

## CHAPTER 2 PRIMARY PREVENTION

Studies on the primary prevention of Colorectal Cancer encompass a range of disciplines including molecular genetics, cell biology, animal research, human nutrition and epidemiology. Endpoints range from gene expression, cell proliferation, apoptosis, and aberrant crypt formation to adenomas (benign tumours) and Colorectal Cancer. Although the strongest evidence has Colorectal Cancer as an endpoint, adenomas also provide useful information. As most Colorectal Cancers arise from adenomas (see Chapter 9), epidemiological studies that use adenomas as an endpoint can provide information about environmental influences on the early stages of colorectal carcinogenesis.

Several molecular pathways to Colorectal Cancer are now recognised. The chromosomal instability pathway is characterised by proto-oncogenic activation (e.g. K-ras) and suppressor gene loss (APC, P53 and DCC), and the microsatellite instability (MSI) pathway by mismatch repair deficiency.<sup>1</sup> *De novo* cancer pathways, independent of a precursor adenoma, also exist. Dietary protection could well be pathway-specific, quite possibly accounting for differences in findings reported in some observational and interventional studies.

This chapter will focus principally on studies using Colorectal Cancer as an endpoint but, where appropriate, information derived from studies on colorectal adenomas will also be included. Data relating to physical activity and obesity have matured in recent observational studies, so advice relating to these has been prioritized in this edition.

### 2.1 Physical activity

The evidence that physical activity protects against colorectal cancer is strong but varies by site in the bowel.<sup>2</sup> It is strongest for colonic cancer. In cohort studies, two of six studies not differentiating by site and eight of fourteen colonic cancer studies (two with mortality outcomes) showed protection, but neither of two rectal cancer studies showed benefit. Respective results for case-control studies were three of seven colorectal, ten of fifteen colonic, and one of ten rectal studies. Some of these studies showed statistical benefit restricted to one gender, specific age ranges, intense but not moderate levels of exercise, or only with one of either recreational or occupational exercise categories.<sup>2,3,4</sup> Levels of activity needed to protect against colon cancer are 30–60 minutes per day of moderate to vigorous physical activity, and the relationship is dose-dependent.<sup>5</sup>

Various mechanistic hypotheses are postulated. These include reduced bile acid secretion, stimulation of intestinal transit, immune and hormonal changes, and a reduction in levels of insulin-like growth factor (trophic to the colonic mucosa).<sup>2,6</sup>

### 2.2 Obesity

Obesity, particularly central obesity, is an independent but not as strong a risk factor for Colorectal Cancer and adenomas.<sup>2,7,8</sup> Obesity interacts with other lifestyle variables in a manner only recently being untangled in epidemiology where it persisted as an independent risk factor.<sup>9</sup>

The 2002 IARC report summarizes the relationship of Colorectal Cancer risk and body mass index. For cohort studies, two of seven studies of colonic cancer showed increased relative risk with obesity, and all but one showed, at least for men, a trend between increasing obesity and Colorectal Cancer risk. There was no such trend in the one rectal cancer cohort study. In case-control studies, four of seven studies had significant increased relative risks for colonic cancer, but none of four rectal cancer studies showed this. Again, some of these significant outcomes were gender restricted, with the risk generally being found more in men than in women.<sup>2</sup> The IARC report concluded that there is sufficient evidence to support a link between weight gain and cancer of the colon, and certain other types of cancer, but inadequate evidence to show that intentional weight loss reduces cancer risk for

any site (data not shown here). The report also concluded that regular physical activity reduces the risk of colon cancer, independently of weight control.

The American Cancer Society Cohort Study of over 900,000 American adults identified relative risks of cancer death in the morbidly obese compared to those of normal weight of 1.52 (CI 1.13–2.05) for men and 1.62 (CI 1.40–1.87) for women. There was also a significant association between body mass index (BMI) and death rates for both colon cancer and rectal cancer.<sup>10</sup> In a Canadian prospective study, the greater risk associated with obesity was mainly in premenopausal women.<sup>11</sup> Intentional weight loss was associated with a reduction in colon cancer risk.<sup>8,12</sup>

Weight gain is also related to adenoma occurrence.<sup>2,13</sup>

### Should physical activity and weight control be advised to reduce the risk of Colorectal Cancer?

Guideline — Physical activity and obesity	Level of evidence		Practice recommendation		Refs
	Cancer	Adenoma	Cancer	Adenoma	
Engage in moderate to vigorous physical activity for 30–60 minutes/day, and avoid excessive weight gain.	III-2	III-2	Recommend	Recommend	2,3,4,5,6,12
Weight should be maintained in the healthy weight range of BMI	III-2	III-2	Recommend	Recommend	2,6,7,8,9,10,11,13

## 2.3 Alcohol

With some exceptions, total alcohol intake is more consistently associated with Colorectal Cancer risk than specific types of alcohol.<sup>14</sup>

In cohort studies, significant associations between alcohol intake and risk have been found in four of five colon cancer studies;<sup>9</sup> three of three rectal cancer studies;<sup>9</sup> and two of three studies of Colorectal Cancer (sub-site not distinguished).<sup>9</sup> A United States cohort study of men showed a particularly strong association of alcohol intake with the development of Colorectal Cancer and adenomas in individuals with low folate or methionine intakes.<sup>15</sup>

In case-control studies, significant associations between alcohol intake and increased risk have been found in nine of 18 studies of colon cancer and nine of 17 studies for rectal cancer.<sup>9</sup> This effect is generally stronger in men than women. Australian studies have found a similar positive association with beer drinking in men.<sup>16,17</sup> The positive association of alcohol intake and development of colon cancer is not as strong for wine intake, especially in women.<sup>9,18</sup> Rectal cancer does not seem to be related to wine drinking.<sup>18</sup>

A recent pooled analysis of eight cohort studies reports a modest increase in risk for cancer with consumption of three or more drinks per day (RR 1.41, CI 1.16–1.72), a risk that was not site-specific within the large bowel.<sup>14</sup>

Colorectal adenomas, especially advanced adenomas, also are related to high alcohol intake.<sup>19</sup> Postulated mechanisms of action include solvent effects of alcohol, microsomal enzyme induction of pro-carcinogens, inhibition of DNA repair and concurrent nutritional deficiency.

### Should alcohol intake be restricted to reduce Colorectal Cancer risk?

Guideline — Alcohol	Level of evidence		Practice recommendation		Refs
	Cancer	Adenoma	Cancer	Adenoma	
Alcohol consumption should be limited or avoided. For people who do drink alcohol, recommended amounts for men are no more than 2 standard drinks per day and for women no more than one standard drink a day.	III-2	III-2	Strongly recommend	Recommend	9,14, 17-20

## 2.4 Tobacco smoking

Of 51 case-control or cohort studies, 22 show a 50% increase in risk from tobacco smoking, and ten are statistically significant. The evidence is stronger for rectal than colonic cancer, and risk is increased for those who have smoked for a longer period.<sup>21,22</sup> Mortality from Colorectal Cancer is also increased.<sup>23</sup> Data are even more consistent for adenomas, with 22 of 27 case-control or cohort studies showing at least a 50% increase in risk. Nineteen are significant and nine of ten have a positive dose response.<sup>2</sup> Thus, the main effect of smoking seems to occur early in the process, during adenoma formation, and applies especially to distal sites in the large bowel.<sup>24</sup>

Smoking is also recognisable as a risk factor in vegetarians.<sup>25</sup>

Smoking may cause specific mutations<sup>26</sup> and may induce metabolic activation (CYP1A2) of heterocyclic amines,<sup>27</sup> particularly in relation to MSI high cancers.<sup>28</sup>

### Does smoking tobacco increase the risk of Colorectal Cancer?

Guideline — Tobacco smoking	Level of evidence		Practice recommendation		Refs
	Cancer	Adenoma	Cancer	Adenoma	
Avoid tobacco smoking	III-2	III-2	Recommend	Recommend	2,21-24

## 2.5 Energy Intake

Case-control studies consistently show a positive association between energy intake and Colorectal Cancer risk. As fat intake is closely associated with energy intake, it has been difficult to differentiate between the two. Attempts to correct for energy by multivariate analysis in cohort studies have indicated that energy derived from fat sources predominates in risk, focusing attention on fat intake itself.<sup>29</sup>

However, a meta-analysis of 13 case-control studies of diet and Colorectal Cancer found little evidence of any energy-independent effect of either total fat or saturated fat intake.<sup>30</sup> The authors

concluded that substituting other sources of calories for fat is unlikely to reduce Colorectal Cancer risk.

A role for insulin and/or insulin-like growth factor 1 as an endogenous hormone trophic to colorectal neoplastic lesions has been suggested. Epidemiological studies provide mixed evidence to support this. The Women’s Health Study of 39,876 health professionals recently reported a positive association (relative risk (RR) 2.85, 95% confidence intervals (CI) 1.40–5.80) for dietary glycaemic load, ( $p = 0.004$  for trend across quintiles), supporting this hypothesis.<sup>31</sup> Total carbohydrate intake was also significantly related (RR 2.41, CI 1.10–5.27), especially with respect to non-fibre carbohydrate ie sugar (RR 2.60, CI 1.22–5.54). However, a United States prospective cohort study of 49,124 women showed no association between Colorectal Cancer incidence and glycaemic load or total carbohydrate or sugar consumption.<sup>32</sup>

### Should energy intake be restricted to reduce Colorectal Cancer risk?

Guideline — Energy Intake	Level of evidence		Practice recommendation		Refs
	Cancer	Adenoma	Cancer	Adenoma	
Limit energy intake in most men to <2500 calories (10,480 kJ) per day and in most women to <2000 calories (8360 kJ) per day.					9,29, 30
	III-2	-	Strongly recommend	-	

## 2.6 Fat Intake

Many case-control and cohort studies demonstrate a direct relationship between dietary fat intake and Colorectal Cancer risk<sup>33</sup> although this has come into recent question from the Boston group of epidemiologists, who favour red meat rather than fat as the risk factor.<sup>34,35</sup> The incidence of Colorectal Cancer is high when fat intake is high and conversely, low when dietary fat intake is low. Summarising the case-control and cohort studies of fat and Colorectal Cancer risk, Potter found that six of ten studies (three null and one inverse) showed this positive association.<sup>36</sup> Other analyses of case-control studies suggest a null association, pointing more to total energy as the key relationship.<sup>30</sup>

In animal models, a higher intake of dietary fat — whether saturated or polyunsaturated — leads to increased hepatic synthesis of cholesterol and bile acids, elevating their concentration in the colon and faeces. Bacterial flora (particularly anaerobes) can convert these sterols into tumour-promoting cholesterol metabolites and oxidised bile acids, increasing chances of DNA replication errors and modulation of apoptosis and cell proliferation.<sup>37</sup>

High intake of monounsaturated fat, typified by olive oil in the ‘Mediterranean diet’, may not be associated with increased risk for Colorectal Cancer or may even be beneficial.<sup>38</sup> Evidence for a beneficial effect was found in a randomised controlled trial reporting on the total incidence of cancer.<sup>39</sup>

Three randomised controlled trials have studied the effect of fat reduction using adenoma recurrence as an endpoint. The Toronto Polyp Study showed no benefit, although the results were not differentiated by adenoma size at outcome.<sup>40</sup> The Australian Polyp Prevention Project demonstrated a significant benefit ( $p = 0.05$ ) with low-fat diets (<25% calories as fat) after two and four years of intervention on the occurrence of large (10 mm or more in diameter) adenomas.<sup>41</sup> The result became more significant ( $p < 0.03$ ) in the group randomised to low fat and added wheat bran (25 g wheat bran supplement). This effect was seen without any change in the weight of participants, suggesting an effect on carcinogenesis intrinsic to dietary fat intake. However, the National Cancer Institute’s trial of a combined low fat (<20% of total calories), high fibre (18 gm per 1000 kcals) and high fruit and

vegetable (3.5 serves/1000 kcals) diet found no difference in the incidence of adenomas after four years of intervention.<sup>42,43</sup>

Omega-3 fatty acids may provide an important exception to the relationship between dietary fat and colorectal neoplasia. There is some evidence of an inverse correlation between intake of fish and fish oil and incidence of Colorectal Cancer, but the epidemiological evidence is inconsistent. The ratio of fish oil to animal fat intake may be important in determination of risk.<sup>44</sup> Fish oil also reduces the proliferation of rectal epithelial cells.<sup>45</sup>

### Should dietary fat be restricted to reduce Colorectal Cancer risk?

Guideline — Dietary fat	Level of evidence		Practice recommendation		Refs
Reduce dietary fat to <25% of calories as fat.	Cancer	Adenoma	Cancer	Adenoma	29,30,36-38,40,42,43
	III-2	II	Recommend		

## 2.7 Major food groups

### 2.7.1 Meat

A meta-analysis of studies on red meat and Colorectal Cancer risk showed a modest effect attributable to red meat: 12–17% increase per 100 gm per day of all meat or red meat consumed. Much of the risk was associated with processed meat.<sup>46</sup> In another meta-analysis, relative risk was 1.27 (CI 1.11–1.45) for red meat and 1.39 (CI 1.09–1.76) for processed meat.<sup>47</sup> A combined prospective study of vegetarians showed that the risk for Colorectal Cancer was no different from non-vegetarians, diminishing the likelihood of an association between the intake of red meat and the risk of Colorectal Cancer.<sup>48</sup> A recently published large cohort study bears mention<sup>49</sup>. In this study of 478,040 people across Europe, the adjusted (for many confounding variables) hazards ratio of highest (>160gm per day) vs lowest (<20gm per day) intake of red and processed meat was 1.35 (CI 0.96 to 1.88), with protection from high fish (80gm vs 20gm) intakes where the hazard ratio was 0.69 (CI 0.54 to 0.88), but not from poultry. However, for nearly all sub-analyses, the risk was higher for processed meat than red meat, and lean red meat was not differentiated from overall red meat intake.

Separating the effects of dietary fat intake from those of red meat is difficult in observational epidemiology. The first report of the American Institute for Cancer Research and World Cancer Research Fund<sup>9</sup> attributed observed increases in risk more to red meat than to fat. That report did not take into account the qualitative higher rating of evidence from randomised controlled trials. It has received criticism for the strength of its conclusions about a ‘probable’ association.<sup>50</sup> In the Australian Polyp Prevention Project,<sup>41</sup> fat reduction was achieved without reduction in red meat intake. The observed inhibition of adenoma growth in this study was therefore attributed to fat reduction rather than red meat reduction. The evidence relating lean red meat to Colorectal Cancer risk remains weak and insufficient to allow the disadvantages of avoiding lean red meat (e.g. decreased intake of iron, calcium, zinc, magnesium, vitamin B12 and other vitamins) to be ignored.

One effect of high-temperature cooking (such as barbecuing) of red meat is the production of heterocyclic amines.<sup>51</sup> Metabolism of heterocyclic amines includes oxidation and acetylation and eventual formation of carcinogens, which are measurable as DNA (deoxyribonucleic acid) adduct formation. N-oxidation (a P4501A2 — otherwise known as CYP1A2 — catalysed step in the liver) and acetylation (NAT2) are genetically controlled and readily identified. Rapid CYP1A2 and rapid NAT2 phenotypes produce more DNA adducts. Indeed, acetylator status has been shown to positively correlate with Colorectal Cancer risk, particularly when taking red meat into account as a co-variable.<sup>52</sup> Some studies,<sup>27,53-55</sup> but not all,<sup>56-58</sup> support this observation. There is inconsistent evidence

that increased intake of heavily browned meat *per se*, or high values of other indicators of intake of heterocyclic amines produced as a result of cooking meat, increases risk of Colorectal Cancer.<sup>56,59,60</sup> It is less certain whether the increased risk associated with well-done red meat is linked to the presence of known mutagens such as heterocyclic amines. In some studies, the risk relationship survives in the genetically susceptible (rapid phenotype for both NAT and CYP1A2) regardless of measured heterocyclic amines in stool.<sup>61,62</sup>

### Should red meat intake be altered to reduce colon cancer risk?

Guideline — Meat	Level of evidence		Practice recommendation		Refs
	Cancer	Adenoma	Cancer	Adenoma	
Moderate intakes of lean red meat can be eaten as part of a mixed diet including carbohydrates (breads and cereals), vegetables and fruit, and dairy products. Charring of red meat is best avoided. Consumption of processed meats should be limited.	III-2	III-2	Equivocal	Equivocal	9,29, 36, 41, 49, 50

#### 2.7.2 Dietary fibre - general

Fibre is a heterogeneous group of plant non-starch polysaccharides and non-carbohydrates that resist digestion in the upper digestive tract. Epidemiological and animal studies have been complicated by the different types and mix of fibres investigated. In a systematic review, Potter found an inverse correlation between plant food intake and cancer risk in eight of ten case-control or cohort studies.<sup>36</sup> Similar findings were observed in a systematic review of case-control studies. Of these studies, 12 out of 13 showed a decreased risk of Colorectal Cancer with increased fibre intake.<sup>63</sup> A cohort study involving United States nurses showed no effect on Colorectal Cancer risk when fibre was analysed by solubility and source.<sup>32</sup> However, overall fibre intake was low and the range of intakes was narrow in that study.

Perhaps the most compelling evidence comes from the EPIC prospective cohort study. A total of 519,978 participants with a wide range of intakes were followed through 1,939,011 person-years; the adjusted relative risk for Colorectal Cancer was 0.58 (CI 0.41–0.85) for highest *versus* lowest quintiles of fibre intake.<sup>64</sup>

Fibre may act by increasing bulk (and decreasing carcinogen concentration), by reducing transit time (and thus carcinogen exposure time), or by acting through its bacterial fermentation products — short chain fatty acids. The production of short chain fatty acids decreases luminal pH, inhibits bacterial enzymes capable of producing carcinogens, and also acts as an important fuel for the colonocyte.<sup>65</sup> Butyrate can induce differentiation in malignant cell lines, slow proliferation and increase apoptosis, and is associated with inhibition of tumorigenesis *in vivo*.<sup>66</sup> Butyrate can also hypermethylate DNA, counterbalancing the loss of methyl groups, which is one of the early steps in the molecular progression to cancer.<sup>67</sup>

#### 2.7.3 Vegetables and fruit

Case-control and cohort studies have shown more consistent protection against Colorectal Cancer from vegetables and fruit compared to cereals.<sup>36</sup> This may be due to non-fibre vegetable components such as phytonutrients. Vegetable intake, especially consumption of cruciferous vegetables (which include bok choy, broccoli, brussel sprouts, cabbage, cauliflower, Chinese cabbage, collards, kohlrabi,

mustard greens, swedes and turnips) appears to be important in conferring this protection.<sup>68</sup> However, the National Cancer Institute trial found that the incidence of adenomas was no lower in those randomised to high fibre/high fruit and vegetable diets when compared to controls.<sup>42,43</sup> Animal models of Colorectal Cancer provide evidence of protection for a range of vegetables<sup>69</sup>, including cruciferous vegetables and also juice extracts and berries<sup>70</sup>. However, the evidence is not strong enough at this stage to conclude that preferentially eating cruciferous vegetables will reduce the risk of Colorectal Cancer.<sup>70</sup>

Characterising the active components of protective vegetables continues to be a promising scientific avenue of pursuit, given the strong epidemiological data on protection. The results of antioxidant trials using betacarotene indicate that, although it is the most prevalent carotenoid antioxidant in cruciferous vegetables, betacarotene does not appear to be responsible for tumour suppression.<sup>36</sup> Protection from cancer by fruit and vegetables may be associated with their low energy density, controlling weight gain. Despite the National Institutes of Health randomized controlled trial, the overall conclusion remains that a higher intake of vegetables probably lowers the risk of Colorectal Cancer.<sup>69</sup>

In contrast to the data for vegetables, evidence for a protective effect from fruits is more limited and has been inconsistent both for colon and rectal cancer and for adenomas. However, a recent study on a large cohort of United Kingdom vegetarians pointed more to fruit than to vegetables as being protective, despite finding no overall reduction in cancer in the vegetarians (RR 0.84, CI 0.55–1.32).<sup>25</sup> The protection may be more for MSI-H (high) cancers exhibiting methylated promoter silencing of MLH mismatch repair genes,<sup>71</sup> highlighting the need for more studies on genotypically-characterised cancers and adenomas.<sup>72</sup>

### Should fresh fruit and vegetable intake be increased to reduce Colorectal Cancer risk?

Guideline — Fresh vegetables	Level of evidence		Practice recommendation		Refs
	Cancer	Adenoma	Cancer	Adenoma	
Eat five or more serves per day of a variety of vegetables. National nutrition guidelines also advise two serves of fruit daily ("Go for 2 and 5")					32, 36, 41, 43, 63, 64, 68
	III-2	-	Equivocal	-	

#### 2.7.4 Cereals and bread

Recent animal studies on the relative solubility of different cereal fibres support the hypothesis that poorly soluble fibres, such as wheat bran, continue to be fermented throughout the colon.<sup>73</sup> As cereal fibres are digested, short chain fatty acids, including butyrate, are released along the length of the colon and rectum.<sup>74</sup>

Several human studies have investigated the role of specified fibre sources on the development of Colorectal Cancer. The study of rectal cancer by Freudenheim et al showed greater protection from insoluble than soluble cereal fibre. There was also protection afforded by vegetable fibre in this study.<sup>75</sup> A recent cohort study reported protection with fibre from vegetables, fruit and whole grains.<sup>76</sup> The Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial, involving 33,971 participants, found fewer adenomas at screening flexible sigmoidoscopy in those in the highest quintile of fibre intake compared to the lowest intake (RR 0.73, CI 0.62–0.86).<sup>51</sup> This association was strongest for grains and cereals and for fruit. As discussed above, the Australian Polyp Prevention

Project used poorly-soluble cereal fibre (25g/day of unprocessed wheat bran) as its fibre intervention.<sup>41</sup> De Cosse et al showed a protective effect of wheat bran (Kellogg's All Bran<sup>®</sup>) in patients with familial adenomatous polyposis (FAP) in a randomised control trial, but only on the basis of actual intake.<sup>77</sup>

While recognising a protective effect, the report from the World Cancer Research Fund placed less emphasis on the importance of cereal fibre than on other fibre sources.<sup>9</sup> The benefits of wheat bran were null in the Arizona intervention trial,<sup>78</sup> a larger study than the Australian study. This has substantially reduced the strength of evidence for wheat bran. However, all trials and observational studies are still consistent with a synergistic effect of unprocessed wheat bran and a low fat diet in reducing Colorectal Cancer risk.<sup>79</sup>

### Should cereal fibre be selected to reduce Colorectal Cancer risk?

Guideline — Cereal fibre	Level of evidence		Practice recommendation		Refs
	Cancer	Adenoma	Cancer	Adenoma	
Select poorly soluble cereal fibres (e.g. wheat bran), especially if at increased risk of Colorectal Cancer.	III-2	II	Equivocal	Equivocal	9, 41, 51, 73-76

#### 2.7.5 Resistant starch

Attention has focused on the possible benefits of those carbohydrates escaping digestion in the small intestine. Although animal data have not been supportive, ecological studies suggest otherwise.<sup>80</sup> The short chain fatty acid hypothesis should hold as well for resistant starch as for fibre. Indeed, resistant starch in the diet produces the highest level of faecal butyrate.<sup>81</sup> The way in which various forms of resistant starch behave with respect to fermentability in the colon is under active investigation. Strains of maize and wheat have been genetically selected or chemically modified to resist digestion and promise protective benefit. One such product is under investigation in a phase III clinical trial on FAP (the CAPP1 study)<sup>82</sup> and another on hereditary non-polyposis Colorectal Cancer (HNPCC) (the CAPP2 study).

#### 2.7.6 Dairy foods

At present there is insufficient evidence to advise for or against dairy products with respect to Colorectal Cancer risk. NHMRC dietary guidelines recommend and the Australian Government's Australian Guide to Healthy Eating recommend including milk, yoghurt, cheese, and/or alternatives in a healthy diet.

## 2.8 Micronutrients

### 2.8.1 Calcium and vitamin D

Although early studies suggested that in the presence of a high-calcium diet there is a modest protective effect for the development of colorectal tumours, recent systematic reviews do not show a significant effect.<sup>83,84</sup> However, *post hoc* analysis showed that dietary calcium intakes above 1068 mg protected against adenoma recurrence in the Arizona interventional wheat bran trial (RR 0.56, CI 0.39–0.80).<sup>85</sup> In combination, dietary and *supplemental* calcium showed a modest reduction in cancer incidence in a cohort study involving over 125,000 persons (RR 0.87, CI 0.67–1.12, p = 0.02 for trend).<sup>86</sup> The effect was stronger for supplements alone. A threshold of 700 mg/day of dietary calcium

for protection against Colorectal Cancer was suggested in analyses of results of the prospective Nurses Health Study (on women) and the Health Professionals Follow-up Study (on men).<sup>87</sup>

Adults should be advised to bring their calcium intake to 1000–1200 mg per day, in keeping with general dietary guidelines.

Dietary vitamin D intake, as distinct from serum 25-(OH) vitamin D levels, appears to have no effect on the development of colorectal tumours.

### Does calcium supplementation reduce Colorectal Cancer risk?

Guideline — Calcium	Level of evidence		Practice recommendation		Refs
	Cancer	Adenoma	Cancer	Adenoma	
Ensure a total calcium intake of 1000–1200 mg/day in keeping with general dietary guidelines.			Cancer	Adenoma	83-87
	III-2	II	Equivocal	Equivocal	

### 2.8.2 Folate

Folate (folic acid, folacin) is abundant in wheat bran, baker's yeast, cruciferous vegetables, spinach, peanuts and liver of all types.<sup>88</sup> A review of prospective and retrospective studies indicated that high folate diets are associated with a decreased risk for colorectal adenomas (RR 0.27 to 0.84) and Colorectal Cancer (RR 0.31 to 1.03),<sup>15</sup> especially in male habitual alcohol consumers.<sup>89-91</sup> One study showed that dietary folate consumption was associated with a greater reduced risk of colon cancer in women having a first-degree relative with colon cancer (RR 0.48 CI 0.28–0.83), compared to those without a family history (RR 0.88 CI 0.62–1.07). Moderate to heavy alcohol consumption increased the familial risk.<sup>92</sup>

Low folate status is associated with increased risk for adenoma formation and cancer.<sup>93</sup> This is enhanced in individuals with the thymine-thymine (TT) genotype for methylenetetrahydrofolate reductase.<sup>94</sup> The effect may be especially relevant to microsatellite unstable Colorectal Cancers, which are characterised by perturbations in methylation.<sup>95,96</sup> Indeed, methyl-poor diets (low folate, low methionine and high alcohol) confer a greater risk compared with methyl-rich diets, the latter perhaps offering a 40% reduction in Colorectal Cancer incidence.<sup>97,98</sup>

At present, no recommendation on folate in terms of Colorectal Cancer risk can be provided.

### 2.8.3 Phytonutrients

It is known that there are several naturally occurring compounds in foods of plant origin (vegetables, fruits and cereals) that have strong protective effects against Colorectal Cancer over and above effects related to their fibre content.<sup>83</sup> The vegetables of particular importance include members of the cruciferous vegetable family (cabbage, cauliflower, broccoli, Brussels sprouts), members of the allium family (garlic, onion, chives), leafy vegetables and tomatoes, as well as fruits and cereals containing carotenoids, vitamin C and vitamin E.<sup>83</sup> These phytonutrient compounds include, among others, carotenoids, vitamin C, vitamin E, folate, indoles, linolenic acid, allylic sulfides, and lycopene. Increasing evidence also points to tea (containing catechins) as being protective.<sup>99,100</sup>

The bulk of the evidence on phytonutrients is epidemiological and underlines the need for a high and varied vegetable, fruit and cereal diet as an important dietary protective factor for colorectal tumours.<sup>83</sup>

## 2.9 Nutritional supplements

Dietary micronutrients and micronutrient supplements should be differentiated, since it is very likely that whole foods will be found to have many more anti-cancer substances than those identified so far. For this reason, it is a good nutritional practice to promote eating whole foods rather than advocating nutritional supplements, except in certain well-defined situations.

### 2.9.1 Calcium

A recent large cohort study has demonstrated protection with supplemental calcium (RR 0.69, CI 0.49–0.96). In an interventional trial conducted by Baron et al, 1.2 g elemental calcium reduced the incidence of new adenomas in the Calcium Polyp Prevention randomised controlled trial.<sup>101</sup> More detailed analysis suggested that the benefit of calcium supplementation was largely in the sub-group with serum 25-(OH) vitamin D levels above the median for the group.<sup>102</sup> These findings are supported by a European trial that also tested the effect of soluble fibre.<sup>103</sup>

### 2.9.2 Folate

Human interventional studies of folate supplementation have commenced but only on a small scale to date.<sup>104</sup>

### 2.9.3 Selenium

Selenium is an essential trace element in humans. It is a part of the enzyme glutathione peroxidase which catalyses the removal of intracellular hydrogen peroxide, thereby reducing the formation of oxygen radicals and the risk of oxidative damage to DNA. Deficiency of selenium may occur with diets lacking whole grains and vegetables and with foods derived from soils low in selenium. North American studies of populations deficient in selenium have suggested an increased incidence and mortality from Colorectal Cancer, but dietary selenium intakes and serum levels in Australia do not show good correlations, weakening a link Colorectal Cancer risk.<sup>105</sup>

Clark and co-workers from the Nutritional Prevention of Cancer Study Group performed a multicentre double-blind, randomised placebo-controlled cancer prevention trial to test whether selenium supplementation decreased the incidence of carcinoma of the skin.<sup>106</sup> Among the secondary endpoints of the study were total cancer incidence and incidence of Colorectal Cancer. The intervention agent was 200 mcg of selenium supplied as a 500 mg brewer's yeast tablet or matched placebo per day. After a total follow up of 8271 person-years, there were eight Colorectal Cancers in the selenium group versus 19 in the placebo group (RR 0.42; CI 0.18–0.95;  $p = 0.03$ ). The total number of carcinomas was 59 in the selenium-treated group and 104 in the placebo group (RR, 0.55; CI, 0.40–0.77;  $p = 0.001$ ). The selenium dose of 200 mcg per day was estimated to be twice the typical dietary intake of these patients and three to four times the recommended daily allowance. Because the results relating to Colorectal Cancer were from a secondary endpoint analysis, the effect requires confirmation in an independent trial of appropriate design before public health recommendations regarding selenium supplementation should be made.

Further support comes from geo-epidemiological observations. Serum selenium levels related inversely to large adenomas in a low soil selenium area in Spain.<sup>107</sup> However, other evidence is not so supportive. Prediagnostic serum selenium levels did not predict recurrent adenomas in a nested case-control study.<sup>108</sup>

## Does selenium supplementation reduce Colorectal Cancer risk?

Guideline — Selenium	Level of evidence		Practice recommendation		Refs
	Cancer	Adenoma	Cancer	Adenoma	
Selenium supplementation for chemoprevention is promising but requires confirmation.	Cancer	Adenoma	Cancer	Adenoma	106-109
	II	-	Equivocal	Equivocal	

### 2.9.4 Antioxidants/carotenoids

One population-based case-control study of Colorectal Cancer found a statistically significant protective effect from the use of multivitamin and vitamin C-containing supplements, an effect independent of other dietary risks.<sup>17</sup> A prospective cohort study of 35,215 Iowa women did find a protective association for highest compared with lowest quartile of vitamin E intake (RR, 0.3; CI, 0.19–0.54).<sup>110</sup> In contrast, randomised controlled trials of the antioxidant vitamins A, C and E and betacarotene have been almost universally negative. The Dartmouth randomised intervention trial (betacarotene 25 mg/day; vitamin C 1 g/day and vitamin E 400 mg/day and placebo),<sup>111</sup> a Canadian trial of vitamin C and vitamin E (vitamin C 400 mg/day; vitamin E 400 mg/day),<sup>112</sup> the Australian Polyp Prevention Project<sup>41</sup> (betacarotene 25 mg/day) and the De Cosse et al interventional study in familial adenomatous polyposis (vitamin C 4 g/day and vitamin E 400 mg/day)<sup>77</sup> all showed no benefit.

## Does antioxidant vitamin supplementation reduce Colorectal Cancer risk?

Guideline — Antioxidant vitamins	Level of evidence		Practice recommendation		Refs
	Cancer	Adenoma	Cancer	Adenoma	
Antioxidant vitamin supplementation is <i>not</i> advised at present to protect against Colorectal Cancer.	Cancer	Adenoma	Cancer	Adenoma	41,77,109, 111,112
	II	II	Recommend	Recommend	

### 2.9.5 Phytonutrients

Specific phytonutrients, including indoles (cruciferous vegetables), S-methyl methane thiosulfonate (cruciferous vegetables); garlic extract, green tea and black tea extracts, and curcuma B supplements (from tumeric) have been found to have anti-Colorectal Cancer properties in experimental models.<sup>83</sup> Some epidemiological studies support these experimental findings. However, at present, phytonutrient supplementation is on an experimental basis and controlled human studies are required.

### 2.9.6 Fibre supplements

Based on their ability to undergo fermentation, commercial fibre preparations could be predicted to provide protection against Colorectal Cancer. Limited information from human studies is available. The European Cancer Prevention trial showed that psyllium gave weak protection against adenomas.<sup>103</sup>

## 2.10 Other chemopreventive candidate agents

### 2.10.1 Aspirin and nonsteroidal anti-inflammatory drugs

The Melbourne Colorectal Cancer Study, which examined 715 patients and 727 controls, was the first to show that regular consumption of aspirin was statistically significantly protective (40% protection) against both colon and rectal cancer in men and in women.<sup>113</sup> Since that report, numerous case-control and cohort studies have supported this association. In addition, several studies have shown protective effects against colorectal adenoma.<sup>114,115</sup>

There have been four prospective randomised clinical trials of aspirin intervention. The first, the Physicians' Health Study, involved use of aspirin in a dose of 325 mg every second day.<sup>116</sup> Although this study showed that aspirin gave no protection against Colorectal Cancer, the findings are difficult to interpret because of the relatively brief duration of treatment and the failure to exclude polyps or cancer at the start of the study. The Dartmouth randomised controlled trial conducted in the USA of aspirin 80 mg/day versus placebo showed a 19% reduction in adenoma incidence. Curiously, aspirin 325 mg/day did not show benefit in the same study.<sup>117</sup> In a parallel study in patients after Colorectal Cancer resection, aspirin 325 mg/day was effective in reducing the incidence of metachronous adenomas during follow up.<sup>118</sup>

Using the less gastrototoxic lysine acetylsalicylate, Benamouzig et al also demonstrated a significantly lower incidence of small and large adenomas at one year in those randomised to aspirin compared with placebo.<sup>119</sup>

Non-aspirin, nonsteroidal anti-inflammatory agents (NSAIDs) have also been found to provide a degree of protection for Colorectal Cancer. With the exception of sulindac,<sup>114</sup> adverse side effects have been a deterrent to large-scale controlled human studies.

Cyclo-oxygenase-2 specific inhibitors have recently been developed to minimise the gastrointestinal side effects of aspirin and of NSAIDs. They have been shown to decrease the number of rectal and duodenal polyps in FAP.<sup>120,121</sup> The rofecoxib "APPROVe" trial was successful in meeting its primary endpoint of reducing the proportion of "higher risk" adenoma patients (mostly those with advanced adenoma features at entry - 78% of the total group) with adenomas over 3 years of treatment (RR 0.75, CI 0.67-0.83). Secondary endpoints evaluating the total group, and cumulative reduction in adenoma number and size were also highly significant.<sup>122</sup> However, both of the two large international trials of COXII inhibitors in sporadic adenoma patients have recently been aborted because of an increased risk of myocardial infarction and stroke emerging after 18 months of treatment, especially in the higher dosage.<sup>122,123</sup> In the rofecoxib trial comparing 25mg vs placebo, there was a relative risk of 1.92 (CI 1.19 3.11; p=0.008)<sup>122</sup> whereas in the celecoxib trial the hazard ratio at 2.8 to 3.1 years was 3.4 (CI 1.4 -7.8) comparing 800mg with placebo, with a non-significant trend apparent with the 400mg arm.<sup>123</sup> Deaths from cardiovascular disease were not significantly different. These have dampened the enthusiasm for chemoprevention with these drugs. Both of these trials recruited in Australia.

Several mechanisms of the action of aspirin and non-aspirin NSAIDs as colorectal tumour chemopreventive agents have been elucidated. These include an anti-proliferative effect, an enhanced apoptotic effect, an anti-angiogenic effect and possibly also, immune modulation.<sup>114,115</sup> This anti-tumour action appears to be related in part to the ability of aspirin and other NSAIDs to inhibit the enzyme COX-2, and in part to mechanisms that appear to be independent of COX-2 inhibition.

Collective evidence of epidemiological studies strongly suggests that a reduction of about 40% in Colorectal Cancer risk can be associated with regular aspirin intake<sup>124</sup> and possibly also with regular NSAID use. Up to now, aspirin has not had broad scientific approval for use as a colorectal tumour chemopreventive in individuals at average risk of because of uncertainties about the optimal dosage,

the optimal duration of use, and adverse side effects. Furthermore, there has not been an assessment of the balance between benefit and risk involved in prolonged aspirin use. This assessment is crucial, as the use of aspirin or NSAID chemoprevention will depend largely on this balance. The lessons apparent from the COXII trials make this especially cogent.

Dosage of aspirin has been informative in two recent studies. In an analysis of the Nurses Health Study, the protective advantage of aspirin was shown to be dose dependent. The analysis showed that 0.5–1.5 standard tablets per week have a RR of 0.80 (CI 0.70–0.93), 2–5 tablets/week have a RR of 0.74 (CI 0.62–0.88), 6–14 tablets per week have a RR of 0.72 (CI 0.61–0.85), and more than 14 tablets per week have a RR of 0.49 (CI 0.36–0.65,  $p < 0.001$  for trend). Increasing duration did not increase the benefit.<sup>125</sup> However, a European cohort study of low-dose use (maximum 150 mg per day) did not show an effect in 29,470 people.<sup>126</sup>

The risk–benefit ratio for aspirin or NSAID prophylaxis is likely to be more favourable for individuals at high risk for Colorectal Cancer, but this risk–benefit ratio is still difficult to quantify. FAP and HNPCC gene carriers are currently participating in randomised controlled trials on the basis of improved risk–benefit ratio,<sup>82</sup> but results are so far unavailable. Several controlled trials are currently in progress, using aspirin alone, aspirin and folate, aspirin and resistant starch, sulindac alone, sulindac and curcumin, and sulindac with difluoromethylornithine (DFMO), as well as COX-2 specific inhibitors alone or in combination with selenium.<sup>106</sup> The results of these studies, to be published over the next few years, should answer some of the unresolved questions. Early indications from a nested case-control study suggest that the benefits may be less, although still significant, when COX-2 inhibitors are compared with non-selective NSAIDs.<sup>127</sup>

For the present, it is reasonable to consider aspirin as prophylaxis in adenoma bearers. The trial by Baron et al showed that a low dose of aspirin may be sufficient.<sup>117</sup>

### Do anti-inflammatory drugs reduce Colorectal Cancer risk?

Guideline — Anti-inflammatory drugs	Level of evidence		Practice recommendation		Refs
	Cancer	Adenoma	Cancer	Adenoma	
Aspirin should be considered as prophylaxis against further adenoma development in those with a previous removal of an adenoma.	II	II	Recommend	Recommend	113-119,124-126

### 2.10.2 Hormone replacement therapy

A meta-analysis of 18 observational studies showed a 20% reduction in colon cancer incidence among women who had ever used hormone replacement therapy (HRT) (RR 0.80, CI 0.74–0.86),<sup>128</sup> a finding supported by the randomised controlled Women’s Health Initiative (RR 0.63 CI 0.43–0.92).<sup>129</sup> However, those cancers detected were at a more advanced pathologic stage in the HRT group versus the control group, tempering the observation of reduced incidence in that study.<sup>130</sup> A reduction in incidence may be particularly true for MSI tumours (RR 0.67, CI 0.59–0.77).<sup>131</sup> These results are mirrored by improvements in survival.<sup>97</sup> Risk is also reduced in rectal cancer (RR 0.81, CI 0.72–0.92). HRT protects against colorectal adenomas.<sup>132</sup>

Any benefits must be balanced against the possibly increased risks for breast cancer, stroke, pulmonary embolism and other adverse outcomes.<sup>129</sup>

## Should hormone replacement therapy be recommended to reduce risk of Colorectal Cancer?

Guideline — Hormone replacement therapy	Level of evidence		Practice recommendation		Refs
	Cancer	Adenoma	Cancer	Adenoma	
HRT <i>cannot be recommended</i> as prophylaxis against Colorectal Cancer because of its possible collateral risks, including breast cancer.					128-132
	III-2	III-2	Equivocal	Equivocal	

### 2.10.3 Other agents

Difluoromethylornithine inhibits ornithine decarboxylase, an essential enzyme in the process of cell proliferation. Loss of hearing acuity has emerged as a drawback to its use in human trials.<sup>133</sup> Oltipraz is a compound related to dethiolthionines, which are found in cruciferous vegetables. It is already in use as an anti-schistosomiasis agent. Oltipraz has reached the stage of human clinical trials as a chemopreventive agent. Ursodeoxycholic acid is a 'trace' bile acid in humans. It can neutralise some toxic effects of bile and it is under clinical trial for adenoma prevention. There is evidence that it decreases incidence of colorectal neoplasia in ulcerative colitis, and reduces development of adenomas with high grade dysplasia in patients with previous adenomas.<sup>134, 135</sup>

Other agents under investigation as specific extracts rather than foods include green tea extracts, magnesium hydroxide, curcumin, tumeric, genistein (a soy extract), and vitamin D, some of which are being studied in clinical trials.

### 2.11 Conclusions

Modifiable dietary and life-style factors have been estimated to account for 70% of the attributable risk for Colorectal Cancer in Western populations.<sup>136</sup>

The guidelines and recommendations espoused in this chapter fit into what is currently recommended as a healthy lifestyle in general, with some special emphasis on certain aspects of Colorectal Cancer prevention that may be relevant to some high-risk groups. It is worth repeating that appropriate dietary changes, together with regular physical activity and maintenance of healthy weight could, in time, substantially reduce the incidence of Colorectal Cancer.

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