POINT OF VIEW

Colorectal cancer: influence of diet and lifestyle factors

A. Franco^{1,2}, A. K. Sikalidis¹ and J. A. Solís Herruzo³

¹Department of Nutritional Sciences. University of California. Berkeley, USA. ²Division of Gastroenterology. University of California. San Francisco, USA. ³Division of Digestive Diseases. Hospital 12 de Octubre. Madrid, Spain

Franco A, Sikalidis AK, Solís Herruzo JA. Colorectal cancer: influence of diet and lifestyle factors. *Rev Esp Enferm Dig* 2005; 97: 432-448.

INTRODUCTION

Colorectal cancer (CRC) is one of the most commonly diagnosed cancers, with more than 944,000 cases and 492,000 cancer-related deaths reported worldwide in 2000 (1). Migrant and temporal studies suggest that colorectal cancer is determined largely by environmental exposures, as it is shown by large rate variations between different countries and by dramatic increases in incidence among populations migrating from low-risk to high-risk areas (2). Based on such epidemiological studies, it has been estimated that as much as 70-80% of colorectal cancer could be attributed to the contribution of environmental and lifestyle factors (3,4). These observations suggest the importance of potentially modifiable factors that may be largely preventable.

On the other hand, although the environment is central to the etiology of most cases of colorectal cancer, individual, genetically-determined susceptibility is also im-

portant and plays a decisive role through its interaction with the other different etiologic factors, as it is shown by the recent discoveries related to the interaction between gene, environment and diet. At this point, the implications of environmental causes of colon cancer are evident. If we could identify and modify these relevant factors, then we might be able to prevent most colorectal cancer incidence. The challenge is to discover the environmental factors that are responsible for this disease and then change them.

DIET

Diet is one of the most important lifestyle factors and has been studied widely. The first major report was a review of the available evidence on diet and cancer published by the USA National Academy of Science in 1982 (5). This report found convincing evidence that diet played an important role in human cancer and included a series of recommendations that at that time emphasized a reduction in total fat intake (6,7). Since the early 1980s many different investigations (animal experiments, retrospective and prospective epidemiological studies, clinical trials) have addressed the potential effects of diet on cancer incidence. Later on, in 1997, a comprehensive review of diet and cancer was published (8), and even since that time new major results have been reported.

Although much has been learned, progress has been slower and more difficult than it was anticipated. For instance, different trials with a variety of nutritional modifications (e.g., increases in fiber, fruits, and vegetables, lower fat intake, or supplementation with various whole foods or with one or more vitamins or minerals) have shown limited effects in colorectal neoplasia prevention (9). Nonetheless, several lines of evidence support a role for dietary modifications in the prevention of colorectal neoplasia. A large number of observational studies sug-

This article has been realized with the support of a grant of Universidad Complutense, Madrid and the University of California.

Recibido: 26-04-05.
Aceptado: 29-04-05.

Correspondencia: Alejandro Franco Ugidos. Paseo de la Esperanza, 8, P3, 7D. 28005 Madrid. e-mail: afrancougidos@hotmail.com

gest that vegetables, fruits, a high-fiber diet, and certain micronutrients might be protective against CRC; while heavy alcohol intake, and red meat (and the way it is cooked and prepared) might increase CRC risk (9-11). At the same time, several animal studies confirmed that dietary changes might reduce cancer risk (12-14). The following sections describe these data.

Dietary fat and meat intake

Previous old studies suggested a positive correlation between dietary fat and CCR risk (6,7,15), which resulted in dietary recommendations based on a reduction in total fat intake. The mechanism postulated for the possible relation between a high-fat diet and colonic cancer resides on the association between fat intake and the production of bile acids. Primary bile acids, also called conjugated bile salts, are produced by the liver to participate in the absorption of fat from the small intestine. Although primary bile acids are very efficiently reabsorbed and redirected to the liver at the ileum, a small percentage, approximately 1-2%, is not absorbed but rather escapes into the colon, where it becomes metabolized by the colonic microflora into secondary bile acids, which are known to be mutagenic (18).

However, several recent studies (16-21) indicate that there is essentially no association of fat intake with risk of colorectal cancer, independently of the kind of fat (total, saturated, monounsaturated or polyunsaturated), and it seems that at least part of the high colon cancer rates in Western countries previously attributed to fat intake are probably due to a sedentary lifestyle with high energy intakes (22,23). Another concern is the possible association between trans-fatty acids (found in soft margarine and baked goods) with colorectal neoplasia; although there is some preliminary evidence available (24,25), the data are not yet conclusive.

Only one study (26) has found an increased risk with fat intake, and it was attributable to animal fat intake, and not to vegetable one. Other further analyses in this last study indicated that red meat intake, a major source of animal fat, was the fact associated with the increased risk of colon cancer. Nowadays, it appears that the association of fat intake with colorectal cancer is specific to fat from animal sources and may be attributed to red meat intake, rather than fat *per se* (27,28).

Related to meat intake, the majority of studies have shown an increased risk of colorectal cancer with high intakes of red meat, with a relative risk of 1.35 (95% CI: 1.21-1.51) (21,26,28,29,31,32), sometimes even stronger with processed meat (20,29-31), especially when long-term consumption was examined. "Red" meat refers to beef, pork and lamb as main meals, and processed meat includes sausages, hamburgers, smoked, cured, salted, and canned meat. The fact, previously discussed, that fat intake does not seem to be associated with colon cancer,

suggests that the findings related to meat intake could be explained by the non-fat components of meat. It has been suggested that cooking methods at high temperature may influence the production of carcinogenic components (heterocyclic amines, polyaromatic hydrocarbons) on the surface of meats cooked during long periods of time or in direct contact with fire (28-30,34). At the same time, humans have different enzymes involved in the metabolism of these compounds, and individuals whose phenotypes provide a higher predisposition to transform them into more active molecules, as the "fast" acetylator phenotype, could be at increased risk of developing polyps and large bowel cancer (35). Furthermore, processed meat may also increase the presence of possible carcinogenic factors as nitrosamine precursors (30,33,34). Finally, there have also been some suggestions that an excessive iron intake, especially in the heme form found in red meat, may also be associated with an increased risk of colorectal cancer (29,33). As proposed mechanisms, heme has been shown to produce cytotoxic effects over colonocytes (36,37), and an increase in the fecal concentrations of N-nitrous compounds (36).

Non-red meat sources of animal protein, including low-fat dairy products, fish, and poultry, either have not been associated with a higher risk of colon cancer or even have been related to a lower risk (16,20,21,32).

To summarize this part: recent data suggest that dietary fat does not seem to be a major risk factor for CRC. On the other hand, red meat intake, and in particular processed meat, seems to be associated with a higher risk of colon cancer, so it has been strongly suggested that it should be eaten less frequently, and maybe avoiding its preparation at high temperatures, in direct contact with fire, or in a very-well cooked way (as it occurs when it is grilled) in order to minimize CCR risk (8,33,38,40).

Fiber

The hypothesis that fiber (mainly found in fruits, vegetables and cereals) reduces the risk of colon cancer has been popular since the 1970's, when Denis Burkitt observed that African natives that consumed a high-fiber diet exhibited low rates of colorectal cancer (39). Many potential mechanisms of action have been proposed (41-44): diluting and binding potential carcinogens and speeding their transit through the colon; affecting different mechanisms of carcinogen activation after altering the colonic flora and reducing the pH; or even serving as the substrate for the generation of short-chain fatty acids (especially butyrate), which may be protective through their ability to modulate gene expression, inhibit the growth of tumorigenic cell lines, induce apoptosis and promote differentiation.

The strongest evidence supporting the fiber hypothesis is the remarkable consistency of the protective effect on epidemiological observations in populations with a high

intake of fiber-rich foods (44), strengthened by a meta-analysis of case-control studies that shows a dose-dependent protective effect (45). However, recent studies have cast doubt on the cancer-preventing effects of fiber: some large prospective studies conducted in specific populations do not support this protective effect (21,26,40,46-48). Furthermore, even no randomized interventional studies have assessed the effect of high-fiber intakes in CRC prevention, most of the trials studying the prevented effect of high fiber diets in the growth of adenomas have shown a lack of effect (49,50) or a very modest protective effect (16,51). However, a recent cohort study conducted in ten European countries has shown a clear protective effect of fiber with a dose-response relationship (52).

Why the results differ is not clear (58). As in the studies about fruit and vegetables, this could be due to some kind of bias, for example: in the duration of studies, in the selection process, secondary to some uncontrolled confounding factors, and so on. Many questions yet remain unsolved in regards to the relation between dietary fiber and the development of CRC: its real effect, its mechanism, how to differentiate it from other potential anticarcinogens present in fiber-rich foods. And if finally it is a protective agent: the exact type and source of fiber, the way to administer it, the amount required, when and during what period of time and in what target group (e.g. those without prior adenomas, or even for everybody). In the near future, results from some trials with different approaches (different type of fiber administered in a different way to specific groups or using other efficacy measures of the intervention) may also enhance the understanding of fiber's chemopreventive potential.

Nevertheless, despite a lack of complete scientific evidence and regardless of a few publications that do not consider that higher consumption of fiber foods or supplements can reduce the risk of colon cancer (53), there are still reasons to think that consuming a high-fiber diet may be protective against colon cancer. Furthermore, we also have to consider its positive effects on the gastrointestinal system (as a preventive factor against constipation, hemorrhoids and diverticulosis), as well as in the cardiovascular one. Thus, it is still reasonable to recommend a total fiber intake of at least 30-35 g/day (8,38,40,44).

Fruits and vegetables

The role of fruits and vegetables in colorectal carcinogenesis has been controversial, especially in recent years. Initially, the majority of case-control studies showed that a high intake of vegetables and fruits was associated with a lower risk of colon cancer (32,54-56). However, more recent prospective studies have found no protective effect (21,26). This absence of association has also been supported by randomized intervention studies with fruits and vegetables (49), and also with dietary antioxidants (57)

(including vitamins A, C, and E, commonly found in fruits and vegetables) that used colorectal adenomas as their end point.

The causes of discrepancy between studies remains unclear (58). As in the studies about fiber, it could be due to different types of bias in the investigations, or as a result of the many different biologically active chemicals found in fruits and vegetables that may potentially reduce cancer incidence, for example: carotenoids, folic acid, vitamin C, flavonoids, phytoestrogens, isothiocyanates, fiber, and so on (55); and nowadays it is unknown which of them are responsible for these possibly reduced risk. The identification of the specific protective constituents, or the combination of them, as well as the types and amounts of fruits and vegetables that may be particularly protective could help provide better guidance.

However, despite the lack of conclusive data, it is still believed that a higher intake of fruits and vegetables (especially vegetables) could be beneficial to prevent CRC. And considering its other health benefits, their consumption should be encouraged (8,38,40,53,58,59).

Micronutrients

Calcium and vitamin D

There is a large body of epidemiological evidence that supports a protective effect of calcium against colorectal cancer. Case-control and prospective epidemiological studies show moderate inverse association (a decrease around 25%) between calcium intake and CRC risk (60,61). There are also interesting data from randomized clinical trials that show that calcium supplementation (1,200-2,000 mg per day) produces a modest, but rapid decrease in the incidence of recurrent colorectal adenomas (62-66), although in one of the studies (66) such an effect was only observed in subjects with higher levels of vitamin D, suggesting that perhaps both calcium and adequate levels of vitamin D are required for the protective effect to be exerted.

Different mechanisms have been proposed for calcium's potential to reduce the risk of colorectal cancer: from binding secondary bile acids and fatty acids, sequestering these mutagenic substances from contact with epithelial cells, to a direct action decreasing colonic epithelial cell proliferation and promoting its differentiation, through a calcium-sensing receptor (67-69).

Furthermore, related to the possible protective effect of vitamin D, *in vitro* and *in vivo* studies have shown that vitamin D and its analogs can inhibit colonic epithelial cell proliferation, induce differentiation and promote apoptosis, as well as their positive effects on calcium absorption and transportation (67-69). In addition, a large epidemiological study has reported a 29% reduction in the risk of CRC among men with the highest vitamin D intakes from dietary or supplemental sources (70). Any-

way, these are still preliminary results, and there are no prospective studies yet (40,71).

As a summary, the most recent studies support the notion of a modest protective effect of calcium in CRC risk, in the range of about 20 to 30%. Based on these data, on its benefits to bone health, and on the fact that many people in western countries do not achieve the recommended daily allowance, some experts suggest starting to consider calcium supplementation (about 1200 mg/day) (8,38,73) at least for individuals at high risk for colon cancer. However, there are also some data against its use, especially in men, provided by a study where it was positively associated with a higher risk of prostate cancer (72), and considering the fact that the protective effect appears to depend upon other different variables as colon subsite, gender, source (dietary or supplemental), and lifestyle factors such as smoking or dietary intake of vitamin D, it seems reasonable to wait for future studies incorporating a thorough examination of these variables (40,71).

Selenium

There is some evidence from epidemiological and animal studies that insufficient selenium intake is related to an increased risk for colon and other types of cancer (74,75). In a recent study designed to assess the use of selenium supplements in the prevention of non-melanoma skin cancers, those receiving supplements had, in an unexpected result, a decreased risk for colon and other types of cancer (lung, prostate), although they developed somewhat more skin cancers (76). However, in case-control and cohort studies correlations between the levels of selenium in the blood or nails and reductions in colorectal neoplasia have been inconsistent (9,77,78). Possible mechanisms for these beneficial effects could include actions on DNA repair, as well as an antioxidant or apoptosis inducing role (79,80).

These results need confirmation, but the protective effect of selenium in colorectal cancer is a plausible possibility.

Iron

Some data have led to speculation that dietary iron could increase the risk of colon cancer. Iron is a pro-oxidant that via the production of oxygen radicals -known to damage protein, lipids, and DNA- could promote the induction of somatic mutations that may favor the development of CRC (81-83). At the same time, in animal studies luminal iron concentrations also increase mucosal colonic proliferation (84). Finally, a prospective study has shown that high iron consumption could be associated with an increased risk of colorectal cancer (85). All these data need to be confirmed.

On the other hand, the effect of total body iron is not clear, and data in that regard are still contradictory (86,87).

Antioxidant vitamins

It has been proposed that the probable protective effects of diets rich in fruits and vegetables against the development of colorectal cancer are due to their content of vitamins with antioxidant properties, particularly carotenoids (vitamin A precursors), retinoids (vitamin A), ascorbic acid (vitamin C), and α -tocopherol (vitamin E) (54,56). Anti-oxidants vitamins may inhibit free-radical reactions and thereby prevent oxidative damage to DNA, as well as be involved in cellular proliferation as part of signaling cascades (for example vitamin E) (82). In addition, certain studies suggest that antioxidants may also inhibit tumorigenesis by stimulating the immune system (88).

Prospective data, however, do not support this hypothesis. Vitamin supplementation (A, C, E or a combination of them) has been evaluated in several large prospective studies (89-94). All found no protective effect of vitamin supplementation against adenoma or cancer incidence. Additionally, there are studies which show that individuals randomized to beta-carotene may actually have higher rates of certain tumors such as lung cancer (95,96). However, more recently another study suggested a reduction in recurrent adenomas in subjects who neither smoked nor drank alcohol with beta-carotene supplementation, but an increase among participants who used tobacco or alcohol (97).

All these contradictory results require confirmation in other trials, but there is now little reason to recommend anti-oxidant vitamins for the prevention of colorectal cancer (38,40).

Folate and methionine

Lower folic acid and methionine intakes have been associated with an increased risk of colon adenoma and colon cancer (98-100). At the same time, the long-term use (for more than 15 years) of multivitamins containing folic acid has been associated with a lower risk of colon cancer (91,101), and the protective effect (91) was seen to be primarily due to the folic acid component of multivitamins, rather than anti-oxidant vitamins.

Folate status may be also an important determinant of neoplastic risk in persons with ulcerative colitis (UC). A reverse association between red blood cell folate concentrations and colorectal dysplasia has been reported (102), and also a reduced risk of colorectal dysplasia among patients who receive folate supplements (103). The relationship between inflammatory bowel disease and low folate levels is also well known secondary to the use of

some drugs (e.g. azathioprine), which may enhance the risk of cancer.

The protective mechanism is unknown, but both folic acid (found essentially in fruit and vegetables) and methionine (found in high concentrations in red meat, chicken and fish) serve as methyl donors; methyl groups are necessary for DNA synthesis, methylation and repair (104); for the translation and function of proteins; and possibly to diminish mucosal proliferation (105).

Dietary and genetic factors may modulate the proposed chemopreventive effects of folate and methionine. Certain studies have shown that heavy alcohol consumption and polymorphisms in the enzyme methylenetetrahydrofolate reductase may reduce the availability of folate or methionine (58,98,99,106). It also seems that the protective effect of folic acid comes from supplements (91) rather than higher dietary intake, maybe because of a loss of folic acid during food preparation due to its water soluble nature, or because of its lower bioavailability when in food (9).

Nowadays there is controversy on how to increase folic acid levels in the general population, which are frequently diminished even in Western societies. The promotion of higher fruit and vegetables intakes (even though folic acid from these foods has a lower bioavailability) has been considered, as well as the fortification of some specific meals, and even a recommendation of daily RDA level supplementation (400 mcg/day). In the U.S.A., the enrichment act of 1998 postulated the mandatory fortification of cereals with folate, with an expectation to minimize the incidence of neural tube defects in newborns, and to reduce the risk of cardiovascular disease (CVD) associated with high homocysteine levels, which are lowered by folic acid. A significant reduction in the incidence of neural tube defects was achieved, but the success rate regarding CVD has proven difficult to assess, and there is no information available for colorectal cancer risk (149). Whether the benefits of additional folate may be greater for some groups –e. g., those who consume alcohol on a daily basis, those taking medications reducing its levels, or those with a higher risk of colon cancer for any reason– is also debated.

In the near future, with all these data and the upcoming results of interventional studies, recommendations about folate and methionine as preventive factors for CRC will be clearer.

LIFESTYLE

Energy balance

It has been suggested that energy imbalance (the difference between energy consumption and energy intake) is one of the factors involved in the increased rates of colorectal cancer among economically developed popula-

tions. Several animal models support this hypothesis –for example, studies in mice have shown that energy (caloric) restriction can profoundly reduce the rate of mucosal proliferation and the development of tumors, including colonic ones (107); at the same time, chemically induced carcinogenesis experiments in rats reveal that the risk of colon cancer varies with the type of diet (e.g. increased by 50% in rats fed with high-energy diets) (150). However, these results are difficult to interpret because they may be dependent on other factors such as physical activity (which appears to be protective) or obesity (which seems to increase the risk).

Nowadays the indicators of energy balance used in humans are growth rates and body weight. Thus, adult height could provide an indirect indicator of pre-adult nutrition, and adult weight gain and obesity could reflect a long-term positive energy balance later in life.

Regarding height, taller adults –even after controlling for body weight– have been associated with an increased risk of colon cancer (20,23,108), maybe reflecting the importance of nutrition in the early stages of life, or maybe just because of its close correlation with the total length of the human colon.

Obesity

A significant body of epidemiological studies suggests that obesity, defined as a high body mass index (BMI), is a risk factor for colon cancer (8,20,23,38,108,113), while weight loss seems to be protective (40). At the same time, in animal models obesity has also been associated with an increased risk of colon cancer (151). The association is clearer for colon neoplasias, but less clear for rectal ones, and it appears to be more consistent for men and young women (less than 55 years), diminishing then in aging women (114,115). This last fact is probably related to the menopausal status and the different origin of estrogens between premenopause and postmenopause periods, since estrogens appear to be a protective factor, as seen in postmenopausal women using replacement estrogens who have a lower risk (116). Some data also indicate that a tendency for central distribution of adiposity (visceral adiposity), as typically found in men, increases the risk independently of BMI (23).

Physical activity

Many studies conducted in diverse populations show that more physically active individuals, especially life-long, are at a lower risk for colon cancer, with a reduced incidence by up to 50% (8,22,23,38,109,110,112,113, 117,118). This effect is independent of other risk factors such as diet and body weight, and it appears with different types of physical activity (at work or during leisure time), although some studies also suggest that more in-

tense activity may confer greater protection than less intense activity (110,117,118). But even a relatively moderate level of activity—for example, walking fast for one hour daily or moderate jogging 3-4 hours per week, which can be achieved by many individuals even in highly industrialized countries—can markedly reduce colon cancer risk (40,112). As with BMI, the relationship between physical activity and colon cancer risk is less clear for rectal neoplasias (8).

The underlying mechanisms by which obesity increases risk and why exercise is protective are being studied. One hypothesis is that insulin resistance and compensatory hyperinsulinemia, as components of the metabolic syndrome (syndrome X) related to obesity and lack of physical inactivity, may enhance the risk of colon cancer. Some studies have found that type 2 diabetes mellitus (119-122) and higher insulin concentrations (123) are associated with a higher risk of colon adenomas and cancer. As potential mechanisms, insulin has growth-promoting effects by itself, and it also promotes insulin-like growth factor-I (IGF-I) tumorigenic actions (124). Although obesity is probably the most important influence on this syndrome, the degree of physical activity, genetic factors, and selected dietary components may also influence it. Two dietary patterns that have been related to the induction of these situations are: an abundant intake of foods with a high dietary glycemic index (white bread, rice, potatoes, cereals) showing fast carbohydrate absorption; and a high sucrose intake (cakes, desserts and refined sugar); both of them could be associated with an increased risk of colon cancer (20,125-127).

It has also been postulated that leptin, a hormone produced by fat cells and associated with colon cancer in some experimental studies, may play a role in its pathogenesis, maybe inducing colonic cell proliferation (128-130). Other potential mechanism include an increased release of cytokines from adipose tissue, which may play a role in the inflammatory state associated with CRC (131).

Furthermore, other proposed mechanisms to explain why physical activity may diminish colon cancer risk include a reduction in intestinal transit time, which would limit the period of contact between the colon mucosa and cancer promoting contents (secondary bile acids, dietary toxics). It also may reduce body mass index and insulin resistance (132).

With all these data, the current recommendation is to be physically active, and to avoid overweight and obesity in order to prevent CRC (8,38,40).

Smoking

The majority of recent studies show an association between cigarette smoking, colorectal adenomas, and cancer (20,120,133-137). This association depends on the number of cigarettes smoked, the amount of time exposed to them, and the age when the habit started, so the

relation with colorectal cancer appears after a sufficiently long and continuous period of exposure (up to 35-40 years). Despite the fact that a precise explanation for the increased risk with cigarette smoking is unknown, cigarette smoke contains over 60 carcinogens and free radicals, which could affect the colorectal mucosa—for example, altering the expression of important cancer-related genes (137). Whether tobacco use is linked predominantly to specific subgroups of colorectal cancer, such as those with p53 mutations (138) or those categorized by microsatellite instability (139), requires further study to identify susceptible individuals. These are just a few reasons added to many other public health implications regarding why people should be recommended not to smoke cigarettes.

Alcohol

Alcohol has been consistently linked with an increased risk for colon adenomas, and in the majority of studies also with CRC, although the magnitude of this relationship is modest (8,27,58,62,91,98,99,109,120,140-143). This association has been found for both colon and rectal cancer in a dose-response relationship, starting in moderate drinkers (more than two drinks a day). Regarding whether or not this is related to beverage-type specific effects (wine, beer, spirits), evidence is not clear (144). Furthermore, a greater elevation in colorectal cancer or adenoma risk is also seen among individuals with high intakes of alcohol and low intakes of folate (91,98-100,145-147). This higher risk may be related to the antagonist effect of alcohol on folate metabolism (148).

The mechanisms of alcohol as a colorectal carcinogen include increased mucosal cell proliferation, activation of intestinal procarcinogens, changes in bile composition, and increased nitrosamine levels (144).

CONCLUSION

Although many mechanisms remain unclear, there is convincing evidence from epidemiological and experimental studies that dietary, environmental, and/or lifestyle factors are likely to have a major influence on the risk of colorectal cancer. Data available suggest that diets high in red meat—especially if cooked at high temperatures— or in processed meat (smoked, cured, salted and canned), and perhaps in refined carbohydrates, increase this risk. Regarding fiber, fruits and vegetables, despite previous data recent epidemiological studies have tended not to support a strong protective effect of their intake on CRC risk; however, some micronutrients in these foods could be beneficial and, considering other health benefits, their consumption should be encouraged. Folic acid is one of those micronutrients that has been shown to be a protective factor and is being studied in randomized

intervention trials. There is also recent evidence supporting a protective effect of calcium and vitamin D. On the other hand, excessive alcohol consumption, probably in combination with a diet low in certain micronutrients such as folate and methionine, and smoking during a long period of time appear to increase risk. Physical inactivity and excess body weight are also consistent risk factors for colon cancer.

It is also important to recognize that the clear benefits of screening for colorectal cancer make it the primary method of prevention nowadays; and that promising chemopreventive pharmacological agents, as some nonsteroidal anti-inflammatory drugs, are also currently being evaluated.

To conclude, overwhelming evidence indicates that primary prevention is feasible for colon cancer at least to some extent, and it has been suggested that as many as 70% of colon cancers may be preventable by moderate changes in diet and lifestyle. Thus, current data are sufficiently strong to justify provisional dietary and lifestyle recommendations, which in combination with efforts at screening, chemopreventive treatment and surveillance will allow progress against this frequent, complex, and also preventable disease.

Furthermore, a more effective, individualized guidance will be possible in the near future once the relationship between specific genetic patterns and individual predisposition to the effects—whether protective or casual—of different environmental factors is assessed.

KEY POINTS AND RECOMMENDATIONS

—Epidemiological evidence indicates that a high proportion of CRC is due to dietary and lifestyle factors.

—Red meat intake (and especially processed meat: smoked, cured, salted and canned)—maybe related to the way it is cooked—is associated with an increased risk of CRC, though mechanisms are unclear.

—Although evidence is not clear, a high-fiber diet may reduce CRC risk and also exert other benefits on the gastrointestinal system and general health.

—Despite a lack of clear evidence, fruits and especially vegetables may be protective against CRC.

—Calcium supplements, in the presence of adequate levels of vitamin D, may help protect against CRC.

—An appropriate folate and methionine status seems to be a protective factor for CRC. Folate supplementation, especially for some groups (heavy alcohol drinkers, some inflammatory bowel disease patients), could help protect them against CRC.

—With the exception of calcium and folate, there is little reason to recommend supplementation (e.g., antioxidant vitamins) with the idea of reducing CRC risk.

—Smoking increases CRC risk.

—Alcohol consumption, especially high intakes, increases the risk of CRC, particularly in the presence of low folate levels.

—Obesity increases CRC risk, while physical activity decreases it. Physical activity and avoidance of overweight and obesity are recommended in order to prevent CRC.

REFERENCES

1. Parkin DM, Bray F, Ferlay J, Pisani P. Estimating the world cancer burden: Globocan 2000. *Int J Cancer* 2001; 94: 153-6.
2. Parkin DM, Muir CS, Whelan SL, et al. Cancer incidence in five continents. IARC Sci Publ 1992; (120): 45-173. Oxford: Oxford University Press.
3. Doll R, Peto R. The causes of cancer. *J Natl Cancer Inst* 1981; 66: 1191-308.
4. Willett WC. Diet, nutrition and avoidable cancer. *Environ Health Perspect* 1995; 103 (Supl. 8): 165-70.
5. Committee on Diet, Nutrition, and Cancer, Assembly of Life Sciences, National Research Council. Diet, Nutrition, and Cancer. Washington, D.C.: National Academy Press, 1982.
6. Walker AR, Burkitt DP. Colonic cancer: hypotheses of causation, dietary prophylaxis, and future research. *Am J Dig Dis* 1976; 21: 910-7.
7. PWynder EL. The epidemiology of large bowel cancer. *Cancer Res* 1975; 35: 3388-94.
8. World Cancer Research Fund in association with American Institute for Cancer Research. Food, Nutrition and the Prevention of Cancer: A Global Perspective. Washington, DC: eAmerican Institute for Cancer Research, 1997.
9. Hawk ET, Umar A. Colorectal cancer chemoprevention: an overview of the science. *Gastroenterology* 2004; 126: 1423-47.
10. Slatery ML. Diet, lifestyle, and colon cancer. *Semin Gastrointest Dis* 2000; 11: 142-6.
11. Steinmetz KA, Potter JD. Vegetables, fruit, and cancer prevention: a review. *J Am Diet Assoc* 1996; 96: 1027-39.
12. Corpet DE, Pierre F. Point: from animal models to prevention of colon cancer. Systematic review of chemoprevention in min mice and choice of the model system. *Cancer Epidemiol Biomarkers Prev* 2003; 12: 391-400.
13. Lamson DW, Brignall MS. Natural agents in the prevention of cancer. Part one: human chemoprevention trials. *Altern Med Rev* 2001; 6: 7-19.
14. Lamson DW, Brignall MS. Natural agents in the prevention of cancer, part two: preclinical data and chemoprevention for common cancers. *Altern Med Rev* 2001; 6: 167-87.
15. Boyle P, Zaridze DG, Smans M. Descriptive epidemiology of colorectal cancer. *Int J Cancer* 1985; 36: 9-18.
16. Giovannucci E, Stampfer MJ, Colditz G, et al. Relationship of diet to risk of colorectal adenoma in men. *J Natl Cancer Inst* 1992; 84: 91-8.
17. Howe GR, Aronson KJ, Benito E, et al. The relationship between dietary fat intake and risk of colorectal cancer evidence from the combined analysis of 13 case-control studies. *Cancer Causes Control* 1997; 8: 215-28.
18. Van Munster IP, Nagengast FM. The role of carbohydrate fermentation in colon cancer prevention. *Scand J Gastroenterol Suppl* 1993; 200: 80-6.
19. Stemmermann GN, Nomura AM, Heilbrun LK. Dietary fat and the risk of colorectal cancer. *Cancer Res* 1984; 44: 4633-7.
20. 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.
21. Giovannucci E, Rimm EB, Stampfer MJ, et al. Intake of fat, meat, and fiber in relation to risk of colon cancer in men. *Cancer Res* 1994; 54: 2390-7.
22. Martínez ME, Giovannucci E, Spiegelman D, et al. Leisure-time physical activity, body size, and colon cancer in women. Nurses' Health Study Research Group. *J Natl Cancer Inst* 1997; 89 (13): 948-55.

23. Giovannucci E, Ascherio A, Rimm EB, et al. Physical activity, obesity, and risk for colon cancer and adenoma in men. *Ann Intern Med* 1995; 122: 327-34.
24. Slattery ML, Benson J, et al. Trans-fatty acids and colon cancer. *Nutr Cancer* 2001; 39 (2): 170-5.
25. McKelvey W, Greenland S, et al. A case-control study of colorectal adenomatous polyps and consumption of foods containing partially hydrogenated oils. *Cancer Epidemiol Biomarkers Prev* 1999; 8 (6): 519-24.
26. 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.
27. Potter JD. Nutrition and colorectal cancer. *Cancer Causes Control* 1996; 7: 127-46.
28. Kushi L, Giovannucci E. Dietary fat and cancer. *Am J Med* 2002; 113 (9B): 63S-70S.
29. Chao A, Thun MJ, et al. Meat consumption and risk of colorectal cancer. *JAMA* 2005; 293: 172-82.
30. Le Marchand L. Meat intake, metabolic genes and colorectal cancer. *IARC Sci Publ* 2002; 156: 481-5.
31. Norat T, Lukanova A, et al. Meat consumption and colorectal cancer risk. *Int J Cancer* 2002; 98: 241-56.
32. 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.
33. Willett WC. Diet and cancer. *JAMA* 2005; 293: 233-5.
34. Cummings JH, Bingham SA. Diet and the prevention of cancer. *BMJ* 1998; 317: 1636-40.
35. Roberts-Thompson IC, Ryan P, et al. Diet, acetylator phenotype, and risk of colorectal neoplasia. *Lancet* 1996; 347: 1372-4.
36. Cross AJ, Pollock JRA, Bingham SA. Heme, not protein or inorganic iron, is responsible for endogenous intestinal N-nitrosation arising from red meat. *Cancer Res* 2003; 63: 2358-60.
37. Sesink AL, Termont DS, et al. Red meat and colon cancer: the cytotoxic and hyperproliferative effects of dietary heme. *Cancer Res* 1999; 59: 5704-9.
38. Burt RW, Winawer SJ, Bond JH, et al. Preventing Colorectal Cancer: A Clinician's Guide. American Gastroenterological Association, 2004.
39. Burkitt DP. Epidemiology of cancer of the colon and rectum. *Cancer* 1971; 28: 3-13.
40. Castells A, Marzo M, Bellas B, et al. Guía de Práctica Clínica de Prevención del Cáncer Colorrectal. *Gastroenterol Hepatol* 2004; 27 (10): 573-634.
41. Harris PJ, Ferguson LR. Dietary fibre: its composition and role in protection against colorectal cancer. *Mutat Res* 1993; 290: 97-110.
42. Klurfeld DM. Dietary fiber-mediated mechanisms in carcinogenesis. *Cancer Res* 1992; 52 (Supl.): 2055s-9s.
43. Kritchevsky D. Cereal fibres and colorectal cancer: a search for mechanisms. *Eur J Cancer Prev* 1998; 7 (Supl. 2): 33-9.
44. Young-In K, et al. American Gastroenterological Association medical position statement: impact of dietary fiber on colon cancer occurrence. *American College of Gastroenterology. Gastroenterology* 2000; 118 (6): 1233-4.
45. Friedenreich CM, Brant RF, Riboli E. Influence of methodologic factors in a pooled analysis of 13 case-control studies of colorectal cancer and dietary fiber. *Epidemiology* 1994; 5: 66-79.
46. Fuchs CS, Giovannucci EL, et al. Dietary fiber and the risk of colorectal cancer and adenoma in women. *N Engl J Med* 1999; 340 (3): 169-76.
47. Steinmetz KA, Kushi LH, et al. Vegetables, fruit, and colon cancer in the Iowa Women's Health Study. *Am J Epidemiol* 1994; 139: 1-15.
48. Riboli E, Norat T. Epidemiologic evidence of the protective effect of fruit and vegetables on cancer risk. *Am J Clin Nutr* 2003; 78: 559S-69S.
49. Schatzkin A, Lanza E, et al. Lack of effect of a low-fat, high-fiber diet on the recurrence of colorectal adenomas. *Polyp Prevention Trial Study Group. N Engl J Med* 2000; 342: 1149-55.
50. Asano T, McLeod R. Dietary fibre for the prevention of colorectal adenomas and carcinomas. *The Cochrane Library*. Chichester, UK: John Wiley & Sons Ltd, 2003.
51. MacLennan R, Macrae F, Bain C, et al. Randomized trial of intake of fat, fiber, and beta carotene to prevent colorectal adenomas. *J Natl Cancer Inst* 1995; 87: 1760-6.
52. Bingham SA, Day NE, Luben R, et al. Dietary fibre in food and protection against colorectal cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC): an observational study. *Lancet* 2003; 361: 1496-501.
53. Willett WA. Goals for Nutrition in the Year 2000. *CA Cancer J Clin* 1999; 49: 331-52.
54. Trock B, Lanza E, Greenwald P. Dietary fiber, vegetables, and colon cancer: Critical review and metaanalyses of the epidemiologic evidence. *J Natl Cancer Inst* 1990; 82: 650-61.
55. Steinmetz KA, Potter JD. Vegetables, fruit, and cancer. I: Epidemiology. *Cancer Causes Control* 1991; 2: 325-57.
56. Block G, Patterson B, Subar A. Fruit, vegetables, and cancer prevention: A review of the epidemiological evidence. *Nutr Cancer* 1992; 18: 1-29.
57. Greenberg ER, Baron JA, Tosteson TD, et al. A clinical trial of antioxidant vitamins to prevent colorectal adenoma. *N Engl J Med* 1994; 331: 141-7.
58. Giovannucci E. Diet, body weight, and colorectal cancer: a summary of the epidemiologic evidence. *J Womens Health* 2003; 12 (2): 173-82.
59. The American Cancer Society 1996 Advisory Committee on Diet, Nutrition, and Cancer Prevention. Guidelines on diet, nutrition, and cancer prevention: reducing the risk of cancer with healthy food choices and physical activity. *CA Cancer J Clin* 1996; 46: 325-41.
60. Wu K, Willett W, et al. Calcium intake and risk of colon cancer in women and men. *J Nat Cancer Inst* 2002; 94: 437-46.
61. Norat T, Riboli E. Dairy products and colorectal cancer. A review of possible mechanisms and epidemiological evidence. *Eur J Clin Nutr* 2003; 57: 1-17.
62. Bonithon-Kopp C, Kronborg O, et al. Calcium supplementation in prevention of colorectal adenoma recurrence: a randomised intervention trial. *Lancet* 2000; 356: 1300-6.
63. Baron J, Beach M, Mandel J, et al. Calcium supplements for the prevention of colorectal adenomas. *N Engl J Med* 1999; 340: 101-7.
64. Bostick R, Fosdick L, Wood J, et al. Calcium and colorectal epithelial cell proliferation in sporadic adenoma patients: a randomized, double-blinded, placebo-controlled clinical trial. *J Nat Cancer Inst* 1995; 87: 1307-15.
65. Hofstad B, Almendingen K, Vatn M, et al. Growth and recurrence of colorectal polyps: a double-blind 3-year intervention with calcium and antioxidants. *Digestion* 1998; 59: 148-56.
66. Grau MV, Baron JA, Sandler RS, et al. Vitamin D, calcium supplementation, and colorectal adenomas: results of a randomized trial. *J Natl Cancer Inst* 2003; 95: 1765-71.
67. Lamprecht SA, Lipkin M. Chemoprevention of colon cancer by calcium, vitamin D and folate: molecular mechanisms. *Nat Rev Cancer* 2003; 3 (8): 601-14.
68. Martínez ME, Willett WC. Calcium, vitamin D, and colorectal cancer: a review of the epidemiologic evidence. *Cancer Epidemiol Biomarkers Prev* 1998; 7: 163-8.
69. Garland CF, Garland FC, Gorham ED. Calcium and vitamin D. Their potential roles in colon and breast cancer prevention. *Ann N Y Acad Sci* 1999; 889: 107-19.
70. McCullough ML, Robertson AS, et al. Calcium, vitamin D, dairy products, and risk of colorectal cancer in the cancer prevention study II nutrition cohort (United States). *Cancer Causes Control* 2003; 14: 1-12.
71. Chia V, Newcomb PA. Calcium and colorectal cancer: some questions remain. *Nutr Rev* 2004; 62 (3): 115-20.
72. Giovannucci E, Rimm EB, Wolk A, et al. Calcium and fructose intake in relation to risk of prostate cancer. *Cancer Res* 1998; 58: 442-7.
73. Bresalier RS. Calcium, chemoprevention, and cancer: a small step forward (a long way to go). *Gastroenterology* 1999; 116 (5): 1261-3.
74. Clark LC. The epidemiology of selenium and cancer. *Fed Proc* 1985; 44: 2584-9.
75. Ip C. The chemopreventive role of selenium in carcinogenesis. *Adv Exp Med Biol* 1986; 206: 431-47.
76. Clark LC, Combs GF Jr, Turnbull BW, et al. Effects of selenium supplementation for cancer prevention in patients with carcinoma of the skin: a randomized controlled trial: Nutritional Prevention of Cancer Study Group. *JAMA* 1996; 276: 1957-63.

77. Knekt P, Aromaa A, Maatela J, et al. Serum selenium and subsequent risk of cancer among Finnish men and women. *J Natl Cancer Inst* 1990; 82: 864-8.
78. Nelson RL, Davis FG, et al. Serum selenium and colonic neoplastic risk. *Dis Colon Rectum* 1995; 38: 1306-10.
79. Narayanan BA, Narayanan NK, Desai D, et al. Effects of a combination of docosahexaenoic acid and 1,4-phenylene bis(methylene) selenocyanate on cyclooxygenase 2, inducible nitric oxide synthase and beta-catenin pathways in colon cancer cells. *Carcinogenesis* 2004; 25 (12): 2443-9.
80. Nelson RL, Abcarian H, et al. The effect of dietary selenium deficiency on acute colorectal mucosal nucleotoxicity induced by several carcinogens in the rodent. *Am J Surg* 1996; 172 (1): 85-8.
81. Lund EK, S, Wharf G, et al. Oral ferrous sulfate supplements increase the free radical-generating capacity of feces from healthy volunteers. *Am J Clin Nutr* 1999; 69: 250-5.
82. Babbs CF. Free radicals and the etiology of colon cancer. *Free Radic Biol Med* 1990; 8: 191-200.
83. Weinberg ED. The role of iron in cancer. *Eur J Cancer Prev* 1996; 5: 19-36.
84. Lund EK, Wharf SG, et al. Increases in the concentrations of available iron in response to dietary iron supplementation are associated with changes in crypt cell proliferation in rat large intestine. *J Nutr* 1998; 128: 175-9.
85. Wurzemann JI, Silver A, et al. Iron intake and risk of colon cancer. *Cancer Epidemiol Biomarkers Prev* 1996; 5: 503-7.
86. Shaheen NJ, Silverman LM, et al. Association between hemochromatosis (HFE) gene mutation carrier status and the risk of colon cancer. *J Natl Cancer Inst*. 2003; 95 (2): 154-9.
87. Kato I, Dnistrian AM, et al. Iron intake, body iron stores and colorectal cancer risk in women: a nested case-control study. *Int J Cancer* 1999; 80 (5): 693-8.
88. Biasco G, Paganelli GM, et al. Chemoprevention of colorectal cancer: role of antioxidant vitamins. *Eur J Cancer Prev* 1992; 1 (Supl. 3): 87-91.
89. Malila N, Virtamo J, et al. The effect of alpha-tocopherol and beta carotene supplementation on colorectal adenomas in middle-aged male smokers. *Cancer Epidemiol Biomarkers Prev* 1999; 8: 489-93.
90. Hennekens CH, Buring JE, Manson JE, et al. Lack of effect of longterm supplementation with beta carotene on the incidence of malignant neoplasms and cardiovascular disease. *N Engl J Med* 1996; 334: 1145-9.
91. Giovannucci E, Stampfer MJ, Colditz GA, et al. Multivitamin use, folate, and colon cancer in women in the Nurses' Health Study. *Ann Intern Med* 1998; 129: 517-24.
92. Greenberg ER, Baron JA, Tosteson TD, et al. A clinical trial of antioxidant vitamins to prevent colorectal adenoma. *N Engl J Med* 1994; 331: 141-7.
93. Hofstad B, Almendingen K, et al. Growth and recurrence of colorectal polyps: a double-blind 3-year intervention with calcium and antioxidants. *Digestion* 1998; 59: 148-56.
94. Malila N, Virtanen M, et al. A comparison of prospective and retrospective assessments of diet in a study of colorectal cancer. *Nutr Cancer* 1998; 32: 146-53.
95. Hennekens CH, Buring JE, Manson JE, et al. Lack of effect of long-term supplementation with beta carotene on the incidence of malignant neoplasms and cardiovascular disease. *N Engl J Med* 1996; 334: 1145-9.
96. The Alpha-Tocopherol Beta-Carotene Cancer Prevention Study Group. The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. *N Engl J Med* 1994; 330: 1029-35.
97. Baron JA, Cole BF, et al. Neoplastic and antineoplastic effects of betacarotene on colorectal adenoma recurrence: results of a randomized trial. *J Natl Cancer Inst* 2003; 95: 717-22.
98. Giovannucci E, Stampfer MJ, Colditz GA, et al. Folate, methionine, and alcohol intake and risk of colorectal adenoma. *J Natl Cancer Inst* 1993; 85: 875-84.
99. Giovannucci E, Rimm EB, Ascherio A, et al. Alcohol, low-methionine-low-folate diets, and risk of colon cancer in men. *J Natl Cancer Inst* 1995; 87: 265-73.
100. Freudenheim JL, Graham S, Marshall JR, et al. Folate intake and carcinogenesis of the colon and rectum. *Int J Epidemiol* 1991; 20: 368-74.
101. White E, Shannon JS, Patterson RE. Relationship between vitamin and calcium supplement use and colon cancer. *Cancer Epidemiol Biomarkers Prev* 1997; 6: 769-74.
102. Lashner BA. Red blood cell folate is associated with the development of dysplasia and cancer in ulcerative colitis. *J Cancer Res Clin Oncol* 1993; 119: 549-54.
103. Lashner BA, Provencher KS, Seidner DL, et al. The effect of folic acid supplementation on the risk for cancer or dysplasia in ulcerative colitis. *Gastroenterology* 1997; 112: 29-32.
104. Choi SW, Mason JB. Folate and carcinogenesis: an integrated scheme. *J Nutr* 2000; 130: 129-32.
105. Kim YI, Baik HW, Fawaz K, et al. Effects of folate supplementation on two provisional molecular markers of colon cancer: a prospective, randomized trial. *Am J Gastroenterol* 2001; 96: 184-95.
106. Ma J, Stampfer MJ, Giovannucci E, et al. Methylenetetrahydrofolate reductase polymorphism, dietary interactions, and risk of colorectal cancer. *Cancer Res* 1997; 57: 1098-102.
107. Weindrich R, Walford RL. Dietary restriction in mice beginning at 1 year of age: effect on life-span and spontaneous cancer incidence. *Science* 1982; 215: 1415-8.
108. Chute CG, Willett WC, Colditz GA, et al. A prospective study of body mass, height, and smoking on the risk of colorectal cancer in women. *Cancer Causes Control* 1991; 2: 117-24.
109. Wu AH, Paganini-Hill A, Ross RK, et al. Alcohol, physical activity and other risk factors for colorectal cancer: A prospective study. *Br J Cancer* 1987; 55: 687-94.
110. IARC Working Group on the Evaluation of Cancer-Preventive Agents. Weight control and physical activity. Handbooks of cancer prevention, vol. 6. Lyon: IARC Press, 2002.
111. Le Marchand L, Wilkins LR, Mi MP. Obesity in youth and middle age and risk of colorectal cancer in men. *Cancer Causes Control* 1992; 3: 349-54.
112. Martínez ME, Giovannucci E, Spiegelman, et al. Leisure-time physical activity, body size, and colon cancer in women. Nurses' Health Study Research Group. *J Natl Cancer Inst* 1997; 89: 948-55.
113. Giovannucci E. Insulin, insulin-like growth factors and colon cancer: a review of the evidence. *J Nutr* 2001; 131: 3109-20S.
114. Terry P, Giovannucci E, Bergkvist L, et al. Body weight and colorectal cancer risk in a cohort of Swedish women: relation varies by age and cancer site. *Br J Cancer* 2001; 85: 346-9.
115. Terry P, Miller AB, Rohan TE. Obesity and colorectal cancer risk in women. *Gut* 2002; 51: 191-4.
116. La Vecchia C, Brinton LA, McTiernan A. Menopause, hormone replacement therapy and cancer. *Maturitas* 2001; 39: 87-115.
117. Colditz G, Cannuscio C, Frazier A. Physical activity and reduced risk of colon cancer: Implications for prevention. *Cancer Causes Control* 1997; 8: 649-53.
118. Oliveria SA, Christos PJ. The epidemiology of physical activity and cancer. *Ann N Y Acad Sci* 1997; 833: 79-90.
119. Hu FB, Manson JE, Liu S, et al. Prospective study of adult onset diabetes mellitus (type 2) and risk of colorectal cancer in women. *J Natl Cancer Inst* 1999; 91: 542-7.
120. Le Marchand L, Wilkens LR, Kolonel LN, et al. Associations of sedentary lifestyle, obesity, smoking, alcohol use, and diabetes with the risk of colorectal cancer. *Cancer Res* 1997; 57: 4787-94.
121. Kono S, Honjo S, Todoroki I, et al. Glucose intolerance and adenomas of the sigmoid colon in Japanese men (Japan). *Cancer Causes Control* 1998; 9: 441-6.
122. Nilsen TI, Vatten LJ. Prospective study of colorectal cancer risk and physical activity, diabetes, blood glucose and BMI: Exploring the hyperinsulinaemia hypothesis. *Br J Cancer* 2001; 84: 417-22.
123. Schoen RE, Tangen CM, Kuller LH, et al. Increased blood glucose and insulin, body size, and incident colorectal cancer. *J Natl Cancer Inst* 1999; 91: 1147-54.
124. Ma J, Pollak MN, Giovannucci E, et al. Prospective study of colorectal cancer risk in men and plasma levels of insulin-like growth factor (IGF)-I and IGF binding protein-3. *J Natl Cancer Inst* 1999; 91: 620-5.
125. Slattery ML, Benson J, Berry TD, et al. Dietary sugar and colon cancer. *Cancer Epidemiol Biomarkers Prev* 1997; 6: 677-85.
126. Franceschi S, Favero A, La Vecchia C, et al. Food groups and risk of colorectal cancer in Italy. *Int J Cancer* 1997; 72: 56-61.

127. Slattery ML, Boucher KM, Caan BJ, et al. Eating patterns and risk of colon cancer. *Am J Epidemiol* 1998; 148: 4-16.
128. Hardwick JC, Van Den Brink GR, Offerhaus GJ, et al. Leptin is a growth factor for colonic epithelial cells. *Gastroenterology* 2001; 121 (1): 79-90.
129. FitzGerald AJ, Mandir N, Goodlad RA. Leptin, cell proliferation and crypt fission in the gastrointestinal tract of intravenously fed rats. *Cell Prolif* 2005; 38 (1): 25-33.
130. Stattin P, Lukanova A, Biessy C, et al. Obesity and colon cancer: does leptin provide a link? *Int J Cancer* 2004; 109 (1): 149-52.
131. Itzkowitz SH, Yio X. Inflammation and cancer IV. Colorectal cancer in inflammatory bowel disease: the role of inflammation. *Am J Physiol Gastrointest Liver Physiol* 2004; 287 (1): G7-17.
132. Shephard RJ, Shek PN. Associations between physical activity and susceptibility to cancer: possible mechanisms. *Sports Med* 1998; 26: 293-315.
133. Giovannucci E, Colditz GA, Stampfer MJ, et al. A prospective study of cigarette smoking and risk of colorectal adenoma and colorectal cancer in U.S. women. *J Natl Cancer Inst* 1994; 86: 192-9.
134. Giovannucci E, Rimm EB, Stampfer MJ, et al. A prospective study of cigarette smoking and risk of colorectal adenoma and colorectal cancer in U.S. men. *J Natl Cancer Inst* 1994; 86: 183-91.
135. Kuper H, Boffetta P, Adami HO. Tobacco use and cancer causation: association by tumour type. *J Intern Med* 2002; 252: 206-24.
136. Giovannucci E, Martínez ME. Tobacco, colorectal cancer, and adenomas: a review of the evidence. *J Natl Cancer Inst* 1996; 88: 1717-30.
137. Giovannucci E. An updated review of the epidemiological evidence that cigarette smoking increases risk of colorectal cancer. *Cancer Epidemiol Biomarkers Prev* 2001; 10 (7): 725-31.
138. Freedman AN, Michalek AM, Marshall JR, et al. The relationship between smoking exposure and p53 overexpression in colorectal cancer. *Br J Cancer* 1996; 73: 902-8.
139. Slattery ML, Curtin K, Anderson K, et al. Associations between cigarette smoking, lifestyle factors, and microsatellite instability in colon tumors. *J Natl Cancer Inst (Bethesda)* 2000; 92: 1831-6.
140. Klatsky AL, Armstrong MA, Friedman GD, et al. The relations of alcoholic beverage use to colon and rectal cancer. *Am J Epidemiol* 1988; 128: 1007-15.
141. Hirayama T. Association between alcohol consumption and cancer of the sigmoid colon: Observations from a Japanese cohort study. *Lancet* 1989; 2 (8665): 725-7.
142. Kune GA, Vitetta L. Alcohol consumption and the etiology of colorectal cancer: A review of the scientific evidence from 1957 to 1991. *Nutr Cancer* 1992; 18: 97-111.
143. Longnecker M, Orza M, Adams M, et al. A metaanalysis of alcoholic beverage in relation to risk of colorectal cancer. *Cancer Causes Control* 1990; 1: 59-68.
144. Pedersen A, Johansen C, Gronbaek M. Relations between amount and type of alcohol and colon and rectal cancer in a Danish population based cohort study. *Gut* 2003; 52(6): 861-7.
145. Su LJ, Arab L. Nutritional status of folate and colon cancer risk: evidence from NHANES I epidemiologic follow-up study. *Ann Epidemiol* 2001; 11: 65-72.
146. Kato I, Dnistrian AM, Schwartz M, et al. Serum folate, homocysteine and colorectal cancer risk in women: A nested case-control study. *Br J Cancer* 1999; 79: 1917-22.
147. Baron JA, Sandler RS, Haile RW, et al. Folate intake, alcohol consumption, cigarette smoking, and risk of colorectal adenomas. *J Natl Cancer Inst* 1998; 90: 57-62.
148. Giovannucci E, Willett WC. Dietary factors and risk of colon cancer. *Ann Med* 1994; 26: 443-52.
149. Rader JL. Folic acid fortification, folate status and plasma homocysteine. *J Nutr* 2002; 132 (8 Supl.): 2466S-70S.
150. Kritchevsky D. Diet and cancer: what's next? *J Nutr* 2003; 133 (11 Supl. 1): 3827S-9S.
151. Weber RV, Stein DE, Scholes J, et al. Obesity potentiates AOM-induced colon cancer. *Dig Dis Sci* 2000; 45 (5): 890-5.