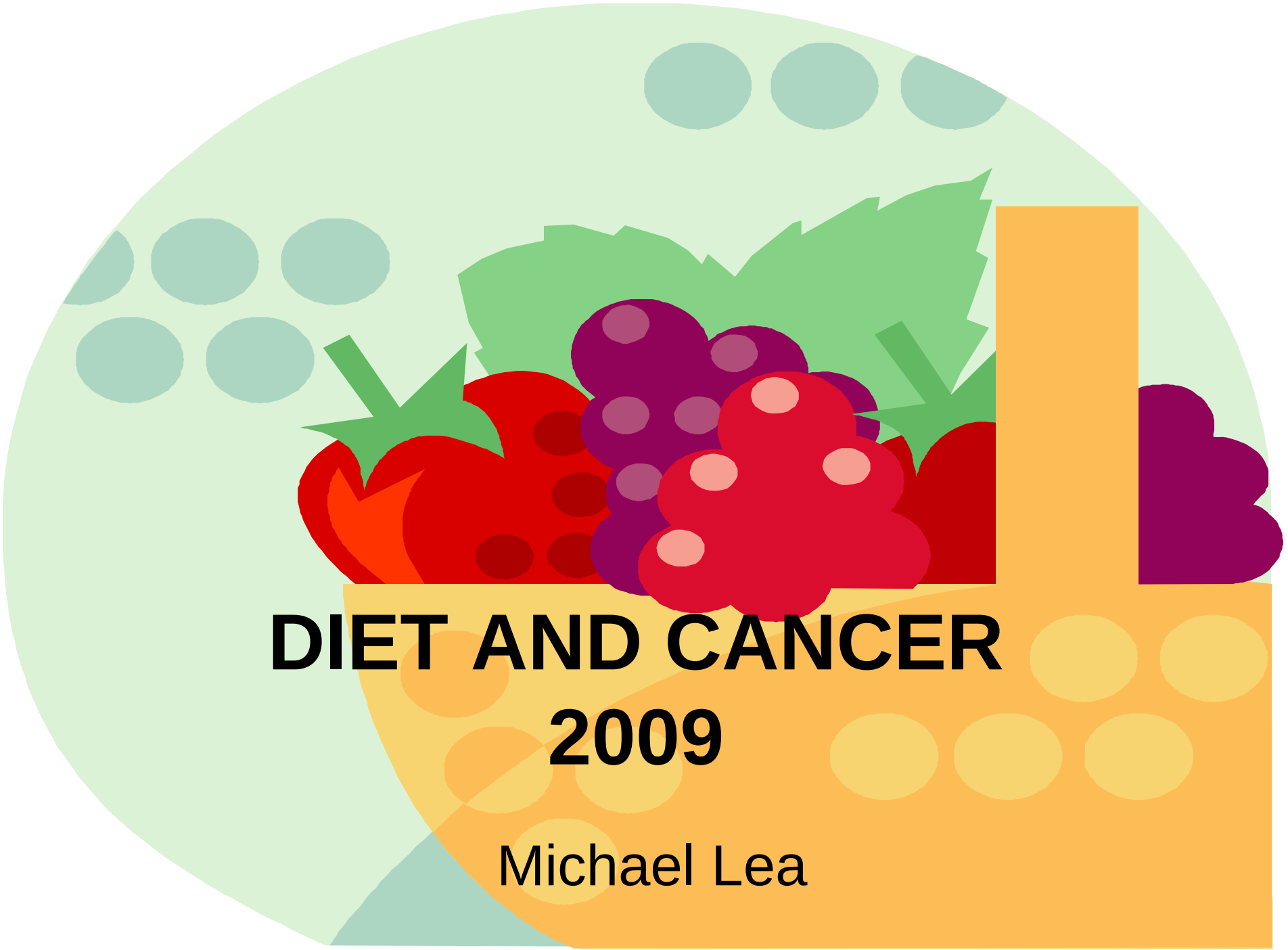

DIET AND CANCER 2009

Michael Lea

DIET AND CANCER - Lecture Outline

- Dietary recommendations
- Caloric consumption
- Fat and Obesity
- Natural carcinogens
- Fiber
- Cooking
- Salt
- Preservatives and Additives
- Vitamins
- Selenium
- Calcium and Vitamin D
- Coffee
- Allyl sulfur compounds
- Antioxidants

DIET AND CANCER

- Although epidemiological data suggests that diet is a major determinant of cancer incidence, the role of specific dietary constituents is fraught with controversy. Recommendations have become a matter of judgment based on conflicting data.
- There is no consensus but the guidelines in the following three tables are representative of recommendations that are frequently offered for a prudent diet.

Table NAS. Summary of the Dietary Guidelines Proposed by the Committee on Diet, Nutrition and Cancer, National Academy of Sciences

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1. Reduction of consumption of both saturated and unsaturated fats in the average U.S. diet.

An appropriate target was considered to be a reduction from 40% to 30% of total calories in the diet.

2. Inclusion in the diet of fruits (especially citrus fruits) and vegetables (especially carotene-rich and cruciferous vegetables).

3. Consumption of food preserved by salt-curing (including salt-pickling) or smoking should be minimized.

4. Efforts should be made to minimize contamination of foods with carcinogens from any source.

5. Further efforts should be made to identify mutagens in food and, where feasible and prudent, mutagens should be removed on their concentration minimized.

6. If alcoholic beverages are consumed, it should be in moderation.

American Cancer Society Guidelines on Nutrition and Cancer

The following guidelines have been recommended by the American Cancer Society for adults of all ages in good health.

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1. Maintain a desirable body weight.
2. Cut down on total fat intake.
3. Include a variety of both vegetables and fruits in the daily diet.
4. Eat more high fiber foods, such as whole grain cereals, legumes, vegetables, and fruits.
5. Limit consumption of alcoholic beverages if you drink at all.
6. Limit consumption of salt cured, smoked and nitrite-preserved foods.
7. Eat a varied diet.

Reference: Doyle, C. et al., Nutrition and physical activity during and after cancer treatment: an American Cancer Society Guide for informed choices. CA Cancer J Clin 56: 323-353, 2006

American Institute for Cancer Research 2008

Recommendations for Cancer Prevention

1. Be as lean as possible within the normal range of body weight.☐
2. Be physically active as part of everyday life.☐
3. Limit consumption of energy-dense foods. Avoid sugary drinks.
4. ☐Eat mostly foods of plant origin.☐
5. Limit intake of red meat and avoid processed meat. ☐
6. Limit alcoholic drinks.
7. Limit consumption of salt. Avoid moldy cereals (grains) or pulses (legumes). ☐
8. Aim to meet nutritional needs through diet alone.

Special Population Recommendations

- Mothers to breastfeed; children to be breastfed. ☐
- Cancer survivors to follow the recommendations for cancer prevention.

And always remember : do not smoke or chew tobacco.

Study Details 30-Year Increase in Calorie Consumption

By ANAHAD O'CONNOR

We knew we ate more; we knew we had gained weight. Now a new study that looked at 30 years of Americans' eating habits has pinned down how many more calories, carbohydrates and fats are eaten daily.

From 1971 to 2000, the study found, women increased their caloric intake by 22 percent, men by 7 percent.

Much of the change was found to be due to an increase in the amount of carbohydrates we have been eating. The findings may reinforce the current trend, among those sometimes known as carb-avoids, of reducing or even eliminating foods like breads and pasta.

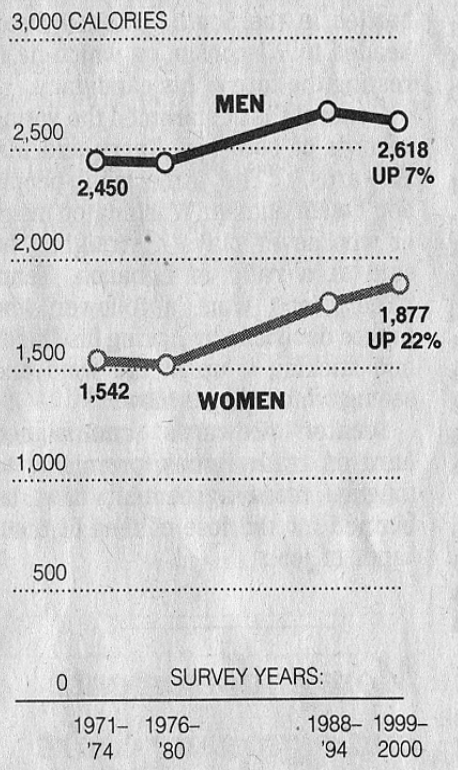
And while the percentage of calories Americans get from fat, especially saturated fats, has decreased, the numbers might be deceiving. The actual amount of fat eaten daily has gone up. It just makes up a smaller percentage of the total caloric pie now that we are eating so many more carbs.

The study, conducted by the Centers for Disease Control and Prevention and reported in the current edition of its Morbidity and Mortality Weekly Report, found that in 1971 women ate 1,542 calories on average, compared with today's 1,877, while men went from 2,450 calories a day to 2,618. Those numbers dwarf the government's recommendations of 1,600 calories a day for women and 2,200 for men.

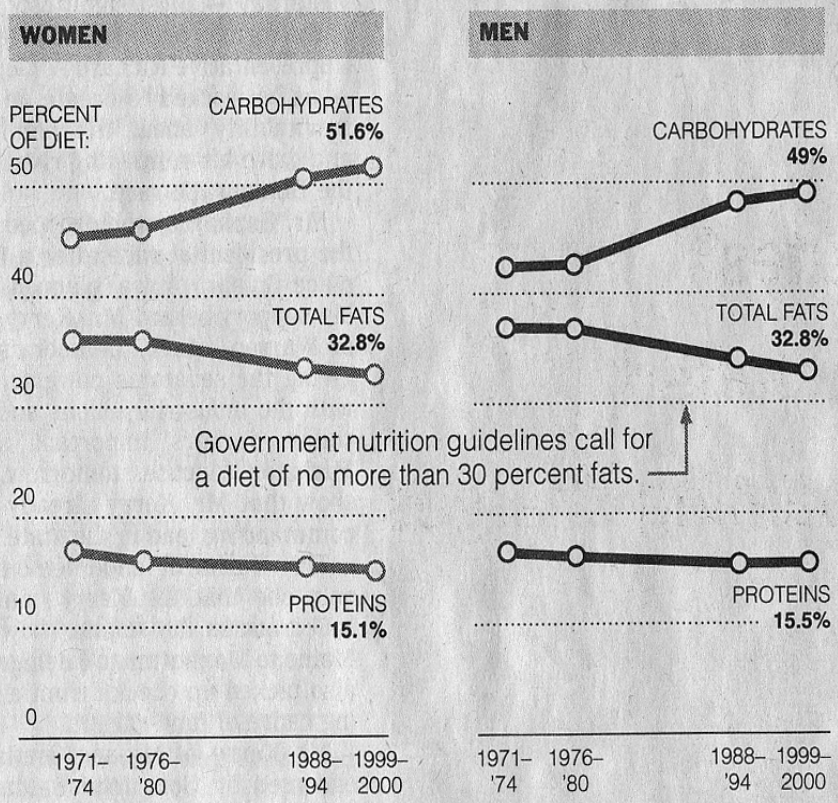
More Food, and More of It Carbohydrates

A 30-year survey has found that the amount of fat people eat has remained steady but that its share of the diet has dropped as carbohydrate consumption has soared.

TOTAL CALORIE INTAKE Average calories consumed daily among adults age 20-74.



CHANGING DIETS Percentage of calories from carbohydrates, fats and proteins among adults age 20-74.



Source: Centers for Disease Control and Prevention

The New York Times

1. CALORIES

The early studies of Tannenbaum suggested that caloric intake could be an important determinant of cancer incidence in experimental animals. More recent studies have supported this conclusion. The epidemiological data for humans has not, so far, indicated a strong link between increased caloric consumption and tumor incidence. However, Weidruch et al. noted that five out of seven case-control studies found a positive association between total caloric intake and cancer risk. The Committee on Diet, Nutrition and Cancer concluded that it does not appear that nutrient-to-energy ratios are critical for the enhancement of tumor development by high fat diets. They noted that the epidemiological evidence supporting total intake as a risk factor for cancer was slight and largely indirect. Much of it was based on associations between body weight or obesity and cancer. The Committee concluded that studies that have evaluated both caloric intake and fat intake suggest that fat intake is the more relevant variable.

1. CALORIES

In the large follow-up study by Willett et al., no association was found between caloric intake and breast cancer risk. This may be contrasted with a study of mammary cancer in rats which concluded that caloric intake was a more stringent determinant of tumor growth than fat intake. Some support for an influence of caloric intake on the risk of colon cancer in humans was provided by a case-control in Majorca. Colorectal cancer was found associated with dietary intake of total calories and, surprisingly, no effects were found with increased consumption of lipids and saturated fats.

If the data for rodents can be extrapolated to humans, and that has not been established, then some effort at caloric restriction may be preferable to *ad libitum* consumption of food.

2. FAT AND OBESITY

The modulating role of dietary fat in carcinogenesis has been well documented in animals. The relationship has been studied most extensively with respect to the positive correlation between fat consumption and cancer of the breast and colon.

The situation is less clear for human cancer. The epidemiological data correlates best with saturated fat consumption. On the other hand, formation of reactive epoxides might be anticipated to be greater with unsaturated fat and there is much data from animal studies to suggest a greater risk with unsaturated fat. The epidemiological data tends to be related to the ratio of meat and vegetables in the diet and may reflect other factors in addition to the fat content. Comparisons between countries have suggested a greater risk than have case-control studies which have at best indicated only modest increases in the relative risk of cancer on high fat diets. It has been noted that the differences in fat consumption in case-control studies have generally been less than those in international comparisons. A decrease in the percentage of calories derived from fat from present average levels close to 40% in the United States to a value of 30% has been advocated by several groups. Even this would be considerably higher than values for some traditional oriental diets. An optimal level of 20% of calories has been suggested.

It is widely felt that the data to support strong recommendations is lacking. Doll doubted whether we shall be able to reach a definite conclusion about the role of fat without an intervention study with random allocation of diets.

FAT and OBESITY (Continued)

Obesity is an indication of caloric imbalance and often of excessive consumption of fat. Doll has concluded that obesity is an established cause for cancer of the endometrium and gall bladder. Endometrial cancer has been attributed to estrogen production by adipose tissue unopposed by other hormones after the menopause. The association of obesity with breast cancer is regarded as more uncertain. The great majority of epidemiological studies have found a positive correlation between body weight and cancer incidence. Obesity has been associated with increased risk of cancer mortality in both men (1.33) and women (1.55) in the United States.

While it has been said that one cannot be too rich or too thin, this may not apply to the risk of cancer. After several studies had indicated that thinness was associated with an elevated risk of lung cancer, Knekt and colleagues attempted to rule out a number of potential confounding factors such as smoking, dietary habits, general health state, lung diseases or occult cancer. From their analysis of data obtained in Finland they were unable to reject the hypothesis that leanness is an independent risk factor for lung cancer. It would seem that the aim should be not too fat and not too thin, at least until we have a better understanding of the mechanisms underlying the epidemiological data.

FAT and OBESITY (Continued)

Low-Fat Dietary Pattern and Risk of Invasive Breast Cancer: The Women's Health Initiative Randomized Controlled Dietary Modification Trial

JAMA 295 (6): 629-642 (2006)

Conclusions: Among postmenopausal women, a low-fat dietary pattern did not result in a statistically significant reduction in invasive breast cancer risk over an 8.1 year average follow-up period. However, the nonsignificant trends observed suggesting reduced risk associated with a low-fat dietary pattern indicate that longer, planned, nonintervention follow-up may yield a more definitive comparison.

3. NATURAL CARCINOGENS AND ANTICARCINOGENS

The publications of Bruce Ames have drawn attention to observation that food may contain a large number of compounds that are carcinogens or anticarcinogens. Ames et al. have suggested that 99.99% by weight of the pesticides in the American diet are chemicals that plants produce to defend themselves. Of 52 natural pesticides that had been tested in high dose animal cancer tests, 27 were rodent carcinogens. This percentage is similar to that found for synthetic pesticides that are carcinogens.

Food can contain a variety of naturally occurring substances that may act as anticarcinogens including fiber, indoles, isothiocyanates, diallyl sulfides, protease inhibitors, selenium , retinoids, ascorbic acid and some polyphenolic compounds including quercetin, ellagic acid, chlorogenic acid and (-)-epigallocatechin-3-gallate. These materials are found most commonly in grains, fruits and vegetables. (-)-epigallocatechin-3-gallate is a constituent of green tea that has been shown to inhibit carcinogenesis in some animal models.

Table 2.8 A sampling of Bruce Ames's roster of carcinogens identified in the normal diet[a]

Foodstuff	Compound	Concentration in foodstuff
Black pepper	piperine	100 mg/g
Common mushroom	agaritine	3 mg/g
Celery[b]	furocoumarins, psoralens	1 μg/g, 0.8 μg/g
Rhubarb	anthraquinones	varies
Cocoa powder	theobromine	20 mg/g
Mustard, horseradish	allyl isothiocyanate	varies
Alfalfa sprouts	canavanine[c]	15 mg/g
Burnt materials[d]	large number	varies
Coffee	caffeic acid	11.6 mg/g

[a]Ames has cited 37 naturally occurring compounds that have registered as carcinogens in laboratory animals; one or more have been found in each of the following foodstuffs:
absinthe, allspice, anise, apple, apricot, banana, basil, beet, broccoli, Brussels sprouts, cabbage, cantaloupe, caraway, cardamom, carrot, cauliflower, celery, cherries, chili pepper, chocolate, cinnamon, cloves, coffee, collard greens, comfrey herb tea, coriander, corn, currants, dill, eggplant, endive, fennel, garlic, grapefruit, grapes, guava, honey, honeydew melon, horseradish, kale, lemon, lentils, lettuce, licorice, lime, mace, mango, marjoram, mint, mushrooms, mustard, nutmeg, onion, orange, paprika, parsley, parsnip, peach, pear, peas, black pepper, pineapple, plum, potato, radish, raspberries, rhubarb, rosemary, rutabaga, sage, savory, sesame seeds, soybean, star anise, tarragon, tea, thyme, tomato, turmeric, and turnip
[b]The levels of these can increase 100-fold in diseased plants.
[c]Canavanine is indirectly genotoxic because of oxygen radicals that are released, perhaps during the inflammatory reactions associated with elimination of canavanine-containing proteins.
[d]On average, several grams of burnt material are consumed daily in the form of bread crusts, burnt toast, and burnt surfaces of meats cooked at high temperature.

Adapted from B.N. Ames, Dietary carcinogens and anticarcinogens, *Science* 231:1256–1264, 1983; B.N. Ames and L.S. Gold, Dietary pesticides (99.99% all natural), *Proc. Natl. Acad. Sci. USA* 87:7777–7781, 1990; and L.S. Gold, B.N. Ames and T.H. Slone, Misconceptions about the causes of cancer, in D. Paustenbach, ed., Human and Environmental Risk Assessment: Theory and Practice, New York: John Wiley & Sons, 2002, pp. 1415–1460.

4. FIBER

The term fiber has been generally applied to undigestible plant material in food. The observations of Burkitt in East Africa led him to suggest an inverse correlation between consumption of fiber and the incidence of colon cancer.

Several mechanisms have been suggested that might relate the fiber content of the diet and decreased colon cancer. These include an increase in fecal bulk and decreased transit time; dilution of carcinogens; changes in intestinal flora and increased binding of mutagens such as pyrolysate products of proteins.

4. FIBER

Rogers and Longnecker concluded that most epidemiological studies of fiber consumption in relation to colon cancer are consistent with a very small inverse association or no association. Differences in fiber content may be a factor in discrepancies noted between fat consumption and colon cancer. Thus, the lower incidence of colon cancer in Finland than in Denmark despite a similar fat consumption may be related to the higher fiber content of the diet in Finland.

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4. FIBER (continued)

There has been uncertainty arising from the heterogeneous nature of fiber. Doll suggested that , what matters from the point of view of colonic and rectal disease, may be the amount of material that reaches the large bowel that is capable of digestion by the bacterial flora and this may include a substantial proportion of the intake of starch. The effectiveness of the diet may be judged by the lowering of fecal pH. This parameter has been reported to be lower for populations at low risk of colorectal cancer.

4. FIBER (continued)

The potential importance of starch as opposed to fiber is suggested by the study of Caderni et al., which found that starch was protective against the effects of the carcinogen, dimethylhydrazine, in rats on a high fat, low calcium, low cellulose diet. In humans, starch malabsorption has been reported to be a possible protective factor in colon carcinogenesis.

4. FIBER (continued)

Bartram et al. found that starch malabsorption was accompanied by changes in fecal bile acid and neutral sterol excretion.They concluded that the decreased concentration of the potential (co)carcinogen 4-cholesten-3-one and the diminished fecal excretion of deoxycholic and lithocholic acids, which are known promoters of colon carcinogenesis, may explain how starch malabsorption may protect against colon cancer.

4. FIBER (Continued)

In an analysis of the literature on the potential protective effect of a high fiber diet against colon cancer, Trock et al. concluded that there is strong support for a reduction in colon cancer risk of approximately 40% among individuals consuming diets with high vegetable and grain content. They found a more consistent association with fiber than with micronutrients such as beta-carotene and ascorbic acid.

Materials classed as fiber differ in their solubility and the degree to which they are fermented by intestinal flora. The protective effect of fiber may be related to the site of fermentation. Colon cancer is more common in the distal than in the proximal large bowel. It is not known to what degree a protective effect of fiber may be related to fermentation yielding butyrate. However, there is evidence that wheat bran may be fermented less readily than more soluble fiber such as oat bran and may be associated with greater effects on the luminal environment of the distal large bowel. This in turn may be related to a greater protective effect against colon cancer.

It has been recommended that intake of fiber be increased to 20 to 30 g but not to exceed 35 g per day, which would entail doubling the average intake in the U.S. diet. An increase in fiber consumption can most readily be achieved by increased intake of fruit, grains and vegetables. Since such a dietary change would be supported by other epidemiological data, the recommendation can be made with more enthusiasm than would be warranted solely by the evidence available for fiber alone.

5. COOKING

Hi-temperature cooking can cause a multitude of chemical rearrangements in food constituents. Superficial examination of browned or, particularly, blackened food would arouse suspicion of the presence of polycyclic hydrocarbons but in recent years there has been considerable focus on heterocyclic amines, notably 2-amino-3-methylimidazole[4,5 -*f*]quinoline (IQ). The presence of IQ has been established in broiled sardines, cooked beef, beef extract and other cooked meat and the carcinogenicity of this compound has been reported in nonhuman primates. It has been noted that mutagens are produced in charred meat and fish during the pyrolysis of proteins that occurs when foods are cooked at very high temperatures.

6. SALT

Most case-control studies have found a positive association between the consumption of salt or salty foods and the risk of gastric cancer. Other positive risk factors for gastric cancer revealed by several studies include starchy foods and alcohol. The marked decline in the incidence of gastric cancer in the United States during the twentieth century may be associated with better conditions for the storage of food. Lessened dependence on preservation of food with salt may be a factor. Whatever the mechanism the decrease in gastric cancer is the most impressive for any site and suggests that we are doing something right.

6. SALT

Of the salts consumed in the diet, nitrites have received more attention than sodium chloride as risk factors for cancer. This arises from the potential role of nitrite in the formation of nitrosamines. The association of nasopharyngeal cancer with consumption of salted fish as eaten in South China has been considered a presumptive dietary cause of cancer and may be related to nitrosamine formation.

At the experimental level, Deschner et al. presented evidence that dietary use of a sodium salt in mice can contribute to the enhancement of chemically induced colon cancer. Advice to minimize consumption of salt-cured, salt-pickled or smoked foods have been included in NCI dietary guidelines and American Cancer Society guidelines have recommended limiting consumption of salt-cured, smoked and nitrite-cured foods. However, Bal and Foerster have suggested that there should be less emphasis on these recommendations on the basis that the contribution of these factors to cancer in the United States appears to be small.

7. PRESERVATIVES AND ADDITIVES

Preservatives may be added to foods to inhibit microbial growth, for example nitrite, or to inhibit oxidation, as in the case of butylated hydroxytoluene (BHT) and butylated hydroxyanisole (BHA). The present trend is to limit nitrite as much as possible due to the danger of nitrosamine formation in the stomach. BHT and BHA have been shown to inhibit chemical carcinogenesis in a number of systems but there have been models in which BHT has acted as a tumor promoter. Such studies favor the use of BHA as an antioxidant. Additives may be included in food for a variety of reasons such as to give color or to alter the physical properties of the food. Since dyes have only esthetic value and some dyes are carcinogenic, limitation on their inclusion in food is prudent. Sweeteners have received close scrutiny. It may be debated whether the prohibition of cyclamate was justified and whether the weak promoting effects of saccharin merit further restriction. In general, there is no substantial evidence that substances now used as preservatives and additives, and generally recognized as safe, present a significant cancer risk.

8. VITAMINS

Of fifty-four studies of ß carotene, 49 yielded evidence of protection against cancers of different organs with a median relative risk of 0.62 for high consumers compared with low. Comparison of serum ß carotene with vitamin E and selenium suggested that ß carotene may be a more effective prophylactic agent. Consumption of carrots was found to decrease the risk of ovarian cancer with an odds ratio of 0.3 for high ß carotene intake. ß carotene is largely converted to vitamin A during absorption through the intestinal mucosa. There is evidence that carotenoids rather than total vitamin A are associated with lowered lung-cancer risk. The mechanism of action is not known and there may be a distinction between antioxidant properties of ß carotene and anti-proliferative and cell-differentiating properties of vitamin A. The antiproliferative effects of the naturally occurring retinoid molecules has led to the synthesis of synthetic analogs. In addition to their frequent antiproliferative effects, retinoids can act as differentiating agents for some cancer cell lines. On the other hand three recent epidemiological trials have indicated that Vitamin A supplements either had no affect or even increased the risk of lung cancer in smokers.

8. VITAMINS (Continued)

Epidemiological studies on the relationship between consumption of ascorbic acid and cancer mortality or incidence have been reviewed by Henson et al. Of 46 reports, 33 were judged to have described significant protective effects on cancer mortality or incidence. There was strong epidemiologic evidence that ascorbic acid, or other fruit components, was protective against cancer of the esophagus, larynx, oral cavity and pancreas. There was also evidence for protective effects against cancer of the stomach, rectum, lung, breast and uterine cervix. Experimental evidence indicates that ascorbic acid can inhibit the formation of nitrosamines under the conditions existing in the stomach but the significance of this effect in diminishing cancer risk in human populations is not clear. Ascorbic acid has a number of sites of action in the body. In addition to its antioxidant and free-radical scavenging activities, ascorbic acid can modulate enzyme activities and collagen synthesis. A role in the immune system system has been indicated.

Studies on the role of vitamins have focused particularly on the anti-oxidant character of vitamin E, vitamin C and carotenoids. There is epidemiological evidence that these compounds may be protective against lung cancer among nonsmokers.

9. SELENIUM

As for many micronutrients, the intake of selenium should not be too little and not too much. Epidemiological data have implicated low selenium intake with increased incidence of cancer. Since the selenium content of foodstuffs is related to the concentration in the soil, a diet derived from different geographical areas is likely to yield adequate selenium. In view of the potential toxicity of selenium compounds, any intervention studies in humans would require a cautious design.

10. CALCIUM AND VITAMIN D

An inverse correlation between the risk of colon cancer and levels of calcium and vitamin D was suggested in 1980. Since that time several epidemiological studies have reported inverse relationships between levels of dietary calcium intake and the incidence of colonic cancer. It has been suggested by Newmark and colleagues that calcium will bind bile acids and fatty acids and thereby prevent their stimulation of proliferation of colonic epithelial cells. Using the model of dimethylhydrazine-induced colon cancer in rats, calcium supplementation has been shown to prevent activating mutations of the K-ras oncogene. The antimutagenic effect of dietary calcium supplementation was abolished by concomitant vitamin D deficiency. Augmentation of the diet with 1.25 g calcium carbonate per day was found to decrease the proliferative rate in subjects at high risk for familial colonic cancer. Total intake of 1.8 g calcium per day has been associated with diminished risk of colon cancer. Calcium in the form of calcium carbonate offers an economical dietary supplement.

10. CALCIUM AND VITAMIN D

In the Womens Health Initiative study, daily supplementation of calcium with vitamin D for seven years had no effect on the incidence of colorectal cancer among postmenopausal women.

J. Wactawski-Wende et al., New England Journal of Medicine 354 (7): 684-696, 2006.

11. COFFEE

Caffeine, with its effects on cellular signal transduction and on DNA repair, is a compound that one might anticipate would influence cancer risk. A study by MacMahon et al. suggested that consumption of coffee could be a risk factor for cancer of the pancreas. The design of this study became a subject of debate. Subsequent studies may have calmed the nerves of individuals disturbed by the effects of heavy coffee drinking and contemplation of the potential consequences of the coffee-drinking habit. Rogers and Longnecker concluded that data on coffee consumption in relation to risk of breast cancer consistently demonstrate no association while an association with pancreatic cancer cannot be excluded. Some reassurance might be gained from the case-control study by Ghadirian et al. who observed that coffee drinkers were collectively at lower risk of pancreatic cancer than nondrinkers.

12. ALLYL SULFUR COMPOUNDS

There is epidemiological and experimental data to indicate that consumption of garlic may be associated with a lower incidence of some types of cancer. This action may be associated with allyl sulfur compounds. When garlic is crushed the action of the enzyme alliinase converts odorless alliin to allicin (diallyl thiosulfinate). Allicin has a characteristic garlic odor shared with some other allyl sulfur compounds. Allicin is an unstable molecule that undergoes conversion to other garlic compounds such as diallyl sulfide and diallyl disulfide.

When alliinase from garlic was chemically conjugated to a monoclonal antibody directed against a specific tumor marker, ErbB2. Athymic nude mice bearing a transplanted human tumor were treated with the antibody-bound enzyme and alliin. Inhibition of tumor growth was observed suggesting that targeted delivery of allicin may have therapeutic potential (Miron et al., Mol. Cancer Ther. 2: 1295-1301, 2003), .

There is evidence that allyl sulfur compounds can inhibit the metabolic activation of some compounds and may favor cancer cell differentiation by increasing the acetylation of histones.

13. ANTIOXIDANTS

A variety of antioxidants occur in fruits, vegetables and other dietary components including the following compounds:

Vitamin C

Vitamin E

Beta-carotene in orange vegetables including carrots

Resveratrol in grapes and red wine

Anthocyanins in red and blue fruits and vegetables

Polyphenols such as epigallocatechin gallate (EGCG) in green tea

SUGGESTED READING

The significance of diet in cancer prevention will be considered further in the last lecture of the course.

Suggested reading: Food, Nutrition, Physical Activity, and the Prevention of Cancer: A Global Perspective. Washington DC, American Institute for Cancer Research, 2007