ammonia, amines, phenols and indoles are also formed following deamination, decarboxylation, fermentation and α or β elimination reactions (Figure 1). Concentrations of protein fermentation products are higher in the left sided (distal) colon as compared to the right sided (proximal) colon suggesting that protein fermentation is more prevalent in the distal colon. Once carbohydrate sources are exhausted in the proximal colon, sources of protein material are fermented and metabolised to salvage energy (Gibson, 1996). Although proteins provide a less significant energy source in the large intestine their importance lies mainly in the effects they have on intermediary metabolism of the host and their role as potential systemic toxins.

Products of Colonic Protein Degradation and Metabolism

Ammonia
Ammonia is the most important product of protein degradation in the large intestine. Ammonia concentrations detected in human faeces range from 12 to 30 mM and excretion has been shown to increase with increased protein intake (Cummings et al., 1979; Silvester et al., 1997; Geypens et al., 1997; Hughes, 1999). Fermentable carbohydrates have been shown to decrease ammonia in vitro (Vince et al., 1978; Mortensen et al., 1991; Silvester et al., 1995) and faecal ammonia excretion in humans at low protein intakes (Kelsay et al., 1978). Bacteria assimilate ammonia to form bacterial protein during carbohydrate fermentation, so the concentration of ammonia in the colon at any one time depends upon the balance between amino acid deamination and bacterial protein synthesis. Ammonia exhibits a number of effects that suggest that it may be involved in tumour promotion. Concentrations as low as 5 -10 mM have been shown to alter the morphology and intermediary metabolism of intestinal cells, affect DNA synthesis and reduce the lifespan of cells (Visek, 1978). Moreover, it has been shown to increase the incidence of colon carcinomas induced by N-methyl-N-nitro-N-nitrosoguanidine in rats (Clinton et al., 1988). Uterosigmoidoscopy patients who have a luminal ammonia concentration as high as 100 mM have increased risk of developing tumours distal to the site of ureteric implantation (McConnel et al., 1979; Tank et al., 1973). Normally ammonia is rapidly absorbed into the portal blood, converted to urea in the liver and excreted in the urine. This pathway is interrupted in cases of liver disease resulting in an accumulation of ammonia in body fluids which is associated with hepatic coma (portal systemic encephalopathy) (Weber et al., 1987).

Phenolic Compounds
Phenolic compounds are formed following bacterial degradation of the aromatic amino acids phenylalanine, tyrosine and tryptophan. Degradation products include p-cresol and phenylpropionate (from tyrosine), phenylacetate (from phenylalanine) and indole propionate and indole acetate (from tryptophan). Intestinal bacteria involved in these processes include Clostidia (Elsden et al., 1976) Bacteroides (Chung et al., 1975), Enterobacteria (Botsford and Desmoss, 1972) Bifidobacteria (Aragozzini et al., 1979) and Lactobacilli (Yokoyama and Carlson, 1981). Phenolic compounds are absorbed in the colon, detoxified by the liver and excreted in urine principally as p-cresols (>90% of urinary phenolic compounds) with the remainder being made up of phenol and 4-ethylphenol (Tamm and Villako, 1971). Physiological levels of these compounds in human colonic contents are normally low as bacterial metabolism of aromatic amino acids requires an electron accepting process e.g. nitrate reduction (Young and Rivera, 1985; Bassert et al., 1986). Nevertheless phenolic compounds have been detected in colon contents from sudden death victims and distal concentrations were four times that detected in proximal regions. Simple phenols were the major products of aromatic amino acid metabolism in the
distal bowel supporting the argument that protein metabolism becomes more important in the distal colon as carbohydrate sources are depleted (Smith and MacFarlane, 1996).

Urinary excretion of phenolic compounds is responsive to dietary protein in a positive manner (Cummings et al., 1979; Geypens et al., 1997). In contrast, decreased urinary phenol and cresol excretion has been shown in the presence of readily fermentable carbohydrate (Cummings et al., 1979) and in subjects who changed from a typical Western diet to an uncooked vegan diet (Ling and Hanninen, 1992). Batch culture fermentation studies showed a 60% decrease in the net production of phenolic compounds in the presence of a fermentable carbohydrate (starch) (Smith and MacFarlane, 1996). Like ammonia, it is probable that these nitrogen sources are utilised for bacterial growth when stimulated by carbohydrate fermentation. Longer transit times increased tyrosine and phenylalanine fermentation in an in vitro gut model (Smith and MacFarlane, 1996). This suggests that longer retention times in the gut encourage more efficient proteolytic metabolism.

The relation of phenol production to cancer is unclear. In vitro work has shown that phenol may enhance N-nitrosation of dimethylamine by nitrite and the reaction between phenol and nitrite produces the mutagen diazoquinone (Kikugawa and Kato, 1986).

Amines
Amines found in gut contents include agamatine, tyramine, pyrrolidine, histamine, piperidine, cadaverine, putrescine and 5-hydroxytryptamine (Drasar and Hill, 1974). Species belonging to the genera Clostridium, Bilidobacterium and Bacteroides have been shown to form amines in substantial quantities (Allison and MacFarlane, 1989). Normally, amines produced by colonic bacteria are detoxified by monoamine and diamine oxidases in the gut mucosa and liver. Dimethylamine has been detected in human urinary samples and 50% of the levels detected were of bacterial origin (Asatoor and Simenhoff, 1965). Although amines have been linked to migraine, hypertension, hepatic coma (MacFarlane and MacFarlane, 1997) and tyramine from food has been implicated in heart failure (Smith, 1980), the physiological significance to the host is largely unknown. Cancer patients excrete higher levels of N-acetyl and acetoxy derivatives of putrescine and cadaverine as compared to healthy individuals (Murray et al., 1993). Putrescine has been shown to regulate cell growth and differentiation in the gastrointestinal epithelium (Seidel et al., 1984). An emerging area of interest however is in their role as N-nitrosation precursors resulting in the formation of potentially carcinogenic N-nitrosocompounds as discussed below.

N-nitrosocompounds
Many N-nitroso compounds (NOC) are known to exert carcinogenic/mutagenic effects following the formation of potent DNA alkylating agents during metabolism. Preformed NOC are found in cosmetics, pharmaceutical products and occupational sources. However endogenous formation provides the most potent source of exposure for humans (Ohshima and Bartsch, 1981). NOC are formed following the reaction between nitrosating agents and nitrosatable substrates. This reaction may be acid or bacterially catalysed or cell mediated hence N-nitrosation may occur at a number of sites in the body (Mirvish, 1995; Tricker, 1997). The large intestine provides a site for bacterially mediated N-nitrosation reactions due to the presence of nitrosating agents from dissimilatory nitrate metabolism and nitrogenous residues from endogenous and dietary sources. These nitrosatable substrates include, dietary proteins and peptides, secondary amines, indoles and phenols derived from protein metabolism (Shephard et al., 1987) and glycine derivatives such as the bile acid glycocholic acid (Shuker and Margison, 1997). Large intestinal N-nitrosation has previously received little attention due to analytical difficulties. The development of a group selective method for total NOC detection however has allowed NOC detection in several biological fluids including faeces (Tricker, 1997). NOC detected by this method are referred to as apparent total NOC (ATNC) as the method may be susceptible to false positives from S-nitrosothiols and nitric acids (Walters et al., 1978). Using this approach large intestinal N-nitrosation was demonstrated in rats and shown to be dependant upon the presence of a gut microflora (Massey et al., 1988). In vitro studies have demonstrated a positive correlation between bacterial nitrate reductase activity and N-nitrosation (Calmels et al., 1985, 1988). Denitrifying bacteria are more potent nitrosators than non-denitrifying bacteria following induction under anaerobic conditions in the presence of nitrate or nitrite (Leach et al., 1987). Bacterial strains belonging to Escherichia, Pseudomonas, Proteus, Klebsiella and Neisseria families have been shown to nitrosate the amine morpholine in the presence of nitrite (Calmels et al., 1985, 1988; Leach et al., 1987). Bacterial N-nitrosation was later shown to be dependant upon the presence of nitrate and nitrite reductase genes probably through the production of NO or NO+ like species (Calmels et al., 1996). Despite evidence from in vitro studies the exact mechanism of bacterial nitrosation remains unknown. In terms of colonic nitrosation, the majority of the microorganisms mentioned above are facultative anaerobes and the majority of human large intestinal microorganisms are obligate anaerobes with numbers of facultative anaerobes being many orders of magnitude lower (Gibson, 1996). Nevertheless, ATNC have been detected in faecal samples from healthy human volunteers and excretion is related to dietary nitrate (Rowland et al., 1991) and red meat consumption (Bingham et al., 1996; Silvester et al., 1997; Hughes, 1999). Nitrate and red meat may contribute to large intestinal N-nitrosation due to the formation of nitrosating agents from dissimilatory nitrate metabolism and nitrogenous residues from colonic protein degradation.

Table 2 summarises quantitative results from some recent studies. All studies referenced in Table 2 reported a high interindividual variation in faecal ATNC excretion which may be due to individual variations in gut flora composition especially nitrate and nitrite reducing bacteria. In addition recent work has shown that faecal ATNC concentration is positively associated with intestinal transit time and inversely related to faecal output (Hughes, 1999). This
Table 2. Human Studies Showing an Effect of Diet on Faecal ATNC Excretion

<table>
<thead>
<tr>
<th>Reference</th>
<th>n</th>
<th>Intervention</th>
<th>Mean faecal ATNC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rowland et al., 1991</td>
<td>8</td>
<td>low nitrate</td>
<td>82 µg/kg</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>300 mg/d nitrate</td>
<td>307 µg/kg</td>
</tr>
<tr>
<td>Bingham et al., 1996</td>
<td>8</td>
<td>60 g/d meat</td>
<td>40 µg/d</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>600 g/d red meat</td>
<td>113 µg/d</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>600 g/d red meat + 20g bran*</td>
<td>138 µg/d</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>600 g/d white meat</td>
<td>56 µg/g</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>60 g/d meat</td>
<td>61 µg/d</td>
</tr>
<tr>
<td>Silvester et al., 1997</td>
<td>8</td>
<td>60 g/d meat</td>
<td>35 µg/d</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>600 g/d red meat</td>
<td>114 µg/d</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>600 g/d red meat + 37g RS</td>
<td>151 µg/d</td>
</tr>
<tr>
<td>Hughes, 1999#</td>
<td>8</td>
<td>No meat</td>
<td>51 µg/d</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>60 g/d red meat</td>
<td>47 µg/d</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>240 g/d red meat</td>
<td>136 µg/d</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>420 g/d red meat</td>
<td>181 µg/d</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>420 g/d red meat</td>
<td>132 µg/d</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>420 g/d red meat + 400 g/d vegetables#</td>
<td>160.9 µg/d</td>
</tr>
</tbody>
</table>

* phytate-free wheat bran, RS resistant starch.
* vegetables as broccoli, petits pois and brussel sprouts.
† significantly different to the low nitrate diet, p < 0.01.
‡ significantly different to the low meat diet, p < 0.05.
§ p < 0.0001 for a dose response effect of red meat on faecal ATNC.
# p < 0.0001 for a dose response effect of red meat + 400 g/d vegetables.
#* significantly different to the no meat and 60 g/d meat diets, p < 0.01.

The toxicological significance of increased faecal ATNC excretion is not known as the group selective method for NOC detection gives no information on the individual NOC present. Attempts to characterise the compounds have shown that they are water-soluble, and 50% have a molecular weight less than 3000. Such compounds can cross cell walls and exert effects at the cellular level. Compounds known to be present include acidic and basic nitrosamines which may be genotoxic upon activation by cytochrome P450 enzymes (Silvester et al., 1997).

**Sulphur and Sulphur Metabolites**

The biology of sulphur in the human gut has escaped serious attention until recently, and thus very little is known of the amounts and sources of sulphur in the diet, and their subsequent digestion and absorption from the intestine. An understanding of the microbial metabolism of sulphur is however well advanced, and in anaerobic ecosystems, like the large intestine, reduced sulphur compounds such as hydrogen sulphide (H₂S), which are highly noxious, can be formed. Emerging evidence suggests sulphide may be toxic to the colonic epithelium. The chief sources of sulphur in the diet are derived from dietary inorganic sulphur (sulphate, sulphite) and the sulphur amino acids, methionine, cysteine, cystine and taurine. Sulphur also occurs naturally in the form of sulphur-containing glucosinolates in brassica vegetables. Intake of inorganic sulphate in humans has been estimated to range between 1.5 and 16 mmol/day (Florin et al., 1991), where dietary sources include fermented beverages, some commercial breads, and dried fruits (Florin et al., 1993). The consumption of sulphur amino acids fluctuates with protein intake. In humans, faecal sulphide concentrations increased from (mean(sem)) 0.22 (0.02) mmol/day to 3.38 (0.31) mmol/day when meat intake increased from 0g/day to 600g/day and this was dose related (p<0.01). This result was confirmed by in vitro modeling of protein fermentation (Magee et al., in press). In this study the main dietary contribution to protein intake was meat. The effect of other protein sources so far is unknown.
It is difficult to determine the physiological significance of increased faecal sulphide excretion to the host as the exact conditions under which sulphides are toxic to epithelial cells are unknown. Several lines of experimental evidence however implicate sulphide as a damaging agent in inflammatory bowel disease and ulcerative colitis (UC). Perfusion for 4 h of isolated rat colon with 0.2 to 1.0 mmol/L sulphide produced increased mucosal apoptosis and goblet cell depletion (Aslam et al., 1992). Roediger et al. (1993a; 1993b) demonstrated inhibition of n-butyrate oxidation in vitro in both rat and human colonocytes at a concentration of 2 mmol/L. Using human colon tissue, Christl et al. (1994) showed that sulfide at 1 mmol/L significantly increased cell proliferation rates and other changes seen classically in ulcerative colitis. Diminished n-butyrate oxidation was demonstrated during perfusion of sulfide into the proximal rat colon (Roediger and Nance, 1986; 1990).

The production of sulphide via sulphur amino acid fermentation has been examined in vitro in batch culture experiments. Faecal slurries from healthy volunteers were spiked with 10 mmol/L-cysteine resulting in a net sulphide generation of approximately 3 µmol/g/48 h (Florin, 1991). Greater sulphide production has been demonstrated in similar experiments using a methionine spike of 5 mmol/L. Using human colon tissue, Florin et al. (1992) showed that sulfide at 1 mmol/L significantly increased cell proliferation rates and other changes seen classically in ulcerative colitis. Diminished n-butyrate oxidation was demonstrated during perfusion of sulfide into the proximal rat colon (Roediger and Nance, 1986; 1990).

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Conclusions

Experimental studies have shown that faecal and urinary excretion of protein metabolites (ammonia, phenols and indoles, NOC and sulphides) are elevated as a consequence of increased meat intakes. Colonic protein metabolism may be one mechanism to explain the epidemiological relationship between red meat intake and colorectal cancer risk as certain products of colonic protein degradation such as ammonia, NOC and possibly sulphides, are known to exert toxic effects. Fermentable carbohydrates have been shown to decrease ammonia in vitro (Vince et al., 1978; Mortensen et al., 1991; Silvester et al., 1995) and urinary phenol and cresol excretion in humans (Cummings et al., 1979). This may reflect increased carbohydrate metabolism at the expense of protein metabolism as carbohydrate is the energy supplying nutrient favoured by the gut microflora (MacFarlane and Cummings, 1991). There are in vivo studies, however, showing no effect of fermentable carbohydrate intake on faecal excretion of ammonia (Cummings et al., 1979; Frourie et al., 1986; Sugawara et al., 1991) and NOC (Bingham et al., 1996; Silvester et al., 1997). In the later studies, fermentable carbohydrate sources were given with a high protein load which may have outweighed the effects of carbohydrate metabolism. Dietary protein intake in relation to fermentable carbohydrate intake may be important when considering the influence of diet on colonic protein metabolites. Faecal measurements reflect metabolite concentrations (typically protein metabolites) in the distal colon, the subsite most prone to disease, more-so than the whole colon. Little is known about colonic NOC and sulphide absorption and the toxicological significance of these compounds to colon health has yet to be elucidated despite known in vitro and in vivo toxic effects. Recently, diets high in meat and fat and low in dietary fibre have been shown to increase human faecal water genotoxicity (Reiger et al., 1999). Epidemiologically, these diets are associated with increased colorectal cancer risk. It is probable that toxic products from colonic protein metabolism contribute to this increased genotoxicity.

References


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