

Invited commentary

Probiotics and colorectal cancer risk

The role played by dietary components in the aetiology of human cancer is a topic that has attracted widespread interest. It has been estimated that about three-quarters of cancer deaths can be attributed to diet and lifestyle factors, with diet accounting for about 50 % of these deaths (World Cancer Research Fund, 1997). The evidence for dietary modulation of cancer risk is greatest for colorectal cancer, which is one of the major causes of death from malignant disease in Europe and North America. In 2000, the number of new cases of this cancer reported in Europe reached 363 000 and it affects 6 % of men and women by the age of 75 years (International Agency for Research on Cancer, 2000). In its advanced form it is quite refractory to the normal therapeutic regimens of radiation, surgery and chemotherapy, so approaches based on prevention of the disease are of particular importance.

Case-control and prospective studies have implicated, *inter alia*, vegetables, cereal fibre and folic acid as potentially important dietary factors in colorectal cancer risk reduction (Bingham, 2000). At first sight it might seem unlikely that probiotics, i.e. live microbial food ingredients with benefits for health (Salminen *et al.* 1998), such as the strains of lactobacillus and bifidobacterium used in the paper presented in this issue of the *British Journal of Nutrition* by Oberreuther-Moschner *et al.* (2004), could influence the risk of colorectal cancer. Indeed, there is a paucity of consistent epidemiological data to support such a contention and what data there are come from studies on yoghurt and fermented milks. A case-control study by Boutron *et al.* (1996) showed a significant inverse relationship between consumption of moderate amounts of yoghurt and the risk of large colonic adenomas (benign tumours) in both women and men. Kampman *et al.* (1994a) reported a inverse relationship (though non-significant) between colonic adenomas and yoghurt consumption. Two other case-control studies have provided additional evidence of inverse associations of colorectal cancer risk and consumption of fermented dairy products (Young & Wolf, 1988) and yoghurt (Peters *et al.* 1992). These findings, however, were not corroborated in a case-control study in the Netherlands of colorectal cancer risk and fermented dairy products, nor in two cohort studies that found no significant associations between cancer risk and yoghurt or fermented milk products (Kampman *et al.* 1994b,c; Kearney *et al.* 1996). It should be noted however that yoghurt and fermented milks usually contain only two types of lactic acid-producing bacteria (*Lactobacillus delbrückii* subsp. *bulgaricus* and *Streptococcus thermophilus*) that are not considered as probiotics and also contain

other components with potential cancer-preventing properties, such as Ca (Gill & Rowland, 2003).

In contrast, studies conducted in laboratory animals, which encompass a wide range of tumour models and shorter-term, predictive assays conducted under diverse conditions, have provided extensive and quite compelling evidence for anti-cancer effects of specific probiotic bacteria. For example, 25–50 % inhibition of carcinogen-induced pre-cancerous colon lesions (aberrant crypt foci) has been reported in rats fed strains of *Bifidobacterium longum* in the diet (Kulkarni *et al.* 1994; Rowland *et al.* 1998). Furthermore, administration of dietary *B. longum* (1×10^{10} live bacterial cells/d) completely suppressed colon tumours induced by the compound 2-amino-3-methyl-3H-imidazo(4,5-f)quinoline, which is a carcinogen found in the human diet (Reddy & Rivenson, 1993). McIntosh *et al.* (1999) reported that *L. acidophilus* markedly reduced both the number and size of colon tumours induced by another carcinogen, 1,2-dimethylhydrazine (DMH). Interestingly, there was also a difference in the type of tumours: in the rats given *L. acidophilus*, in contrast to the ones given DMH alone, only benign tumours were seen, suggesting that probiotics may inhibit the development of malignant disease.

In a study of particular relevance to that of Oberreuther-Moschner *et al.* (2004), it has been shown that a number of strains of lactobacilli and bifidobacteria (although not *Streptococcus thermophilus*), prevent DMH-induced DNA damage in the colon mucosa of rats (Pool-Zobel *et al.* 1996). Thus, it is possible to make an association between an event such as prevention of DNA damage in the colon and suppression of tumour incidence. There is also a mechanistic link between the two, since damage and mutation in oncogenes and tumour suppresser genes is known to be a critical factor in the initiation and development of colorectal cancer (Vogelstein *et al.* 1988).

Given the strength of the animal data, it is important to undertake well-controlled intervention trials in human subjects, which, unlike epidemiological studies, can provide evidence of causal relationships between nutritional factors and a disease. However, for carcinogenesis this is extremely difficult. For such trials, cancer is an impractical endpoint in terms of numbers of subjects, cost, study duration and ethical considerations, although there have been dietary interventions using recurrence of colonic adenomas as an endpoint (for review, see Gill & Rowland, 2002). The long lag-phase (10–30 years) between exposure to carcinogenic stimuli and appearance of tumours is a particular problem. The alternative strategy is to use early or

intermediate biomarkers of cancer: these may be biochemical, molecular, cellular or based on pathological changes, such as increased cell proliferation (Rafter *et al.* 2004). Many of these markers require invasive interventions (biopsies of the rectal or colon mucosal), which limits their usefulness, so the idea of non-invasive methodologies utilizing faecal samples is attractive (if indeed such a term could be used to describe faeces). Rafter *et al.* (1987) first proposed that the supernatant fraction formed after centrifugation of faeces (faecal water) would be a source of potential bioactive compounds involved in the aetiology of colon cancer and demonstrated cytotoxic activity in the samples. This concept has been further developed (Venturi *et al.* 1997; Glinghammar *et al.* 1997; Rieger *et al.* 1999) to encompass measurements of genotoxicity, which, as mentioned earlier, has great relevance to the whole process of carcinogenesis (Vogelstein *et al.* 1988).

Although further work is needed to validate faecal water genotoxicity as a biomarker for cancer risk, the current study by Oberreuther-Moschner *et al.* (2004) has clearly demonstrated that consumption by healthy volunteers of a large pot of yoghurt (300 g/d) containing probiotic strains can modify the genotoxicity of faecal samples, in comparison with a non-probiotic yoghurt, thus providing direct evidence suggesting probiotic consumption may have a beneficial influence on events related to colon cancer in human subjects. The study has also demonstrated the practicalities of using the marker in dietary interventions with relatively small numbers of subjects.

Despite the very encouraging results from current studies, there are some big gaps in our knowledge, the prime one being the mechanisms involved in anticancer effects of probiotics. Changes in gut bacterial enzymes that generate carcinogens and tumour promoters such as NH_3 and secondary bile acids, stimulation of immune surveillance, suppression of inflammatory processes, binding of carcinogens in the gut, are just some of the suggestions, which have varying levels of scientific support (Burns & Rowland, 2000). Without well-defined mechanisms, it is difficult to develop more effective, targeted probiotics that can be evaluated for activity in human intervention trials.

Ian Rowland

Northern Ireland Centre for Food and Health
School of Biomedical Sciences

University of Ulster
Coleraine BT52 1SA

UK

i.rowland@ulster.ac.uk

References

- Bingham SA (2000) Diet and colorectal cancer prevention. *Biochem Soc Trans* **28**, 12–16.
- Boutron MC, Faivre J, Marteau P, Couillaud C, Senesse P & Quipourt V (1996) Calcium, phosphorous, vitamin D, dairy products and colorectal carcinogenesis: a French case-control study. *Br J Cancer* **74**, 145–151.
- Burns AJ & Rowland IR (2000) Anti-carcinogenicity of probiotics and prebiotics. *Curr Issues Intest Microbiol* **1**, 13–24.
- Gill C & Rowland IR (2003) Cancer. In *Functional Dairy Products*, [T Mattila Sandholm and M Saarela, editors]. pp. 19–53. Boca Raton, FL: CRC Press.
- Gill CIR & Rowland IR (2002) Diet and cancer: assessing the risk. *Br J Nutr* **88**, Suppl. 1, S73–S87.
- Glinghammar B, Venturi M, Rowland IR & Rafter JJ (1997) Shift from a dairy product-rich to a dairy product-free diet: influence on cytotoxicity and genotoxicity of fecal water—potential risk factors for colon cancer. *Am J Clin Nutr* **66**, 1277–1282.
- International Agency for Research on Cancer (2000) GLOBOCAN 2000: Cancer Incidence, Mortality and Prevalence Worldwide. Lyon: IARC.
- Kampman E, Giovannucci E, van't Veer P, Rimm E, Stampfer MJ, Colditz GA, Kok FJ & Willett WC (1994b) Calcium, vitamin D, dairy foods, and the occurrence of colorectal adenomas among men and women in two prospective studies. *Am J Epidemiol* **139**, 16–29.
- Kampman E, Goldbohm RA, van den Brandt PA & van't Veer P (1994c) Fermented dairy products, calcium, and colorectal cancer in The Netherlands Cohort Study. *Cancer Res* **54**, 3186–3190.
- Kampman E, van't Veer P, Hiddink GJ, van Aken Schneijder P, Kok FJ & Hermus RJ (1994a) Fermented dairy products, dietary calcium and colon cancer: a case-control study in The Netherlands. *Int J Cancer* **59**, 170–176.
- Kearney J, Giovannucci E, Rimm EB, Ascherio A, Stampfer MJ, Colditz GA, Wing A, Kulkarni N & Reddy BS (1994) Inhibitory effect of *Bifidobacterium longum* cultures on the azoxymethane induced aberrant crypt foci formation and faecal bacterial β -glucuronidase. *Proc Soc Exp Biol Med* **207**, 278–283.
- McIntosh GH, Royle PJ & Playne MJ (1999) A probiotic strain of *L. acidophilus* reduces DMH-induced large intestinal tumors in male Sprague Dawley rats. *Nutr Cancer* **35**, 153–159.
- Oberreuther-Moschner DL, Jahreis G, Rechkemmer G & Pool-Zobel BL (2004) Dietary intervention with the probiotics *Lactobacillus acidophilus* 145 and *Bifidobacterium longum* 913 modulates the potential of human faecal water to induce damage in HT29clone19A cells. *Br J Nutr* **91**, 925–932.
- Peters RK, Pike MC, Garabrant DH & Mack TM (1992) Diet and colon cancer in Los Angeles County, California. *Cancer Causes Controls* **3**, 457–473.
- Pool-Zobel BL, Neudecker C, Domizlaff I, Ji S, Schillinger U, Rumney C, Moretti M, Vilarini I, Scasellati-Sforzolini R & Rowland IR (1996) Lactobacillus and Bifidobacterium mediated antigenotoxicity in the colon of rats. *Nutr Cancer* **26**, 365–380.
- Rafter J, Govers M, Martel P, Pannemans D, Pool-Zobel B, Rechkemmer G, Rowland I, Tuijtelars S & van Loo J (2004) PASSCLAIM- Diet-related cancer. *Eur J Nutr* (In the Press).
- Rafter JJ, Child P, Anderson AM, Alder R, Eng V & Bruce WR (1987) Cellular toxicity of fecal water depends on diet. *Am J Clin Nutr* **45**, 559–563.
- Reddy BS & Rivenson A (1993) Inhibitory effect of *Bifidobacterium longum* on colon, mammary, and liver carcinogenesis induced by 2-amino-3-methylimidazo[4,5-f]quinoline, a food mutagen. *Cancer Res* **53**, 3914–3918.
- Rowland IR, Rumney CJ, Coutts JT & Lievens LC (1998) Effect of *Bifidobacterium longum* and inulin on gut bacterial metabolism and carcinogen-induced aberrant crypt foci in rats. *Carcinogenesis* **19**, 281–285.
- Rieger MA, Parlesak A, Pool-Zobel BL, Rechkemmer G & Bode C (1999) A diet high in fat and meat but low in dietary fibre increases the genotoxic potential of 'faecal water'. *Carcinogenesis* **20**, 2311–2316.

- Salminen S, Bouley C, Boutron-Ruault MC, Cummings JH, Franck A, Gibson GR, Isolauri E, Moreau MC, Roberfroid M & Rowland I (1998) Functional food science and gastrointestinal physiology and function. *Br J Nutr* **80**, Suppl. 1, S147–S171.
- Venturi M, Hambly RJ, Glinghammar B, Rafter JJ & Rowland IR (1997) Genotoxic activity in human faecal water and the role of bile acids: a study using the alkaline comet assay. *Carcinogenesis* **18**, 2353–2354.
- Vogelstein B, Fearon ER, Hamilton SR, Kern SE, Preisinger AC, Leppert M, Nakamura Y, White R, Smits AM & Bos JL (1988) Genetic alterations during colorectal-tumor development. *New Engl J Med* **319**, 525–532.
- World Cancer Research Fund (1997) Diet, Nutrition and the Prevention of Cancer: A Global Perspective. Washington, DC: WCRF/American Institute for Cancer Research.
- Young TB & Wolf DA (1988) Case-control study of proximal and distal colon cancer and diet in Wisconsin. *Int J Cancer* **42**, 167–175.