Diet and colorectal cancer prevention

S. A. Bingham

Medical Research Council, Dunn Human Nutrition Unit, MRC Welcome Trust Building, Cambridge CB2 2XY, U.K.

Abstract

The majority of cancers are sporadic and epidemiological estimates suggest that up to 80% of colorectal cancer is attributable to diet. Epidemiologically, cross-sectional comparisons, case-control studies and trends in food intake 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

Key words: ammonia, meat, N-nitroso compounds.

Abbreviations used: NSP, non-starch polysaccharides; SCFA, short-chain fatty acids; NOC, N-nitroso compound.

Received 6 August 1999
support these findings although estimates of relative risk are not high. Existing prospective studies have however used crude indices of diet subject to substantial measurement error, and interactions with genetic polymorphisms in, for example, phase-I and -II enzymes have been studied only rarely. The association between meat consumption and colorectal cancer is usually attributed to the formation of heterocyclic amines in meat when it is cooked. In addition, in humans high-meat diets increase the level of nitrosatable material entering the colon so that faecal N-nitroso compounds (NOCs) increase in a dose-responsive manner following endogenous synthesis in the colon. Some of the mutations and guanine adducts accumulated during colorectal cancer progression are characteristic of alkylative damage, which would be compatible with NOC exposure. To date, NSP, resistant starch and vegetables have not reduced faecal NOC levels.

Introduction

Up to 80% of bowel cancers in Western populations are currently attributed to diet, so potentially this is a preventable disease [1]. However, the extent to which diet is capable of causing somatic alterations in genes known to be involved in the causation of bowel cancer, or is able to prevent or mitigate these alterations, is an emerging area of research. For the time being, evidence linking diet with colorectal cancer is limited to epidemiological associations with support from experimental studies and plausible hypotheses. A major problem in epidemiological studies of large-bowel cancer is the absence of an easily accessible intermediate risk marker, known to alter in response to diet, that can be used to link dietary intake and the presence of the disease in either intervention or prospective studies. Information being collected from all participants in the European Prospective Investigation of Cancer (EPIC) includes not only estimates of diet but also the collection of biological specimens which will be used to link diet and cancer registrations with intermediate markers of risk such as hormonal status, DNA adducts, biomarkers of diet and genotypic risk factors [2].

Epidemiology of diet and colorectal cancer

Armstrong and Doll attributed much of the international variation in large-bowel cancer incidence between countries to dietary differences, especially meat and fat consumption [3]. Results of cohort studies set up several years ago are now beginning to appear in the literature, but the need for accuracy in dietary assessment has only recently been recognized, hence very crude assessments of dietary intake, mainly based on short lists of food, food-frequency questionnaires, were used in most of these. These assessments would have been associated with a substantial degree of measurement error, not amenable to correction [4]. For example, if meat is associated with increased risk, lower rates for cancer would be expected in vegetarians. In a recent meta analysis of five cohorts, meat eaters were not at greater risk than non-meat eaters, although the standardized mortality ratios for all cohorts were low, and the amount of meat consumed by meat eaters was unable to be established [5]. Nevertheless, two recent analyses of the literature have concluded on the basis of available evidence that there is moderately consistent evidence that diets with less red meat are associated with reduced risk of colorectal cancer [6] and that red meat probably increases risk [7]. These reports have also concluded that higher intakes of non-starch polysaccharides (NSP; dietary fibre) and vegetables would reduce the risk of colorectal cancer [6,7].

Starch, NSP and fermentation

Carbohydrate, mainly as NSP and starch resisting digestion, entering the large bowel stimulates anaerobic fermentation, leading to the production of short-chain fatty acids (SCFA), acetate, propionate, butyrate, gas and an increase in microbial cell mass. The SCFA are absorbed by the intestinal mucosa where they stimulate sodium absorption and bicarbonate production. The stimulation of bacterial growth, together with water binding to residual unfermented NSP, leads to an increase in stool weight, dilution of colonic contents and faster transit time through the large gut [8]. There is a strong inverse association between high stool weight and colorectal cancer incidence [9]. Low stool weight leads to constipation, which together with use of cathartics are risk factors for colorectal cancer [10,11]. The association between low stool weight and bowel disease including cancer is the basis of recommendations for an 18-g population average intake of NSP, a 50% increase for the U.K. and most Western populations [6,7].

During fermentation, approximately 60, 20 and 20% molar ratios of acetate, propionate and butyrate respectively are formed in the large gut [8]. Butyrate was suggested as a protective agent in
colon cancer in 1981 [12]. In cultured cell lines, it is a well-recognized anti-proliferative agent, arresting cell growth in G1, inducing differentiation, inhibiting histone deacetylase and stimulating apoptosis [13,14]. In vivo, the effect of butyrate on proliferation is less clear since it is a primary fuel for the colonocyte and replacement of butyrate may result in increased proliferation [15]. Rodent studies have shown that luminal butyrate levels are inversely associated with colonic cell proliferation, and positively associated with histone acetylation [16]. However, studies using direct-acting carcinogens in rodents have not shown a protective effect against carcino genesis of large amounts of butyrate added to drinking water or food [17,18], and there are conflicting reports in animals fed starch from which increased levels of butyrate are presumed to arise [19–21].

Fermentation may be important in prevention of colorectal cancer via other effects as well [8]. The production of SCFA reduces luminal pH, and bacterial \( \alpha \)-dehydroxylase activity, and hence conversion of primary to the secondary bile acids deoxycholic and lithocholic acids is inhibited [22]. Production of phosphatidylincholine diacylglycerol, one of two intracellular messengers formed from phosphatidyl inositol, is enhanced in human fermentation systems by the presence of deoxycholic acid [23]. Diacylglycerol increases the affinity of protein kinase C for calcium and renders it active at physiological levels of this ion, phosphorylating serine and threonine residues in many target organs. Phorbol esters are well-known promoters because they resemble diacylglycerol but are not degraded. Increased levels of protein kinase C have been reported in colonic tumour tissue [24]. Total faecal diacylglycerol levels have been shown to be reduced by a 15-g supplement of wheat bran in women [25].

**Meat and nitrogen metabolism in the colon**

The association between meat consumption and colorectal cancer is usually attributed to the formation of heterocyclic amines in meat when it is cooked. In rodents, heterocyclic amines are carcinogenic in a wide variety of organs, mainly liver but including skin, lung, colon and mammary gland. One, PhIP [2-amino-1-methyl-6-phenylimidazo(4,5-b)pyridine] has attracted particular attention because it tends to be the most abundant, and colon tumours that are produced in rats from it have a high frequency of microsatellite instability that is similar to that seen in human inherited and sporadic colorectal cancers [26]. Furthermore, G/C base-pair mutations are produced in cell lines, which are similar to those produced in APC gene mutations of colon tumours in rodents [27]. Present estimates of risk from these compounds are however rather low when extrapolated from animal carcinogenicity data, for example 0.25% of all colon cancers [28]. However, as judged by species differences in adduct formation to these compounds, the human colon may be more susceptible to the effects of these compounds than the colon of rodents [29].

Meat also alters nitrogen metabolism and enhances the production of endogenous promoters and possible carcinogens, such as N-nitroso compounds (NOCs), within the colon. The amount of nitrogen entering the large bowel, mainly in the form of protein, peptides and amino acids, can be increased by increasing protein intake [31]. There are many different types of proteolytic bacteria found in the large gut which, depending on pH and substrate availability, may respond to active carbohydrate fermentation in the right colon, or to protein released from bacterial cell lysis in the left colon when readily fermented carbohydrates, such as pectin, are exhausted. Some versatile bacteria deaminate to form ammonia, SCFA and a variety of other products including phenols and branched-chain fatty acids [8].

In humans, the increase in nitrogen entering the colon as a result of consuming high-meat diets increases faecal ammonia concentration. Ammonia is a promoter of carcinogenesis in rodent models [32,33] and patients with urostomies who have very high luminal ammonia concentrations have a greatly increased risk of developing tumours distal to the site of ureteric implantation [34].

NOCs are also found in the colon and are formed endogenously because the amines and amides produced primarily by bacterial decarboxylation of amino acids can be N-nitrosated in the presence of a nitrosating agent, such as NO, from stimulated macrophages in the large-bowel mucosa, together with nitrite produced from reduced nitrate diffusing into the gut. Chemical N-nitrosation may occur under neutral or alkaline conditions (as in the small and large intestine). In the anaerobic large bowel, nitrate, entering the body partly in food and water, is reduced to nitrite in the colon during dissimilatory nitrate metabolism by the colonic flora [8]. Supplements of nitrate have therefore been shown to elevate faecal NOC levels [35]. A number of facultative and anaerobic colonic
bacteria are able to catalyse the formation of NOCs at an optimum pH of 7.5 [36].

In humans, increased intake of red meat induced a significant (P < 0.024) 3-fold increase from 40 ± 7 (± S.E.) to an average of 113 ± 25 μg per day of NOCs, mainly as acidic and basic nitrosamines [37]. Subsequent studies have confirmed this effect of red meat, and shown that there is a dose response to 0, 60, 240 and 420 g of meat per day [38,39]. Contrary to expectation that NOCs would also be reduced when high-red-meat diets are supplemented with 20 g f phytate-free wheat bran in six volunteers, there was no reduction in NOC levels. However, faecal weight increased and hence the contents of the lumens were diluted. Transit time is inversely related to faecal weight. The net result would have been less contact between the NOCs arising from a high-red-meat diet and the colonic mucosa with the high-bran diet [37]. Later studies have also shown no reduction with resistant starch on faecal NOC levels, nor with vegetables, but similar effects on faecal weight, transit time and hence contact of NOC with the large-bowel mucosa [38,40].

Conclusion

Despite interesting possibilities, a direct link between the epidemiology of most dietary factors, intermediate risk markers and the end points of cancer in humans has yet to be established. The study of diet in relation to different genotypes at risk for cancer is likely to emerge as a key area, perhaps explaining low estimates of relative risk within populations despite strong relationships internationally between dietary habits such as high meat consumption and the occurrence of this disease. A direct relation between dietary habits and DNA damage relevant to current models of colorectal cancer has yet to emerge. For example, the ras mutations most commonly involved in colon cancer are G→A transitions at the second G of a GG pair at codon 12 or 13 of K-ras and these are characteristic of alkylating agents such as NOCs [41]. One preliminary study has shown an increase in relative risks for mutations in the K-ras gene and meat consumption in colon-cancer cases [42]. However, another study has shown no relation with meat, but a significant elevation in relative risks for animal and total protein to 1.5 (1.0–2.1) for codon-12 mutations only, and a reduction to 0.4 (0.2–1.0) (ranges shown are 95% C.I.) for codon-13 K-ras mutations [43]. It is likely that more studies of this type, linking somatic mutations, diet and cancer, will be published. Meanwhile, there are public-health recommendations to increase vegetable and NSP consumption in order to increase stool weight and thus decrease risk of large-bowel cancer and other large-bowel disorders [6,7]. The type, amount, processing, cooking and dose responses of meat or protein increasing risks of cancer are, however, uncertain.

References

1 Willett, W. C. (1995) Env. Health Perspect. 103 (suppl. 8), 165–170
This paper examines the biochemistry of the uptake and metabolic route of two groups of plant phenolic secondary metabolites which are synthesized by plants for defensive purposes. Many foods and beverages contain high levels of phenolic compounds. Certain phenolics in the diet are particularly bioactive and have pronounced effects on mammalian cells. These effects, together with epidemiological studies and animal models, have led to the hypothesis that dietary phenolics contribute to the health benefits of a diet rich in fruit and vegetables. The paper examines the biochemistry of the uptake and metabolic route of two groups of plant phenolics, the flavonoids and hydroxycinnamates.

**Introduction**

Flavonoids and cinnamates are widespread phenolic secondary metabolites which are synthesized by plants and play important structural roles in the plant cell wall, act as a defence against UV light, protect against pathogen ingress and are involved in repair of injury. Consequently, many foods and beverages contain high levels of phenolic compounds, which often provide colour, taste, astringency and other sensory characteristics. Most plants store phenolics attached to a hydrophilic moiety such as a sugar. This renders the phenolic less biologically active, more soluble and more easily handled by the plant. Certain phenolics in the diet are particularly bioactive and have pronounced effects on mammalian cells. These effects, together with epidemiological studies and animal models, have led to the hypothesis that dietary phenolics contribute to the health benefits of a diet rich in fruit and vegetables. This paper examines the human metabolic pathways of dietary flavonoids and cinnamates.