Cancer Causes and Control 1996, 7, pp. 127–146

Nutrition and colorectal cancer

John D. Potter

(Received 26 April 1995; accepted in revised form 23 August 1995)

Epidemiologic evidence on the relation between nutrition and colorectal cancer is reviewed. Colon cancer varies approximately 20-fold internationally. Although there is clear evidence of genetic predisposition to colon cancer, much of this variation appears to be related to differences in dietary habits. At present, the data suggest that vegetables are associated with lower risk, and that fiber alone does not account for this association. Further, meat consumption is associated with increased risk but this, too, is not explained solely by its fat content. Several microconstituents of the diet may be associated with reduced risk – including folate and calcium – but phytochemicals of other sorts may be relevant. Mutagenic compounds, particularly heterocyclic amines, produced when protein is cooked, plausibly explain the meat association. The most consistent inverse association is with physical activity. Alcohol is associated, though inconsistently, with increased risk. Rectal cancer is less well studied but, at present, there are few data to suggest that the dietary risk factors are markedly different. Physical activity does not appear to be associated with a lower risk. Colorectal adenomatous polyps also appear to share the spectrum of risk factors seen with colon cancer, although, for adenomas, tobacco smoking is also a clear and consistent risk factor. There are a variety of links between the dietary epidemiology and physiology of colorectal neoplasia and the relevant pathologic and molecular changes. Other causal connections remain to be explicated. *Cancer Causes and Control* 1996, 7, 127-146

Key words: Adenomatous polyps, colon cancer, diet, epidemiology, genetics, molecular biology, review.

Introduction

Colon cancer incidence rates vary approximately 20-fold around the world.[1,2] The developed world – North America, western Europe, Australasia – shows the highest rates with age-adjusted (world standard) incidence rates of 25 to 35 per 100,000 in the late 1980s.[2] It is notable that the formerly relatively low rates in northern Italy are now higher (>30 per 100,000 for males) than in England and Wales (<20 per 100,000).[2,3] The formerly very low rates in Japan have risen now to a level comparable to those in England and Wales.[2,3] The lowest rates are seen in India (1 to 3 per 100,000).[3]

Colon cancer is essentially the only cancer that occurs with approximately equal frequency in men and women.[4] However, in North America and Australia (high rates) and Japan and Italy (rapidly rising rates) in particular, the age-adjusted rates in men now exceed those in women by as much as 20 percent. The differences are less marked in England and Wales. The male and female rates in New Zealand non-Maoris (around 30 per 100,000) are equal. The tendency remains for the rates to be similar between the genders or to or show an excess among women before the age of 50, and always to show an excess among men after that age.[2,3] The risk of cancer varies by subsite within the colon.[2,3,5] Subsite risk has been shown to vary by gender and age: women have higher rates of right-sided neoplasms; males develop cancer at somewhat older ages and more distally.[4,6]

Migrant data suggest that the 20-fold international difference may be explained largely by differences in dietary and other environmental factors. The one interesting exception appears to be the Maoris (Polynesians) who show an unexpectedly low incidence in New Zealand (11.4 per 100,000 in males and 13.7 per 100,000 in females) despite the apparent similarity of their nutrient intakes with their non-Maori compatriots.[3,7] There are some possibilities that specific foods eaten may be markedly different.[8]

Address correspondence to Dr Potter, Cancer Prevention Research Program, Fred Hutchinson Cancer Research Center, 1124 Columbia Street, Seattle, WA 98104, USA.

The Polynesians of Hawaii also had been reported previously to be at a lower risk than expected and comparable to that seen in New Zealand. This lower risk now is seen only in women (13.7 per 100,000), with the male Polynesians showing a rate of 28.0 per 100,000 – similar to that seen in the United States White populations.[3] This male-female difference (more than twofold), if not a consequence of noncomparable denominators, is markedly higher than that seen in any other population group.

More than 90 percent of cancers of the colon are adenocarcinomas.[9] Very little is known about the etiology of colonic lymphomas and carcinoids which comprise almost all of the remaining histologic types.[9]

Five-year relative survival following the diagnosis of colon cancer is almost 60 percent in the US,[10] with similar proportions reported in other parts of the developed world.[11] Survival rates are not well described in many areas of the world.

Migrant studies, as suggested above, as well as the recent rapid changes in incidence rates in Italy, Japan, and perhaps male Polynesians in Hawaii, have shown that the disease is particularly sensitive to changes in environment. Incidence rates reach those of the host country within one or two generations, even within the migrating generation.[12-15] On the other hand, colon cancer has long been known to occur more frequently in some families[16] and there are several rare genetic syndromes which carry an excess risk of colon cancer.[17-19] It is, therefore, a disease for which there are both established genetic predisposition and causal environmental exposures.

Epidemiology of colon cancer

Ecologic studies of diet

Many of the etiologic hypotheses for colon cancer were generated from ecologic studies and clinical observations[13,20-22] on fat, meat, and animal protein on the one hand, and fiber and cereals on the other. Comparisons almost always have been incidence and mortality from colorectal cancer and Food and Agriculture Organization (FAO) (United Nations) food disappearance data (the restricted usefulness of these data is well understood) or, much less commonly, within-country data. Many of the reported studies, therefore, are not so much replications as repetitions of the same analysis. The studies of the International Agency for Research on Cancer (IARC) Intestinal Microecology Group[23] and Jensen *et al*,[24] however, involved the measurement of diet and specific intermediate biology in individuals.

Of the 13 ecologic studies of fat, meat, and protein, 11[23,25-34] reported correlations of 0.7 or greater with mortality or incidence. Only the study of Jensen *et al*[24] failed to confirm such an association, while Enstrom[35] reported only a weak relation within the US. Nonetheless, similar relations with population ownership of motor vehicles[26] and Gross National Product[27] suggest that affluence may be as good as the dietary variables in predicting international variation. Of the seven studies of fiber and cereals, six[23,29,31-34] reported inverse associations between bowel cancer incidence and plant-foods with correlation of approximately −0.7. Again, the study of Jensen *et al*[24] failed to confirm an association. McKeown-Eyssen and Bright-See[34] concluded that total fat and fiber consumption together accounted for 67 percent of inter-country variation in colon cancer death rates among men.

Analytic studies of diet

Nutrients and food. Analytic studies of colon cancer, both case-control and cohort, are relatively consistent with these ecologic findings,[36] but more importantly, have provided data on associations with specific nutrients and classes of foods. Interpretation of the impact of any one dietary constituent on risk of colon cancer, however, has been hampered by the failure to take account of the high degree of collinearity among major nutrients. Although methods to separate out the individual effects of fat, protein, and total energy have been proposed,[37-39] the problem of collinearity is an issue that is more intrinsically complicated than can be solved by statistical methods. Nutrients are intimately bound to the foods in which they are found (both in the physical and statistical sense), and the presence or absence of association in a given population may be, in part, a consequence of the pattern of foods that are consumed. Most foods contain many nutrients and, as in the case of plant foods, also contain a wide variety of substances that have been shown in animal studies and *in vitro* to have potent effects; these are poorly measured in human diets.[40-42] The consequence of this is that associations between disease risk and some nutrients may be stronger than others because those constituents are better measured, not because they are casually relevant.

More than 40 case-control and cohort studies of associations between dietary factors and risk of colon cancer have been reported, some represented by more than one publication.[13,43-103] Studies with primitive dietary methods, with very small populations, with significant methodologic shortcomings, or with an unclear design[13,43-45] have been excluded from consideration here.

The majority of studies used some form of food frequency questionnaire (FFQ), although only a few of these have been examined for their reproducibility and comparability with other methods such as diet records.[58,59,72,89] The more widely used and better characterized instruments have between 50 and 150 items.

Of the dietary factors, the inverse associations between vegetable consumption and risk is the most consistent observation. Of the 28 studies that have published findings for vegetables, 23 reported an inverse association. Inverse associations with fruit are much less frequent. When attention is confined to those studies, both case-control and cohort, with at least 100 cases, with a FFQ of at least 50 items, and a response rate among cases (case-control studies only) of at least 60 percent, there are nine[60,62,70,73,77,81,83,86,91] studies that have reported on vegetables, of which only the study of Peters *et al*[91] failed to find a reduced risk in association with higher intake of one or more measures of vegetable intake. Four other similar studies[55,67,76,94] lacking only data on resonse rates showed comparable findings. The related finding, that foods high in fiber (often also a measure of vegetable as well as grain intake) are inversely associated with colon cancer risk, also has been noted in 11 of 17 studies and seven[73,77,80,84,85,87,95] of 12[57,68,73,7477,80,84,87,88,91,95] of the larger, better conducted studies as defined above. Three[53,67,94] of four other studies,[53,67,75,94] again lacking only data on response rates, reported similar findings. Meyer and White[95] showed that fiber differentiated between cases and controls, but suggested that the source of this difference itself differed between the genders – cereal fiber in men, fruit fiber in women. Howe and colleagues[104] completed a formal meta-analysis of 13 case-control studies using original data and reported that there was a consistently lower risk in association with higher overall fiber intake – odds ratios (OR) of 1.0, 0.79, 0.69, 0.63, 0.53 for each quintile of consumption from lowest to highest (P trend < 0.0001). However, in those populations where cereal consumption is high – southern Europe and Asia, particularly – there is a puzzling observation that risk is higher in association with higher consumption of rice (Japanese)[47] or pasta and rice (southern Europe).[67,78,92] In the four large prospective studies,[88,98,100,102] inverse associations between intake of fiber and risk of colon cancer have been weak or nonexistent. Individual foods were not reported in all of these prospective studies; nonetheless, associations with vegetables or fiber from vegetables and fruits also have not been as clear as those seen in the case-control studies.

Meat, protein, and fat are related consistently, almost universally, positively to risk. Of the 19 studies that have reported on the association with fat and protein, 15 have shown an increased risk with one or both of these nutrients. Only the studies of Macquart-Moulin[67] in France and Tuyns[75] in Belgium, the Iowa Women's Health Study (USA),[98] and the Netherlands cohort[100] failed to find an association; sugar was the only nutrient associated with increased risk in these latter two studies. (One study,[63] using a 24-hour recall, found an inverse association with fat in the Japanese Hawaiian cohort.) Seventeen of 29 studies have reported an increase in risk associated with higher meat consumption. (Hirayama,[16] using a three-item questionnaire in a very large cohort study in Japan, found an inverse association). When attention is confined to the better conducted studies, eight[60,62,71,73,83,85,88,91] of 12 studies[60,62,71,7381,83,85,88,91,94,98,100] show a positive association with meat intake. Four studies[49,55,73,88] have shown an inverse association with fish or seafood.

These data suggest a positive association between fat or animal protein intake and risk of colon cancer. Nonetheless, an unpublished pooled analysis of many of the better case-control studies (Geoffrey Howe, Columbia University, NY, USA. Personal communication, 1995) and several of the recent large prospective studies have provided less support for a specific effect of dietary fat. Many of the case-control studies have reported that cases have higher total energy intake than controls. This is despite the fact that differences in body size in the case-control studies sometimes have been small (*cf* section on body size below). Further, there is evidence (see below) of an inverse association between risk of colon cancer and physical activity, which suggests that we should see reduced, rather than elevated, food intake among those who subsequently develop colon cancer. Is the association between fat intake and colon cancer secondary to the relationship with total energy intake? The above-mentioned pooled analysis of 13 case-control studies (Howe, personal communication, 1995) confirmed the strong overall association between total energy intake and colon cancer risk but, after adjusting for total energy intake, failed to find an association with dietary fat.

The recent large prospective studies of diet and colon cancer[88,98,100,102] find no evidence of a positive association between energy intake and risk of colon cancer. Indeed, two of the studies[98,100] found inverse associations. These findings are consistent with a protective effect of physical activity (see below), and suggest a major methodologic bias, a consequence of selective participation or survival, differential recall of past diet, or some combination of these, has occurred in the case-control studies. There is little evidence that either total dietary fat or animal fat are risk factors in three of these prospective studies.[98,100,102] In the Nurses' Health Study (USA),[88] the positive association between animal fat and colon cancer risk no longer remained when controlled for red meat consumption, whereas the association with red meat remained statistically significant in the presence of a fat variable (W. Willett, Harvard School of Public Health. Personal communication, 1995). A similar association with red meat and meat protein was seen in the Health Professionals Follow-up Study (USA)[102] and processed meats, but not fresh meat were associated with risk in the Dutch cohort.[100]

In summary, these data are consistent with a positive association between red meat consumption and risk of

colon cancer that is probably not accounted for solely by its fat content.

Eggs. Eight case-control studies[60,71,76,78,79,85,92,105] and two cohort studies[66,106] have reported on egg consumption and colon cancer risk. Nine of the 10 presented risk estimates consistent with a positive association, with ORs or relative risks (RR) in the range of 1.1 to 8.2 for high *cf* low intake; in three of these studies, the association was statistically significant, as evidenced by a *P*-value less than 0.05 for a trend test, a *P*-value less than 0.0.5 for the OR for the uppermost consumption level, or a 95 percent confidence interval (CI) that excluded 1.0 for the uppermost consumption level. Four studies reported ORs of 2.0 or greater for high *cf* low intake. Each of the eight studies that met specific design criteria, similar to those noted above, reported a positive association; in two of these studies, the association was statistically significant. Four studies[67,73,107,108] have reported on risk of colon and rectal cancers combined, but not separately. Each of the three studies[73,107,108] that met the better design criteria (defined above), reported statistically significant findings consistent with a positive association for egg consumption.

Calcium and vitamin D. The calcium/vitamin D question has been the focus of interest following the development of a specific mechanistic hypothesis;[109] a number of intervention studies in patients with adenomatous polyps have been completed recently or are in progress.

Several ecologic studies have demonstrated inverse associations between calcium, vitamin D, and milk intake and colorectal cancer mortality (*e.g.* refs. 110-111). Many of the analytic epidemiologic studies that have addressed calcium,[67,73,75,77,83,85,88,91,112-116] Vitamin D,[85,88,91,112,117] or dairy products[45,60,62,66,67,73,83,85,91,113,116,118,119] in relation to colonic neoplasms are methodologically problematic and have yielded inconsistent results.

Of 13 analytic epidemiologic studies (nine case-control studies and four cohort studies) that have investigated the association between calcium and colon cancer, eight suggested inverse associations; three[75,85,116] reported statistically nonsignificantly elevated risks with higher calcium; and no direction of association was reported in two. Of the eight studies suggesting inverse associations, statistically significant decreased risk was found in three of the case-control studies[73,91,113] and in two of the cohort studies.[112,114] One of the studies that reported no association with calcium and that did not provide a measure of the strength of association was the Nurses' Health Study.[88] The strongest associations were reported by Garland *et al*,[112] Slattery *et al*,[113] and Peters *et al*.[91] Of the two studies [75,85] that suggest positive associations of calcium intake with risk of colon cancer, one[85] reported only univariate results even though total energy intake was associated positively with colon cancer. No other features of the studies appear to provide a simple explanation for the diversity of findings.

Of five analytic epidemiologic studies (three cohort studies and two case-control studies) that investigated the association between vitamin D and colon cancer, three[85,112,117] suggest an inverse association; one reported a null association[91] and one, the Nurses' Health Study, reported that there was no significant association, but, as with calcium, did not report its direction. The inverse associations in the other two cohort studies were statistically significant.[112,117]

Folate. Giovannucci *et al*[103] recently have reported finding an association between lower risk of colon cancer in men and higher intakes of folate and methionine. They further noted that this increase in risk with low folate and methionine was marked particularly in those with higher alcohol intakes. Indeed, among those with high folate intakes, there appeared to be little association with alcohol intake. These findings for folate are essentially identical to an earlier report from the same group of researchers on adenomas (see below) and similar to those from the Upstate New York Study of rectal cancer (see below).

Other micronutrients and minerals. The data on selenium are interesting but derived largely from ecologic data.[120] The human analytic data do not provide clear evidence of association specifically with colon cancer[12,122] although there are data suggesting associations between prediagnostic levels of selenium and cancer in general[123] and gastrointestinal cancer in particular.[124]

The data on specific micronutrients such as ascorbate and β-carotene are often, particularly among the early studies, in the form of indices derived by combining rich sources of the nutrient of interest.[50] A number of researchers have reported reduced risks in associations with specific micronutrients, *e.g.*, vitamin C[49,63,73] and various measures of dietary carotenoids,[49,78,80,87,94] but others have failed to confirm these (*e.g.*, ref. 96). Many studies have not reported on these dietary components. Further and most importantly, it has become clear that the association between (usually reduced) risk and consumption of specific micronutrients is explained as plausibly by consumption of plant foods in general, or the many substituent bioactive compounds that they contain, as it is by one of the 'established' micronutrients. It is a matter, largely, of what can be measured rather than what is causal and, in most studies using food tables derived, for instance, from United States Department of Agriculture data, the levels of any but the most long-established essential nutrients (such as ascorbate and a composite carotene variable) are not available.

Meal frequency. Potter and McMichael[69] originally postulated an association between frequency of food intake and risk of colon cancer. They reasoned that, as bile acids are secreted into the bowel with each intake of food and as the concentration of secondary bile acids in bile is determined, in part, by the frequency of recirculation, risk of colon cancer would rise with frequency of food consumption. The Adelaide (Australia) case-control study did not unequivocally confirm this hypothesis[69] showing an OR of 1.7 (CI = 0.9-3.1) for women consuming more than four meals per day compared with those consuming three or fewer after controlling for total energy intake. The findings were similar for men and there was no association with rectal cancer in either gender. Subsequently, three other studies[78,79,85] have shown statistically significantly higher ORs (1.3 to 2.1) in association with a greater meal frequency. Whether the nature of the food consumed differs among those with different eating frequencies has yet to be elucidated.

Food mutagens. Sugimura and Sato[125] originally proposed that specific heterocyclic amines, potent mutagens present in cooked food, were important in the etiology of colon cancer. Several separate classes of these compounds have been identified[126] and have been shown to be carcinogenic in animals.[126,127] Evidence for their importance in humans is derived from three sources. First, the original observations on the role of meat, fat, and protein, described above, are consistent with a more specific, correlated exposure as the causal agent. Second, the degree to which meat has been cooked has been sought as a specific datum in a case-control study (there are several others currently in the field). In the one published study of Gerhardsson de Verdier *et al*,[128] an OR for colon cancer of 2.7 (CI = 1.4-5.9) was reported for the most frequent consumers of fried meat with a heavily browned surface (top 40 percent cf lower 60 percent of consumption) and an even higher risk (OR = 6.0) for rectal cancer. The third area relevant to this hypothesis is the genetic variability of the capacity to metabolize arylamines (see below).

Physical activity

Reduced physical activity has emerged as the factor that, perhaps, is associated most consistently with an increased risk of colon cancer. Most studies have concentrated on occupational activity,[87,91,129-138] although studies examining leisure time and total activity[80,84,87,115,129,139-142] and participation in college athletics[141] also have shown a reduced risk for the more active. The association has been observed in both genders.

Occupational studies have examined usual lifetime occupation, while most other studies have examined activity levels two to three years prior to diagnosis. The time at which physical activity may have its greatest impact is not established, although some data exist: Lee *et al*[141] showed that individuals who reported high levels of activity throughout their lives were at the lowest risk for developing colon cancer, whereas those who reported high levels of activity more recently were less well protected. This finding could suggest either that the lower risk is, indeed, a result of higher lifetime physical activity or merely that those who report consistently high levels of activity over longer period of time, as opposed to recently, are the most physically active. Studies of those in sedentary jobs for a larger part of their working life also indicate the importance of lifetime activity.[136] Increased activity in early adulthood, as reported retrospectively, was not associated with decreased risk in women in one case-control study.[143] Studies that have examined dietary intake and body size as well as physical activity have found that neither confounds the association with physical activity.[80,84,87] It has been suggested that the effects of diets high in fat or protein may be modified by physical activity;[80,87] these interpretations should be viewed with caution, however, because numbers available to evaluate interactions were small. Studies that have examined rectal cancer alone do not consistently show an inverse association with physical activity.[136,137,140,141]

Body size

Individuals who consume more energy than they expend through physical activity may be at increased risk of colon cancer.[144] Those who are overweight may be at increased risk of colon cancer because of this energy imbalance. Most studies have relied upon recalled weight and height from some time period prior to diagnosis and have calculated a body mass index (BMI)(wt/ht^2). Associations with body size have been inconsistent. Some studies have found that men and women who are in the highest body size quantile are at as much as a twofold increased risk of colon cancer,[66,77,81,115,138,140,142,146] but others have reported no association.[50,54,147] Increased stature, independent of weight, is associated with increased colon cancer risk, with ORs for men of 2.1 and for women of 1.6.[144,148] Early caloric restriction may diminish cell proliferation, thereby reducing cell number and organ size, or inhibiting some early tumor event.[149,150] It is possible that hereditary factors associated with stature also are related to cancer risk. The distribution of body fat has been examined for its association with risk of colon cancer in two prospective studies: in women, there was no association;[151] but, in men, waist-to-hip ratio (WHR) was a strong predictor.[142] Intriguingly, in men, two studies[142,152] also show that WHR predicts risk of large, but not small, adenomatous polyps.

Alcohol

Stocks[47] first reported an elevated, though not statistically significant, risk of colorectal cancer among daily beer drinkers compared with abstainers (OR = 1.4) in 1957. Subsequently, the association between alcohol and cancers of the large bowel has been explored in other studies. Several different methods of assessing alcohol consumption have been used: in some, exposure status was defined as membership in specific groups, such as those with a history of alcohol abuse or misuse,[153-156] or those employed in the beer industry;[157,158] in others, individual intake was assessed using dietary histories, questions on the frequency of use of specific beverages, or food-frequency questionnaires measuring average intake of over the last year. Intake has been reported as mean grams or milliliters per day, drinks per day or week, kilograms per year, etc. Frequency of consumption (*i.e.*, none, infrequently, occasionally, daily) also has been used. Not all studies considered abstainers as the reference group; some studies used the lowest group of alcohol consumers such as the lowest half, tertile, or quartile. It is not entirely clear what effects these methodologic differences may have on the consistency of findings but they do not help to make associations clearer.

Ecologic studies. Four ecologic studies of alcohol and colon cancer have shown a positive association.[159-162] Geographic differences in cancer mortality have been correlated positively with beer consumption (r = 0.58 - 0.76).[159-162] Changes in *per capita* beer consumption from 1950-52 to 1960-62 have been correlated positively with changes in colon cancer mortality rates from 1960-64 to 1970-74 (to allow for a latency period), in the US, United Kingdom, Australia, and New Zealand.[162] A significant, positive correlation ($r = 0.4$) between wine and cancer mortality rates across 41 US states has been reported.[159] However, a nonsignificant, negative correlation ($r = -0.13$ to -0.23) was found across 29 countries in the only other study that considered this association.[162] Consumption of liquor across 41 states of the US correlated positively with colon cancer mortality rates ($r = 0.5$-0.6).[159]

Cohort studies. Of the eight cohort studies that have investigated the association between alcohol and colon cancer in alcoholics[153-156,163,164] or in people employed in breweries,[157,158] none showed significant associations. Only two of these studies included women.[155,156] In one of these, there was a statistically nonsignificant 60 percent elevated risk of colon cancer mortality among alcoholic women when compared with the general population of the UK.[156]

All of the general population cohort studies[103,165-168] that investigated the effect of alcohol on colon cancer reported significant results. Klatsky *et al*[166] reported a dose-response relationship between alcohol and colon cancer in women but no association in men; these results were not confined to any particular colon subsite or alcoholic beverage. In a study of Japanese adults,[167] there was a fivefold increase in the risk of mortality from sigmoid colon cancer, but no association with risk of proximal colon mortality, among men who drank alcohol daily compared with abstainers; daily beer consumers had a 12-fold elevated risk of sigmoid colon cancer mortality, with less marked associations with sochu and sake. In women, the RR for any alcohol consumption was 1.9 for sigmoid colon cancer mortality. The Health Professionals Follow-up Study[103] found an increased risk for colon cancer among both current and past drinkers. The association was particularly marked among, and indeed essentially confined to, those with a low intake of folate or methionine.[103]

Case-control studies. A significant, positive association between alcohol and colon cancer has been reported in eight[13,69,76,90,91,118,169,173] of 16[13,47,60,69,76,82,90,91,118,169-175] case-control stud-ies. Of the three studies that included only men,[82,173,174] one[174] found no association and another[82] reported a nonsignificant 60 percent elevation in risk for men who consumed at least 70 g of ethanol per day; this was not specific to any type of alcoholic drink.

Three[76,90,118] of five[76,90,118,170,172] case-control studies that combined men and women reported a positive association between colon cancer and alcohol. In a study in China,[90] the RR of colon cancer for those who consumed at least 10 kg of ethanol per year compared with those who drank less was 2.0. In Nebraska, commercial beer consumption was associated with at least a 2.7 fold-elevation in risk of colon cancer compared with abstainers, but no association was found for homemade beer or any type of wine.[118] There was also a positive, dose-response relationship between beer and colon cancer in the Belgian study.[76]

Of the seven case-control studies[13,47,60,69,169,171,175] that stratified on gender, one[69] reported a positive association between one or more measures of alcohol exposure and colon cancer in women and three reported similar findings in men.[13,69,169] Four studies[47,60,171,175] showed no association in either men or women. The data from the Third National Cancer Survey (USA)[169] showed a positive relationship between colon cancer and total alcohol as well as beer, wine, and liquor in men but not in women. Consumption of liquor, but not beer, wine, or total alcohol was associated positively in men and in women in an Australian study,[69] this association was specific for the

proximal colon. One study[73] considered potential modifying effects, particularly of calcium and vitamin D, on the association between alcohol and colon cancer, noting that, in men, high alcohol intake was associated with increased risk of proximal cancer only in those with a low calcium and vitamin D intake.

Summary. Although cross-cultural, ecologic comparisons are consistent with a positive association between alcohol consumption and colon cancer, cautious interpretation of these results is clearly warranted. Of the 20 general population studies that have examined alcohol and colon cancer, 12 have reported a positive association (12 of the 19 alcohol-rectal cancer studies showed a positive association – see below). Inconsistencies in results may be a consequence of the small number of cases in some studies or the result of differences in control groups, in methods of assessing consumption, and in preferred beverages across countries and between the genders.

Caffeine and coffee

Caffeine or coffee intake has been associated with approximately a twofold increased risk in populations that are predominantly members of the Church of Jesus Christ of the Latter Day Saints (LDS), commonly known as Mormon,[175] and Seventh-day Adventists (SDA),[66] and with a much smaller level of risk in one other case-control study.[77] In other populations, coffee intake has been associated with decreased risk (risk estimates in the range of 0.6 to 0.7) or has been reported to have no association.[48,83,85,91,176-178] Some of these differences in findings could be a consequence of differences in the type and quantity of coffee consumed. For instance, in the study by Bjelke,[49,50] where a reduced risk was observed at the highest level of intake, those in the intermediate level of intake (two to three cups a day) were at an increased level of risk similar to those observed in LDS and SDA populations where the upper level of intake was only two to three cups. Studies that have found an inverse association with caffeine have proposed that the relation is a consequence of the capacity of caffeine to increase serum cholesterol levels by decreasing excretion of cholesterol;[179] low serum cholesterol levels are associated with increased colon cancer risk in some populations,[180] although the temporality of the association is not clear. The finding that caffeine or coffee increases risk are consistent with the observation that coffee is mutagenic in the Ames test.[181,182] The balance between constituents that increase and decrease risk may vary by bean roasting and coffee preparation, thus accounting for the inconsistencies reported here. Random variation is a more prosaic but equally plausible explanation.

Epidemiology of rectal cancer

The rectum is distinguished from the colon in that it tends to have a shallower epithelium and is considered usually to be empty except immediately prior to defecation, although there are data to suggest that this is not always the case even in normal healthy individuals.[183] The rectum appears to have few metabolic functions with the exception of water absorption. In very few studies has rectal cancer been studied as a discrete entity in relation to diet,[184] although it has been reported on separately in several papers–see below. There is, in addition, a substantial literature on rectal cancer in relation to alcohol consumption and this is presented in detail below.

Diet

By and large, the published data on diet do not suggest that the risk factors for rectal cancer differ substantially from those of colon cancer although the rectum does not appear to share other risk factors such as reproductive history, physical activity, and meal frequency.[4,68,69,185] Indeed, some authors have argued that there is a greater distinction to be drawn between the proximal and distal large bowel (including rectum) than between the colon and rectum.[173]

Freudenheim *et al*[184] reported, in a study of 422 case-control pairs, that risk decreased with increasing intake of fiber from vegetables (but not grains), vitamin C, and carotenoids (these relations were unaffected when controlling for fat), and increased with increasing intakes of total energy and fat (but also carbohydrate) and intake of iron. Potter and McMichael,[69] in a study of 199 matched case-control triplets, showed that there was a lower risk of rectal cancer in women (and possibly men) for higher intakes of vitamin C and, similar to the findings of Freudenheim, found a suggestion of lower risk in the presence of higher vegetable fiber intake but not cereal fiber intake. Bidoli *et al*[92] (125 cases and 699 controls) showed a higher risk for red meat, cheese, and eggs, but also white bread and polenta. They reported lower risks in association with higher intake of spinach, carrots, and whole-grain bread. Hu and colleagues,[90] on the other hand, reported that, in a case-control study of 225 rectal cases and 225 controls, lower consumption of meat and eggs was associated with higher risk. They noted also that higher intakes of vegetables, particularly chives and celery, and higher grain consumption were associated with lower risk. Overall, these findings in a Chinese population suggest that dietary quality and variety (possibly related to bioactive compounds in both plant and animal foods) are significant determinants of rectal cancer risk – a finding consistent with observations made earlier in a Western younger male population.[69] Nonetheless, the data available at this stage do not make a strong case for

regarding the dietary associations of rectum and colon as different.

Alcohol

Rectal cancer has been correlated positively with alcohol consumption in all of the geographic and time-trend studies considered; no gender differences were reported.[159-162] Geographic differences in rectal cancer mortality rates were positively correlated with beer consumption ($r = 0.71$-0.81).[159,160,162] Changes in *per capita* beer consumption from 1950-52 to 1960-62 were associated positively with changes in rectal cancer mortality rates from 1960-64 to 1970-74, in the US, UK, Australia, and New Zealand.[161]

Seven cohort studies examined the association between alcohol and rectal cancer in either alcoholics[153-156,163,164] or people employed in the beer industry.[157,158] In the only study that found an association[157] there was an elevated rectal cancer mortality rate among male brewery workers compared with that of skilled and unskilled workers in Dublin, Ireland (SMR = 1.6); each of these employees was allowed to consume two pints of stout or other beer daily, free of charge. However, no association was found in the only other study of brewery workers;[158] although the daily free ration of beer in the this Danish study was higher than the Dublin study (six pints *cf* two pints), it consisted of a lighter lager-type of beer. The conflicting results from these two studies suggest that there may be congeners in stout beers (that are made from highly charred grain) that lead to elevated risks of rectal cancer that are not present in lighter beers. A dose-response relationship between alcohol and rectal cancer was observed in all three cohort studies of the general population.[166-168] There was no difference between males and females in the only study that included both genders, nor was the association specific to either wine, beer, or spirits.[166] Beer was associated significantly with rectal cancer in men who consumed 15 liters of beer per month compared with abstainers (RR = 3) in them Japanese-Hawaiian cohort.[168]

Alcohol was associated positively with rectal cancer in nine of 16 case-control studies. Two[173,174] of the three studies that included only males[82,173,174] found a significant, positive association between rectal cancer and at least one category of total alcohol intake. In one of these, conducted in Korea,[174] there was a fivefold elevated risk of rectal cancer in heavy alcohol consumers compared with abstainers. Gender-specific associations were not assessed in five[63,77,118,170,172] of the 15 case-control studies that included both males and females. There was no association between rectal cancer and either total alcohol consumption[170,172] or any type of alcoholic beverage[63,88,118] in any of these studies.

One[48] of the nine case-control studies that stratified on gender found no association between alcohol and rectal cancer in either males or females. Six studies reported a significant association with at least one type of alcoholic beverage in males[13,69,90,171,186,187] and three[69,169,188] reported a significant association in females. The study by Miller *et al*[60] reported a nonsignificant inverse association with alcohol consumption in both males and females. ORs for rectal cancer in males ranged from 0.5 in men who consumed < 47.7 grams of ethanol (excluding beer) per day[60] to 2.1 in men who consumed at least six kg of ethanol per year.[90] In females, ORs were approximately 2.0 for the highest level of consumers compared with abstainers.[169,187] There was a positive association between beer and rectal cancer in three[13,171,186] of five studies[13,60,169,171,186] for males. Beer was not associated significantly with rectal cancer in females in any of these five studies; however, the association was inverse in at least two studies.[60,186] There was a positive relationship between wine and rectal cancer only in the Australian study by Potter and McMichael[69] and this was confined to females. However, inverse associations with wine were reported for males and females by Williams *et al*.[169] There was a significant positive association with liquor,[69] and an inverse association between liquor and rectal cancer in the study by Kune *et al*,[171] in both of these studies the finding was confined to males.

In summary, among studies of alcoholics or brewery workers, the risk of rectal cancer was elevated in four of seven studies (RRs ranged from 1.0 to 3.3), although only the study of brewery workers from Dublin showed a significant association (RR = 1.6). There may not have been enough power to detect a significant association in many of the studies, given the small number of cases. Of the 19 general population studies that have examined alcohol and rectal cancer, 12 reported a positive association (as noted above, 12 of the 20 alcohol/colon-cancer studies showed a positive association). Beer appeared to be related positively to cancer of the rectum in men more often than in women, in whom there were nonsignificant inverse associations in two of 10 studies.

Epidemiology of colorectal, adenomatous polyps

Adenomatous polyps are accepted widely as precursors of colorectal cancer in humans. These nonmalignant neoplastic lesions have themselves been the subject of a number of studies since 1986 when Hoff and colleagues[188,189] published on risk factors thought to be important in the etiology of colon cancer itself. There are a total of 16 studies in the literature where the roles of diet and alcohol have been addressed. It is worth bearing in mind that the issues that make the interpretation of case-control studies of diet and cancer difficult – particularly recall bias – may be marginally less problematic in studies of

polyps where it is theoretically possible (and especially so in screening studies) to collect dietary data prior to diagnosis. However, selection bias is a much greater problem in studies of this precursor where self-referral is often the norm and where finding controls derived from the same population, but known to be without disease, is a problematic issue.

Dietary factors and alcohol have been studied in a total of 16 studies, though some of these have produced more than one report;[189-212] there are three cohort studies,[193-195] and 13 case-control studies. There are reports of one study in the literature of 'recurrent' (metachronous) polyps.[205,208]

Of the nine studies that reported associations between risk of adenomas and fat, one showed an increase,[206] two[189,198] reported an increase in men and one[205] in women, and three were null.[190,193,199] One study noted increased risk in association with polyunsaturated fat, but no relation with total or saturated fat;[204] another found a decreased risk in association with polyunsaturates and, again, no association with saturated or total fat[210] The study of metachronous polyps showed a positive association with fat in women but not in men.[205] One study[194] reported that beef consumption was higher in male cases than controls, and two studies[198,205] noted a high red-meat-to-chicken-and-fish ratio as a risk factor. Two studies[190,199] showed an elevated risk with simple carbohydrates.

As with colon cancer, the most consistent finding appeared to be with plant foods with eight [189,190,194,198,199,204,206,210] of ten[193,205] studies showing lower risk with higher consumption. The reported data are clearest for fiber, both cereal and vegetable-and-fruit: five of seven studies showed lower risk overall and the other two reported lower risk in men or women only. Polyp recurrence was also lower in women (but not men) with higher fiber intakes.[205]

Alcohol is associated relatively consistently with increased risk;[191,192,196,197,200,207,211,212] however, some studies[195,196,199] had null results and one small study[94] suggested a difference between men and women.

Physical activity was lower in cases than non-cases in all three[193,199,203] of three studies that reported on this variable.

Mechanisms

In a recent paper,[213] I attempted to integrate some of the epidemiologic findings with what is known about the biology of colon cancer. Much of what follows is an update of that paper.

Physiologic and biochemical models

The earliest mechanistic model of colon carcinogenesis was the bile acid hypothesis[24] – modified by an increasing understanding of colonic fermentation, volatile fatty acid production, and a variety of resultant anticarcinogenic effects.[215,216] (More recently, the effect of cooking on food, resulting in both potential carcinogens such as heterocyclic amines[125-127] and promoters,[217] combines the old search for human gut carcinogens with some new ideas).

These physiologic hypotheses are neither mutually exclusive nor incompatible with the epidemiologic observations. Specifically, fat increases bile acid production, ultimately increasing the exposure of the bowel mucosa to the toxic, trophic, and promoting effects of (particularly secondary) bile acids.[214] Fiber binds bile acids, reduces transit time, increases stool bulk, ferments to volatile fatty acids which may be directly anti-carcinogenic[215] and which, by lowering pH, may reduce the conversion of primary to secondary bile acids.[216] Thus, the meat-and-vegetables hypothesis and the bile-acid/volatile-fatty-acid hypothesis appear to represent a one-to-one mapping of epidemiologic on physiologic models.

The cooked-food hypothesis proposes, however, that the association with fat is incomplete. High-fat diets contain greater amounts of heterocyclic amines from meat proteins[125] and promoters as a consequence of cooking at a higher temperature (cooking in fat produces higher temperatures than cooking in water).[217] Thus, argue the proponents of this idea, the meat/vegetable hypothesis is really the 'high-temperature: increased-carcinogens /low-temperature: low-carcinogens' hypothesis. These, again, are not incompatible models and, rather than simplifying the picture, really may provide evidence for a complex, interactive etiology, where one environmental exposure may act at several stages in the carcinogenic process.

Vegetables, particularly, have a variety of anti-carcinogenic properties at both physiologic (via stool bulking, transit time, *etc.*) and molecular levels (see below).[40-42] Calcium, it has been proposed, lowers risk by binding bile acids and fatty acids, thereby reducing exposure to these toxic, trophic, and co-carcinogenic compounds. Additionally, calcium may reduce cell proliferation directly.[109] To date, evidence for these mechanisms from human studies is scarce.

One other aspect of gut physiology is worthy of consideration – endocrine metabolism. There is substantial evidence that subsite and age differences in colon cancer risk themselves vary by gender;[4,68,218] there is a female excess of right-sided colon cancers at all ages and a male excess of left-sided cancers. There is evidence, also, of increased risk in association with having fewer children[185,219,220] though this, intriguingly, is sometimes,[220] but not always, different between men and women![115] Further, there are physiologic correlates for these observations: men and women differ, under controlled experi-

mental conditions, on transit time, stool bulk, volatile fatty acid production, and bile acid production; these differences are, by and large, consistent with the epidemiologic observations.[68,221-223] These data suggest differences in gut metabolism between the genders that may be mediated, ultimately, by hormones but also may suggest differences in colonic bacterial populations, fermentation rates, and general colonic milieu.

At epidemiologic and physiologic levels, our current models of the etiology of colon cancer are relatively consistent. However, the influences of fat, fiber, calcium, and vegetables, of cooked food, of reproduction, of alcohol, and of exercise seem to work each through multiple and different but, in some cases, overlapping pathways to carcinogenesis. The variety of exposures – ingested foods and host responses and states – primarily determines what the colonic cell ultimately is exposed to; *i.e.*, these factors determine and condition the growth media[213,224] – both luminal and plasma – in which the colonic cells are bathed. Thus, each of epidemiologic risk factors operates through a variety of pathways that reasonably can be thought of as physiologic cascades.[213] For example, meat and fat are a source of DNA-interacting carcinogens and increase hepatic bile-acid production. Other factors, including bacterial species, bacterial enzyme production, and transit time will alter the production and concentration of secondary bile acids, thereby modifying the process of cell damage and repair and causing changes in gut surface area. The increase in cellular workload will increase cell replication rates.

Ingested vegetables, on the other hand, increase the fiber content of the large bowel which may bind bile acids and may undergo fermentation, thus increasing both bacterial mass and VFA production. This, in turn, produces effects on cell replication and cell maturation and inhibits secondary bile-acid production by reducing intra-luminal pH. Meanwhile, the fiber and the increased bacterial mass increase stool bulk and increase the workload of gut musculature and reduce transit time.[221,225]

On the plasma side of the colonic cells, there is not only the opportunity for exposure to carcinogens and anti-carcinogens, but also the likelihood that specific relationships – both accelerating and controlling growth – exist between fibroblasts and epithelial cells; these may be mediated particularly by endogenous growth factors.[226,227] The recent findings[228] suggesting lower risk in association with NSAID use provide empirical evidence for this possible mechanism. Whether growth factor paracrine/autocrine loops are related also to some of the other established risk factors seems to be a reasonable and testable question.[229]

Overall risk of colon cancer, under this model, might be regarded as the summation, over long periods, of the moment-to-moment outcomes of these physiologic cascades and molecular loops.[213]

Cell/crypt model

The target cells of colon carcinogenesis are (probably progenitor) crypt epithelial cells. Thus, increasing attention has focused on the transition from normal to malignant cell and from macroscopically normal mucosa through adenomatous polyps to cancer. The adenoma/carcinoma sequence, as originally proposed by Hill, Morson, and Bussey,[230] is now the accepted description of this process and one that makes intervention in those with polyps an attractive substitute for large-scale, cancer-prevention trials. However, the agents hypothesized by these authors to explain both international differences and the transitions, in individuals, from one state to the next remain to be elucidated.

A likely marker for increased adenoma/carcinoma risk is a persistently rapid, cellular replication rate.[231] Again, this is important because, if indeed the hypothesized adenoma/carcinoma sequence is preceded by a normal cell/adenoma sequence, even smaller and more rapid tests of the anticarcinogenic potential of specific agents (and even behavioral strategies) become feasible. One other 'stage' in this process has been proposed – the aberrant crypt or the microadenoma;[232] its appropriateness for human studies is not yet established but it has been used as an endpoint in animal studies[217] – and may represent evidence of a normal cell/adenoma sequence.

There are two lines of inquiry that can be integrated with the micro-anatomical changes described above. The first is the work at the molecular level that provides some confirmatory evidence for the coherence of the adenoma/carcinoma sequence and, further, provides some hints that allow understanding of the micro-anatomical changes. The second perhaps is even more interesting – data that may tie the epidemiologic risk factors (particularly the dietary exposures) to the molecular and cellular events.

Molecular models-genetic predisposition

One link across genetic susceptibility, diet, and the DNA-damaging compounds is represented by the consumption and metabolism of arylamines. These compounds are present in large amounts in cooked protein; their metabolism (and therefore the extent to which colonic DNA will be exposed) is under genetic control. The mechanism[233-234] appears to be as follows: heterocyclic amines readily undergo hepatic *N*-oxidation (itself a function of the activity of the phenotypically polymorphic enzyme, $P450_{1A2}$). The *N*-hydroxy metabolites can be transported to the colon via blood. In the colonic epithelial cells or the liver, the *N*-hydroxy derivatives are good substrates for *O*-acetylation (also via a polymorphic enzyme – NAT2), producing *N*-acetoxy arylamines which readily form DNA-adducts.[233,234] Both the *N*-hy-

droxy form and the *N*-acetoxy form appear to be stable enough to be transported directly via plasma; glucuronidation is not a necessary step.[234] Glutathione-*S*-transferases (GSH), however, do appear also to be important in protecting epithelial DNA from adduction by these activated heterocyclic amines.[235] Kadlubar, Lang, and colleagues[236] recently have shown that both NAT2 status and $P450_{1A2}$-status predict risk and that fast acetylators who are also fast *N*-oxidizers (approximately 16 percent of the North American population) are at nearly three times the risk of those who are slow acetylators/slow *N*-oxidizers.

Familial Adenomatous Polyposis (FAP), also called Adenomatous Polyposis Coli, is a rare genetic syndrome.[17,18] It is characterized by the development, as early as childhood, of multiple adenomas, numbering from a few polyps to several thousand. FAP carries an almost 100 percent risk of colorectal adenocarcinoma. Localization of the FAP gene – *APC* – was accomplished independently by Leppert *et al*[237] and Bodmer *et al*,[235] in 1987; the gene was mapped to chromosome 5q. Gardner syndrome also was shown to be linked to the 5q markers.[239] The relevant gene is now sequenced and a variety of germline mutations have been described.[240-243]

Mutations at the *APC* locus are a common and probably a very early somatic event in polyps and cancer,[244] supporting the idea that, for some individuals, the first hit is the germline mutation of the gene and for others, it is an early somatic event. The causes of the somatic events remain to be established. The protein product of *APC* associates in the cell with proteins called catenins.[245,246] This provides evidence that *APC* is involved in some manner with cell adhesion and cell-communication. Whether there are links to diet or other risk factors remains to be established but the APC gene does appear, in the rat, to be vulnerable to mutation by heterocyclic amines, particularly PhIP (see below).

Another form of colon neoplasia that shows familial aggregation is Hereditary Non-polyposis Colorectal Cancer (HNPCC).[247] This syndrome is not easily distinguished from 'sporadic' polyposis and cancer on physical examination. The most clearly distinguishing features of the family history are the tendency to early onset and a pattern of other cancers – particularly those involving endometrium, urinary tract, stomach, and biliary system.[247] An analysis involving two large HNPCC kindreds[248,249] found strong linkage to anonymous microsatellite markers on chromosome 2p15-16[248] and suggested a mechanism different from that associated with the inherited abnormality of tumor suppressor genes – perhaps involving a predisposition to genetic instability and manifesting as widespread alterations in short repeated DNA sequences.[249,250] Other similar genes exist in the human genome and have been linked to HNPCC.[251] A plausible mechanism has been established.[252]

Molecular models – somatic events

Vogelstein and colleagues[253-258] have provided extensive evidence that there is an accumulating (but not necessarily linear) series of specific chromosomal and genetic changes that accompany (and perhaps cause) the transition from normal colonic mucosa to metastatic carcinoma. Further, some of these changes[256] show the importance of cell-cell communication at stages other than those involving APC – perhaps emphasizing the relevance of cell-adhesion both early in carcinogenesis (via disruption of cell communication or impairment of sloughing of cells at the luminal surface) and late (via changes in metastatic potential).

Possible links between epidemiology and molecular events

Are there any data to link the epidemiologic risk factors to the molecular biology? Several lines of inquiry hint at relationships and give insights into the kinds of questions it is increasingly possible to answer.

Abnormalities of DNA methylation appear early in colon neoplasia.[259] Methylation is under genetic control and expression of the methyl transferase gene is increased considerably in the normal mucosa of cancer patients and is even higher in polyp and cancer tissue.[260] Of even greater interest to the discussion here is whether there are environmental influences on DNA methylation. Chronic methionine and choline deficiency produce alterations in DNA methylation and a variety of tumors in rodents.[261] Folate deficiency may have related effects.[262] Giovannucci *et al*[103,200] recently have shown that high folate, low methionine, and high alcohol (itself often associated with low folate) are all associated with increased risk of colonic adenomatous polyps and cancer, suggesting strongly that the abnormalities of methylation seen in early colon neoplasia are plausibly related directly to dietary factors. Do these data point generally to mechanisms by which substances without direct DNA-interacting capacity are, nonetheless, involved at molecular level, in the cancer process? Recently, work from Baylin's lab[263] tentatively has linked this important mechanism with the hormonal and reproductive data briefly discussed above: in a sequence of 45 colon tumors examined, all showed abnormalities of methylation of the ER gene.

Certainly, there is evidence of other dietary influences at the molecular level: one of the most interesting is the hypothesis from Weinstein and colleagues[264,265] that fat is important in colon carcinogenesis because it is a source of diacylglycerol (DAG). These workers point out that in-

tracellular DAG is an important part of the cascade that leads from *ras* activation via a G-protein or from growth factors via receptors to protein kinase C activation, protein phosphorylation, and cell turnover. They have proposed[264] that the interaction of fat, bile acids, and bacteria produces excess intraluminal diacylglycerol which will mimic and amplify these cell replication signals.

Vegetables contain a large number of substances–both micronutrients, such as carotenoids and ascorbate and other bioactive compounds, such as phenols, flavonoids, isothiocyanates, and indoles with a variety of potent anticarcinogenic properties.[40-42] The steps from pro-carcinogen to neoplastic cell replication or (re-) differentiation can be considered broadly as follows: pro-carcinogen is activated to ultimate carcinogen (either of which may be solubilized and excreted by a variety of P450 and Phase II enzymes); carcinogen passes through membranes; carcinogen interacts with DNA; synthesis and replication of abnormal DNA (or DNA repair) occur; cell replication with abnormal DNA and abnormal protein synthesis (or cell differentiation or apoptosis) result. At almost every one of these steps, one or more known phytochemicals can alter the likelihood of carcinogenesis, usually in a favorable direction but sometimes in a way that enhances risk. For example, glucosinolates and indoles, isothiocyanates and thiocyanates, phenols, and coumarins can induce solubilizing and (usually) inactivating enzymes; ascorbate and phenolic compounds can block the formalin of carcinogens such as nitrosamines; carotenoids and flavonoids can act as antioxidants; lipid-soluble compounds such as steroids and carotenoids may alter membrane structure or function; some of the sulphur-containing compounds may suppress DNA and protein synthesis; carotenoids may suppress DNA synthesis and enhance differentiation.

The fermentation of fiber results in the intraluminal production of volatile fatty acids, such as butyrate. Data from Paraskeva's lab[266,267] recently has shown that, in colon tumor cells in culture, at least, VFAs will induce apoptosis – yet another possible explanation for the lower risk that a diet high in fermentable fiber may confer.

It is also possible that dietary constituents could influence both early and later stages of the carcinogenic process via effects on gene expression. For instance, the level of dietary fat has been shown, in experimental animals, both to alter the production of eicosanoids[268,269] (which, in turn, can influence DNA synthesis and tumor production) and the induction of genes coding for Phase I and II metabolizing enzymes.[270,271] Contrary data do exist, however.[272] Further, fasting and refeeding are followed by structural changes in the chromatin at the site of genes involved in metabolic regulation and the degree and kinds of changes are dependent on the amount of fat and protein in the diet;[273] this, via endocrine and paracrine mechanisms could have a major effect on cell replication rates.

Dietary variables with the capacity for direct DNA damaging effects include heterocyclic amines described above.[126] It is worth noting that the transversion and transition mutations seen with high frequency in K-*ras* are plausibly related to the interaction between arylamines and DNA.[274] Work in Nagao's lab recently has shown that, in rats, heterocyclic amines can induce microsatellite instability,[275] the hallmark of mutation of the DNA mismatch repair genes described above. This group has shown further that there is a specific fingerprint, involving deletion of a G from GGGA sequences, associated with PhIP, but not IQ, in the rat APC gene.[276] Such lesions however, have not been described in human APC mutations where, in fact, G deletions appear relatively rare.[244,277,278] It seems plausible that heterocyclic amines could work at two levels – damaging both target genes such as APC and *ras* as well as the HNPCC genes. If the HNPCC genes are mutated somatically or a germline mutation is inherited, such lesions will be poorly repaired and the process of carcinogenesis accelerated. This could provide a link between carcinogenic dietary exposures and the abnormalities in DNA mismatch repair enzymes seen in HNPCC.

The suggestion of coherence among the epidemiology, the physiology, and the molecular biology is encouraging and challenging. Perhaps more importantly, seeking such coherence across etiologic models is a process that may be able to be generalized to other diseases. While the exact mechanisms remain unclear, however, there are sufficient empirical data to establish that diets high in meat (and perhaps fat) are associated with increased risk, as are diets low in plant foods – vegetables, fruit, and perhaps cereals. Alcohol increases risk; physical activity and lower body size reduce risk.The public health recommendations that follow from these associations are clear.

References

1. American Cancer Society. *Cancer Facts and Figures* 1992. Atlanta, GA (USA): ACS, 1992.
2. Muir C, Waterhouse J, Mack T, *et al. Cancer Incidence in Five Continents. Vol 5.* Lyon, France: International Agency for Research on Cancer, 1987; IARC Sci. Pub. No. 88.
3. Parkin DM, Muir CS, Whelan SL, *et al. Cancer Incidence in Five Continents. Vol. 6.* Lyon, France: International Agency for Research on Cancer, 1992; IARC Sci. Pub. No. 120.
4. McMichael AJ, Potter JD. Reproduction, endogenous and exogenous sex hormones, and colon cancer: A review and hypothesis. *JNCI* 1980; **65**: 1201-7.
5. Correa P, Haenszel W. The epidemiology of large bowel cancer. *Adv Canc Res* 1978; **26**: 2-141.

6. McMichael AJ, Potter JD. Host factors in carcinogenesis. Certain bile-acid profiles that selectively increase the risk of proximal colon cancer. *JNCI* 1985; **75**: 185-91.
7. Smith AH, Pearce NE, Joseph JG. Major colorectal cancer aetiological hypotheses do not explain mortality trends among Maori and non-Maori New Zealanders. *Int J Epidemiol* 1985; **14**: 79-85.
8. Ferguson LR, Yee RL, Scragg R, Metcalf PA, Harris PJ. Differences in intake of specific plant foods by polynesians may explain their lower incidence of colorectal cancer compared with Europeans in New Zealand. *Nutr Cancer* 1995; **23** 33-42.
9. Schottenfeld D, Winawer SJ. Large Intestine. In: Schottenfeld D, Fraumeni JF Jr, eds. *Cancer Epidemiology and Prevention*. Philadelphia, PA (USA): WB Saunders Co, 1982: 703-27.
10. Reis LAG, Miller BA, Hankey BF, Kosary CL, Harras A, Edwards BK, eds. *SEER Cancer Statistics Review, 1973-1991: Tables and Graphs*, Bethesda, MD (USA): 1994; National Cancer Institute, NIH Pub No. 94-2789.
11. Bonnett A, Dickman P, Roder D, *et al*. *Survival of Cancer Patients in South Australia*. Adelaide, Australia: South Australian Cancer Registry, 1992.
12. Haenszel W. Cancer mortality among the foreign born in the United States. *JNCI* 1961; **26**: 37-132.
13. Wynder EL, Shigematsu T. Environmental factors of cancer of the colon and rectum. *Cancer* 1967; **20**: 1520-61.
14. McMichael AJ, McCall MG, Hartshorne JM, Woodings TL. Patterns of gastrointestinal cancer in European migrants to Australia: The role of dietary change. *Int J Cancer* 1980; **25**: 431-7.
15. McMichael AJ, Giles GG. Cancer in migrants to Australia: Extending the descriptive epidemiological data. *Cancer Res* 1988; **48**: 751-6.
16. Macklin MT. Inheritance of cancer of the stomach and large intestine in man. *JNCI* 1969; **24**: 551-71.
17. Gardner EJ. A genetic and clinical study of intestinal polyposis, a predisposing factor for carcinoma of the colon and rectum. *Am J Human Genet* 1951; **3**: 167-76.
18. Veale AMO. *Intestinal Polyposis*. Cambridge, UK: Cambridge University Press, 1965.
19. Utsunomiya J, Lynch HT. *Hereditary Colorectal Cancer*. New York, NY (USA): Springer-Verlag, 1990.
20. Hill MJ, Drasar BS. Degradation of bile salts by human intestinal bacteria. *Gut* 1968; **9**: 22-7.
21. Aries V, Crowther JS, Drasar BS, *et al*. Bacteria and the aetiology of cancer of the large bowel. *Gut* 1969; **10**: 334-5.
22. Burkitt DP. Related disease-related cause? *Lancet* 1969; **2**: 1229-31.
23. IARC Intestinal Microecology Group. Dietary fibre, transit time, faecal bacteria, steroids, and colon cancer in two Scandinavian populations. *Lancet* 1977; **2**: 207-11.
24. Jensen OM, MacLennan R, Wahrendorf J. Diet, bowel function, faecal characteristics and large bowel cancer in Denmark and Finland. *Nutr Cancer* 1982; **4**; 5-19.
25. Gregor OR, Toman R, Prusova F. Gastrointestinal cancer and nutrition. *Gut* **10**: 1031-4.
26. Drasar BS, Irving D. Environmental factors and cancer of the colon and breast. *Br J Cancer* 1973; **27**: 167-72.
27. Armstrong B, Doll R. Environmental factors and cancer incidence and mortality in different countries, with special reference to dietary practices. *Int J Cancer* 1975; **15**: 617-31.
28. Howell MA. Diet as an etiological factor in the development of cancers of the colon and rectum. *J Chron Dis* 1975; **28**: 67-80.
29. Schrauzer GN. Cancer mortality correlation studies II. Regional associations of mortalities with the consumptions of foods and other commodities. *Med Hypoth* 1976; **2**: 39-49.
30. Knox EG. Foods and diseases. *Br J Prev Soc Med* 1977; **31**: 71-80.
31. Liu K, Stamler J, Moss D, *et al*. Dietary cholesterol, fat and fibre, and colon cancer mortality. *Lancet* 1979; **2**: 782-5.
32. Meyer F. Relations alimentation-cancer en France. *Gastroenterol Clin Biol* 1977; **1**: 971-82.
33. Rosen P, Horwitz C, Gilat T. Can changes in dietary habits prevent colorectal cancer? In: RA Malt, RCN Williamson, eds. *Colonic Carcinogenesis*. Boston, MA (USA): MTP Press Ltd. 1982; Falk Symposium No 31.
34. McKeown-Eyssen G, Bright-See E. Relationship between colon cancer mortality and fibre consumption: An international study (Abstract). In: Wallace G, Bell L, eds. *Fibre in Human and Animal Nutrition. Proceedings of a Symposium, New Zealand, May 1982*. Wellington, New Zealand: Royal Society of New Zealand, 1983: 35.
35. Enstrom JE. Colorectal cancer and the consumption of beef and fat. *Br J Cancer* 1975; **32**: 432-9.
36. Potter JD. Large bowel cancer: epidemiology and biology. *Ergeb Gastroenterol* 1989; **24**: 137-40.
37. Willett WC, Stampfer MJ. Total energy intake: Implications for epidemiologic analyses. *Am J Epidemiol* 1986; **124**: 17–27.
38. Howe GR, Miller AB, Jain M. re: Total energy intake: implications for epidemiologic analyses (Letter). *Am J Epidemiol* 1986; **124**: 156-7.
39. Pike MC. re: Total energy intake: Implications for epidemiologic analyses (Letter). *Am J Epidemiol* 1989; **129**: 1312-5.
40. Wattenberg LW. Inhibition of chemical carcinogenesis. *JNCI* 1987; **60**: 11-8.
41. Wattenberg LW. Inhibition of carcinogenic effects of polycyclic hydrocarbons by benzyl isothiocyanate and related compounds. *JNCI* 1977; **58**: 195-8.
42. Steinmetz K, Potter J. Vegetables, fruit and cancer. II. Mechanisms. *Cancer Causes Control* 1991; **2** 427-42.
43. Higginson J. Etiological factors in gastrointestinal cancer in man. *JNCI* 1966; **37**: 527-45.
44. Graham S, Dayal H, Swanson M, Mittelman A, Wilkinson G. Diet in the epidemiology of cancer of the colon and rectum. *JNCI* 1978; **61**: 709-14.

45. Tajima K, Tominga S. Dietary habits and gastro-intestinal cancers: A comparative case-control study of stomach and large intestinal cancers in Nagoya Japan. *Jpn J Cancer Res* 1985; **76**: 705-16.
46. Stocks P. Cancer incidence in North Wales and Liverpool region in relation to habits and environment. London, UK: Brit Emp Cancer Campaign, 35th Annual Report, Suppl to Part 2: 1957; 1-127.
47. Wynder EL, Kajutani T, Ishikana S, *et al*. Environmental factors of cancer of the colon and rectum. II. Japanese epidemiological data. *Cancer* 1969; **23**: 1210-20.
48. Haenszel W, Berg JW, Segi M, *et al*. Large bowel cancer in Hawaiian Japanese. *JNCI* 1973; **51**: 1765-79.
49. Bjelke E. *Epidemiologic studies of cancer of the stomach, colon and rectum. Vol III. Case-control study of gastrointestinal cancer in Norway*. Ann Arbor, MI (USA): Univ Microfilms, 1973.
50. Bielke E. *Epidemiologic studies of cancer of the stomach, colon and rectum. Vol IV, Case-control study of digestive tract cancers in Minnesota*. Ann Arbor, MI (USA): Univ Microfilms, 1973.
51. Bjelke E. Epidemiologic studies of cancer of the stomach, colon and rectum; with special emphasis on the role of diet. *Scand J Gastronenterol* 1974; **9**: 124-229.
52. Phillips R. Role of life-style and dietary habits in risk of cancer among Seventh-day Adventists. *Cancer Res* 1975; **35**: 3513-22.
53. Modan B, Barell V, Lubin F, *et al*. Low-fiber intake as an etiologic factor in cancer of the colon. *JNCI* 1975; **55**: 15-8.
54. Dales LG, Friedman GD, Ury HK, *et al*. A case-control study of relationships of diet and other traits to colorectal cancer in American Blacks. *Am J Epidemiol* 1979; **109**: 132-44.
55. Haenszel W, Locke FB, Segi M. A case-control study of large bowel cancer in Japan. *JNCI* 1980; **64**: 17-22.
56. Haenszel W, Kurihara M, Locke FB, *et al*. Stomach cancer in Japan. *JNCI* 1976; **56**: 265-78.
57. Jain M, Cook GM, Davis FG, *et al*. A case-control study of diet and colo-rectal cancer. *Int J Cancer* 1980; **26**: 757-68.
58. Morgan RW, Jain N, Miller AB, *et al*. A comparison of dietary methods in epidemiologic studies. *Am J Epidemiol* 1978; **107**: 488-98.
59. Jain M, Howe GR, Johnson KC, Miller AB. Evaluation of a diet history questionnaire for epidemiologic studies. *Am J Epid* 1980b; **111**: 212-9.
60. Miller AB, Howe GR, Jain M, *et al*. Food items and food groups as risk factors in a case-control study of diet and colorectal cancer. *Int J Cancer* 1983; **32**: 155-61.
61. Hirayama T. A large-scale cohort study on the relationship between diet and selected cancers of digestive organs. WR Bruce, P Correa, M Lipkin, *et al*, eds. *Gastrointestinal Cancer: Endogenous Factors. NY, NY (USA):* Cold Spring Harbor Laboratory, 1981; Banbury report 7: 409-26.
62. Manousos O, Day NE, Trichopoulos D, *et al*. Diet and colorectal cancer. A case-control study in Greece. *Int J Cancer* 1983; **32**: 1-5.
63. Stemmermann GN, Nomura AMY, Heilbrun LK. Dietary fat and the risk of colorectal cancer. *Cancer Res* 1984; **44**: 4633-7.
64. Heilbrun LK, Hankin JH, Nomura AM, Stemmermann GN. Colon cancer and dietary fat, phosphorus and calcium in Hawaiian-Japanese men. *Am J Clin Nutr* 1986; **43**: 306-9.
65. Heilbrun LK, Nomura A, Hankin J, Stemmermann G. Diet and colorectal cancer with special reference to fiber intake. *Int J Cancer* 1989; **44**: 1-6.
66. Phillips RL, Snowdon DA. Dietary relationships with fatal colorectal cancer among Seventh-day Adventists. *JNCI* 1985; **74**: 307-17.
67. Macquart-Moulin G, Riboli E, Cornée J, *et al*. Case-control study on colorectal cancer and diet in Marseilles. *Int J Cancer* 1986; **38**: 183-91.
68. McMichael A, Potter JD. Diet and colon cancer. Integration of the descriptive, analytic and metabolic epidemiology. *JNCI* 1985; **69**: 223-8.
69. Potter JD, McMichael AJ. Diet and cancer of the colon and rectum: A case-control study. *JNCI* 11986; **76**: 557-69.
70. Steinmetz KA, Potter JD. Food group consumption and colon cancer in the Adelaide Case-control Study. I. Vegetables and fruit. *Int J Cancer* 1993 **53**: 711-9.
71. Steinmetz KA, Potter JD. Food group consumption and colon cancer in the Adelaide Case-control Study. II. Meat, poultry, seafood, dairy foods, and eggs. *Int J Cancer* 1993; **53**: 720-7.
72. Rohan TE, Potter JD. Retrospective assessment of dietary intake. *Am J Epidemiol* 1984; **120**: 876-87.
73. Kune S, Kune GM, Watson F. Case-control study of dietary etiologic factors. The Melbourne colorectal cancer study. *Nutr Cancer* 1987; **9**: 21-42.
74. Lyon JL, Mahoney AW, West DW, *et al*. Energy intake: its relationship to colon cancer risk. *JNCI* 1987; **78**: 853-61.
75. Tuyns AJ, Haelterman M, Kaaks R. Colorectal cancer and the intake of nutrients: oligosaccharides are a risk factor, fats are not. A case-control study in Belgium. *Nutr Cancer* 1987; **10**: 181-96.
76. Tuyns AJ, Kaaks R, Haelterman M. Colorectal cancer and the consumption of foods: a case-control study in Belgium. *Nutr Cancer* 1988; **11**: 189-204.
77. Graham S, Marshall J, Haughey B, *et al*. Dietary epidemiology of cancer of the colon in western New York. *Am J Epidemiol* 1988; **128**: 409-503.
78. La Vecchia C, Negri E, Decarli A, *et al*. A case-control study of diet and colo-rectal cancer in northern Italy. *Int J Cancer* 1988; **41**: 492-8.
79. Young TB, Wolf DA. Case-control study of proximal and distal colon cancer and diet in Wisconsin. *Int J Cancer* 1988; **42**: 167-75.
80. Slattery ML, Schumacher MC, Smith KR, *et al*. Physical activity, diet and risk of colon cancer in Utah. *Am J Epidemiol* 1988; **128**: 989-99.
81. West DW, Slattery ML, Robinson LM, *et al*. Dietary intake and colon cancer. Sex and anatomic site-specific associations. *Am J Epidemiol* 1989; **130** 883-94.

82. Peters RK, Garabrant DH, Yu MC, Mack TM. A case-control study of occupational and dietary factors in colorectal cancer in young men by subsite. *Cancer Res* 1989; **49**: 5459-68.
83. Lee HP, Gourley L. Duffy SW, *et al*. Colorectal cancer and diet in an Asian population – a case control study among Singapore Chinese. *Int J Cancer* 1989; **43**: 1007-16.
84. Gerhardsson de Verdier M, Hagman U, Steineck G, *et al*. Diet, body mass and colorectal cancer: a case-referent study. *Int J Cancer* 1990; **46**: 832-8.
85. Benito E, Obrador A, Stiggelbout A, *et al*. A population-based case-control study of colorectal cancer in Majorca. I. Dietary factors. *Int J Cancer* 1990; **45**: 69-76.
86. Benito E, Stiggelbout A, Bosch FX, *et al*. Nutritional factors in colorectal cancer risk: A case-control study in Majorca. *Int J Cancer* 1991; **49**: 161-7.
87. Whittemore AS, Wu-Williams AH, Lee M, *et al*. Diet, physical activity, and colorectal cancer among Chinese in North American and China. *JNCI* 1990; **82**: 915-26.
88. Willett WC, Stampfer MJ, Colditz GA, *et al*. Relation of meat fat and fiber intake to the risk of colon cancer in a prospective study among women. *N Engl J Med* 1990; **323**: 1664-72.
89. Willett WC. *Dietary Epidemiology*. Oxford, UK: Oxford University Press, 1990.
90. Hu J, Liu Y, Yu Y, *et al*. Diet and cancer of the colon and rectum: a case-control study in China. *Int J Epidemiol* 1991; **20**: 362-7.
91. Peters RK, Pike MC, Garabrant D, Mack TM. Diet and colon cancer in Los Angeles County, California. *Cancer Causes Control* 1992; **3**: 457-73.
92. Bidoli E, Franceschi S, Talamini R, *et al*. Food consumption and cancer of the colon and rectum in north-eastern Italy. *Int J Cancer* 1992; **50**: 223-9.
93. Thun MJ, Calle EE, Namboodiri MM, *et al*. Risk factors for fatal colon cancer in a large prospective study. *JNCI* 1992; **84**: 1491-500.
94. Zaridze D, Filipchenko V, Kustov V, *et al*. Diet and colorectal cancer: results of two case-control studies in Russia. *Eur J Cancer* 1993; **29A**: 112-5.
95. Meyer F, White E. Alcohol and nutrients in relation to colon cancer in middle-aged adults. *Am J Epidemiol* 1993; **138**: 225-36.
96. Bostick RM, Potter JD, McKenzie DR, *et al*. Reduced risk of colon cancer with high intake of vitamin E: The Iowa Women's Health Study. *Cancer Res* 1993; **53**; 4230-7.
97. Bostick RM, Potter JD, Sellers TA, McKenzie DR, Kushi LH, Folsom AR. Relation of calcium, vitamin D, and dairy food intake to incidence of colon cancer among older women: The Iowa Women's Health Study. *Am J Epidemiol* 1993; **137**: 1302-7.
98. Bostick RM, Potter JD, Kushi LH, *et al*. Sugar, meat, and fat intake, and non-dietary risk factors for colon cancer incidence in Iowa women (United States). *Cancer Causes Control* 1994; **5**: 38-52.
99. Steinmetz KA, Kushi LH, Bostick RM, Folsom AR, Potter JD. Vegetables, fruit and colon cancer in the Iowa Women's Health Study. *Am J Epidemiol* 1994; **139**: 1-15.
100. Goldbohm RA, van den Brandt PA, van't Veer P. A prospective cohort study on the relation between meat consumption and the risk of colon cancer. *Cancer Res* 1994; **54**: 718-23.
101. Kampman E, Goldbohm A, van den Brandt PA, van 't Veer P. Fermented dairy products, calcium, and colorectal cancer in the Netherlands cohort study. *Cancer* 1994; **54**: 3186-90.
102. Giovannucci E, Rimm EB, Stampfer MJ, Colditz GA, Ascherio A, Willett WC. Intake of fat, meat and fiber in relation to risk of colon cancer in men. *Cancer Res* 1994; **54**: 2390-97.
103. Giovannucci E, Rimm EB, Ascherio A, Stampfer MJ, Colditz GA, Willett WC. Alcohol, low-methionine – low-folate diets and risk of colon cancer in men. *JNCI* 1995; **87**: 265-73.
104. Howe GR, Benito E, Castellato R, *et al*. Dietary intake of fiber and decreased risk of cancers of the colon and rectum: evidence from the combined analysis of 13 case-control studies. *JNCI* 1992; **84**: 1887-96.
105. Iscovich JM, L'Abbeé KA, Castelleto R, *et al*. Colon cancer in Argentina. I: Risk from intake of dietary items. *Int J Cancer* 1992; **51**: 851-7.
106. Steinmetz KA, Potter JD. Egg consumption and cancer of the colon and rectum. *Eur J Cancer Prev* 1994; **3**: 237-45.
107. Martinez I, Torres R, Frias Z, Colón JR, Fernández N. Factors associated with adenocarcinomas of the large bowel in Puerto Rico. In: *Advances in Medical Oncology, Research, and Education, Vol. III*. Oxford, UK: Pergamon Press, 45-52.
108. Modan B, Cuckle H, Lubin F. A note on the role of dietary retinol and carotene in human gastro-intestinal cancer. *Int J Cancer* 1981; **28**: 421-4.
109. Newmark HL, Wargovich MJ, Bruce WR. Colon cancer and dietary fat, phosphate, and calcium: a hypothesis. *JNCI* 1984; **72**: 1323-5.
110. Sorensen AW, Slattery ML, Ford MH. Calcium and colon cancer. A review. *Nutr Cancer* 1988; **11**: 135-45.
111. Emerson JC, Weiss NS. Colorectal cancer and solar radiation. *Cancer Causes Control* 1992; **3**: 95-9.
112. Garland C, Barrett-Connor E, Rossof AH, *et al*. Dietary vitamin D and calcium and risk of colorectal cancer: A 19-year prospective study in men. *Lancet* 1985; **1**: 307-9.
113. Slattery ML, Sorenson AW, Ford MH. Dietary calcium intake as a mitigating factor in colon cancer. *Am J Epidemiol* 1988; **128**: 504-14.
114. Stemmerman GN, Nomura A, Chyou PH. The influence of dairy and non-dairy calcium on subsite large-bowel cancer risk. *Dis Colon Rectum* 1990; **33**: 190-4.
115. Wu AH, Paganini-Hill A, Ross RK, Henderson BE. Alcohol, physical activity, and other risk factors for colorectal cancer: A prospective study. *Br J Cancer* 1987; **55**: 687-94.
116. Negri E, La Vecchia C, D'Avanzo B, *et al*. Calcium dairy products and colorectal cancer. *Nutr Cancer* 1990; **13**; 255-62.
117. Garland CF, Garland FC, Shaw EK, *et al*. Serum 25-hydroxyvitamin D and colon cancer. Eight-year prospective study. *Lancet* 1989; **2**: 1176–8.

118. Pickle LN, Greene MH, Ziegler RG, *et al.* Colorectal cancer in rural Nebraska. *Cancer Res* 1984; **44**: 363-9.
119. Ursin G, Bjelke E, Heuch I, *et al.* Milk consumption and cancer incidence. A Norwegian prospective study. *Br J Cancer* 1990; **61**: 454-9.
120. Schrauzer GN, White DA, Schneider CJ. Cancer mortality correlation studies: III. Statistical associations with dietary selenium intakes. *Bioinorg Chem* 1977; **7**: 23-34.
121. Nomura A, Heilbrun LK, Morris JS, Stemmermann GN. Serum selenium and the risk of cancer, by specific sites: case-control analysis of prospective data. *JNCI* 1987; **79**: 103-8.
122. Schober SE, Comstock GW, Helsing KJ, *et al.* Serologic precursors of cancer. *Am J Epidemiol* 1987; **126**: 1033-41.
123. Salonen JT, Alfthan G, Huttunen JK, Puska P. Association between serum selenium and the risk of cancer. *Am J Epidemiol* 1984; **120**: 120-342.
124. Willett WC, Morris JS, Pressel S, *et al.* Prediagnostic serum selenium and risk of cancer. *Lancet* 1983; **322**: 130-4.
125. Sugimura T, Sato S. Mutagens-carcinogens in foods, *Cancer Res* 1983; **43**: 2415s-21s.
126. Nagao M, Sugimura T. Carcinogenic factors in food with relevance to colon cancer developments. *Mutation Res* 1993; **290**: 43-51.
127. Ohgaki H, Hasegawa H, Kato T, *et al.* Carcinogenicities in mice and rats of IQ, MeIQ, and MeIQx. In: Hayashi Y, Nagao M, Sugimura T, *et al*, eds. *Diet, Nutrition and Cancer*. Tokyo, Japan: Japan Sci Soc Press, 1986: 97-105.
128. Gerhardsson de Verdier M, Hagman U, Peters RK, *et al.* Meat, cooking methods and colorectal cancer: a case-referent study in Stockholm. *Int J Cancer* 1991; **49**: 520-5.
129. Severson RK, Nomura AMY, Grove JS, Stemmermann GN. A prospective analysis of physical activity and cancer. *Am J Epidemiol* 1989; **130**: 522-9.
130. Slattery ML, Adb-Elghany N, Kerber R, Schumacher MC. Physical activity and colon cancer: A comparison of various indicators of physical activity to elevate the association. *Epidemiology* 1990; **1**: 481-5.
131. Brownson RC, Chang JC, Davis JR, Smith CA. Physical activity on the job and cancer in Missouri. *Am J Public Health* 1991; **81**: 639-42.
132. Fredriksson M, Bengtson NO, Hardell L, Axelson O. Colon cancer, physical activity, and occupational exposures. *Cancer* 1989; **63**: 1838-42.
133. Paffenbarger RS, Hyde RT, Wing AL. Physical activity and incidence of cancer in diverse populations: a preliminary report. *Am J Clin Nutr* 1987; **45**: 312-7.
134. Gerhardsson de Verdier M, Broderus B, Norell SE. Physical activity and colon cancer risk. *Int J Epidemiol* 1988; **17**: 743-6.
135. Gerhardsson M, Norell SE, Kiviranta H, *et al.* Sedentary jobs and colon cancer. *Am J Epidemiol* 1986; **123**: 775-80.
136. Vena JE, Graham S, Zielezny M, *et al.* Lifetime occupational exercise and colon cancer. *Am J Epidemiol* 1985; **122**: 357-65.
137. Garabrant DH, Peters JM, Mack TM, Bernstein L. Job activity and colon cancer risk. *Am J Epidemiol* 1984; **119**: 1005-14.
138. Kato I, Tominaga S, Ikari A. A case-control study of male colorectal cancer in Aichi Prefecture, Japan: with special reference to occupational activity level, drinking habits and family history. *Jpn J Cancer Res* 1990; **81**: 115-21.
139. Ballard-Barbash R, Schatzkin A, Albanes D, *et al.* Physical activity and risk of large bowel cancer in the Framingham Study. *Cancer Research* 1990; **50**: 3610-3.
140. Gerhardsson de Verdier M, Steineck G, Hagman U, *et al.* Physical activity and colon cancer: a case-referent study in Stockholm. *Int J Cancer* 1990; **46**: 985-9.
141. Lee IM, Paffenbarger RS, Hsieh C-c. Physical activity and risk of developing colorectal cancer among college alumni. *JNCI* 1991; **83**: 1324-9.
142. Giovannucci E, Ascherio A, Rimm EB, Colditz GA, Stampfer MJ, Willett WC. Physical activity, obesity, and risk for colon cancer and adenoma in men. *Ann Intern Med* 1995; **122**: 327-34.
143. Marcus PM, Newcomb PA, Storer BE. Early adulthood physical activity and colon cancer risk among Wisconsin women. *Cancer Epidemiol Biomark Prev* 1994; **3**: 641-4.
144. Albanes D, Taylor PR. International differences in body height and weight and their relationship to cancer incidence. *Nutr Cancer* 1990; **14**: 69-77.
145. Nomura A, Heilbrun LK, Stemmermann GN. Body mass index as a predictor of cancer in men. *JNCI* 1985; **74**: 319-23.
146. Dietz AT, Newcomb PA, Marchs PM, Storer BE. The association of body size and large bowel cancer risk in Wisconsin (United States) women. *Cancer Causes Control* 1995; **6**: 30-6.
147. Berry EM, Zimmerman J, Peser M, *et al.* Dietary fat, adipose tissue composition, and the development of carcinoma of the colon. *JNCI* 1986; **77**: 93-7.
148. Albanes D, Jones DY, Schatzkin A, *et al.* Adult stature and risk of cancer. *Cancer Res* 1988; **48**: 1658-62.
149. Bullough WS. Mitotic activity and carcinogenesis. *Br J Cancer* 1950; **4**: 329-36.
150. Winick M, Noble A. Cellular response in rats during malnutrition at various ages. *J Nutr* 1966; **89**: 300-6.
151. Bostick RM, Potter JD, Kushi LH, *et al.* Sugar, meat, and fat intake, and non-dietary risk factors for colon cancer incidence in Iowa women (United States). *Cancer Causes Control* 1994; **5**: 38-52.
152. Shinchi K, Kono S, Honjo S, *et al.* Obesity and adenomatous polyps of the sigmoid colon. *Jpn J Cancer Res* 1994; **85**: 479-484.
153. Sundby P. *Alcoholism and Mortality*. Oslo, Norway: Universitetsforlaget, 1967.
154. Halulinen T, Lehtimaki L, Lehtonene M, Teppo L. Cancer morbidity among two male cohorts with increased risk of alcohol consumption in Finland. *JNCI* 1974; **52**; 1711-4.
155. Monson RR, Lyon JL. Proportional mortality among alcoholics. *Cancer* 1975; **36**: 1077-9.
156. Adelstein A, White G. Alcoholism and mortality. *Population Trend* 1976; **6**: 7-13.

157. Dean G, MacLennan R, McLoughlin H, Shelley E. Causes of death of blue-collar workers at a Dublin brewery, 1954-73. *Br J Cancer* 1979; **40**: 581-9.
158. Jensen OM. Cancer morbidity and causes of death among Danish brewery workers. *Int J Cancer* 1979; **23**: 454-63.
159. Breslow NW, Enstrom JE. Geographic correlations between cancer mortality rates and alcohol-tobacco consumption in the United States. *JNCI* 1974; **53**: 631-9.
160. Enstrom JE. Colorectal cancer and beer drinking. *Br J Cancer* 1977; **35**: 674-83.
161. McMichael AJ. Alimentary tract cancer in Australia in relation to diet and alcohol. *Nutr Cancer* 1979; **1**: 82-9.
162. Potter JD, McMichael AJ, Hartshorne JM. Alcohol and beer consumption in relation to cancers of bowel and lung: An extended correlation analysis. *J Chron Dis* 1982; **35**: 833-42.
163. Robinette CD, Hrubec Z, Fraumeni JF. Chronic alcoholism and subsequent mortality in World War II veterans. *Am J Epidemiol* 1979; **109**: 687-700.
164. Schmidt W, Popham RE. The role of drinking and smoking in mortality from cancer and other causes in male alcoholics. *Cancer* 1981; **47**: 1031-41.
165. Gordon T, Kannel WB. Drinking and mortality: the Framingham Study. *Am J Epidemiol* 1984; **120**: 97-107.
166. Klatsky AL, Armstrong MA, Freidman GD, Hiatt RA. The relations of alcoholic beverage use to colon and rectal cancer. *Am J Epidemiol* 1988; **128**: 1007–15.
167. Hirayama T. Association between alcohol consumption and cancer of the sigmoid colon: observations from a Japanese cohort study. *Lancet* 1989; **334**:725-7.
168. Stemmermann GN, Nomura A, Chyou PH, *et al*. Prospective study of alcohol intake and large bowel cancer. *Digest Dis Sci* 1990; **35** 1414-20.
169. Williams RR, Horm JW. Association of cancer sites with tobacco and alcohol consumption and socioeconomic status of patients: interview study from the Third National Cancer Survey. *JNCI* 1977; **58**: 525-47.
170. Tuyns AJ, Péquignot G, Gignoux M, Valla A. Cancers of the digestive tract, alcohol and tobacco. *Int J Cancer* 1982; **30**: 9-11.
171. Kune S, Kune GA, Watson LF. Case-control study of alcoholic beverages as etiologic factors: the Melbourne colorectal cancer study. *Nutr Cancer* 1987; **9**: 43-56.
172. Ferraroni M, Negri E, La Vecchia C, *et al*. Socioeconomic indicators, tobacco, and alcohol in the aetiology of digestive tract neoplasms. *Int J Epidemiol* 1989; **18**: 556-62.
173. Longnecker MP. A case-control study of alcoholic beverage consumption in relation to risk of cancer of the right colon and rectum. *Cancer Causes Control* 1990; **1**: 5-14.
174. Choi SY, Kahyo H. Effect of cigarette smoking and alcohol consumption in the etiology of cancer of the digestive tract. *Int J Cancer* 1991; **49**:381-6.
175. Slattery ML, West DW, Robinson LM, *et al*. Tobacco, alcohol, coffee, and caffeine as risk factors for colon cancer in a low-risk population. *Epidemiology* 1990; **1** :141-5.
176. Rosenberg L, Werler MM, Palmer JR, *et al*. The risks of cancers of the colon and rectum in relation to coffee consumption. *Am J Epidemiol* 1989; **130**: 859-903.
177. La Vecchia C, Ferraroni M, Negri E, *et al*. Coffee consumption and digestive tract cancers. *Cancer Res* 1989; **49**: 1049-51.
178. Jacobsen BK, Bjelke RE, Dvale G, Heuch I. Coffee drinking, mortality, and cancer incidence: results from a Norwegian prospective study. *JNCI* 1986; **76**: 823-31.
179. Jacobsen BK, Thelle DS. Coffee, cholesterol, and colon cancer: is there a link? *Br Med J* 1987; **294**: 4-5.
180. Schatzkin A, Hoover RN, Taylor PR, *et al*. Serum cholesterol and cancer in the NHANES I epidemiology follow-up study. *Lancet* 1987; **11**: 298-301.
181. Levin RE. Influence of caffeine on mutations induced by nitrosoguanidine in Salmonella typhimurium tester strains. *Environ Mutagen* 1982; **4**: 689-94.
182. Kosugi A, Nagoa M, Suwa Y, *et al*. Roasting coffee beans produces compounds that induce prophage in E cole and S. typhimurium. *Mutat Res* 1983; **116**: 179-84.
183. McNeil NI, Ramptons DS, Phil D. Is the rectum usually empty? A quantitative study in subjects with and without diarrhoea. *Dis Col Rect* 1981; **24**: 596-9.
184. Freudenheim JL, Graham S, Marshall JR, Haughey BP, Wilkinson G. A case-control study of diet and rectal cancer in western New York. *Am J Epidemiol* 1990; **131**: 612-24.
185. Potter JD, Slattery ML, Bostick RM, Gapstur SM. Colon cancer: a review of the epidemiology. *Epidemiology* 1993; **15**: 499-545.
186. Kabat GC, Howson CP, Wynder EL. Beer consumption and rectal cancer. *Int J Epidemiol* 1986; **15**: 494-501.
187. Freudenheim JL, Graham S, Marshall JR, Haughey BP, Cholewinski S, Wilkinson G. Folate intake and carcinogenesis of the rectum and colon. *Int J Epidemiol* 1991; **20**: 368-74.
188. Hoff G, Foerster A, Vatn MH, Gjone E. Epidemiology of polyps in the rectum and sigmoid colon. *Scand J Gastroenterol* 1986; **20**: 677-83.
189. Hoff G, Moen IE, Trygg K, *et al*. Epidemiology of polyps in the rectum and sigmoid colon. *Scand J Gastroenterol* 1986; **21**: 199-204.
190. Macquart-Moulin G, Riboli E, Cornée J, Kaaks R, Berthezene P. Colorectal polyps and diet: a case-control study in Marseilles. *Int J Cancer* 1987; **40**: 179-188.
191. Kikendall JW, Bowen PE, Burgess MB, *et al*. Cigarettes and alcohol as independent risk factors for colonic adenomas. *Gastroenterology* 1989; **97**: 660-4.
192. Kono S, Ikeda N, Yanai F, Shinchi K, Imanishi K. Alcoholic beverages and adenomatous polyps of the sigmoid colon: a study of male self-defence officials in Japan. *Int J Epidemiology* 1990; **19**: 848-52.
193. Kono S, Shinchi K, Ikeda N, Yanai F, Imanishi K. Physical activity, dietary habits and adenomatous polyps of the sigmoid colon: a study of self-defence officials in Japan. *J Clin Epidemiol* 1991; **44**: 1255-61.
194. Kune GA, Kune S, Read A, MacGowan K, Penfold C, Watson LF. Colorectal polyps, diet, alcohol and family

history of colorectal cancer: a case-control study. *Nutr Cancer* 1991; **16**: 25-30.
195. Riboli E, Cornée J, Macquart-Moulin G, Kaaks R, Casagrande C, Guyader M. Cancer and polyps of the colorectum and lifetime consumption of beer and other alcoholic beverages. *Am J Epidemiol* 1991; **134**: 157-219.
196. Cope GF, Wyatt JI, Pinder IF, *et al.* Alcohol consumption in patients with colorectal adenomatous polyps. *Gut* 1991; **32**: 70-2.
197. Honjo S, Kono S, Shinchi K, *et al.* Cigarette smoking, alcohol use and adenomatous polyps of the sigmoid colon. *Jpn J Cancer Res* 1992; **83**: 806-11.
198. Giovannucci E, Stampfer MJ, Colditz G, Rimm EB, Willett WC. Relationship of diet to risk of colorectal adenoma in men. *JNCI* 1992; **84**: 91-8.
199. Benito E, Cabeza E, Moreno V, Obrador A, Bosch FX. Diet and colorectal adenomas: a case-control study in Majorca. *Int J Cancer* 1993; **55**: 213-9.
200. Giovannucci E, Stampfer MJ, Colditz GA, *et al.* Folate, methionine, and alcohol intake and risk of colorectal adenoma. *JNCI* 1993; **85**: 875-84.
201. Kono S, Imanishi K, Shinchi K, Yanai F. Relationship of diet to small and large adenomas of the sigmoid colon. *Jpn J Cancer Res* 1993; **84**: 13-9.
202. Lee WC, Neugut AI, Garbowski GC, *et al.* Cigarettes, alcohol, coffee, and caffeine as risk factors for colorectal adenomatous polyps. *Ann Epidemiol* 1993; **3**: 239-44.
203. Little J, Logan RFA, Hawthin PG, Hardcastle JD, Turner ID. Colorectal adenomas and energy intake, body size and physical activity: a case-control study of subjects participating in the Nottingham faecal odccult blood screening programme. *Br J Cancer* 1993; **67**: 172-6.
204. Little J, Logan RFA, Hawthin PG, Hardcastle JD, Turner ID. Colorectal adenomas and diet: a case-control study of subjects participating in the Nottingham faecal occult blood screening programme. *Br J Cancer* 1993; **67**: 177-84.
205. Neugut AI, Garbowski GC, Lee WC, *et al.* Dietary risk factors for the incidence and recurrence of colorectal adenomatous polyps. *Ann Int Med* 1993; **118**: 91-5.
206. Sandler RS, Lyles CM, Peipins LA, McAuliffe CA, Woosley JT, Kupper LL. Diet and risk of colorectal adenomas: macronutrients, cholesterol, and fiber. *JNCI* 1993; **85**: 884-91.
207. Sandler RS, Lyles CM, McAuliffe C, Woosley JT, Kupper LL. Cigarette smoking, alcohol and the risk of colorectal adenomas. *Gastroenterol* 1993; **104**: 1445-51.
208. Jacobson JS, Neugut AI, Murray T, *et al.* Cigarette smoking and other behavioral risk factors for recurrence of colorectal adenomatous polyps (New York City, NY, USA). *Cancer Causes Control* 1994; **5**: 215-20.
209. Kampman E, Giovannucci E, van 't Veer P, *et al.* Calcium, vitamin D, dairy foods, and the occurrence of colorectal adenomas among men and women in two prospective studies. *Am J Epidemiol* 1994; **139**: 16-29.
210. Olsen J, Kronbor O, Lynggaard J, Ewertz M. Dietary risk factors for cancer and adenomas of the large intestine. A case-control study within a screening trial in Denmark. *Eur J Cancer* 1994; **30A**: 53-60.
211. Martinez ME, McPherson RS, Annegers JF, Levin B. Cigarette smoking and alcohol consumption as risk factors for colorectal adenomatous polyps. *JNCI* 1995; **87**: 274-9.
212. Boutron M-C, Faivre J, Dop M-C, Quipourt V, Senesse P. Tobacco, alcohol, and colorectal tumors: A multistep process. *Am J Epidemiol* 1995; **141**: 1038-46.
213. Potter JD: Reconciling the epidemiology, physiology, and molecular biology of colon cancer. *JAMA* 1992; **268**: 1573-7.
214. Hill MJ, Aries VC. Faecal steroid composition and its relationship to cancer of the large bowel. *J Path* 1971; **104**: 129-39.
215. Stephen A, Cummings J. Mechanism of action of dietary fibre in the human colon. *Nature* 1980; **284**: 283-4.
216. Cummings J. Fermentation in the human large intestine: evidence and implications for health. *Lancet* 1983; **I**: 1206-9.
217. Corpet D, Stamp D, Medline A, Minkin S, Archer M, Bruce WR. Promotion of colonic microadenoma growth in mice and rats fed cooked sugar or cooked casein and fat. *Cancer Res* 1990; **50**: 6955-8.
218. McMichael AJ, Potter JD. Do intrinsic sex differences in lower alimentary tract physiology influence the sex-specific risks for bowel cancer and other biliary and intestinal diseases? *Am J Epidemiol* 1983; **118**: 620-7.
219. Weiss NS, Daling JR, Chow WH. Incidence of cancer of the large bowel in women in relation to reproductive and hormonal factors. *JNCI* 1981; **67**: 57-60.
220. Potter JD, McMichael AJ. Large bowel cancer in relation to reproductive and hormonal factors: a case-control study. *JNCI* 1983; **71**: 703-9.
221. Stasse-Wolthuis M, Albers HFF, van Jeveren JGC, *et al.* Influence of dietary fiber from vegetables and fruits, bran or citrus pectin on serum lipids, faecal lipids, and colonic function. *Am J Clin Nutr* 1980; **33**: 1745-56.
222. Stephen AM, Wiggins HS, Englyst HN, Cole TJ, Wayman BJ, Cummings JH. The effect of age, sex and level of intake of dietary fibre from what on large-bowel function in thirty healthy subjects. *Br J Nutr* 1986; **56**: 349-61.
223. Lampe JW, Slavin JL, Potter JD. Sex differences in colonic function: a randomized trial. *Gut* 1993; **34**: 531-6.
224. McMichael AJ, Potter JD. Dietary influences upon colon carcinogenesis. In: Hayashi Y, Nagar N, Sugimura T, *et al*, eds. *Diet, Nutrition and Cancer*. Tokyo, Japan: Japan Sci Soc Press, 1986; 275–90.
225. Lampe JW, Slavin Jl, Melcher EA, Potter JD. Effects of cereal and vegetable fiber feeding on potential risk factors for colon cancer. *Cancer Epi Bio Prev* 1992; **1**: 207-11.
226. Anzano MA, Riemann D, Pritchett W, Bowen-Pope DF, Grieg R. Growth factor production by human colon carcinoma cell lines. *Cancer Res* 1989; **49**: 2898-04.
227. Mukaida H, Hirabayashi N, Hirai T, Iwata T, Saeki S, Toge T. Significance of freshly cultured fibroblasts from different tissue in promoting cancer growth cells. *Int J Cancer* 1991; **48**: 423-7.
228. Thun MJ, Namboodiri MM, Heath CW. Aspirin use

and reduced risk of fatal colon cancer. *N Eng J Med* 1991; **325**: 1593-6.

229. Ross JA, Potter JD, Severson RK. Platelet-derived growth factor and the epidemiology of colorectal cancer: a hypothesis. *Eur J Cancer Prev* 1993; **2**: 197-210.
230. Hill MJ, Morson BC, Bussey HJR. Aetiology of adenoma-carcinoma sequence in large bowel. *Lancet* 1978; **I**: 245-7.
231. Lipkin M. Biomarkers of increased susceptibility to gastrointestinal cancer: new application to studies of cancer prevention in human subjects. *Cancer Res* 1988; **48**: 235-45.
232. Bird RP. Observation and quantification of aberrant crypts in the murine colon treated with a colon carcinogen: preliminary findings. *Cancer Lett* 1987; **37**: 147-51.
233. Turesky RJ, Lang N, Butler MA, Teitel CH, Kadlubar FF. Metabolic activation of carcinogenic heterocyclic aromatic amines by human liver and colon. *Carcinogenesis* 1991; **12**: 1417-22.
234. Kaderlik KR, Minchin RF, Mulder GJ, *et al.* Metabolic activation pathway for the formation of DNA adducts of the carcinogen 2-amino-1-methyl-6-phenylimidazol (4,5-*b*)pyridine (PhIP) in rat extrahepatic tissues. *Carcinogenesis* 1994; **15**:1703-9.
235. Lin D, Meyer DJ, Ketterer B, Lang NP, Kadlubar FF. Effects of human and rat glutathione *S*-transferases on the covalent DNA binding of the *N* Acetoxy derivatives of heterocyclic amine carcinogens *in Vitro*: A possible mechanism of organ specificity in their carcinogenesis. *Cancer* 1994; **54**: 4920-6.
236. Kadlubar FF, Butler MA, Kaderlik KR, *et al.* Polymorphisms for aromatic amine metabolism in humans: relevance for human carcinogenesis. *Environ Health Persp* 1992; **98**: 69-74.
237. Leppert M, Dobbs M, Scambler P, *et al.* The gene for familial polyposis coli maps to the long arm of chromosome 5. *Science* 1987; **238**: 1411-3.
238. Bodmer WF, Bailey CJ, Bodmer J, *et al.* Localization of the gene for familial adenomatous polyposis on chromosome 5. *Nature* 1987; **328**: 614-6.
239. Leppert M, Burt R, Hughes J, *et al.* Genetic analysis of an inherited predisposition to colonic cancer in a family with a variable number of adenomatous polyps. *New Engl J Med* 1990; **32**: 904-8.
240. Groden J, Thliveris A, Samowitz W, *et al.* Identification and characterization of the familial adenomatous polyposis coli gene. *Cell* 1991; **66**: 589-600.
241. Kinzler K, Nilbert M, Su L-K, *et al.* Identification of FAP locus genes from chromosome 5q21. *Science* **253**: 661-5.
242. Joslyn G, Carlson M, Thliveris A, *et al.* Identification of deletion mutations and three new genes at the familial polyposis locus. *Cell* 1991; **66**: 601-13.
243. Spirio L, Otterud B, Stauffer D, *et al.* Linkage of a variant or attenuated form of adenomatous polyposis coli to the adenomatous polyposis coli (APC) locus. *Am J Hum Genet* 1992; **51**: 92-100.
244. Powell SM, Zilz N, Beazer-Barclay Y, *et al.* APC mutations occur early during colorectal tumorigenesis. *Nature* 1992; **359**: 235-7.
245. Su LK, Vogelstein B, Kinzler KW. Association of the APC tumor suppressor protein with catenins; *Science* 1993; **262**: 1734-7.
246. Rubinfeld B, Souza B, Albert I, *et al.* Association of the apc gene product with b-Catenin. *Science* 1993; **262**: 1731-4.
247. Lynch HT, Lynch JF, Cristofaro G. Genetic epidemiology of colon cancer. In: Lynch HT, Hirayama T, eds. *Genetic Epidemiology of Cancer*. Boca Raton, FL (USA): CRC Press: 251-77.
248. Peltomaki P, Aaltonen LA, Sistonen P, *et al.* Genetic mapping of a locus predisposing to human colorectal cancer. *Science* 1993; **260**: 810-2.
249. Aaltonen LA, Peltomaki P, Leach FS, *et al.* Clues to the pathogenesis of familial colorectal cancer. *Science* 1993; **260**: 812-6.
250. Thibideau SN, Bren G, Schald D. Microsatellite instability in cancer of the proximal colon. *Science* 1993; **260**: 816-9.
251. Papadopoulos N, Nicolaides NC, Wei Y-F, *et al.* Mutation of a *mutL* homolog in hereditary colon cancer. *Science* 1994; **263**: 1625-9.
252. Fishel R, Ewel A, Lee S, Lescoe MK, Griffith J. Binding of mismatched microsatellite DNA sequences by the human MSH2 protein. *Science* 1994; **266**: 1403-5.
253. Baker S, Fearon E, Nigro J, *et al.* Chromosome 17 deletions and p53 gene mutations in colorectal carcinomas. *Science* 1989; **244**: 217-22.
254. Vogelstein B, Fearon E, Kern S, *et al.* Allelotype of colorectal carcinomas. *Science* 1989; **244**: 207-12.
255. Kinzler K, Nilbert M, Vogelstein B, *et al.* Identification of a gene located at chromosome 5q21 that is mutated in colorectal cancers. *Science* 1991; **251**: 1366-70.
256. Fearon E, Cho K, Nigroo J, *et al.* Identification of a chromosome 18q gene that is altered in colorectal cancers. *Science* 1990; **247**: 49-56.
257. Fearon ER, Vogelstein B. A genetic model for colorectal tumorigenesis. *Cell* 1990; **61**: 759-67.
258. Nishisho I, Nakamura Y, Miyoshi Y, *et al.* Mutations of chromosome 5q21 genes in FAP and colorectal cancer patients. *Science* 1991; **253**: 665-9.
259. Feinberg A, Vogelstein B. Hypomethylation of ras oncogenes in primary human cancers. *Biochem Biophys Res Comm* 1983; **111**: 47-54.
260. El-Deiry WS, Nelkin BD, Celano P, *et al.* High expression of the DNa methyltransferase gene characterizes human neoplastic cells and progression stages of colon cancer. *Proc Nat Acad Sci* 1991; **88**: 3470-4.
261. Hoffman RM. Altered methionine metabolism, DNA methylation and oncogene expression in carcinogenesis. *Biochem Biophys Act* 1984; **738**: 49-87.
262. Yunis JJ, Soreng AL. Constitutive fragile sites and cancer. *Science* 1984; **226**: 1199-204.
263. Issa JPJ, Ottaviano YL, Celano P, Hamilton SR, Davidson NE, Baylin SB. Methylation of the oestrogen receptor CpG island links aging and neoplasia in human colon. *Nature Genetics* 1994;**7**: 536-40.

264. Morotomi M, Guillem J, LoGerfo P, Weinstein IB. Production of diacylglycerol, an activator of protein kinase C, by human intestinal microflora. *Cancer Res* 1990; **50**: 3595-9.
265. Guillem JG, Weinstein IB. The role of protein kinase C in colon neoplasia. In: Herrar L, ed. Familial Adenomatous Polyposis. New York, NY (USA): Alan R Liss, 1990; 325-32.
266. Hague A, Manning AM, Hanlon KA, Huschtsha LI, Hart D, Paraskeva C. Sodium butyrate induces apoptosis in human colonic tumor cell lines in a p53-independent pathway–implications for the possible role of dietary fibre in the prevention of large bowel cancer. *Int J Cancer* 1993; **55**: 498-505.
267. Hague A, Elder DJE, Hicks DJ, Paraskeva C. Apoptosis in colorectal tumour cells: induction by the short chain fatty acids butyrate, propionate and acetate and by the bile salt deoxycholate. *Int J Cancer* 1995, in press.
268. Rosenthal MD. Fatty acid metabolism of isolated mammalian cells. Prog Lipid Res 1987; **26**: 87-124.
269. Nicosia S, Patrono C. Eicosanoid biosynthesis and action: novel opportunities for pharmacological intervention. *FASEB J* 1989; **3**: 1941-8.
270. Rutten AAJJL, Falke HE. Influence of high dietary evels of fat on rat hepatic phase I and II biotransformation enzyme activities. *Nutr Rep Int* 1987; **36**: 109.
271. Kim HJ, Choi ES, Wade AE. Effect of dietary fat on the induction of hepatic microsomal cytochrome P450 isozymes by phenobarbital. *Biochem Pharmacol* 1990; **39**:1423.
272. Guillem JG, Hsieh LL, O'Toole KM, *et al.* Changes in expression of oncogenes and endogenous retrovital-like sequences during colon carcinogenesis. *Cancer Res* 1988; **48**: 3964.
273. Castro EC. Nutrient effects on DNA and chromatin structure. *Ann Rev Nutr* 1987; **7**: 407.
274. Beland FA, Kadlubar FF. Formation and persistence of arylamine DNA adducts *in vivo*. *Environ Health Perspect* 1985; **62**: 19-30.
275. Canzian F, Ushijima T, Serikawa T, Wakabayashi K, Sugimura T, Nagao M. Instability of microsatellites in rat colon tumors induced by heterocyclic amines. *Cancer Res* 1994; **54**: 6315-7.
276. Kakiuchi H, Watanabe M, Ushijima T, *et al.* Specific 5′-GGGA-3′ → GGA-3′ mutation of the *Apc* gene in rat colon tumors induced by 2-amino-1-methyl-6-phenylimidazo(4,5-*b*)pyridine. *Proc Natl Acad Sci* 1995; **92**: 910-4.
277. Miyoshi Y, Nagase H, Ando H, *et al.* Somatic mutations of the APC gene in colorectal tumors: mutation cluster region in the APC gene. *Hum Mol Genet* 1992; 1: 229-33.
278. Miyaki M, Konishi M, Kikuchi-Yanoshita R, *et al.* Characteristics of somatic mutation of the adenomatous polyposis coli gene in colorectal tumors. *Cancer Res* 1994; **54**: 3011-20.