Cancer of the colon and rectum is the second most common cause of cancer mortality in Westernized countries [1]. Incidence rates vary approximately 20-fold around the world. The international differences, migrant data, and recent rapid changes in incidence rates in Italy, Japan, urban China, and male Polynesians in Hawaii [1] show that this cancer is highly sensitive to changes in diet and other aspects of the environment. Diet appears to have a particularly strong association with the occurrence of this cancer and thus offers promise for intervention. In this chapter, current research on diet and risk for and primary prevention of colorectal cancer, with an emphasis on epidemiologic studies, is summarized.

Fat and Meat

The hypothesis that dietary meat and/or fat increases risk of colon cancer is one of the oldest and most investigated. Certainly, intake of meat that is high-fat, processed, smoked, salted, etc., from the evolutionary perspective, is a historically recent phenomenon [2]. Highly plausible explanatory hypotheses have been developed in support of a causal relationship between meat and fat intake and colon cancer (summarized in Table 1) and the data from animal and metabolic studies in support of these hypotheses have been substantial [3]. The oldest hypothesis is that fat intake increases the production of bile acids which are mutagenic and cytotoxic. In metabolic epidemiologic studies, increased fecal concentrations of bile acids have been found in populations with higher rates of colon cancer as well as in patients with colonic neoplasms (although not entirely consis-
Table 1. Hypothesized mechanisms of increased risk of colon cancer from high intakes of meat or fat\(^1\)

<table>
<thead>
<tr>
<th>Fat increases bile acid production</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bile acids damage DNA</td>
</tr>
<tr>
<td>Bile acids are toxic to colon cells resulting in compensatory colonic epithelial cell proliferation</td>
</tr>
<tr>
<td>Bile acids in meat eaters vs. vegetarians more readily transform into potential carcinogens</td>
</tr>
</tbody>
</table>

High fat intake associated with increased oxidative mitogenic and cytotoxic damage

Meat (especially red meat) increases fecal iron which catalyzes oxidative reactions, leading to increased oxidative mitogenic and cytotoxic damage

Meat cooked at high temperatures contains higher amounts of carcinogenic heterocyclic amines

\(^1\) Potential mechanisms may not be mutually exclusive, but may be additive or synergistic.

In animals, the tumor-enhancing effects of bile acids are increased after enzymatic modification by intestinal bacteria. Among humans, the capacity of colonic flora to transform bile acids into potential carcinogens has been found to be greater in populations with high rates of colon cancer and among meat eating populations than in vegetarian populations. Furthermore, this capacity is reduced when the intake of beef fat is reduced. In animals, a high intake of saturated and unsaturated fat increased chemically induced colon tumorigenesis (although not entirely consistently).

Of at least 41 analytic epidemiologic studies investigating the meat/colon cancer association, 24 found a direct association, one an inverse association, and 16 no definite association \([1, 3–8]\). The only study to find an overall inverse association was an older prospective mortality study in Japan, a society generally at low risk for colon cancer. Other studies have found inverse associations with poultry or fish. A second prospective mortality study, this one in Seventh Day Adventists, reported a null association, and a third, a small cohort in White males \([5]\), found a direct association. Of five prospective studies of incident colorectal cancer, one, the Nurses' Health Study, reported a direct association; a second, the Iowa Women's Health Study, using the same food frequency questionnaire as the Nurses' study, reported a null association; a third, the Norwegian National Health Screening Service cohort with 143 cases found a null association for total meats but a direct association for sausage limited to women \([6]\); a fourth, in Seventh Day Adventists, in contradistinction to the earlier mortality study, found a direct association \([7]\), and the fifth, a Finnish cohort study, found direct associations with smoked, salted fish, cured meat, and meats with N-nitroso compounds \([8]\).
Of 25 studies investigating the fat/colon cancer association, 10 found a direct
association, one an inverse association, and 14 no definite association [1, 3, 4, 6,
9, 10]. The only studies to find an overall inverse association were a prospective
study of Hawaiians of Japanese descent, and a case-control study of Montreal
francophones that found nonsignificant odds ratios (ORs) of 0.78 and 0.71 for
total and saturated fats, respectively [9]. However, another study found a statisti-
cally significant inverse association (OR = 0.6) with the ratio of polyunsaturated
to saturated fatty acids [10]. Only three other prospective studies have examined
the association; one, the Nurses’ Health Study, reported a direct association; the
second, the Iowa Womens’ Health Study, using the same dietary assessment
instrument, reported a null association; and the third, the Norwegian National
Health Screening Service cohort study [6], found a null association for total fat
and for various types of fat.

Of interest is that the Iowa Womens’ Health Study, the Nurses’ Health Study,
and several, but not all other studies that investigated different types of meats in
relation to colon cancer, reported associations that involved higher fat meats (red
meats, processed meats, etc.) and were consistent with increased risk, while associ-
ations that involved fish and/or other seafoods or skinless white meat poultry
were consistent with decreased risk [1, 3, 4].

Although associations between fat and meat and colon cancer have now been
investigated in over 40 analytic epidemiologic studies, and although direct associa-
tions were found in approximately one half to two thirds of these studies, find-
ings are too inconsistent to establish causal relationships. Furthermore, the inter-
pretation of many studies is hampered by the common finding of a direct associa-
tion between total energy intake and colon cancer risk, thus raising uncertainty as
to whether it is the total amount of food consumed or the fat or meat components
of the diet that is etiologically important. Other hypothesized explanations for
differences in the findings across studies are differences in populations; study
designs, dietary assessment methodologies, and data analysis procedures; and
population ranges of dietary intakes, cooking practices, genotypic or phenotypic
susceptibility, and molecular characteristics (implying possible differences in eti-
ologies) of the cancers. Null associations in many studies may be related to dietary
or cooking method homogeneity within populations, the lack of accuracy of cur-
rently available dietary assessment instruments, and mix of genetically suscepti-
bile individuals or tumors of given molecular characteristics/etiologies.

For example, some, but not all, studies that have examined the association of
meat doneness or method of preparation have found a stronger risk with cooking
at higher temperatures or to greater degrees of doneness, as surrogates of hetero-
cyclic amine exposure [4]. Even more recently, some studies have found even
stronger associations with indicators of heterocyclic amine exposure from cook-
ing meat with rapid activity of some enzymes that metabolize heterocyclic
amines. In these studies N-acetyltransferase activity was indicated by either phe-
notyping using model compounds or genotyping for polymorphisms of NAT1 and
Table 2. Hypothesized colon anticarcinogenic mechanisms of dietary fiber

<table>
<thead>
<tr>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increases stool bulk, diluting fecal mutagens</td>
</tr>
<tr>
<td>Decreases stool transit time, decreasing fecal mutagen contact time</td>
</tr>
<tr>
<td>Binds or dilutes bile acids, reducing their mutagenic and cytotoxic effects</td>
</tr>
<tr>
<td>Binds or dilutes carcinogens</td>
</tr>
<tr>
<td>Ferments</td>
</tr>
<tr>
<td>To volatile fatty acids that are potentially anticarcinogenic</td>
</tr>
<tr>
<td>To volatile fatty acids that decrease pH</td>
</tr>
<tr>
<td>Reducing conversion of primary to more carcinogenic secondary bile acids</td>
</tr>
<tr>
<td>Reducing solubility, thus carcinogenic activity of free bile acids</td>
</tr>
<tr>
<td>Leading to release of bound calcium which may bind bile acids</td>
</tr>
<tr>
<td>Induces different patterns of colonic bacteria, thus influencing type and degree of relevant metabolic reactions</td>
</tr>
</tbody>
</table>

1 Potential mechanisms may not be mutually exclusive, but may be additive or synergistic.

NAT2. One study suggested that the risk from beef was more associated with tumors that were p53-negative [11], but a second study found no associations with various groupings of meat regardless of the p53 status of the tumors [12].

Opposite findings within many studies for higher fat meats (increased risk) vs. fish or seafoods (decreased risk) may have etiologic implications and suggest the need to investigate various meat groupings more vigorously [3]. For example, if the mechanism of the hypothesized meat/colon cancer relationship is more a matter of low-fat meats vs. high-fat meats, then the bile acid explanatory hypothesis may be more tenable than the cooked meat hypothesis. Alternative explanations, however, include other unidentified or accounted for healthy behaviors associated with low-fat meat consumption, potential protective effects of ω-3 fatty acids in seafoods (for example, ω-3 fatty acids have reduced colonic epithelial cell proliferation in a small clinical trial in humans), and different cooking methods associated with red meats vs. seafoods.

Fiber

The hypothesis that fiber decreases the risk of colorectal cancer is also one of the oldest and has also been heavily studied. From the evolutionary perspective, a low intake of fiber is a historically recent phenomenon [2]. Mechanistic hypotheses are summarized in Table 2 [13]. It is becoming more apparent, however, that looking at dietary fiber as a single entity may be misleading and oversimplifying the fiber-colon cancer association. Fiber classifications that may be important etiologically include nonstarch polysaccharides (cellulose, hemicelluloses, pectin,
gums, mucilages) vs. non-polysaccharides (lignin), water-soluble (pectin, gums, mucilages, and some hemicelluloses) vs. water-insoluble (cellulose, lignin, and most hemicelluloses), fermentable vs. nonfermentable, cereal vs. vegetable, etc. [13]. For example, cellulose and wheat bran have been shown to decrease fecal bile acid concentrations, whereas oat and corn bran have been shown to increase concentrations. Insoluble fiber tends to increase fecal bulk and decrease transit time, whereas soluble fiber has less effect. (Cellulose is found primarily in root and leafy green vegetables and legumes; hemicellulose primarily in cereal brans; pectin in fruit, and gums in legumes and oats.)

Furthermore, results of animal studies involving fiber feeding and colon cancer have been mixed [13]. Part of the inconsistency may be due to feeding different types of fiber. Wheat bran, although not in every study, has been the fiber most consistently providing an apparent protective effect. Results of studies of oat bran, corn bran, and pectin have been more mixed.

The results of observational epidemiologic studies of fiber and colon cancer have been mixed, but generally supportive of the fiber-colon cancer hypothesis [1, 3, 4, 14]. Of 19 case-control studies assessing fiber intake as a specific dietary constituent, eight provided strong support for a protective effect, five provided moderate support, four no support, and two suggested an increased risk with increased fiber intake. A meta-analysis of 13 case-control studies (using original data) found a statistically significant approximate halving of risk for those in the highest quintile of fiber intake compared to those in the lowest quintile. The results of three prospective cohort studies have not provided strong support for dietary fiber, on the whole, as being protective against colon cancer. In the Nurses’ Health Study, total dietary fiber, vegetable fiber, fruit fiber, and cereal fiber, were not associated with risk. In the Iowa Women’s Health Study, total dietary fiber was not associated with risk, although the relative risk for cancer of the distal colon was 0.66 (95% CI 0.34–1.29) for the highest quartile compared to the lowest, but there was no suggestion of a dose-response. In the Norwegian National Health Screening Service cohort there was no apparent association of fiber and risk of colon cancer [6]. Two recent case-control studies had the capacity to estimate intakes of a wider variety of types of fiber. In one, a large hospital-based case-control study in Italy [15], inverse, but not statistically significant, associations were found for total fiber (nonstarch polysaccharides), soluble noncellulose polysaccharides, total insoluble fiber, cellulose, insoluble noncellulose polysaccharides, lignan, vegetable fiber, and fruit fiber, but not for cereal fiber. A second, large population-based case-control study in a racially diverse population in Hawaii [16], found evidence for decreased risk in association with dietary fiber, nonstarch polysaccharides, soluble fiber, insoluble fiber, cellulose, and noncellulose polysaccharides, but it appeared that these associations were all primarily due to fiber from vegetable sources. There was also evidence to suggest that there was an association of vegetable fiber independent of other potential mechanisms of vegetables as potential reducers of risk.
On the whole, then, the idea that at least some types of dietary fiber may afford protection against colon cancer is highly plausible, and the animal experimental and human observational literature is generally supportive of the hypothesis. Much work needs to be done to (1) sort out which type(s) of fiber, if any, are protective; (2) include more valid estimates of intake of different fiber types in more observational epidemiologic studies, and (3) conduct fiber-feeding trials in humans.

**Vegetables and Fruit**

Vegetables and fruit contain a myriad of potentially anticarcinogenic compounds, and as a food group have been more consistently associated with risk (a reduced risk) of colon cancer than any other dietary factor [1, 3, 4, 14]. From the evolutionary perspective, a low intake of plant-based foods is a relatively recent population phenomenon [2]. Potential anticarcinogenic agents in plants (Table 3) include fiber (reviewed above), antioxidants and antioxidant enzyme-associated micronutrients and folate (reviewed further below) [13]. Other potential anticarcinogenic compounds for which there has of yet been little study in humans include: dithiolthiones, glucosinolates and indoles, isothiocyanates and thiocyanates, coumarins, flavonoids, phenols, protease inhibitors, plant sterols, isoflavones, saponins, inositol hexaphosphate, allium compounds, and limonene [13]. Plant potential anticarcinogenic compounds, including the lesser studied ones, have both complementary and overlapping mechanisms of action, including the induction of detoxification enzymes, inhibition of nitrosamine formation, provision of substrate for formation of antineoplastic agents, dilution and binding of carcinogens in the digestive tract, alteration of hormone metabolism, antioxidant effects, and others [13].

Potter et al. [1] postulated that a diet regularly high in plant foods is the one to which humans are most adapted. This diet, then, provides regular high amounts of substances to which the human metabolism is dependent for optimum health, some of which have not been identified as essential nutrients. Many of these substances can serve to keep inducible enzyme systems “tuned” to handle occasional high intakes of carcinogens; inhibit the formation of other carcinogens; reduce the capacity of transformed cells to proliferate, and act as antioxidants, etc. Thus, abandonment of the vegetable and fruit anticarcinogen “cocktail” to which we are adapted may increase the risk of colon cancer.

The analytic epidemiologic literature on the association of vegetables and fruit and colon cancer is very consistent. Of 31 analytic epidemiologic studies (28 case-control studies and three cohort studies) that investigated the possible association of vegetables and fruit and the incidence of colon cancer, 29 were in an inverse direction (23 were statistically significant), and two were in the direction of increased risk [1, 3, 4, 14]. There has been more consistency for vegetable intake
### Table 3. Potentially anticarcinogenic constituents of vegetables and fruit, their common sources, and potential mechanisms

<table>
<thead>
<tr>
<th>Constituents</th>
<th>Common plant sources</th>
<th>Potential anticarcinogenic mechanisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fiber</td>
<td>All plants</td>
<td>See Table 2</td>
</tr>
<tr>
<td>Antioxidants</td>
<td>All plants</td>
<td>Protect against oxidative damage</td>
</tr>
<tr>
<td>Folate</td>
<td>Leafy green vegetables</td>
<td>Protects against DNA hypomethylation</td>
</tr>
<tr>
<td>Dithiolthiones</td>
<td>Cruciferous vegetables</td>
<td>Increase glutathione</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Increase glutathione reductase</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Increase glutathione transferase</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Increase quinone reductase</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Increase glucose-6-phosphate dehydrogenase</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Increase 6-phosphogluconate dehydrogenase</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Block reaction of electrophilic carcinogens with cellular macromolecules</td>
</tr>
<tr>
<td>Glucosinolates</td>
<td>Cruciferous vegetables</td>
<td>Increase mixed-function oxidase activity</td>
</tr>
<tr>
<td>Indoles</td>
<td>Cruciferous vegetables</td>
<td>Increase mixed-function oxidase activity</td>
</tr>
<tr>
<td>Isothiocyanates</td>
<td>Cruciferous vegetables</td>
<td>Inhibit DNA methylation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Induce phase-II xenobiotic metabolizing enzymes</td>
</tr>
<tr>
<td>Thiocyanates</td>
<td>Cruciferous vegetables</td>
<td>Inhibit DNA methylation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Induce phase-II xenobiotic metabolizing enzymes</td>
</tr>
<tr>
<td>Coumarins</td>
<td>Vegetables, citrus fruit</td>
<td>Induce glutathione S-transferase activity</td>
</tr>
<tr>
<td>Flavonoids</td>
<td>Most vegetables, fruit</td>
<td>Antioxidant properties</td>
</tr>
<tr>
<td>Phenols</td>
<td>Variety of vegetables, fruit</td>
<td>Some are antioxidants, flavonoids, coumarins</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Some inhibit N-nitrosation reactions</td>
</tr>
<tr>
<td>Phenol</td>
<td>Most plants, especially in seeds, legumes, potatoes, sweet corn</td>
<td>Competitively inhibit proteases</td>
</tr>
<tr>
<td>Plant sterols</td>
<td>Most plants</td>
<td>Possible beneficial effects on cell membranes</td>
</tr>
<tr>
<td>Isoflavones</td>
<td>Variety of plants, especially soybeans</td>
<td>Weak estrogenic activity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inhibit tyrosine kinase</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inhibit certain P450 enzymes</td>
</tr>
<tr>
<td>Saponins</td>
<td>Variety of plants, especially soybeans</td>
<td>Bind bile acids</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reduce colonic epithelial cell proliferation</td>
</tr>
<tr>
<td>Inositol</td>
<td>Variety of plants, especially soybeans and cereals</td>
<td>Decrease lipid peroxidation</td>
</tr>
<tr>
<td>hexaphosphate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allium compounds</td>
<td>Allium vegetables (e.g., onions, garlic)</td>
<td>Induce glutathione S-transferase</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Induce microsomal monoxygenase</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inhibit bacterial conversion of nitrate to nitrite</td>
</tr>
<tr>
<td>Limonene</td>
<td>Citrus fruit</td>
<td>Induces glutathione S-transferase</td>
</tr>
</tbody>
</table>

1 Potential mechanisms may not be mutually exclusive, but may be additive or synergistic.
Table 4. Hypothesized colon carcinogenic mechanisms of sucrose

<table>
<thead>
<tr>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>When cooked, contains compounds that are genotoxic</td>
</tr>
<tr>
<td>Increases colon transit time, increasing carcinogen contact time</td>
</tr>
<tr>
<td>Increases fecal concentration of total and secondary bile acids</td>
</tr>
<tr>
<td>Increases colorectal epithelial cell proliferation</td>
</tr>
<tr>
<td>May increase aberrant crypt foci formation</td>
</tr>
<tr>
<td>High glycemic index promotes hypertriglyceridemia, hyperinsulinemia, insulin resistance</td>
</tr>
</tbody>
</table>

Potential mechanisms may not be mutually exclusive, but may be additive or synergistic.

In summary, a decreased risk of colon cancer with an increased consumption of vegetables and fruit is biologically plausible and supported by the most consistent analytic observational epidemiologic literature of any diet-colon cancer association; however, more prospective data are needed. The multiplicity of potential mechanisms, rather than detracting from the plausibility of a protective effect of vegetables and fruit, makes a strong case for the potential of increased vegetables and fruit in the primary prevention of colon cancer.

Sucrose

It has long been known that a high intake of sucrose is a prominent distinguishing feature of the high-risk Western-style diet [2]. Little attention, however, has been paid to the possibility that this historically recent prominent dietary constituent might be etiologically linked to colon carcinogenesis. Potential mechanisms are summarized in Table 4 [3].

To date, 17 analytic epidemiologic studies have reported investigating the association of sucrose and colon neoplasia; of these, 15 reported an association in the direction of increased risk (findings were significant in seven, one reported an OR of exactly 1.0, and one reported a statistically nonsignificant inverse association).
Nutrition and Colon Cancer Prevention

Among the six studies that found a significantly increased risk with higher sucrose intakes, the prospective Iowa Womens’ Health Study reported a RR of 2.0, a Belgian case-control study of incident colon cancer reported an OR of 2.31 with more evidence of a dose-response relationship, a French case-control study of incident colorectal adenoma reported an OR of 2.17 but with more evidence for a limitation to the highest intake grouping, a US multicenter case-control study [17] found an OR of 1.59, a Uruguayan case-control study [18] an OR of 2.18 (6.07 if also highest quantile of protein), and an Italian case-control study [19] an OR of 1.4. A Spanish case-control study and an Italian case-control study also reported risk estimates of about 2.0 but that narrowly missed statistical significance at the p ≤ 0.05 level [3]. One Italian study found an increased risk with pastries but not candy bars [20]. Another of the studies that suggested a direct association (RR = 2.0) was the only previous prospective study to investigate the sucrose-colon cancer association; however, the study endpoint was colon cancer mortality, the number of cases was small (n = 41), and the sucrose exposure measurement was limited to consumption of cake or pie [3]. The only study to suggest an inverse association was a small hospital-based case-control study in Greece [3].

The Iowa Womens’ Health Study, the only prospective study to address sucrose intake and colon cancer incidence, found a nearly twofold increased risk of colon cancer in women associated with high intakes of sucrose and sucrose-containing foods [3]. Among the sucrose-containing foods, no individual foods or groupings of foods appeared to contribute disproportionately to the overall association, and the association for sucrose was approximately the same as for the total sucrose-containing food grouping. No multiplicative interactions were seen between meat and sucrose-containing foods or between fat and sucrose. These observations suggest that it is increased sucrose consumption *per se* that is associated with increased risk of colon cancer rather than the consumption of sucrose in combination with something else or sucrose that has been used in a certain way (e.g., cooked vs. uncooked). There was a suggestion, however, that the association involving a grouping of all sucrose-containing foods was stronger after removing the calcium-rich food items (ice cream and ice milk). This suggests a hypothesis that a protective effect of calcium may have been partially negating a risk-enhancing effect of sucrose.

The sucrose findings of the several studies, then, in relation to incident colon cancer are fairly consistent, and several are not only statistically significant but are relatively strong for diet-disease associations. Taken as a whole, the findings of the analytic epidemiologic studies are generally supportive of the possibility of a causal relationship and, as discussed above, are biologically plausible.
Calcium

The estimated average intake of calcium in modern Western diets is 740 mg daily, an amount that from the evolutionary historical perspective is low [2]. The calcium intake of all mammalian species (including chimpanzees) other than modern man is equivalent to a human intake of 1,500–2,000 mg daily, an amount that corresponds to the estimated intake of Paleolithic man [2]. Given that, on average, only about 30% of calcium consumed is absorbed from the gut, it is plausible that the mammalian gut is best adapted for high enteral levels of calcium. If enough calcium is consumed (estimated at 1,500–2,000 mg daily) for absorption for physiologic needs and to bind free phosphate in the gut there will be sufficient free enteral calcium to bind bile acids, thereby preventing their mutagenic and cytotoxic effects [3]. Furthermore, in human colonocyte cell culture, calcium has been shown to reduce cell proliferation and increase differentiation [3]. The mechanisms by which calcium affects cell cycle are not clear; however, several lines of research indicate that calcium may exert such effects by interacting with cyclic AMP, calmodulin, tyrosine kinase, and ornithine decarboxylase [3]. In addition, calcium may influence other mechanisms; for example, cell adhesion mechanisms involving E-cadherin, a calcium-dependent cell adhesion molecule that interacts in complex fashion with the adenomatous polyposis coli gene product [3]. Calcium has been consistently shown to reduce colon carcinogenesis in animals [3].

The analytic observational epidemiologic literature on the association of calcium and colon cancer is somewhat inconsistent, but inverse associations have more frequently been found. Of 23 analytic epidemiologic studies (15 case-control studies and eight cohort studies) that investigated the possible association of calcium and colon cancer, 17 suggested inverse associations, and three positive associations (no direction of association was reported in two studies) [1, 3, 4]. None of these studies found a statistically significant increased risk associated with higher calcium intake. A statistically significant decreased risk associated with higher calcium intake was found in six of the case-control studies and in three of the cohort studies (limited to the sigmoid colon in one of the latter and to those with no family history of colon cancer in another). The cohort studies that reported no association were the Nurses’ Health Study (OR = 0.7) [21], the Health Professionals Follow-up Study (OR = 0.75) [22], the Iowa Women’s Health Study (OR = 0.68) [3] (all three used virtually identical food frequency questionnaires), and a prospective study in the Netherlands (nested case-control, OR = 0.92) [3]. Of the three studies suggesting positive associations of calcium intake with risk of colon cancer, one reported only univariate results even though total energy intake was positively associated with colon cancer, a second reported OR was 1.1, a figure not meaningfully different from 1.0, and the third, a Belgian case-control study, reported an OR of 1.34 [3].
In clinical trials, calcium has been found to normalize the proliferative zone in colon crypts [3]. More importantly, calcium supplementation statistically significantly reduced adenoma recurrence by approximately 20% in a recent US multicenter clinical trial [23]. This 20% figure is remarkably similar to the risk reduction estimates from the US cohort studies.

**Vitamin D**

Compared to calcium, similar but less extensive evidence exists to support a role for vitamin D in lowering colorectal cancer risk. The colonic epithelium contains vitamin D receptors, and vitamin D is intimately related to calcium metabolism, has reduced cell proliferation in human colon cell lines in vitro, has reduced colonic epithelial cell proliferation in rodents, was a necessary cofactor in reducing k-ras G to A mutations in colorectal neoplasms in rats, and has reduced tumorigenesis in rats [3].

Of 12 analytic epidemiologic studies (five cohort studies and seven case-control studies) that investigated the possible association of vitamin D and colon cancer, ten suggested an inverse association, one reported a null association, and none reported a direct association [1, 3, 4, 21, 22]. All five of the cohort studies found inverse associations ranging from RRs of 0.3 to 0.73 [3, 21, 22]; of these, three were statistically significant. All seven of the case-control studies found inverse associations ranging from ORs of 0.4 to 0.93; of these, two were statistically significant.

**Milk Products**

Although milk products have received little attention in laboratory experiments related to colon cancer, they are major sources of calcium and vitamin D in the American diet.

Of 17 analytic epidemiologic studies (12 case-control studies and five cohort studies) which investigated the possible association of milk and colon cancer, 12 suggested an inverse association, four a positive association, and one no association (OR = 1.0) [1, 3, 4, 22]. None of these studies found a statistically significant positive association. The inverse associations were statistically significant in five case-control studies. Observed associations were not statistically significant in the remaining studies; however, of the studies that reported strength of association, seven (including the five cohort studies) [3, 22] were in the direction of decreased risk and four were in the direction of increased risk. One of the five cohort studies reported a positive association (OR = 1.09) [22] and all studies reporting positive associations were hospital-based. The only two studies that reported strong inverse associations were the population-based Utah and Seattle, Wash., case-control studies.
Antioxidants and Antioxidant Enzyme-Associated Micronutrients

Antioxidant-related micronutrient intake has been of great interest in relation to risk of colorectal cancer. From the evolutionary perspective, the density of antioxidant-related and other micronutrients in modern diets is low [2]. Oxidizing agents from endogenous and exogenous sources are believed to be both initiators and promoters of carcinogenesis [3]. These agents damage DNA, are cytotoxic, and modulate gene expression. The colonic luminal contents expose the colonic epithelium to tremendous levels of oxidative stress. Micronutrients such as vitamin E, vitamin C and the carotenoids have direct antioxidant activity. Other micronutrients such as selenium, riboflavin, niacin, zinc, and manganese are essential components of important antioxidant enzymes. Various antioxidant micronutrients appear to enhance or even to be essential to the antioxidant effects of one another. Vitamin E, the carotenoids, vitamin C, and selenium can also stimulate the immune system and may protect against the development of cancer by enhancing immune surveillance. Vitamins E and C can also reduce nitrite, inhibiting the production of nitrosamines and nitrosamides, compounds that induce tumors in experimental animals and possibly in humans. β-Carotene and selenium may also inhibit cell proliferation by effects independent of their antioxidant activities. Vitamin E, carotenoids, vitamin C, and selenium were found to reduce colon tumorigenesis in animals. Furthermore, in several studies, antioxidant micronutrients enhanced the effects of one another, emphasizing their interdependence.

The analytic observational epidemiologic evidence for an association of vitamin E and risk for colorectal cancer is mixed, but the evidence from prospective studies is consistent with an inverse association. In the prospective Iowa Women’s Health Study (n = 35,215) [3], an adjusted RR of 0.32 (95% CI 0.19–0.54) was found for those in the highest quintile of intake of total vitamin E compared to those in the lowest quintile of intake. The association was even more striking in the youngest age group (55–59 years old) for which the RR was 0.16 (95% CI 0.04–0.70). Several years later the association was again investigated, this time according to a family history of colon cancer [24]. An inverse association was found among persons without a history of a first-degree relative who had colon cancer, but not among persons with a positive family history. Findings in five prospective studies suggested that the prediagnostic serum level of α-tocopherol was lower in subjects who subsequently developed colorectal cancer than in non-cases [3]. Differences were not statistically significant in any one of the five studies, but when the original data from the five studies were pooled and analyzed, the OR for the highest quartile of serum α-tocopherol concentration compared to the lowest was 0.6 (95% CI 0.4–1.0) with and 0.7 (95% CI 0.4–1.1) without adjustment for serum cholesterol.

Assessment of dietary intake of carotenoids until recently has been limited to estimates of β-carotene and vitamin A. Furthermore, human study of carotenoids
as potential anticarcinogenic agents has been somewhat inhibited by findings of increased risk of lung cancer in smokers in two clinical trials of β-carotene. Findings in older analytic observational epidemiologic studies are mixed [3]. Findings in two prospective studies were null. In more recent studies, all case-control studies, five of seven found inverse associations and two found no association. Two of the studies were able to examine various types of carotenoids. In one, inverse associations were found for multiple carotenoids but not for β-carotene [9]; in the other, no associations were found for any type of carotenoid or for total carotenoids [25].

The analytic observational epidemiologic evidence for vitamin C has also been mixed, with most studies finding either weak inverse associations or no association [3].

Selenium has also been found to be inversely associated with colon cancer. Because the selenium content of food varies with soil and growing conditions, dietary intake of selenium cannot be measured accurately in larger, analytic epidemiologic studies [3]. In ecologic studies, internationally and within the US, dietary selenium, local plant selenium levels, and blood selenium concentrations were significantly inversely correlated with age-adjusted mortality from cancer of the colorectum [3]. In three cohort studies that measured serum selenium levels, a marginal association was observed in one; lower mean levels of selenium were found in individuals who developed colon cancer in a second, and a null association was found in the third [3]. In another prospective cohort study, toenail selenium levels were marginally, but not statistically associated with risk of colon cancer [3]. In the prospective Iowa Women’s Health Study, the adjusted RR of colon cancer for those taking selenium supplements compared to those who were not was 0.6 (95% CI 0.27–1.32) [3].

Despite the strong plausibility for a protective effect against cancer, riboflavin, niacin, zinc, and manganese have received little attention in animal or human studies; however, the limited data are generally, but not entirely, supportive for a protective effect for them too [3].

Four small clinical trials in humans suggest that antioxidants can reduce colorectal epithelial cell proliferation [3]. Although five preliminary clinical trials of antioxidant micronutrient supplements and adenoma recurrence all suggested beneficial effects, a large-scale, well-conducted, randomized, controlled trial found no efficacy of administering a combination of vitamin E (400 mg), β-carotene (25 mg), and vitamin C (1,000 mg) in reducing adenoma recurrence over a 4-year period [3].

There are few clinical trial data pertaining to the efficacy of antioxidants in reducing the incidence or mortality of cancer, and the colon cancer data are even more limited. There have been two reported clinical trials testing the efficacy of antioxidants in reducing the cancer incidence or mortality in which colon cancer incidence was monitored. One study, a randomized, double-blind, placebo-controlled trial in 29,133 fifty- to sixty-nine-year-old Finnish male smokers tested
α-tocopherol (50 mg daily) and β-carotene (20 mg daily), each alone and in combination, vs. placebo over 5–8 years [3]. The primary endpoint of the trial was lung cancer incidence, but colon cancer incidence was monitored. Although there was an 18% increase in the incidence of lung cancer in men on β-carotene alone (but no increase in those on α-tocopherol alone or in combination with β-carotene, perhaps again emphasizing their interdependence), there was a nonstatistically significant decrease in the incidence of colon cancer in those on α-tocopherol, but no apparent effect from β-carotene alone. Data on α-tocopherol and β-carotene in combination in relation to colon cancer were not presented. In the second, a randomized, double-blind, placebo-controlled, clinical trial of selenium and skin cancer in which colon cancer incidence was also monitored, there was a statistically significant decrease in the risk of colorectal cancer with selenium supplementation relative to placebo [26].

**Folate**

Folate intake as a potential protective factor against colon carcinogenesis has been of recent interest. Global DNA hypomethylation is consistently found in colon neoplasms [1, 3, 4]. It also appears to be an early event in the multi-step process of colon carcinogenesis, occurring in non-neoplastic tissue prior to the development of the neoplasm. Hypomethylation may be initiated by inadequate cellular levels of the methyl donor, S-adenosylmethionine, the production of which is dependent on the vitamin, folate, and the amino acid, methionine, as well as vitamins B6 and B12. Diets deficient in folate and methionine may cause DNA hypomethylation. In addition, alcohol, a methyl group antagonist, may cause DNA hypomethylation. Thus, a high alcohol intake, in combination with a diet low in folate, methionine, B6 and B12 may cause even greater DNA hypomethylation. A major source of dietary folate is plant foods, and that of methionine, animal products. In addition to these biochemical findings providing biological plausibility for the hypothesis that folate and methionine may protect against colon cancer, is that methyl-deficient diets have been shown to cause various cancers in animals.

In human analytic observational epidemiologic studies, an inverse association between folate and the risk of colon cancer has been reported in five recent case-control studies and three cohort studies [1, 3, 4]. Using the same food frequency questionnaire as in the male cohort study, the authors of one of the male cohort studies also found an inverse association with colon adenoma in two cohorts. In the cohort studies the association was strongest in those with high alcohol consumption. One cohort study found a stronger association among persons homozygous for mutant MTHFR, but a case-control study did not find a substantial difference according to MTHFR polymorphism.
Coffee and Tea

Although associations of coffee and tea with risk for colorectal cancer have been investigated previously, only recently have strong, biologically plausible mechanisms, such as antioxidant activity, been articulated [1, 27–29]. Among five recent studies that investigated tea, one found an inverse association (primarily with rectal cancer), one found a direct association (for colon, but a null association for rectum), and the others no association. The study finding an inverse association was a population-based, case-control study in Shanghai that investigated green tea [28]. The study finding a direct association was a small, nested, case-control study in a clinical trial cohort of older Finnish male smokers; tea exposure was primarily black tea, which was not widely or heavily consumed [29]. The null studies were all Western (Italy, Switzerland, Netherlands, Argentina) case-control studies in which tea consumption was primarily black tea, which was not widely or heavily consumed.

Other Aspects

Other aspects of diet have been examined in basic, animal, and a few human studies. Investigated factors have included dietary diversity; dietary patterns; other specific foods, nutrients, micronutrients, and non-nutrients; cooking vs. raw foods; N-nitroso compounds, and others. There is as yet not enough human evidence to discern a pattern or lack thereof for many of these aspects of diet.

Needed Research

Some areas of needed research are summarized in Table 5. Increased understanding of the molecular basis of colon carcinogenesis is opening up opportunities to increasing the understanding of the environmental determinants of colorectal cancer. Figure 1 shows a schema summarizing current knowledge of molecular events involved or associated with colon carcinogenesis [4], where diet may have an impact, and what genes/proteins and gene expressions could be assessed for impact.

Conclusions

Diet and nutrition clearly play a role in the etiology and primary prevention of colon cancer. The most consistent dietary factor associated with colon cancer is vegetable and fruit intake, with a high intake being associated with a decreased risk. Many of the dietary constituents that have been less well studied, but are
Table 5. Some future directions for research into the role of diet and nutrition in the etiology and primary prevention of colon cancer

Sorting out the competing and complementary effects of:
- Energy balance, total energy intake, fat, meat, meat cooking methods, methionine and other constituents of meats, and metabolic phenotypes
- Constituents of plant foods, cooking methods, and metabolic phenotypes
- Refined sugars, grains, potatoes, carbohydrates, glycemic response, and insulin resistance

Elucidating interactions of various aspects and constituents of diet with metabolizing and other enzymes

Elucidating interactions of various aspects and constituents of diet with the various genes, gene products, and other proteins involved or associated with the multi-step process of colon carcinogenesis (Fig. 1)

emerging as at least fairly consistently associated with a decreased risk of colon cancer, are nutritive and non-nutritive substances that are most abundant (or could be most abundant; e.g., calcium) in vegetables and fruit: fiber, calcium, antioxidants, and folate. In addition to many of these relatively well-studied constituents of vegetables and fruit, there is a myriad of other compounds in vegetables and fruit that may plausibly reduce the risk of colon cancer but have not yet received a great deal of study. Many of the dietary constituents of the modern Western diet that are most consistently associated with an increased risk of colon cancer are found in abundance in diets low in vegetables and fruit: fat, sucrose, and high-fat red meat cooked at high temperatures. An explosion in the understanding of the molecular basis of colon carcinogenesis is beginning to fuel a leap forward in understanding the contributions of diet to modulation of risk. Individualization of prescriptions for risk reduction as well as substantial reductions in population risk are within sight.

Fig. 1. A model of the molecular biology of colorectal cancer showing potential points of action and study of the effects of dietary agents on colorectal carcinogenesis. ACF = Aberrant crypt foci; Metas. = metastases; Mut. = mutation; β-Cat. = β-catenin; Hypermeth. = hypermethylation; Exog. = exogenous; LOH = loss of heterozygosity; MMR = mismatch repair; MSI = microsatellite instability.
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References

Discussion

Dr. Meier: Do you think sex plays a role in the fiber prevention studies, because more studies show positive results in men than in women?

Dr. Bostick: There appears to be some evidence that estrogens may interact with fiber in some way to affect the risk of colon cancer [1, 2].

Dr. Meier: Maybe time plays a role? Perhaps you should start with fiber intake as a child. There are epidemiological studies showing that in countries where the fiber intake is higher than in Europe, they have less cancer, less diverticulosis, and less constipation.

Dr. Bostick: That would make sense. Colon cancer is a multistep process that occurs over a very long period of time, so those things that increase or decrease the risk will probably be more effective if applied throughout that long time period. I don’t think one should be thinking in terms of what particular thing causes colon cancer or what particular thing will prevent it, but rather that there are various things that increase or decrease the probability of moving along that pathway. It’s the balance of these aspects of our diet and lifestyle that create the environment in the colon that affects the risk of these genetic events occurring. So it certainly makes sense that the proper environment over a lifetime would be more influential than making a sudden change late in life. By that time you may have already accumulated so many genetic changes that it’s beyond the point of reversal.

Dr. Asprer: Can dietary intervention possibly change the course of a patient with a genetic or hereditary background for colon carcinoma? And if so, following the earlier question, how long would that dietary modification have to be in place to make sure that the interaction of environment and heredity does not take effect in the direction of colon cancer?

Dr. Bostick: There is evidence that even in persons genetically predisposed to colon cancer, such as those with familial adenomatous polyposis and hereditary non-polyposis colon cancer, you can affect their risk of getting the disease [3]. There’s evidence both at the human level and at the animal level. There have been antigen-presenting cell and knock-out models that show that you can reduce tumorigenesis with various interventions [3]. Up to now, most of those interventions have been pharmacologic, such as the use of non-steroidal anti-inflammatory drugs (NSAIDs). In humans we’ve also found that we can actually decrease the number of adenomas or the size of their growth with NSAIDs in patients with familial adenomatous polyposis, which is strongly genetically determined. It has been shown that the genes that are defective or mutated in these genetic syndromes are the ones that are
most commonly mutated in the sporadic colon cancers. So whether you acquire it through the germline or through somatic mutation doesn’t seem to matter; in both cases there are exposures that seem to modulate the risk of these events occurring. Cox 2 looks as though it’s going to be really important because we’ve shown that you can modulate it with NSAIDs [3], and that may point us towards foods we can eat that may modulate Cox 2, and towards what kind of foods may modulate some other aspects of molecular carcinogenesis.

**Dr. Asper:** Has it been shown that foods can alter the natural history of familial syndromes?

**Dr. Bostick:** Not yet, that I know of.

**Dr. Lim:** You mentioned that physical activity is probably more important than diet as an etiological factor in the causation of colorectal cancer. Could you elaborate on that and tell us the possible mechanisms?

**Dr. Bostick:** I don’t know that physical activity is more important; it’s just that the observational literature is more consistent for physical activity. Thus of 27 studies, 25 have been in the direction of an inverse association. The reason why physical activity doesn’t get discussed as much as some other factors is that we really don’t have many good ideas as to why it might reduce risk. There have been people who have claimed that it increases the transit time through the colon, but when you take a close look at reports on the frequency of bowel movements and so on, that doesn’t really seem to be a strong association. The only thing I’ve seen recently that might suggest a potential mechanism is that exercise may modulate Cox 2 activity. Perhaps there is something about a positive energy balance that creates a metabolic environment that favors the development of colon cancer.

**References**