Plenary Lecture

Diet and cancer prevention: the Concerted Action Polyp Prevention (CAPP) Studies

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A presentation by a geneticist to The Nutrition Society is a little unusual. For that presentation to be focused on prevention of cancer by dietary means is liable to prompt the reader to check for an error in the title. Despite the apparent incongruity, there is a powerful argument for drawing together the two fields, especially in approaches to the management of colo-rectal cancer (CRC), a disorder which is usually environmental and always genetic.

CRC is the commonest cause of cancer death in non-smokers. It shows marked variation in prevalence, being very common in Western societies and rare among rural populations in underdeveloped countries (Burkitt, 1969). Strategies which explore approaches to prevention are needed since survival after development of a symptomatic cancer remains poor. A dietary contribution is accepted but the mechanisms which are unclear. There is a strong inverse correlation between CRC incidence and ingestion of starch (Cassidy et al. 1994). This correlation is illustrated in Fig. 1 which shows CRC incidence with starch intake in different countries.

There is strong epidemiological evidence in favour of non-steroidal anti-inflammatory drugs (NSAID) being protective against CRC which is summarized in Fig. 2 (Burn et al. 1995). All studies to date have pointed to a relative risk of CRC in regular users of NSAID of approximately 0.5. The one exceptional study involved a group with a mean age of 73 years (Paganini-Hill et al. 1989; Fig. 2).

Resistant starch

This term is used to describe any starch which is not digested in the upper gastrointestinal tract (Bingham, 1988). Some is inaccessible in seeds, for example, while some is in a crystalline form which makes it resistant to pancreatic amylase (EC 3.2.1.1). Early claims for the benefit of fibre (Burkitt, 1969) confused fermentable carbohydrate, or resistant starch (RS), with NSP ('true fibre'). Starches which reach the colon undigested are fermented by bacteria to short-chain fatty acids. Of these, butyrate in particular appears to have a beneficial anti-neoplastic effect. The literature supporting a major beneficial role for RS and butyrate continues to grow. Butyrate has a protective effect in the rat model (McIntyre et al. 1993) while in human subjects, RS has been shown to reduce mucosal proliferation, the level of secondary bile acids and the mutagenicity of faecal water (van Munster et al. 1994). In transformed cells terminal differentiation is induced, resulting in programmed cell death or apoptosis (Hague et al. 1993).

An hypothesis for the molecular mechanism of action of butyrate has been proposed by Kruh et al. (1994) who suggest that butyrate acts at two levels. The initial effect is to inhibit histone deacetylase, resulting in hyperacetylation of histones and increased accessibility of DNA to factors controlling gene expression. Second, butyrate, directly or indirectly, alters the binding of regulatory transacting proteins to specific DNA sequences which control the expression of the gene.

In vitro, butyrate reduces upper crypt cell proliferation when the latter is induced by the co-carcinogenic secondary bile acid deoxycholate (Scheppach, 1994). Butyrate may also influence tumourigenesis at a much later stage by inhibiting colonocyte secretions of urokinase (EC 3.4.21.31), which appears to be involved in control of cell migrations and invasiveness (Kruh et al. 1994).

At the epidemiological level, as illustrated in Fig. 1, the correlation between the starch content of population diets and their colon cancer incidence is striking. The negative correlation for starch intake v. cancer rates was 0.76 and was the most highly correlated of all food components. A major attraction of RS is that it is indistinguishable from

Abbreviations: CAPP, Concerted Action Polyp Prevention; CRC, colo-rectal cancer; FAP, familial adenomatous polypl; HNPCC, hereditary non-polyposis colon cancer; NSAID, non-steroidal anti-inflammatory drugs; RS, resistant starch.

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of colonic carcinoma in the dimethylhydrazine rat animal model (Davis & Patterson, 1994). Oshima et al. (1996) have recently shown that the polymorphic variant COX2, prevalent in the colonic mucosa, plays an early role in adenoma development in the Apc716 knockout mouse, reinforcing the biological case for the hypothesis that aspirin will suppress adenoma development. Aspirin is produced by acetylation of salicylate, a naturally occurring anti-inflammatory found originally in willow (Salix alba) bark (Leutwyler, 1994). Salicylate is an important mediator of plant resistance (Delaney et al., 1994), and is present in substantial amounts in a wide range of green vegetables. Salicylate assists in plant resistance by induction of apoptosis at the site of infection. Given the relationship between salicylate levels and plant infection, it is likely that the modern Western diet will have relatively little salicylate as a result of modern farming methods which aim to minimize plant infection. Ingestion of currently available green vegetables does not elevate salicylate blood levels (Janssen et al., 1996).

Salicylate induces apoptosis in colo-rectal tumour cell lines (Elder et al., 1996). Sulindac is an NSAID metabolized to a more active form in the gut and has been shown to cause adenoma regression in controlled studies with patients with familial adenomatous polyposis (FAP; Giardiello, 1994; Debinski et al., 1995). In vitro studies have shown that this agent also inhibits cell growth by the induction of apoptosis (Piazza et al., 1995; Shiff et al., 1996). This effect is not considered to occur via inhibition of prostaglandin synthesis (Boolbol et al., 1996).

**Study populations with a genetic predisposition to colon cancer**

Genetic predisposing factors for CRC are thought to account for up to 10% of population variance (Stephenson et al., 1991). Two dominantly inherited single gene conditions, FAP and hereditary non-polyposis colon cancer (HNPPC), confer a particularly high risk. FAP accounts for about 1% of CRC (Burn et al., 1994) and results from a defect in the APC gene. This gene acts as the ‘gatekeeper’ of the adenoma–carcinoma sequence. In 1993–4, a series of reports demonstrated mutations in a group of genes responsible for DNA mismatch repair in families with NHPCC (Kolodner et al., 1994). This phenotype, also known as Lynch syndrome, is characterized by a high risk of colon cancer, up to 80% lifetime risk in most studies. Discovery of the gene defects has confirmed that these often large families have a distinct genetic predisposition and that it is now possible and desirable to identify ‘at risk’ individuals in order to ensure they are offered regular colonoscopy.

Genetic predictive testing of a growing number of families with HNPPC, has provided a motivated population with which to test dietary and pharmaceutical interventions. This approach allows shorter duration and fewer participants in intervention trials, as neoplasia is more likely to develop in a short time span. Costs are reduced because high quality endoscopic surveillance is provided as part of standard clinical care. As well as providing valuable

![Graph showing relationship between starch intake and colon cancer incidence](image)

**Fig. 1.** Starch intake and colo-rectal cancer incidence in different countries. r = 0.76. (From Cassidy et al. 1994.)

![Graph showing relative risk of colo-rectal cancer in regular non-steroidal anti-inflammatory drug users](image)

**Fig. 2.** Relative risk of colo-rectal cancer in regular non-steroidal anti-inflammatory drug users. Values are means and standard deviations represented by horizontal bars. (Modified from Burn et al. 1995.)

 normally digestible wheat starch and can be mixed with a variety of other foods, e.g. yoghurts, stews, cereals.

**Aspirin**

As well as the accumulating epidemiological evidence (Fig. 2) for a protective effect of aspirin in CRC, there is also support from animal studies. Aspirin reduces the incidence
information for the management of these high risk families, it is also likely that such trials will produce data which can be extrapolated for use in preventative strategies for the general population. The original trial involving FAP gene carriers was initiated in 1993 with funding from the Biomed programme as Concerted Action Polyposis Prevention (CAPP; Burn et al. 1995). This study, now renamed CAPP1 is likely to reach a conclusion in 1999.

CAPP2 will randomize carriers of HNPCC to 600 mg enteric coated aspirin or placebo and 30 g treatment starch or placebo. The treatment starch to be used for CAPP2 will be a proprietary maize starch. The control will be fully-digestible wheat starch. Each will be mixed with p-aminobenzoic acid, the same compliance marker as that used in CAPP1. Subjects will be carriers of a mismatch repair defect. The diagnosis will depend on the presence of a relevant cancer (colon, uterus, stomach etc.), or dysplastic polyps in a known HNPCC family, or demonstration of a pathological mutation in one of the mismatch repair genes associated with the syndrome.

The primary endpoint for CAPP2 will be the number, size and histological stage of CRC found after 2 years on treatment or placebo. There is a 42% lifetime risk of uterine cancers in female carriers (Dunlop et al. 1997). Details of all extracolonic disease will be recorded. Based on the Finnish observations (Järvinen et al. 1995), during the period of the study, 10% of gene carriers will develop colonic neoplasia. In order to have a 90% probability of being able to demonstrate a reduction to 50%, we would require 606 in each limb, or 1212 in total, using a factorial design.

Conclusion

CRC, the second biggest cause of cancer death, is intimately related to diet but is the result of a series of genetic changes in one or more cells in the colonic wall. In up to 15% of cases, one of the genetic steps is present in the germline, making progression to cancer more predictable and usually at an earlier age than usual. Those at high genetic risk provide an ideal basis for intervention studies to evaluate chemo-prevention and dietary preventative measures. This concept forms the basis of the CAPP studies. CAPP1 is testing aspirin and starch in carriers of FAP before the surgical resection of their colons as a preventive measure. CAPP2 will apply the same interventions to a target population of 1200 carriers of mismatch repair gene defects who are at risk of HNPCC.

It is 30 years since Burkitt’s (1969) famous observation on the role of diet in colon cancer and just over 200 years since William Stone rediscovered the anti-inflammatory effects of willow bark. Both made mistakes in the interpretation of their findings, but they deserve our appreciation nevertheless for the value of their acute powers of observation. There is a certain symmetry in the use of the most sophisticated scientific techniques to establish, with industrial support, that the solution to the second biggest cause of cancer death may lie in learning how to make our food ‘old fashioned’. In addition to making our starch less digestible, we may need to simulate the infections which used to fill our food with salicylate. In his original letter to the Royal Society, William Stone may have touched the essence of the medicinal value of aspirin when he noted that ‘few vegetables are equal in every place’. In our quest for healthy plants, we may argue that we have robbed our diet of an essential nutrient, salicylate.

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References


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