Wheat bran and cancer: The role of dietary fibre

Lynnette R Ferguson[1] DPhil (Oxon) and Philip J Harris[2] PhD (Cantab)

[1]Auckland Cancer Society Research Centre, University of Auckland Faculty of Medicine and Health Science, Auckland, New Zealand and [2]School of Biological Sciences, University of Auckland, Auckland, New Zealand

Wheat bran is known to protect against colorectal cancer. However, although it is a rich source of dietary fibres (plant cell walls), these make up less than 50% of its dry weight. Thus, it is not known whether the dietary fibres or components in the cell contents protect against cancer. Some of these components in the cell contents are known to have anticancer activity and include phytic acid and various phenolics (phenolic acids, lignans and flavonoids). Possible mechanisms of protection by dietary fibres and components in the cell contents are discussed. A major goal of future research on wheat bran should be to determine the role that dietary fibre plays in cancer prevention.

Key words: cancer prevention, dietary fibre, phenolic components, phytic acid, plant cell walls, wheat bran.

Introduction

The fibre hypothesis was first proposed by Burkitt as a consequence of his finding of low rates of colon cancer in regions of Africa which have diets with a high cereal content and hence a high content of dietary fibre (DF).[1] The value of a diet with a high content of DF was also indicated by some subsequent case control studies of colorectal cancer. However, the European Society of Cancer Prevention 'Consensus meeting on cereals, fibre and colorectal and breast cancers' concluded that cereals themselves rather than the DF *per se* may be very important.[2] The epidemiological literature concerning the protective effects of cereals and DF against cancer was re-examined by Hill who also concluded that there was no doubt that cereals were protective, but that there could be dispute over the strength of the protection given by DF.[3] A further analysis of data from Europe, North America and Australasia showed that among various foods rich in DF, cereals were strongly protective, as were vegetables other than starchy root vegetables, whereas fruits appeared neutral.[4] However, in addition to DF, whole grain cereals are known to contain a number of potential anticancer compounds including various phenolics, vitamin E, selenium and phytic acid.[5,6] Most of the DF of cereals as well as these other compounds occur in the outer cell layers of the grain.

To a plant scientist, these outer cell layers of cereals are known as the bran layers and comprise the aleurone, pericarp and seed coat (Fig. 1). These bran layers make up approximately 14% of wheat grains and are separated from the starchy endosperm and embryo during roller milling. However, during roller milling the separation of the bran layers from the starchy endosperm is never complete, and some starchy endosperm is usually left adhering to the bran layers. Thus, wheat bran as bought from the supermarket contains variable amounts of starchy endosperm in addition to the bran layers. Usually the DF content of wheat bran is less than 50%. Nevertheless, wheat bran is a rich source of DF, is palatable and is readily incorporated into the diet.

In intervention studies, wheat bran has been shown to protect against early markers of human colon cancer.[7,8] In animal models, it has also been shown to protect against breast cancer.[9] However, the protective effects of wheat bran have often been assumed to be solely due to the DF despite the presence of other potential anticancer compounds. Indeed, it is unfortunate that the terms wheat bran and 'wheat dietary fibre' or 'wheat fibre' have been used interchangeably in many studies.[10,11]

Definition and composition of wheat bran dietary fibre

Early studies to try to confirm the fibre hypothesis were impeded by a lack of agreement on the definition of DF and also by the lack of good analytical methods for its quantification. We have defined DF as 'consisting of the walls around plant cells as well as components obtained from these walls. The term may also include non-starch polysaccharides from sources other than plant cell walls'.[12] We included in this definition components obtained from cell walls and non-starch polysaccharides from sources other than plant cell walls because these are used as food additives. Nevertheless, more than 95% of the DF in Western diets is from whole plant cell walls. These cell walls are highly organized, complex structures that can vary both in their composition and physical properties.

Cell walls cannot be regarded simply as mixtures of various components.[13] However, some recent definitions of DF, such as that of Kenji *et al.*, do not acknowledge that most DF occurs as whole plant cell walls and not simply as mixtures of components.[14] These authors used the following as their definition: 'Dietary fibre consists of plant cell wall polysaccharides and lignin, which are not hydrolysable by human digestive enzymes, and includes pectin, cellulose, and hemicellulose'. Further confusion is caused by the common use in

Correspondence address: Dr LR Ferguson, Auckland Cancer Society Research Centre, University of Auckland Faculty of Medicine and Health Science, Private Bag 92019, Auckland, New Zealand.
Tel: 64 9 373 7599 (ext. 6372); Fax: 64) 9 373 7502
Email: l.ferguson@auckland.ac.nz

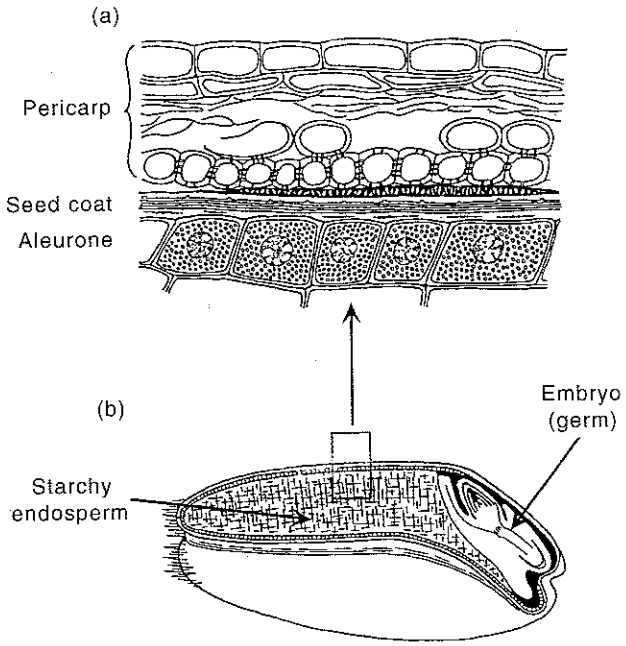

Figure 1. (a) Longitudinal section of the bran layers of a wheat grain showing the different cell types. (b) Longitudinal section through a wheat grain; the rectangle indicates the location of the section shown in 1(a). This figure was modified from K Esau with permission.[73]

epidemiological studies of the term 'fibre type' to refer to plant cell-wall components or fractions. Viewed from the perspective of plant science, the term 'fibre type' is better used to refer only to the different types of plant cell walls in the diet.

Wheat bran contains several different cell types with different wall compositions. In addition to polysaccharides, the walls of the outer cell layers (many of the pericarp cells and the seed coat) contain the complex polyphenolic polymer, lignin (Fig. 2).[15,16] The cell walls of the seed coat also contain cutin, a three-dimensional polyester with similar properties to lignin.[15] In contrast to these pericarp and seed-coat cell walls, the aleurone cell walls contain neither lignin nor cutin. They contain instead a high proportion of the polysaccharide arabinoxylan, which has ferulic acid attached to it by ester links.[16–18]

A variety of methods are used to quantify DF, none of which measure exactly the cell-wall content of a food. The two most commonly used are the Englyst method[19] and the AOAC (Association of Official Analytical Chemists) method of Prosky *et al.*[20] In the Englyst method, DF is measured as non-starch polysaccharides by summing the constituent monosaccharides of these polysaccharides. However, polysaccharides are not the only components of plant cell walls and this method does not include lignin or cutin in the DF value. In the AOAC method, the DF value does include lignin and cutin as well as cell-wall polysaccharides, but the value also includes some resistant starch as well as Maillard browning products.[13] As would be expected, the AOAC method gives higher DF values than the Englyst method. In a comparative study of the two methods in which 12 foods were analysed, the AOAC values were on average 19% higher than the Englyst values.[21]

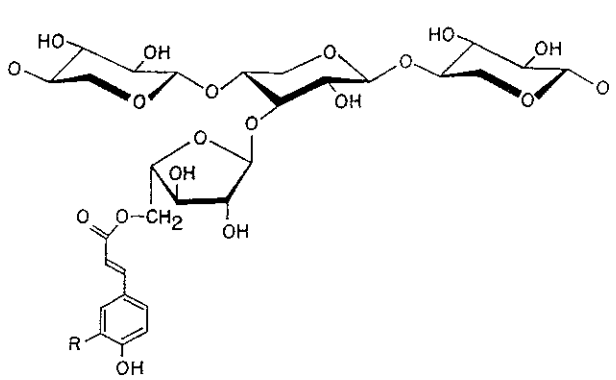

Figure 2. Portion of an arabinoxylan from aleurone cell walls in wheat bran. Ferulic/*p*-coumaric acid is ester-linked to the arabinose residue (R = H = *p*-coumaric acid; R = OCH3 = ferulic acid).

Soluble and insoluble dietary fibre

In addition to determining the total DF content of a food, both methods have adaptations for determining soluble and insoluble DF depending on the solubility of the DF in water or buffer solutions. However, the conditions used to solubilize the soluble DF are very different from the conditions in the gastrointestinal tract.[22,23] Indeed, Monro found that a much smaller proportion of total DF was solubilized *in vivo* in rats than was solubilized in the Englyst method.[23]

Although soluble DF, for example pectic polysaccharides extracted from plant cell walls, are degraded quickly and extensively by colonic bacterial enzymes, simply because a DF is soluble does not mean that it will be degraded.[12] Also, some insoluble DF, such as lignified cell walls, are not degraded by colonic bacterial enzymes; however, this is not true of all insoluble DF. For example, 87% of the DF in wheat bran was insoluble when analysed by the Englyst method.[21] However, only 64% of the wheat bran DF remained undegraded by bacterial enzymes in both rat and human large intestines.[24,25] The pericarp cell walls of wheat bran are lignified and the presence of this lignin protects the cell-wall polysaccharides from degradation by colonic bacterial enzymes. In contrast, the aleurone cell walls are slowly and partially degraded by bacterial enzymes.[24–26] Although walls of aleurone cells are only partly degraded, they do not contain lignin but instead contain ferulic acid ester-linked to polysaccharides; some *p*-coumaric acid is also present in this form (Fig. 2). The degradation leads to the release of feruloylated oligosaccharides, which can then be further degraded to release ferulic acid.[27]

Cell contents of wheat bran

In addition to cell walls or DF, wheat bran contains cell-contents components. Analyses indicate that most of these can be accounted for as protein (mostly from the aleurone cells), starch (from the contaminating starchy endosperm), moisture and ash. In addition, a range of potential anticancer compounds occur in the cell contents. These include various phenolics, vitamin E, selenium and phytic acid.[5,6] Several of these have been independently implicated in cancer protection.

Although many of the phenolic components of wheat bran occur in the cell walls, some also occur in the cell contents. These include phenolic acids, flavonoids, and lignans.[28] Onyeneho and Hettiarachchy identified a number of free phenolic acids in an aqueous extract of durum wheat

bran.[29] The most abundant acid was ferulic, followed in order of abundance by vanillic, *p*-coumaric, protocatechuic, syringic, *p*-hydroxybenzoic, caffeic, and genitisic.

Flavonoids have structures based on a C15 nucleus and are usually grouped in classes (e.g. flavones). The flavone tricin as well as two glycosides of the flavone apigenin have been identified from wheat bran.[30–32] Wheat bran also contains small amounts of the flavanol catechin and proanthocyanidins (also known as condensed tannins) which are oligomers or polymers based on flavanol units.[33] The total flavonoid content of wheat bran varies according to wheat cultivar.

Plant lignans are phenolic dimers with a characteristic dibenzylbutane skeleton.[5,34,35]

Phytic acid is the hexaphosphate of *myo*-inositol. It occurs as a magnesium–calcium salt in the aleurone cells of wheat bran and may comprise approximately 4% of the bran.[36–38]

Wheat bran is an adequate source of vitamin E, β-carotene, and cancer protective minerals including iron, calcium and selenium.[39] It also appears to be a useful source of folic acid.

Mechanisms by which dietary fibres may protect against cancer

As summarized in Table 1, a number of mechanisms have been suggested for DF protection against cancer. Additionally, numerous reviews have appeared on this topic, such as Hill, Harris and Ferguson, Ferguson and Harris, Klurfeld, and Kritchevsky.[4,12,13,40,41]

Possible role of butyrate in cancer protection

Products resulting from DF polysaccharides being degraded by colonic bacterial enzymes are fermented to produce short chain fatty acids (predominantly acetic, propionic, and butyric), hydrogen, methane, carbon dioxide, and water. Numerous authors have suggested that the butyrate produced prevents the development of colon cancer. This forms the basis of the 'butyrate hypothesis' which is probably the most commonly cited mechanism for the protective action of DF. For example, Archer *et al.* claim that butyrate inhibits colon cancer cell growth by two mechanisms, one involving histone hyperacetylation and p21 induction and the other related to impaired epidermal growth factor-responsiveness.[42] Emenaker and Basson studied the effects of short chain fatty acids in inhibiting human (SW1116) colon cancer cell invasion.[43] They suggested that major effects of these were through reducing urokinase plasminogen activator activity, and by modulating amounts of degradative matrix metalloproteinases (MMP) and protective tissue inhibitor matrix metalloproteinases (TIMP). Palmer *et al.* commented on the modulation of p53 expression in cultured colonic adenoma cell lines by butyrate.[44]

Many of the effects of butyrate cited rely on changes in the expression of certain genes, as summarized by Smith *et al.*[45] However, recent research has revealed various activities of butyric acid on isolated cells, especially its ability to modify nuclear architecture and to induce death by apoptosis. It changes the structure of chromatin through its effects on post-translational modifications, especially acetylation and phosphorylation of the nuclear histones. Butyric acid can also modify the differentiation state of cells, overcoming the resistance of cancerous colonic cells to normal programmed cell death.

However, all these studies are at the cellular level, involving tissue culture cells. Smith *et al.* pointed out the difficulties of proving butyrate action *in vivo*, given that the synthesis and site of action of butyric acid are in close proximity.[45] If this mechanism is really important, it would be necessary to show that butyrate is produced in the right place and at the right time, is generated from DF and that this is the most important aspect of DF action. None of this evidence is available. Indeed, studies to show these links have generally been negative. For example, Zoran *et al.* used a series of DF sources with varying amounts of butyrate production and found that protection against colon cancer failed to correlate with butyrate production.[46] In a recent review, Klurfeld concluded:

> There is no reason to believe that a single lumenal or tissue factor will hold the key to understanding the causes of dietary fiber's effect on reducing the risk of colon cancer. In fact, the data suggest that multiple, interacting factors will be revealed... It is quite plausible that the combination of dietary fibre, or its metabolites, in conjunction with other phytochemicals may be necessary to realize inhibition of the tumorigenic process.[40]

Other mechanisms of cancer protection by DF

Dietary fibres may also act directly in a variety of ways to reduce the availability of dietary carcinogens to the colonic mucosa and hence protect against cancer. These ways include the reduction of transit time in the gastrointestinal tract, an increase in faecal bulk, and the adsorption of dietary carcinogens to the DF. Dietary fibre in wheat bran may act by all of these mechanisms.[11,12] In particular, the lignified pericarp cell walls of wheat bran are lignified and lignified cell walls are known to be good at adsorbing dietary carcinogens. These cell walls are known to be undegraded in the colon and hence the adsorbed carcinogens can be carried out of the body in the faeces.[12] To what extent these various mechanisms operate to protect against colorectal cancer is not clear. However, Corpet *et al.* showed that increasing faecal bulk, in the absence of DF or a source of DF, failed to protect against the development of an early marker of carcinogenesis.[47] Recent studies in this laboratory have examined the effects of a wheat bran diet on the absorption, metabolism and excretion of a radiolabelled heterocyclic amine in rats (LR Fergu-

Table 1. Some proposed mechanisms by which dietary fibres have been suggested to protect against cancer

Mechanisms
Modification of carcinogen absorption through:
Decreased transit time
Increased faecal bulk
Increased carcinogen binding
Other mechanisms including modulation of enzyme activity
Hormonal effects
Butyrate effects
Apoptosis
Gene expression
Signal transduction

son *et al.*, unpubl. data., 1998). The data cannot be explained by the simple hypotheses previously suggested.[12]

Another way wheat bran may protect against cancer is via the ferulic acid ester-linked to arabinoxylans in the aleurone cell walls (Fig. 2). Ferulic acid is a good antioxidant[48] and can inhibit carcinogenesis caused by the carcinogen 4-nitroquinoline-1-oxide in a rat tongue model.[49] Phenolic acids in general are known to inhibit carcinogenesis caused by various carcinogens (e.g. Wattenberg, Mori *et al.*, and Mandal and Stoner),[50–52] or to inhibit mutagenesis.[53] Ferulic, caffeic and chlorogenic acids are effective blockers of nitrosamine formation.[54,55] Other authors such as Tanaka *et al.*[49] have suggested that the primary action of phenolic acids in preventing cancer may be through their action as 'blocking compounds', preventing carcinogens from binding to critical targets.[50] It is possible that ferulic acid released from aleurone cell walls can protect against the development of colon cancer.

Possible role of cell content components in cancer protection

Phenolic acids in the cell contents may protect like ferulic acid released from the cell walls, as described above. However, the phenolic acids in the cell contents could be absorbed from the gastrointestinal tract in the stomach or small intestine.

Many of the flavonoids, including proanthocyanidins, have been shown to be powerful antioxidants.[56,57] In various animal models[58] and in some epidemiological studies,[59] a range of flavonoids have proved able to inhibit various stages of tumour development. Some flavonoids, especially flavones and flavonols, may induce and/or otherwise affect the activities of various phase I and phase II enzymes both *in vivo* and *in vitro*.[60,61] Such activities will influence the metabolic activation of a variety of exogenous carcinogens to DNA-reactive forms, as well as enhancing detoxification. For example, Uda *et al.* showed that various flavonoids induced quinone reductase enzymes in murine hepatoma cells,[61] whereas Canivenc-Lavier *et al.* showed that some flavones increased the activities mediated by cytochrome P450 1A1, 1A2, 2B1 and 2B2, as well as modulating the activities of *p*-nitrophenol UDP-glucuronyl transferase and glutathione transferase enzymes in rat livers.[60]

Plant lignans may be converted by fermentation in the large intestine to mammalian lignans which may protect against the development of some hormone-dependent cancers, including breast cancer, as well as other cancers.[62] The effects of lignans were studied in human volunteers by Adlercreutz *et al.*[63] They suggested that lignans affect uptake and metabolism of sex hormones by affecting regulation of the concentrations in plasma of globulin that binds sex hormones. They also suggested that lignans could inhibit cell proliferation by competing with estradiol for type II oestrogen binding sites, which may protect against the development of some hormone-dependent cancers, including breast cancer, as well as other cancers.[62]

The anticancer effects of phytic acid have also been extensively studied. For example, when compared with wheat bran supplementation, 0.4% phytic acid gave better protection against cancer induced by the mammary carcinogen 7,12-dimethylbenz[*a*]anthracene.[64] Phytic acid strongly chelates multivalent metal ions, especially zinc, calcium and iron. Probably because of this, it is a strong inhibitor of iron-mediated generation of the hydroxyl radical, a hazardous oxidant. Phytic acid thus acts as an antioxidant and reduces lipid peroxidation.[65,66] It may also be antineoplastic because of its action on signal transduction pathways, cell cycle regulatory genes, differentiation genes, oncogenes and perhaps tumour suppressor genes.[67] It is also known to affect the metabolic and detoxification capacity of the liver. For example, in mice it increased hepatic concentrations of glutathione S-transferase and cytochrome *P*-450.[68]

β-Carotene and the antioxidant vitamins C and E are well known as free radical trapping agents.[69] In addition, they have been found to contribute to immune stimulation, inhibition of nitrosamine formation, and enhancement of cell communication; they also influence metabolic activation of carcinogens. β-Carotene and vitamin E were found to protect against later stages of carcinogenesis better than wheat bran.[70] The B vitamin folic acid appears to have an influence on DNA methylation and thus on proto-oncogene expression.

Evidence from epidemiology for the role of dietary fibre in cancer protection

Epidemiological studies have shown that eating a diet rich in fruits, vegetables or cereals protects against colorectal cancer.[3,71] However, the question remains as to whether this protection is caused by the dietary fibre or by components in the contents of plant cells, or by a combination of both. Furthermore, as we have indicated above plant cell walls vary widely in their composition and physical properties and thus all types of plant cell walls (DF) are unlikely to be equally protective. For example, the predominant types of plant cell walls in fruits and vegetables have very different compositions and physical properties from those of wheat bran cell walls. Even within wheat bran, the cell walls of the periderm and the aleurone are quite different.

These problems of what components of a diet rich in food plants are protecting against cancer are thus complex and difficult to address experimentally. Nevertheless, we believe that the commonly used approach of simply quantifying DF and correlating this with cancer incidence does not distinguish between plant cell walls which have quite different compositions and physical properties and hence probably different protective properties. The situation is also not improved by quantifying cell-wall components in the diet and describing these as 'types of DF': for example by quantifying soluble and insoluble DF, cellulose, non-cellulosic polysaccharides etc. These are mostly simply indicators of the cell-wall content. However, a high content of soluble DF may indicate a diet rich in fruits and vegetables which mostly have parenchyma cells containing high proportions of pectic polysaccharides. Nevertheless, a high content of soluble DF could also arise from a diet rich in oat or barley grains with cell walls rich in (1→3,1→4)-β-glucans. Cell walls rich in pectic polysaccharides and cell walls rich in (1→3,1→4)-β-glucans may well have quite different effects in terms of cancer risk.

Evidence from human intervention studies for the role of dietary fibre in cancer protection

At least theoretically, human intervention studies should make it possible to determine whether DF or components of

the cell contents are responsible for the protective effect of wheat bran. This could be done by isolating DF from wheat bran and comparing its effects with those of unextracted wheat bran. Because there is currently no unequivocal proof in humans that DF protects against cancer, this would be an important study to do. However, to show statistically significant effects would require a more sensitive biomarker than the polyp assays currently being used in human populations.[7,8] The use of newer and more sensitive markers, such as the comet assay in blood lymphocytes (e.g. Pool Zobel et al.), may provide the necessary sensitivity for such studies.[72]

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References

1. Burkitt D. Related disease – related cause? Lancet 1969; 2: 1229–1231.
2. Anonymous. Consensus meeting on cereals, fibre and colorectal and breast cancers. ECP consensus panel on cereals and cancer. Eur J Cancer Prev 1997; 6: 512–514.
3. Hill MJ. Cereals, cereal fibre and colorectal cancer risk: a review of the epidemiological literature. Eur J Cancer Prev 1997; 6: 219–225.
4. Hill MJ. Dietary fibre and human cancer. Epidemiological data. Adv Exp Med Biol 1997; 427: 27–34.
5. Thompson LU. Antioxidants and hormone-mediated health benefits of whole grains. Crit Rev Food Sci Nutr 1994; 34: 473–497.
6. Slavin J, Jacobs D, Marquart L. Whole-grain consumption and chronic disease: Protective mechanisms. Nutr Cancer 1997; 27: 14–21.
7. De Cosse JJ, Miller HH, Lesser ML. Effects of wheat fibre and vitamins C and E on rectal polyps in patients with familial adenomatous polyposis. J Natl Cancer Inst 1989; 81: 1290–1297.
8. MacLennan R, Macrae F, Bain C. Randomized trial of intake of fat, fiber, and β-carotene to prevent colorectal adenomas. The Aust Polyp Prevention Project. J Natl Cancer Inst 1995; 87: 1760–1766.
9. Zile MH, Welsch CW, Welsch A. Effect of wheat bran fiber on the development of mammary tumors in female intact and ovariectomized rats treated with 7,12-dimethylbenz(a)anthracene and in mice with spontaneously developing mammary tumors. Int J Cancer 1998; 75: 439–443.
10. Ferguson LR, Harris PJ. Does wheat bran or does wheat dietary fibre protect against breast cancer? Int J Cancer 1998; 78: 385–386.
11. Ferguson LR, Harris PJ. Wheat bran protection against cancer: dietary fibre or phytochemicals? Eur J Cancer Prev 1999; 8: 17–25.
12. Harris PJ, Ferguson LR. Dietary fibre: its composition and role in protection against colorectal cancer. Mutation Res 1993; 290: 97–110.
13. Ferguson LR, Harris PJ. Studies on the role of specific dietary fibres in protection against colorectal cancer. Mutat Res 1996; 350: 173–184.
14. Kenji T, Hedio O, Yasuharu O, Iwao Y, Tomohiro S, Katsuya Y, Kiichi M, Shigeru T, Hideki A. Dietary factors and prevention of colon cancer. Nippon Geka Gakkai Zasshi [J Japan Surg Soc] 1998; 99: 368–372.
15. Schwartz PB, Kunerth WH, Youngs VL. The distribution of lignin and other fiber components within hard red spring wheat bran. Cereal Chem 1988; 65: 59–64.
16. Fincher GB, Stone BA. Cell walls and their components in cereal grain technology. In: Pomeranz Y, ed. Advances in Cereal Science and Technology, Vol. 8. St Paul, MO: American Association of Cereal Chemists, 1986; 207–295.
17. Bacic A, Stone BA. Chemistry and organisation of aleurone cell wall components from wheat and barley. Aust J Plant Physiol 1981; 8: 475–495.
18. Smith MM, Hartley RD. Occurrence and nature of ferulic acid substitution of cell wall polysaccharides in graminaceous plants. Carbohydr Res 1983; 118: 65–80.
19. Englyst HN, Quigley ME, Hudson GJ. Determination of dietary fibre as non-starch polysaccharide with gas liquid chromatography, high performance liquid chromatographic or spectrophotometric measurement of constituent sugars. Analyst 1994; 119: 1497–1502.
20. Prosky L, Asp N-G, Schweizer TF, deVries JW, Furda I. Determination of insoluble, soluble, and total dietary fiber in foods and food products: interlaboratory study. J Assoc Off Anal Chem 1988; 71: 1017–1023.
21. Wood R, Englyst HN, Southgate DAT, Cummings JH. Determination of dietary fibre collaborative trials Part IV. A comparison of the Englyst and Prosky (AOAC) procedures for the determination of soluble, insoluble and total dietary fibre. J Assoc Public Anal 1993; 29: 57–139.
22. Monro JA. Dietary fiber pectic substances: source of discrepancy between methods of fiber analysis. J Food Composion Anal 1991; 4: 88–99.
23. Monro JA. A nutritionally valid procedure for measuring soluble dietary fibre. Food Chem 1993; 47: 187–193.
24. Stephen AM, Cummings JH. Mechanism of action of dietary fibre in the human colon. Nature 1980; 284: 283–284.
25. Stevens BJH, Selvendran RR, Bayliss CE, Turner R. Degradation of cell wall material of apple and wheat bran by human faecal bacteria in vitro. J Sci Food Agric 1988; 44: 151–156.
26. Mongeau R, Yiu SH, Brassard R. Chemical and fluorescence microscopic analysis of fiber degradation of oat, hard red spring wheat, and corn bran in rats. J Agric Food Chem 1991; 39: 1966–1971.
27. Kroon PA, Faulds CB, Ryden P, Robertson JA, Williamson G. Release of covalently bound ferulic acid from fiber in the human colon. J Agric Food Chem 1997; 45: 661–667.
28. McCallum JA, Walker JRL. Phenolic biosynthesis during grain development in wheat: changes in phenylalanine ammonia-lyase activity and soluble phenolic content. J Cereal Sci 1990; 11: 35–49.
29. Onyeneho SN, Hettiarachchy NS. Antioxidant activity of durum wheat bran. J Agric Food Chem 1992; 40: 1496–1500.
30. Kruger JE, Reed G. Enzymes and color. In: Pomeranz Y, ed. Wheat: chemistry and technology Vol. 1, 3rd edn. St. Paul, MN: American Association of Cereal Chemists, 1998; 441–500.
31. Feng Y, McDonald CE, Vick BA. C-Glycosylflavones from hard red spring wheat bran. Cereal Chem 1988; 65: 452–456.
32. Feng Y, McDonald CE. Comparison of flavonoids in bran of four classes of wheat. Cereal Chem 1989; 66: 516–518.
33. McCallum JA, Walker JRL. Proanthocyanidins in wheat bran. Cereal Chem 1990; 67: 282–285.
34. Thompson LU, Robb P, Serraino M, Cheng F. Mammalian lignan production from various foods. Nutr Cancer 1991; 16: 43–52.
35. Lewis NG, Davin LB. Evolution of lignan and neolignan biochemical pathways. Am Chem Soc Symp Series 1994; 562: 202–246.
36. Cosgrove DJ. Phytates in Cereals and Legumes. Boca Raton, FL: CRC Press, 1989.
37. Stone BA. Cereal grain carbohydrates. In: Henry RJ, Kettlewell PS, eds. Cereal grain quality. London: Chapman & Hall, 1996; 251–288.
38. Lehrfeld J, Wu YV. Distribution of phytic acid in milled fractions of scout 66 hard red winter wheat. J Agric Food Chem 1991; 39: 1820–1824.
39. Burlingame BA, Milligan GC, Apimerika DE, Arthur JM. The Concise New Zealand Food Composition Tables, 2nd edn. Public Health Commission, Wellington, New Zealand, 1994.
40. Klurfeld DM. Fiber and cancer protection – mechanisms. Adv Exp Med Biol 1997; 427: 249–257.
41. Kritchevsky D. Dietary fibre and cancer. Eur J Cancer Prev 1997; 6: 435–441.
42. Archer S, Meng S, Wu J, Johnson J, Tang R, Hodin R. Butyrate inhibits colon carcinoma cell growth through two distinct pathways. Surgery 1998; 124: 248–253.
43. Emenaker NJ, Basson MD. Short chain fatty acids inhibit human (SW1116) colon cancer cell invasion by reducing urokinase plasminogen activator activity and stimulating TIMP-1 and TIMP-2 activities, rather than via MMP modulation. J Surg Res 1998; 76: 41–46.

44. Palmer DG, Paraskeva C, Williams AC. Modulation of p53 expression in cultured colonic adenoma cell lines by the naturally occurring lumenal factors butyrate and deoxycholate. Int J Cancer 1997; 73: 702–706.
45. Smith JG, Yokoyama WH, German JB. Butyric acid from the diet: actions at the level of gene expression. Crit Rev Food Sci Nutrition 1998; 38: 259–297.
46. Zoran DL, Turner ND, Taddeo SS, Chapkin RS, Lupton JR. Wheat bran diet reduces tumor incidence in a rat model of colon cancer independent of effects on distal luminal butyrate concentrations. J Nutr 1997; 127: 2217–2225.
47. Corpet DE, Tache S, Peiffer G. Carborundum, a bulk similar to dietary fibers but chemically inert, does not decrease colon carcinogenesis. Cancer Lett 1997; 114: 35–38.
48. Rice-Evans CA, Miller NJ, Paganga G. Antioxidant properties of phenolic compounds. Trends Plant Sci 1997; 2: 152–159.
49. Tanaka T, Kojima T, Kawamori T. Inhibition of 4-nitroquinoline-1-oxide-induced rat tongue carcinogenesis by the naturally occuring plant phenolics caffeic, ellagic, chlorogenic and ferulic acids. Carcinogenesis 1993; 14: 1321–1325.
50. Wattenberg LW. Chemoprevention of cancer. Cancer Res 1985; 45: 1–8.
51. Mori H, Tanaka T, Shima H, Kuniyasu T, Takahashi M. Inhibitory effect of chlorogenic acid on methylazoxymethanol acetate-induced carcinogenesis in large intestine and liver of hamsters. Cancer Lett 1986; 30: 49–54.
52. Mandal S, Stoner GD. Inhibition of N-nitrosobenzylmethylamine-induced esophageal tumorigenesis in rats by ellagic acid. Carcinogenesis 1990; 11: 55–61.
53. Wood AW, Huang MT, Chang RL. Inhibition of the mutagenicity of bay region diol epoxides of polycyclic aromatic hydrocarbons by naturally occuring plant phenols: exceptional activity of ellagic acid. Proc Natl Acad Sci USA 1982; 79: 5513–5517.
54. Pignatelli B, Bereziat J-C, Descotes G, Bartsch H. Catalysis of nitrosation in vitro and in vivo in rats by catechin and resorcinol and inhibition by chlorogenic acid. Carcinogenesis 1982; 3: 1045–1049.
55. Keunzig W, Chau J, Norkus E. Caffeic and ferulic acids as blockers of nitrosamine formation. Carcinogenesis 1984; 5: 309–313.
56. Harborne JB, Baxter H, eds. Phytochemical dictionary. London: Taylor & Francis, 1993.
57. Bagchi D, Garg A, Krohn RL. Oxygen free radical scavenging abilities of vitamins C and E, and a grape seed proanthocyanidin extract in vitro. Res Commun Mol Pathol Pharmacol 1997; 95: 179–189.
58. Hollman PC, Katan MB. Absorption, metabolism and health effects of dietary flavonoids in man. Biomed Pharmacother 1997; 51: 305–310.
59. Knekt P, Jarvinen R, Seppanen R. Dietary flavonoids and the risk of lung cancer and other malignant neoplasms. Am J Epidemiol 1997; 146: 223–230.
60. Canivenc-Lavier MC, Vernevaut MF, Totis M. Comparative effects of flavonoids and model inducers on drug-metabolizing enzymes in rat liver. Toxicology 1996; 114: 19–27.
61. Uda Y, Price KR, Williamson G, Rhodes MJ. Induction of the anti-carcinogenic marker enzyme, quinone reductase, in murine hepatoma cells in vitro by flavonoids. Cancer Lett 1997; 120: 213–216.
62. Adlercreutz H. Phytoestrogens: epidemiology and a possible role in cancer protection. Environ Health Perspect 1995; 103 (Suppl. 7), 103–112.
63. Adlercreutz H, Mousavi Y, Clark J. Dietary phytoestrogens and cancer: in vitro and in vivo studies. J Steroid Biochem Mol Biol 1992; 41: 331–337.
64. Vucenik I, Yang GY, Shamsuddin AM. Comparison of pure inositol hexaphosphate and high-bran diet in the prevention of DMBA-induced rat mammary carcinogenesis. Nutr Cancer 1997; 28: 7–13.
65. Graf E, Eaton JW. Dietary suppression of colonic cancer. Fiber or phytate? Cancer 1985; 56: 717–718.
66. Zhou JR, Erdman JW Jr. Phytic acid in health and disease. Crit Rev Food Sci Nutr 1995; 35: 495–508.
67. Shamsuddin AM, Vucenik I, Cole KE. IP6: a novel anti-cancer agent. Life Sci 1997; 64: 343–354.
68. Singh A, Singh SP, Bamezai R. Modulatory influence of arecoline on the phytic acid-altered hepatic biotransformation system enzymes, sulfhydryl content and lipid peroxidation in a murine system. Cancer Lett 1997; 117: 1–6.
69. Hennekens CH. Antioxidant vitamins and cancer. Am J Med 1994; 97: 2S–4S.
70. Alabaster O, Tang Z, Shivapurkar N. Dietary fiber and the chemopreventive model of colon carcinogenesis. Mutat Res 1996; 350: 185–197.
71. Steinmetz KA, Potter JP. Vegetables, fruit and cancer. I Epidemiology. Cancer Causes Control 1991; 2: 325–357.
72. Pool Zobel BL, Bub A, Muller H, Wollowski I, Rechkemmer G. Consumption of vegetables reduces genetic damage in humans – first results of a human intervention trial with carotenoid-rich foods. Carcinogenesis 1997; 18: 1847–1850.
73. Esau K. Plant Anatomy, 2nd edn. New York: John Wiley, 1965.