TOXICOLOGICAL SCIENCES **52 (Supplement),** 72–86 (1999)

Diet and Cancer Prevention: The Fiber First Diet©

Gary M. Williams,*[,1] Christine L. Williams,† and John H. Weisburger*[,]‡

*Department of Pathology, New York Medical College, Valhalla, New York 10595; †Institute of Human Nutrition, Columbia University, New York, New York; and ‡American Health Foundation, Valhalla, New York

Diet can play a major role in cancer prevention. The international differences in cancer incidence are largely accounted for by lifestyle practices that include nutrition, exercise, and alcohol and tobacco use. About 50% of cancer incidence and 35% of cancer mortality in the U.S., represented by cancers of the breast, prostate, pancreas, ovary, endometrium, and colon, are associated with Western dietary habits. Cancer of the stomach, currently a major disease in the Far East, relates to distinct, specific nutritional elements such as excessive salt intake. For these cancers, information is available on possible initiating genotoxic factors, promoting elements, and prophylactic agents. In general, the typical diet in the United States contains low levels of the potent carcinogenic agents, heterocyclic amines, formed during the cooking of meats. It provides only about half the potent appropriate fiber intake and is high in calories. About twice as many calories as would be desirable come from fat, certain kinds of which enhance the development of cancers. Other foods with functional properties, such as soy products and tea, can be beneficial. To achieve reduction in risk of certain cancers, diet must be optimized, primarily to reduce caloric intake and the fat component. The latter should be 20% or less of total caloric intake and fiber should be increased to 25–35 g per day for adults. One approach to achieving these goals is the Fiber First Diet,© a diet designed around adequate fiber intake from grains, especially cereals, vegetables, legumes, and fruits, which thereby reduces both calorie and fat intake. Such dietary improvements will not only reduce cancer and other chronic disease risks, but will contribute to a healthy life to an advanced age. A corollary benefit is a lower cost of medical care.

Key Words: **antioxidant; exercise; fat; food; lifestyle; nutrition; vitamins.**

For centuries, it has been known that food contains a variety of specific healthful or harmful components. The specific contribution of diet to cancer was highlighted at the beginning of this century in a major treatise on cancer, in which W. R. Williams (1908) concluded, “The incidence of cancer is largely conditioned by nutrition.” This insight was extended by a remarkable statistician, E. L. Hoffman (1937), who in an extensive review came to the conclusion that “the underlying cause of cancer is to be found in an excessive intake of foods . . . ” Experimental exploration of the relationship of nutrition to cancer began to be pursued in depth, beginning only in the late 1940s and 1950s, with the pioneering work of Tannenbaum (1959). The substantial influence of nutrition on cancer has become increasingly evident, as this group of diseases, together with cardiovascular disease and stroke, have supplanted infectious disease as the most important cause of premature mortality in Western societies. Knowledge of the role of nutrition in the pathogenesis of cancer has continued to accrue (Clifford and Kramer, 1993; Micozzi and Moon, 1992; Miller *et al.*, 1994; Weisburger and Williams, 1995; Williams and Wynder, 1996; World Cancer Research Fund, 1997), with major evidence coming from ecological correlation, particularly between countries such as the U.S. and Japan, where specific cancers differ greatly in incidence. The first food-borne cancer-causing agents to be identified were benzo-[*a*]pyrene and related polycyclic aromatic hydrocarbons, formed during grilling of meats and fishes. It is not known, however, whether the amounts so-formed constitute a human cancer risk upon oral intake. A subsequently discovered food contaminant from fungi, aflatoxin B_1, causes liver cancer in humans, and especially in persons carrying the hepatitis virus (International Agency for Research on Cancer, 1987). In this paper, we review the nutritional and food-borne factors for which substantial evidence exists concerning their influence on cancer incidence. We suggest appropriate actions for cancer reduction through adjustment in dietary practices and adoption of a healthful diet and exercise plan, beginning in childhood.

Diet and Cancer

In 1998, 1,228,600 new cases of cancer, excluding skin cancer, were estimated to have occurred in the United States (Landis *et al.*, 1998). As in our previous reviews (Weisburger and Williams, 1995; Williams and Wynder, 1996), we have estimated the contribution of known etiologic agents on each specific cancer. From the proportion of the total cases represented by that type of cancer, we arrived at an estimate of the contribution of causative agents to cancer incidence. As shown in Table 1, our analysis leads to the conclusion that about 50% of the anticipated cancer incidence and 30–35% of mortality in Americans in 1998 is related to diet and excessive alcohol use. While there are certainly genetic conditions that predispose to cancer (Bradlow *et al.*, 1997), diet and the other major lifestyle factor, smoking, exert a critical influence on cancer risk, in addition to whatever intrinsic susceptibility exists. That is also the case for risk of coronary artery disease.

[1] To whom correspondence should be addressed. Fax: (914) 594-4163. E-mail: williamsgm@pol.net.

TABLE 1
Estimated Causes of Cancer Mortality in the United States, 1998

Type of cause	% of total
Lifestyle cancers	
Diet-related	
High fat, low fiber, low in vegetables and fruits, high in broiled or fried foods: large bowel, breast, pancreas, prostate, ovary, endometrium	30–35
Salted pickled foods, low in vegetables and fruits: stomach[a]	2–3
Tobacco-related: Lung, larynx, oral cavity, bladder, pancreas, kidneys, stomach	30–35
Tobacco and alcohol-related: oral cavity, esophagus	2–3
Alcohol-related: liver, esophagus	1–2
Sunlight-related: melanoma of skin[a]	1–2
Bacteria	
Helicobacter pylori: stomach	1–2
Viruses	2–5
Human papilloma: cervix, penis, anus; hepatitis B, C: liver; HTLV-1: adult T-cell leukemia; Epstein-Barr: B-cell lymphoma	
Lifestyle and occupational exposures	
Tobacco and asbestos, tobacco and mining, tobacco and uranium, tobacco and radium: lung, respiratory tract	2–3
Genetic	2–3
Tumor suppressor gene mutations, including APC, familial adenomatous polyposis: colon; BRCA1, 2: breast; RB1: retinoblastoma; WT 1: Wilms tumor	
Occupational cancers, various carcinogens: bladder and other organs	1
Iatrogenic	1–2
Radiation, drugs: diverse organs, leukemia	
Unknown	3–25[b]

Note. Landis *et al*, 1998. Basal cell and squamous cell cancers of the skin (which account for about 700,00 cases) were excluded from the data.

[a] *Helicobactor pylori* has an interactive role.

[b] This large variation is a function of the broad range calculated for the main diet and tobacco-associated cancers.

Elements in the diet, including both naturally occurring and synthetic components and nutritional factors, can either inhibit or facilitate the oncogenic process (National Research Council, 1996). Dietary elements that facilitate oncogenesis can do so either by initiating the process, usually through genotoxic effects, or enhancing tumor development through epigenetic promotional activity (Williams, 1993a). Information on the contribution of diet constituents to specific cancers, as regards mechanisms of action, are reviewed herein.

A conventional definition of a nutrient is "a substance obtained from food and used in the body to promote growth, maintenance, and/or repair" (Whitney and Hamilton, 1981). The generally recognized broad classes of nutrients are carbohydrates, fats, proteins, vitamins, minerals, and water. Imbalances in nutrients, either inadequacies or excesses, as well as in other food components, are one of the major ways in which diet contributes to cancer etiology (Table 2). The mechanisms and chemicals involved are diverse, involving effects on hormones and other physiological functions, modulation of enzymes, and perturbation of cell kinetics. Ultimately, cancer is the result of a fundamental mutation in cellular DNA and, as will be discussed, diet can convey the genotoxic as well as modulating factors.

Nutritional Inadequacies

One of the most significant nutrient inadequacies in the Western diet is insufficient consumption of fiber. There is no precise definition of fiber, but it may be considered to be the remnants of ingested plant cells that are resistant to digestion by alimentary enzymes (Trowell, 1974). Some of the components of fiber are lignin, cellulose, and hemicellulose. There are soluble and insoluble fibers, both involved in inhibition of cancer risks by specific mechanisms. Fiber has a number of physiologic effects, including its water-holding capacity, which contributes to fecal bulk (Eastwood, 1992).

A protective effect of dietary fiber against colon cancer has been established by numerous negative associations between colon cancer rates and intake of food groups rich in fiber (Freudenheim *et al.*, 1990; Hill, 1998; Howe *et al.*, 1992; Negri *et al.*, 1998; Potter, 1996). The evidence is particularly strong for fiber in cereals and vegetables (Caygil *et al.*, 1998). Some studies do not report an important protective effect of fiber (Fuchs *et al.*, 1999) because of the low intake of cereal fiber. The human data are even less clear for breast cancer (Howe *et al.*, 1990), although several studies have found a protective effect, particularly by cereal fiber and soluble fibers of vegetable origin (Caygil *et al.*, 1998; La Vecchia *et al.*, 1997). In support of the epidemiological observations, animal studies have revealed a protective effect of fiber, particularly of wheat-bran fiber, for colon and breast cancer (Reddy, 1996; Rose,

TABLE 2
Dietary Impacts on Cancer in 1998

Factor	Estimated importance[a]: Western communities	Asian/African communities
Nutritional excesses	+++	+[b]
Nutritional inadequacies	+	+
Other dietary inadequacies	++	++
Carcinogens formed in food	++	++
Food contaminants and additives	0	++[c]

[a] O, no impact; +, some impact; ++, strong impact; +++, very strong impact.

[b] In Japan, dietary habits are progressively more Western, and the corresponding cancers are increasing.

[c] Mostly aflatoxin and related mycotoxins, and also traditional high salt use.

1990). The mechanism for the protective effect of fiber against colon cancer involves an increase in stool bulk, thereby diluting fecal bile acids, which are promoters of colon cancer. Other effects may also be involved, such as complexing of bile acids (Klurfeld, 1992; Reddy, 1996).

Low intake of fruits and vegetables, i.e., less than 2 servings per day, has been identified epidemiologically to be associated with risk for cancers of the oral cavity (Takezaki *et al.*, 1996), stomach (Neugut *et al.*, 1996; Trichopoulos *et al.*, 1985), lung (Colditz *et al.*, 1987; Le Marchand, *et al.*, 1989), and breast (Chyou *et al.*, 1990; Trichopoulou *et al.*, 1995). Diets low in fruits and vegetables are, of course, usually low in fiber and high in fat, which may confound the interpretation of associations. Nevertheless, the risks associated with such diets have been attributed to inadequate levels of antioxidants, including vitamin C (ascorbic acid), vitamin A, vitamin E, and carotenoids (Byers and Guerro, 1995; Garewal, 1995; Hwang *et al.*, 1994; Nomura *et al.*, 1997; van Poppel and Goldbohm, 1995; Willett and Hunter, 1994; Zhang *et al.*, 1999), although the evidence is not conclusive (Vainio and Rautalahti, 1999). Nevertheless, it is plausible that Vitamin A could be protective since it influences the differentiation of cells in certain tissues. In addition, the protective effects of carotenoids may relate to their function as precursors of vitamin A, in addition to their antioxidant activity. Some carotenoids, such as lycopene, are superior antioxidants in singlet oxygen quenching. Lycopene is present at high levels in tomatoes, and inadequate consumption could increase some cancer risks (Giovannucci, 1999; Grann *et al.*, 1999; Le Marchand *et al.*, 1989). Importantly, lycopene is well absorbed from tomato juice (Pool-Zobel *et al.*, 1998) or cooked tomato products, with small amounts of olive oil, as typically used in Greece and Italy (Weisburger, 1998c). Vitamin C is an antioxidant and its inhibition of formation of N-nitroso compounds from secondary amines has been postulated to be the basis for its protective effect against stomach cancer (Correa, 1992; Mirvish, 1994). However, its role as a free radical scavenger may be equally important. The normal stomach has an active ascorbic acid secretion mechanism which is impaired by infection with *Helicobacter pylori*, a bacterial agent linked to gastric cancer (De Koster *et al.*, 1994; Hwang *et al.*, 1994). Intake of at least 200 mg/day of vitamin C is desirable. Vegetables and fruits are also rich in flavonoids such as quercitin, which have antioxidant activity (see below).

Although the content of fat in the U.S. diet is high, around 35–40% of calories, intake of certain fatty acids may be suboptimal. Fatty acids as nutrients are metabolically incorporated into glycerolipids and processed into phospholipids, which are components of all cells. They are also oxidized by cyclooxygenase and lipoxygenase to eicosanoids, which are key mediators of biochemical processes, such as prostaglandins. The n-3 polyunsaturated fatty acids have 3 carbons separating the methyl end from the first unsaturated bond and include linolenic (C18:3, n-3), eicosapentanoic acid (C20:5, n-3) and docasahexanoic acid (C22:6, n-3). These have been found to have a protective effect against breast and colon cancer (Carroll, 1992; Cave, 1996; Singh *et al.*, 1997). Also, the growth and metastasis of a transplantable human breast tumor in a mouse model system was suppressed by high levels of n-3 fatty acids, but enhanced by n-6-polyunsaturated oils (Rose and Connolly, 1993). The protective mechanisms might involve a metabolic effect (Sardesai, 1992) such as increased biosynthesis of the 3-series prostaglandins (PGE_3) and thromboxanes (TXA_3). These compete with the 2-series compounds, which are biologically active as cancer promoters. Also, n-3 fatty acids inhibit the synthesis of arachidonic acid from linoleic acid, and compete with arachidonic acid as a substrate for cyclooxygenase. In addition, fatty acids are ligands for the peroxisome proliferator-activated receptors (PPARs) (Krey *et al.*, 1997), which are gene transcription factors belonging to the nuclear hormone receptor superfamily.

Deficiencies in specific micronutrients have been related to increases in several cancers under certain circumstances. Imbalances in dietary iodine intake can, to some extent, be the basis for geographic differences in thyroid cancer (Franceschi *et al.*, 1993). The minerals calcium and selenium are anticarcinogenic in animal models, especially as regards the large intestine. Calcium lowers the rate of cell cycling, particularly in the intestinal tract (Lipkin and Newmark, 1995). Several epidemiological studies have found an inverse association between calcium intake and the risk of colorectal cancer (Garland *et al.*, 1985), but not in all (Martinez and Willett, 1998). In addition, calcium is important for other aspects of good health, such as bone strength. Some epidemiological studies suggest that vitamin D intake is inversely associated with colon cancer risk (Martinez and Willett, 1998), but the data are sparse. Such a protective effect could stem from an action on absorption and metabolism of calcium.

Asian countries historically have had low rates of breast, colon, and prostate cancers, which was largely attributable to low-fat diets (see Nutritional Excesses). Current dietary habits in Japan are changing to a Western pattern, with concomitant increase in Western-type cancers (Tominaga and Kuroishi, 1997). These findings provide strong evidence for an association of the Western dietary pattern with the types of cancers frequent in North America. In addition, the traditional diets in Far Eastern countries are comprised of many soy products. These are rich in isoflavones (Fournier *et al.*, 1998; McLaughlin *et al.*, 1995) such as genistein, a functional agent with anticarcinogenic properties, which has been observed in experimental models (see below). Typical Western diets are quite low in isoflavones, and hence, this may constitute a suboptimal condition that could also develop in Asian countries as a shift to Western-type diets progresses.

Nutritional Excesses

Over-nutrition is well established as a cause of increased risk for a number of cancers (Kritchevsky, 1995). This has been corroborated in animal models (Pariza and Boutwell, 1987) in which caloric restriction strongly inhibits carcinogenesis. For some cancers, as will be discussed, the contribution of overnutrition relates to specific dietary excesses, while for others such as renal cell cancer (Wolk *et al.*, 1996), a general energy effect appears to be involved. Also, obesity, which reflects excess energy intake, is associated with greater risk for endometrial neoplasia (Schottenfeld, 1995).

In the United States, fat intake from both plant and animal sources averages about 100 g/day for males and 60g/day for females, accounting for about 35% of total energy (Rolls and Hill, 1998). About 25% of this is contributed by animal products, which are high in saturated fatty acids (Grundy, 1996; Micozzi and Moon, 1992). Substantial evidence is available that excess consumption of total calories or specific food components creates a condition of metabolic overload that leads to increases in cancer (Kritchevsky, 1995; Williams and Wynder, 1996; Wynder and Williams, 1993). In population or ecological studies, high-fat intake is strongly associated with an increased prevalence of colon cancer (Potter *et al.*, 1993), breast cancer (Boyd *et al.*, 1993; Carroll, 1992), and, possibly, cancer of the prostate (Mettlin, 1997) and lung (Swanson *et al.*, 1997). This relationship is sometimes (Hayes *et al*., 1999), but not always, evident in cohort or case-control studies (Kampman *et al*., 1999; Martin-Moreno *et al.*, 1994), the latter perhaps because even the lowest intake group is also overexposed (i.e., >25% calories from fat) in populations with traditional high fat consumption. Nevertheless, case-control studies generally support a positive association for saturated or animal fat intake and breast cancer in postmenopausal women (Howe, 1994). Importantly, the rates in postmenopausal women differ most between countries of high and low fat intake. The amount of fat intake may affect serum estradiol levels (Wu *et al*, 1999). For prostate cancer risk, case-control studies support an association of greater intake of dietary fat, especially saturated fat, whereas all cohort studies have not shown consistency (Nomura and Kolonel, 1991), although some do provide support (Le Marchand *et al.*, 1994). Likewise, increased risk for pancreas cancer has been linked to high-fat intake (Lyon *et al.*, 1993), particularly via meat consumption (Gold and Goldin, 1998; Howe and Burch, 1996; Soler *et al.*, 1998). Studies in animal models generally demonstrate that fat influences cancer development in the breast (Welsch, 1992), colon (Reddy, 1996), and pancreas (Birt *et al.*, 1989), although specific exceptions have been observed. Less experimental evidence is available for prostate cancer, perhaps in part because a good laboratory model to investigate dietary modulation of prostate cancer is not available. The enhancing effects of high-fat diets have been attributed to increased caloric intake, which certainly increases tumor development (Keenan *et al.*, 1997), but analysis of the collective literature reveals an enhancing effect by specific dietary fats (Freedman *et al.*, 1990) as well as a general effect from excessive calories (Birt *et al.*, 1989).

One element in the role of high fat intake appears to be in levels of certain fatty acids. In contrast to the low levels of n-3 fatty acids previously discussed, most plant oils are high in n-6 fatty acids such as linoleic acid (C18: 2nB6), which is positively associated with prostate, breast (postmenopausal), colon (distal), and pancreatic cancer risk (Godley *et al.*, 1996; Micozzi and Moon, 1992). In rodent models, n-6 polyunsaturated oils are stronger promoters than monounsaturated oils, such as olive oil, or n-3 polyunsaturated oils (Carroll, 1992; Cave, 1996), yet, they all provide an identical caloric load. The mechanisms of action of specific oils as regards biosynthesis and degradation of bile acids or estrogen are distinct, and parallel their enhancing action, or lack thereof. Corresponding to the experimental findings, the rates of breast and colon cancer in Mediterranean countries with a high intake of olive oil are appreciably lower than in North America or the United Kingdom (Martin-Moreno *et al*. 1994; Trichopoulou *et al.*, 1995). A further contributing element in the Mediterranean region, however, might be the high intake of vegetables and tomatoes, with protective actions, as discussed above.

Nevertheless, caloric intake and possibly nutrient density may be of importance in humans, especially where overnutrition leads to obesity. It is noteworthy that in animal models, the only modulation of diet that consistently maintains maximal longevity is caloric restriction (Masoro, 1991). In part, this is due to an effect on cell cycling, itself a key factor in carcinogenesis and longevity. No conclusive association, however, has been established between sugar intake and any cancer (Burley 1997, 1998).

Excess salting of foods has been associated with increased risk of stomach cancer (Hwang *et al.*, 1994; Kneller *et al.*, 1992), for which laboratory studies provide support (Chen *et al.*, 1996; Sugimura, 1996; Takahashi *et al.*, 1983). Similar considerations may hold for cancer of the esophagus in China.

Thus, overall, there is strong evidence that nutritional excesses have a significant impact on the occurrence of a number of important types of cancer in Western societies and others (Table 2), as was concluded by W. R. Williams as long ago as 1908. There is also evidence for a role of exercise in reducing cancer risk (Friedenreich and Rohan, 1995), which may relate to diet.

Cancer-Modulating Food Components

Chemicals with carcinogenic activity in animals can be present in food through several different sources (Table 3). These include carcinogens of the type that have the ability to react with DNA and hence are mutagenic, and those that are not chemically reactive but produce other epigenetic cellular effects which bear on cancer development (Williams and Weisburger, 1991).

Food-borne carcinogenic chemicals can be detected by a variety of highly sensitive analytical techniques, and generally, such exposures are currently held to very low levels. Aflatoxins, which are potent carcinogenic mycotoxins produced by

TABLE 3
Sources of Detectable Laboratory Carcinogens in Food

Source	Example
Naturally occurring	
Plant	Cycasin
Microbial	Mycotoxins
Contaminant	
Introduced before processing	DDT
Introduced during processing	Trichloroethylene, methylene chloride
Additive	Butylated hydroxyanisole, saccharin
Formed from food components	
During processing	Nitrosamides/nitrosamines
During cooking	Benzo(a)pyrene and related hydrocarbons, heterocyclic amines
In the body	Nitrosamides/nitrosamines

Note. Many of the agents listed are detectable only at minute levels (i.e., <1 ppm) by highly sensitive analytical techniques.

fungi, were not discovered until 1960, but probably were at significant levels in certain crops such as corn or peanuts prior to that time (Williams, 1994). Aflatoxin has been associated with liver cancer in Asian and African countries, where exposure is high, and chronic hepatitis contributes also. In the United States, reduced mycotoxin exposure, subsequent to its recognition, and/or increased anticarcinogens in the diet, may be speculated to underlie the decline in liver cancer deaths (Williams, 1994). They have diminished from about 12 per 100,000 in males in 1930 to about 5 per 100,000 in 1990 (Landis *et al.*, 1998). Also in the past, nitrate (saltpeter) and salt were used at high levels for food preservation (Jones, 1992), and these may have contributed to the formation of carcinogens suspected to have been involved in the high incidence of stomach cancer prevalent in the early part of this century (Chen *et al.*, 1996; Correa, 1992; Howson *et al.*, 1986; Weisburger and Williams, 1995). However, the evidence has been considered inconclusive (Eichholzer and Gutzwiller, 1998).

A large number of substances that produce liver tumors in rodents, such as organochlorine pesticides, have been present at trace levels in food since their introduction in the 1940s for agricultural use. Obviously, these have not led to an increase in human liver cancer in the U.S., since, as noted, this cancer has declined over the past 50 years.

During the cooking of food, a variety of heterocyclic amines is formed in the browning reaction (Adamson *et al.*, 1995; Felton and Gentile, 1997; Weisburger *et al*., 1998). Prominent among these is 2-amino-1-methyl-6-phenylimidazo{4,5-b}pyridine (PhIP). These DNA-reactive agents are potent multiorgan and multispecies carcinogens, including in primates. It has been postulated that they may be the initiating agents for breast, prostate, pancreas, and colon cancers in Western societies (Weisburger and Williams, 1995), with PhIP estimated to account for half of the incremental cancer risk (Layton *et al.*, 1995). Recently, consumption of well done red meat, a source of heterocyclic amines, has been associated with an increased risk of colorectal adenomas, precursors of carcinomas (Sinha *et al*., 1999)

In the stomach, nitrosation reactions involving nitrates and other components in the diet give rise to nitrosamides and nitrosamines These carcinogens are postulated to be the initiating agents for stomach and esophageal cancer (Correa, 1992; Craddock, 1992), a concept which is supported by the demonstration that certain nitroso compounds induce gastric and esophageal cancer in rodents (Correa, 1992; Craddock, 1992; Mirvish, 1994). A novel direct-acting mutagen, 2-chloro-4-methylbutanoic acid and possible carcinogen for the stomach, was isolated from fish preserved with salt and saltpeter (Chen *et al.*, 1996; Furihata *et al.*, 1996).

Food also can be the source of infectious agents, such as the hepatitis B virus in shellfish and liver flukes in raw fish, which cause chronic tissue injury leading to increases in specific cancers.

Among beverages, alcohol consumed in excessive amounts is clearly associated with liver disease and increased risk of liver cancer, as well as esophageal cancer in association with cigarette smoking (International Agency for Research on Cancer, 1988). Weak and inconsistent positive associations between alcohol consumption and breast cancer have been reported in many epidemiologic studies (Rosenberg *et al.*, 1993), and current observations continue to show weak or absent association (Freudenheim *et al.*, 1995; Holmberg *et al.*, 1995; Longnecker *et al.*, 1995). Increased risk of cancer of the colon is also reported to be associated with alcohol consumption (Kune and Vatetta, 1992; Le Marchand *et al.*, 1997). Also, rectal cancer may be associated with alcohol intake, and metabolism to acetaldehyde has been postulated (Seitz, 1990). These epidemiological observations have not been corroborated in experimental studies and no mechanism has been elucidated. Coffee has also been discussed as a risk factor, particularly for bladder cancer, but a causal association has not been established (International Agency for Research on Cancer, 1991). In fact, caffeine may possibly be antimutagenic (Weisburger, *et al.*, 1998). As discussed below, tea appears to be anticarcinogenic.

Although several synthetic food additives are established experimental carcinogens when administered chronically at high doses, none has been associated with cancer in humans (Williams and Weisburger, 1991). To the contrary, antioxidants such as butylated hydroxyanisole and butylated hydroxytoluene may be functioning as anticarcinogens in the diet (Williams, 1993b, 1994). Generally, carcinogenic agents are not allowed as food additives. However, saccharin, a well-documented rodent bladder carcinogen at high dietary levels, operating through an epigenetic mechanism with a sharp dose-response displaying a no-effect threshold (Whysner and Williams, 1996), has been permitted as an exception. Its unrestricted use for many decades has pro-

TABLE 4
Food-Borne Inhibitors of Experimental Cancer

Food component	Food	Experimental cancer inhibited
Bifidobacterium longum cultures	Fermented dairy products	Large intestine, liver
Calcium	Dairy products	Large intestine
Carotenoids, β-carotene	Green/yellow vegetables, fruits	Large intestine, stomach
Conjugated linoleic acid	Cheese, cooked meats, oils(?)	Breast, forestomach, skin
Diallyl sulfide	Garlic, onions	Esophagus, forestomach, large intestine, liver
Fiber	Bran cereal and bread, vegetables	Breast, large intestine, pancreas
Fructans	Chicory, garlic, onion, asparagus	Large intestine
Indole-3-carbinol (glucobrassicin)	Cruciferous vegetables	Breast, endometrium, forestomach, liver, lung
Minerals		
Calcium	Dairy products	Large intestine, breast
Selenium	Vegetables, meat	Breast, skin, large intestine, liver, lung
Monoterpenes		
D-carvone	Caraway seed	Forestomach, lung
D-limonene	Citrus fruits	Breast, forestomach, lung
Myoinositol (phytate)	Bran cereals and bread	Large intestine, breast
Phenolics (glycosides)		
Catechins	Fruits, vegetables	Large intestine, breast
(-)-epigallocatechin-3-gallate	Tea	Lung, esophagus, skin, breast, small and large intestine
Flavonoids	Vegetables	
Quercetin	Vegetables	Breast, large intestine
Naringenin	Citrus	Breast
Isoflavones	Soy products	Breast, large intestine
Genistein		
Hydroxycinnamic acids	Fruits, vegetables,	Forestomach
Caffeic acid	Soy, cereals	
Chlorogenic acid		Large intestine, liver
Ferulic acid		Forestomach
Tannins	Vegetables	Forestomach, lung
Tannic acid		
Ellagic acid	Fruits	Esophagus, liver, skin
Protease inhibitors		
Bowman-Birk	Soy	Liver
Edi ProA soy protein	Soy	Liver
Soy protein isolate	Soy	Breast, large intestine
Thiocyanates (glucosinolates):	Broccoli, cabbage	Breast, forestomach
Benzyl isothiocyanate	Watercress	Liver, lung
Benzyl thiocyanate		Breast, liver
Phenethyl isothiocyanate		Breast, esophagus, forestomach, lung
Sulforaphane	Broccoli	Breast, large intestine
Vitamins		
Vitamin A	Liver, milk, eggs, vegetables	Liver, lung
Vitamin C (ascorbic acid)	Citrus fruits, vegetables	Kidney, large intestine, lung, stomach
Vitamin E (α-tocopherol)[a]	Seeds, nuts, vegetable and seed oils	Breast, forestomach, large intestine, oral, skin

[a] Foods listed do not provide optimal amounts, and supplementation with 100–200 international units, with the main meal of the day is suggested.

vided evidence that the cancer risks from epigenetic agents are negligible under actual, realistic conditions of use. Nevertheless, one natural food "additive," salt, when used in excess, appears to play a role in stomach cancer (Chen *et al.*, 1996; Kneller *et al.*, 1992; Takahashi *et al.*, 1983). This indicates that high-level exposures to some agents can enhance risk. High salt intake also relates to hypertension. Low consumption of some of these protective components is associated with increased cancer risks, as discussed in Nutritional Inadequacies.

Foods also contain a variety of components that have been demonstrated in animal models to inhibit specific chemical-induced cancers (Table 4). These agents can function as carcinogen-reducing agents, reducing formation or absorption of carcinogens; carcinogenesis-blocking agents, blocking carcinogen reactions with cellular macromolecules; or cancer-suppressing agents, suppressing neoplastic development. Low consumption of some of these protective components is associated with increased cancer risks, as discussed in Nutritional Inadequacies.

TABLE 5
Food-Borne Agents That Influence Human Cancers

Cancer	DNA-reactive carcinogen	Enhancing or promoting factor	Protective factor
Breast	Heterocyclic amines	High-fat diet[a]	Adequate fiber, soy, tea, ?calcium, ?vitamin D
Prostate	?Heterocyclic amines	High fat diet[a]	Soy, lycopene, cooked tomatoes
Lung	(Tobacco smoke)[a] (Occupational exposures)	?High fat diet[a] (Tobacco smoke)	Fruits and vegetables, soy, tea
Large intestine	Heterocyclic amines	High fat diet[a]	Adequate fiber, calcium, vitamin D, soy, tea
Pancreas	(Tobacco smoke) ?Heterocyclic amines	?High fat, meat diet	Soy, tea ?vegetables and fruits
Stomach	?Reactive chloro- or nitroso- compounds	High intake of salted and preserved foods (also *Helicobacter pylori*)	Fruits and vegetables, soy, tea
Liver	Aflatoxins	Alcohol (hepatitis)	
Esophagus	?Nitrosamines (Tobacco smoke)	Alcohol	Tea, ?soy

Note. Agents in parentheses are not food-borne.
[a] Monounsaturated oils, olive or canola oils, do not promote; n-3-polyunsaturated oils are protective.

Specific Human Cancers Influenced by Food-Borne Components

Patterns of food consumption are well established as being associated with incidences of certain cancers, as discussed above, and foods have been documented to contain cancer-modulating agents from a variety of sources (Weisburger, 1998b). The contribution to the main human cancers of specific carcinogens, enhancing or inhibiting factors conveyed in food, is summarized in Table 5. These agents in aggregate account for the 50% of cancer attributable to diet (Table 1).

The potential for modification of diet to determine cancer rates is illustrated strikingly by the decline of stomach cancer in most populations (Correa and Chen, 1994; Howson *et al.*, 1986). Stomach cancer rates in the United States have decreased from about 38 deaths per 100,000 males in 1930 to about 6 per 100,000 in 1990, and from about 28 deaths per 100,000 females to about 4 per 100,000 (Landis *et al.*, 1998). A consistent factor associated with reduced risk was intake of vegetables and fruit (Boeing, 1991, postulated to provide protective vitamin C and β-carotene (Hansson *et al.*, 1994; Steinmetz and Potter, 1991). As described above, vitamin C may inhibit the nitrosation reaction in the stomach that leads to carcinogen formation. Another possible contributor to this dramatic decline is changes in methods of food preservation. The use of salting and nitrates has diminished (Hwang *et al.*, 1994; Weisburger, 1998b; Weisburger and Williams, 1995) in favor of canning, freezing, and refrigeration. Salt and nitrates provide substrates for the formation of carcinogens, and salt is a promoter of stomach cancer in animal models. Thus, reduction of these elements could lessen carcinogenic effects in the stomach.

Another cancer that has declined in the United States in both genders is liver cancer (Landis *et al.*, 1998). This reduction has occurred in spite of increased exposures to food-borne animal liver carcinogens such as organochlorine pesticides. As noted above, one genotoxic liver carcinogen that has been carefully controlled over the past 30 years is aflatoxin, a major contributor to liver cancer in parts of the world with high contamination, and hence this reduction may be in part responsible for the decline. Regardless of the basis for the decline of stomach and liver cancers, their reduction clearly demonstrates that specific cancers can be reduced through effective prophylaxis. The current knowledge of the role of nutrition and other food components in the etiology of major cancers such as colon, breast, pancreas, and prostate (Table 4) offers an attractive opportunity for cancer control.

Strategies for Cancer Prophylaxis

Nutrition

Cancer prevention must focus, beginning in childhood, on managerial approaches to assuring optimal nutrition and balance of food components (Williams, C. L., 1996; Williams, C. L. *et al.*, 1993), since cancer is a "chronic" condition that develops over a long period of time, and certain cancers may have their inception during childhood. In addition, food preferences are established in childhood. As a general guide, an attainable goal after adolescence is a diet comprising 25% *or less* of calories from fat (no more than 40 g per day for an adult) and 25–35 g of fiber (Wynder *et al.*, 1992; Williams and Wynder, 1996). For children, fat consumption after the age of 2 should also be no more than 30% of calories consumed (range 20–30%), and an adequate total fiber intake in g per day should follow the "age plus 5" formula, eventually reaching the minimally desirable adult level of 25g/day by age 20 (Williams, C. L. *et al.*, 1995). A balanced diet should consist of 6 or more servings per day from the grain group (whole grain bread, cereal, rice, and pasta items), 3–5 servings of green and yellow vegetables, 2–4 servings of fruits, and 2 or 3 servings of low-fat or fat-free dairy products, as recommended by

TABLE 6
Fiber First Diet©

Dietary fiber intake per day
2–19 years old, age + 5 in g
≥ 20 years old, 25–35g
50% from grains
30% from vegetables and legumes
20% from fruits
Fluid intake per day: 8–12 glasses (8-ounce)

various authorities (Dwyer, 1993). Whole-grain products are an excellent source of insoluble fiber (Jacobs *et al.*, 1998). As an animal protein source, fish is preferable, because of its content of protective n-3 fatty acids and might be consumed 3 or more times per week. Meat and poultry should be limited to 2–3 small servings, preferably low fat versions, per week. These foods will deliver the desirable daily intakes of 200 mg of vitamin C, 400 units of vitamin D, and 1.0–1.5 g of calcium, which Lachance (1994) proposes as an appropriate Recommended Daily Allowance based upon an "ideal" content. A well-balanced diet should not require supplementation, except perhaps for vitamin E, which is delivered at only about 25 IU in recommended diets. Daily use of multivitamins has been reported to be associated with reduced colon cancer risk (White *et al.*, 1997) although evidence for anticancer activity has not been established (Byers and Guerro, 1995; Greenberg *et al.*, 1994). Nevertheless, use of a multivitamin with at least 200 IU of vitamin E is recommended for reduction of risk of cardiovascular disease. These dietary recommendations will also provide reduced risk for other major diseases, particularly coronary heart disease and stroke (Shils *et al.*, 1994; Sugimura, 1996; Weisburger, 1998b; Weisburger and Williams, 1995; Willett, 1994), and certainly are not expected to do harm.

To achieve these goals, an attractive approach is the Fiber First Diet© (FFD) (Table 6), which emphasizes that fiber be consumed first in the day and first in each meal. The desirable fiber intake for adults is 25–35 g/day. For children, minimal intake is achieved by the "age plus 5" principle, i.e., the g per day is calculated by adding 5 to the child=s age (Williams, 1995a,b; Williams and Bollella, 1995). This results in a progressive intake to age 20 when the adult goal is reached. A healthy range of dietary-fiber intake for children is age + 5 to age + 10 grams per day. The source of fiber should be approximately 50% from grains, including wheat bran, 30% from vegetables and legumes, and 20% from fruits (Fig. 1). This must be accompanied by adequate water and fluid intake to hydrate the fiber in the gut. A desirable source of fluid is fruit and vegetable juices, which, respectively, are sources of bioavailable vitamin C (Weber *et al.*, 1996) and β-carotene or lycopene (Pool-Zobel *et al.*, 1998). These, like tea, discussed below, provide valuable functional effects.

The basic elements of the FFD are given in Table 7, and a comparison with typical meals is provided in Table 8. Most

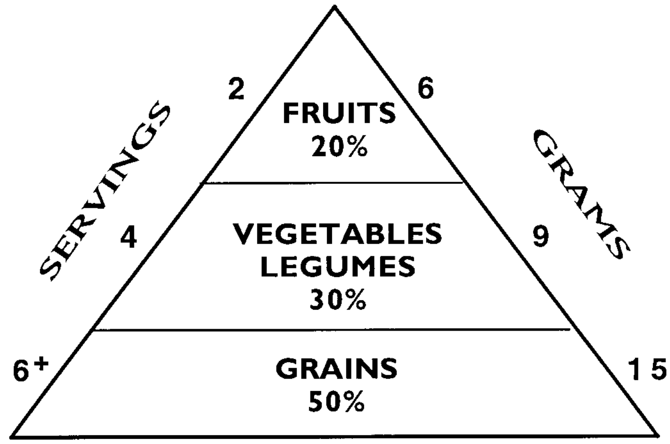

FIG. 1. Adult fiber pyramid.

individuals will be able to achieve the fiber-first diet by consuming a high-fiber breakfast cereal, using whole wheat bread in a sandwich at lunchtime, and consuming 3 to 5 vegetables and 2 fruits throughout each day. In addition to providing adequate fiber and displacing fat in the diet, key components of the FFD (grains, vegetables, legumes, and fruit) furnish important vitamins and minerals. In addition, the FFD provides other functional components that have been associated with reduced cancer risk (Steinmetz and Potter, 1991), discussed below. The FFD should slightly

TABLE 7
Guidelines for Dietary Fiber Intake on Fiber First Diet©

Adult[a]	Child[b]
Breakfast	Breakfast
Wheat bran cereal[c] (8 g)	2 cup wheat bran cereal[c] (4 g)
1 fruit (4 g)	2 fruit (2 g)
1 slice whole wheat toast (2 g)	
Lunch[c]	Lunch[c]
2 slices whole wheat bread[d] (4 g)	2 slices whole wheat bread[d] (4 g)
1 fruit (3 g)	1 fruit (3 g)
	Snack
	1/2 cup fruit (2 g)
Dinner[e]	Dinner[c,e]
1 cup vegetable or legume (4 g)	1/4 cup vegetable or legume (1 g)
1 baked potato w/skin (4 g)	1 baked potato– no skin (2 g)
2 tomato (1 g)	2 cup fruit (2 g)
1 cup lettuce (1 g)	
Total dietary fiber = 31 grams	Total dietary fiber = 20 grams

Note. The listed foods are fiber-containing foods which would be chosen "first" to achieve fiber goal. Other foods and drinks would accompany these to complete dietary requirements.

[a] Adult recommendation for dietary fiber: 25–35 grams per day.

[b] Child, age 10 (recommended range of fiber intake based on age + 5 to 10 guideline = 15–20 g/day).

[c] Include a cup of low fat milk.

[d] Bread as part of a sandwich.

[e] Dinner would also include a serving of lean meat, fish or other source of protein.

TABLE 8
Fiber First Diet© Versus Usual U.S. Diet

Typical U.S. diet 13 g fiber; 1950 calories 34% energy from fat

Meal	Fiber (g)	Fat (g)	KCAL	Calcium (mg)
Breakfast:				
1 corn muffin ($1\frac{1}{2}$ oz.)	1	5	125	
1 tsp. butter	0	5	45	
1 cup beverage[a]	0	0	5	
1 tbsp. half and half	0	2	20	
Lunch:				
1 cheeseburger	2	14	310	200
1 small French fries	2	12	220	
1 small choc. shake	0	5	350	581
Snack:				
banana	4	0	120	
Dinner:				
salad: 1 cup iceburg lettuce	1	0	25	
$\frac{1}{2}$ large tomato	1	0	25	
2 tbsp regular dressing	0	10	90	
$1\frac{1}{2}$ cup white rice	2	0	240	
3 oz. fried chicken[b]	0	15	225	
1 cup regular soda	0	0	150	
DAILY TOTALS	13	68	1950	781

Fiber First Diet© 31.5 g fiber; 1800 calories 24% energy from fat

Meal	Fiber (g)	Fat (g)	KCAL	Calcium (mg)
Breakfast:				
1 cup Raisin Bran	8	1.5	200	
1 cup strawberries, fresh	3.5	0	40	
1 cup milk, 1%	0	2.5	100	300
Lunch:				
2 oz turkey breast	0	2	70	
2 slices whole wheat bread	4	2	160	
1 tbsp lite mayo	0	5	45	
$\frac{1}{2}$ large tomato	1	0	25	
1 cup garden salad	2	0	25	
1 tsp. olive oil + vinegar	0	5	45	
seltzer with lemon	0	0	0	
1 apple, small	3	0	60	
Snack:				
1 Nutrigrain bar[c]	1	3	140	200
1 cup milk, 1%	0	2.5	100	300
Dinner:				
3 oz. broiled salmon	0	9	165	
$\frac{1}{2}$ cup broccoli sauteed	2	0	25	
with 1 tsp. olive oil + garlic	0	5	45	
6 oz. baked potato + skin	4	1	180	
3 tbsp. low-fat sour cream	0	5	45	50
1 cup milk, 1% fat	0	2.5	100	300
Snack:				
$\frac{1}{2}$ cup peaches, fresh	2	0	60	
$\frac{1}{2}$ cup frozen yogurt	0	0	90	450
3 graham crackers, ($2\frac{1}{2}$ in. squares)	1	2	80	
DAILY TOTALS	31.5	48	1800	1600

[a] Tea, coffee.
[b] All white-meat, no skin.
[c] Kellogg.

reduce daily energy intake (Table 8), especially since consumption of high-fiber foods reduces food intake at the next meal (Rolls and Hill, 1998). While adoption of the FFD will usually lower fat intake, wherever possible, reduced fat products such as skim milk should be used. Snacks, especially, should be low in fat. Fruits make wholesome, tasty between-meal snacks. Even potato chips are available in low-fat versions, prepared by baking or frying in non-digestible fat substitutes such as olean.

Functional Foods

In addition to the importance of nutrition in cancer prevention, recognition is growing that foods contain components that have specific effects on genomic, cellular, biochemical, or physiological function, which can protect against disease processes, including cancer and cardiovascular disease. Epidemiological studies reveal that reduced risk of some cancers is associated with consumption of foods such as vegetables (Block *et al.*, 1992), whole grain cereals and breads (Caygill *et al.*, 1998), and soy products (Fournier *et al.*, 1998; Mclaughlin *et al.*, 1995). Specific constituents of these foods that are believed to be responsible for the protective effects have been identified. Those food components that have been demonstrated to have anticarcinogenic effects in experimental systems are listed in Table 5. Among these are phenolics, which occur usually as glycosides in a wide array of foods; carotenoids; phytoestrogens; and minor nutrients such as minerals and vitamins (Wattenberg, 1992). Foods rich in such components have been referred to as "functional foods."

Prominent among functional components of food are antioxidants (Aruoma, 1994). The antioxidants in whole grains have been suggested as contributors to the anticarcinogenicity of these foods (Johnson, 1998), in addition to their fiber effect. An important type of antioxidant in plants is polyphenols, which have properties similar to the synthetic antioxidant phenolics BHA and BHT. The polyphenols present in tea have exhibited anticarcinogenic activity in experimental models (Katiyar and Mukhtar, 1996; Weisburger, 1997b, 1998a; Yang and Wang, 1993) (Table 4). In addition to its antioxidant content, tea is, of course, mainly water, which is an important essential nutrient. Epidemiological studies have not yet yielded strong evidence of cancer risk reduction. However, green-tea drinking in China and Japan is associated with lower rates of esophageal and gastric cancers, which are highly prevalent in these countries, and also of pancreatic, colorectal, and bladder cancers (reviewed by Blot *et al.*, 1996, and Bushman, 1998). Laboratory research showed that green and black teas have similar protective properties as antimutagens and anticarcinogens (Weisburger, 1998a). The known underlying mechanisms, therefore, suggest that tea should be health promoting. Also, several epidemiological studies on tea use have noted a reduced mortality from heart disease, with similar risk factors to those related to the nutritionally-linked cancers. Cocoa is another plant source of polyphenols (Zumbé, 1998). Antioxidants such as polyphenols and flavonoids (Williamson *et al.*, 1998) are also free-radical scavengers, and this activity may be involved in their anticarcinogenicity (Aruoma, 1994).

Carotenoids comprise about 600 pigmented chemicals formed in plants. Some have activity as provitamin A, and most have some antioxidant potential. The association of reduced cancer risks with consumption of fruits and vegetables has been attributed to carotenoids, particularly β-carotene, which has shown anticancer activity in animal models (Toma *et al.*, 1995).

Over 90 plants have been identified as possessing some estrogenic activity (Farnsworth *et al.*, 1975) due to their content of phytoestrogens, which include isoflavones, coumestans, and lignans (Kurzer and Xu, 1997; Reinli and Block 1996). Epidemiologic studies suggest reduced risks of prostate and gastric cancers with consumption of soy foods (Adlercreutz *et al.*, 1993; Fournier *et al.*, 1998), which are the richest dietary source of isoflavones, and include the aglycones: genistein, daidzein, and glycitein. In animal studies, genistein has been reported to inhibit mammary carcinogenesis in rats, but this has not been substantiated, and the biologic properties appear to be quite complex (Barnes, 1997). Oilseeds, such as flaxseed, are the richest plant sources of lignans, such as secoisolariciresinol.

Plants belonging to the genus *Allium* include garlic, onion, leek, and shallot, which contain large amounts of organosulfur compounds, as well as glutathione and flavonols. *Allium* vegetable consumption has been associated, in case-control studies, with reduced cancer risk (Steinmetz and Potter, 1991), although this was not confirmed for lung cancer in a prospective cohort study (Dorant *et al.*, 1994).

Another category of functional foods consists of prebiotics that stimulate the growth in the gut and/or activity of types of bacteria, such as *Lactobacillus acidophilus* and *Bifidobacterium* species, which are beneficial (Gibson and Roberfroid, 1995). The β (2–1)D fructans, inulin and oligofructose, are soluble fibers that are fermented by colonic microflora and stimulate the growth of bifidobacteria. These fructans inhibited the induction of preneoplastic lesions in rat colon (Reddy *et al.*, 1997). Foods such as yogurt are considered probiotics because they contain the beneficial live microbes. While several studies have shown that administration of bifidobacteria or lactobacilli to carcinogen-exposed animals reduced colon preneoplastic or neoplastic lesions, results have not been consistent (Gallaher *et al.*, 1996).

In order for functional components to produce a biological effect, they must, of course, be bioavailable in sufficient amounts. The richest sources of vitamin E are vegetable oils (Sokol, 1996), but since these should be limited in the diet, supplementation is the only practical way to achieve sufficient intake. Vitamin E, and the other fat-soluble vitamins A and D, must be consumed as part of a fat-containing meal to be absorbed. Other components, such as quercitin (Gugler *et al.*, 1975), also are not well absorbed.

Intervention trials are currently underway, in which some of these functional food components, such as β-carotene and vitamin A, are being administered as supplements to various study populations (Boone *et al.*, 1997; Greenwald *et al.*, 1995). Some early results have been disappointing (Vainio and Rautalahti, 1998), and it would be remarkable if change in single minor components of diet could alter the risk of a major cancer, such as lung cancer due to continuing smoking that provides an overpowering carcinogenic stimulus. In fact, the trials with β-carotene have shown increases in lung cancer (The Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group, 1994; Omenn *et al.*, 1996). As discussed by Olson (1996), antioxidants in some situations can exert prooxidant effects, and large doses of β-carotene can inhibit the absorption of other carotenoids, leading to nutritional imbalances.

Synthetic chemicals with functional properties superior to those of natural food components are also available. These include antioxidants such as butylated hydroxyanisole and butylated hydroxytoluene, isothiocyanates, and organoselenium compounds. The potential of such agents for cancer prevention deserves attention. Moreover, consideration needs to be given to combined modification of both nutritional and functional components of the diet, and to the adoption of new dietary patterns, starting in childhood, and based on detailed research in the field of nutrition and health and an understanding of the underlying mechanisms.

CONCLUSIONS

Genetic predisposition is clearly important in the etiology of cancer in some individuals, notably with breast and colon cancer, for which inherited mutations in cancer suppressor genes have been identified. Nevertheless, genetic predisposition as a major determinant is calculated to account for only 2–3%, at most, of the current cancer burden (Table 1). Individuals in any population have varying susceptibilities to cancer, but nutrition and food-borne components clearly affect cancer risk in the majority of populations of the world. Practical approaches to reducing cancer risk through dietary modification are available, including the Fiber First Diet,© described herein, which is compatible with other recommendations. Improved nutrition will also serve to reduce risk of other important chronic diseases. Research will help to further define the optimal diet and lifestyle, both in terms of nutritional and functional components throughout the life span, to best promote and maintain good health.

ACKNOWLEDGMENTS

We thank N. Rivera, P. Morris, and K. Bateman for preparing the manuscript. Research support from the American Cancer Society, Grant CN-157, and gifts from the Texaco Foundation, and the Friends Against Cancer Team.

REFERENCES

Adamson, R. H., Gustafsson, J. A., Ito, N., Nagao, M., Sugimura, T., Wakabayashi, K., and Yamazoe, Y. (Eds.) (1995). Heterocyclic amines in cooked foods: Possible human carcinogens. *Proceedings of the 23rd International Symposium Princess Takamatsu Cancer Research Fund*. Princeton Scientific Publishing, Princeton, NJ.

Adlercreutz, H., Bannwart, C., W≅h≅l≅, K., M≅kel≅. T., Brunow G., Hase, T., Arosemena, P. J., Kellis, J. T., Jr., and Vickery, L. E. (1993). Inhibition of human aromatase by mammalian lignans and isoflavonoid phytoestrogens. *J. Steroid Biochem. Molec. Biol.* **44**, 147–153.

The Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group (1994). The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. *N. Engl. J. Med.* **334**, 1029–1035.

Aruoma, O. I. (1994). Nutrition and health aspects of free radicals and antioxidants. *Food Chem. Toxicol.* **7**, 671–683.

Barnes, S. (1997). The chemopreventive properties of soy isoflavonoids in animal models of breast cancer. *Breast Cancer Res. Treat.* **46**, 169–179.

Birt, D. F., Julius, A. D., White, L. T., and Pour, P. M. (1989). Enhancement of pancreatic carcinogenesis in hamsters fed a high-fat diet *ad libitum* and at a controlled calorie intake. *Cancer Res.* **49**, 5848–5851.

Block, G., Patterson, B., and Subar, A. (1992). Fruit, vegetables, and cancer prevention: A review of the epidemiological evidence. *Nutr. Cancer* **18**, 1–29.

Blot, W. J., Chow, W.-H., and McLaughlin, J. K. (1996). Tea and cancer: A review of the epidemiological evidence. *Eur. J. Cancer Prev.* **5**, 425–438.

Boeing, H. (1991). Epidemiological research in stomach cancer: Progress over the past ten years. *J. Cancer Res. Clin. Oncol.* **117**, 133–143.

Boone, C. W., Bacus, J. W., Bacus, J. V., Steele, V. E., and Kelloff, G. J. (1997). Properties of intraepithelial neoplasia relevant to cancer chemoprevention and to the development of surrogate endpoints for clinical trials. *Proc. Soc. Exper. Biol. Med.* **216**, 151–165.

Boyd, N. F., Martin, L. J., Noffel, M., Lockwood, G. A., and Tritchler, D. L. (1993). A meta-analysis of studies of dietary fat and breast cancer risk. *Br. J. Cancer* **68**, 627–636.

Bradlow, H. L., Fishman, J., and Osborne, M. P. (Eds.). (1997). Cancer, genetics and the environment. *Ann. N Y Acad. Sci.* **833,**

Burley, V. J. (1997). Sugar consumption and cancers of the digestive tract. *Eur. J. Cancer Prev.* **6**, 422–434.

Burley, V. J. (1998). Sugar consumption and human cancer in sites other than the digestive tract. *Eur. J. Cancer Prev.* **7**, 253–277.

Bushman, J. L. (1998). Green tea and cancer in humans: A review of the literature. *Nutr. Cancer* **31**, 151–159.

Byers, T., and Guerrero, N. (1995). Epidemiologic evidence for vitamin C and vitamin E in cancer prevention. *Am J. Clin. Nutr.* **62**, 1385–1392S.

Carroll, K. K. (1992). Dietary fat and breast cancer. *Lipids* **27**, 793–797.

Cave, W. T., Jr. (1996). Fish oil and cancer prevention. In *Nutrition and Cancer Prevention* (R. R. Watson and S. I. Mutfi, Eds.), pp. 81–90. CRC Press, Boca Raton, FL.

Caygill, C. P. J., Charlett, A., and Hill, M. J. (1998). Relationship between the intake of high-fibre foods and energy and the risk of cancer of the large bowel and breast. *Eur. J Cancer Prev.* **7**, S11–17.

Chen, W., Weisburger, J. H., Fiala, E. S., Spratt, T. E., Carmella, S. G., Chen, D. and Hecht, S. S. (1996). Gastric carcinogenesis: 2-Chloro-4-methylthiobutanoic acid, a novel mutagen in salted, pickled Sanma Hiraki fish, or similarly treated methionine. *Chem. Res. Toxicol.* **9**, 58–66.

Chyou, P. H., Nomura, A. M. Y., Hankin, J. H., and Stemmerman, G. N. (1990). A case-cohort study of diet and stomach cancer. *Cancer Res.* **50**, 7501–7504.

Clifford, C., and Kramer, B. (1993). Diet as risk and therapy for cancer. *Med. Clin. North Am..* **77**, 725–744.

Colditz, G. A., Stampfer, M. J., and Willett, W.C. (1987). Diet and lung cancer: A review of the epidemiologic evidence in humans. *Arch. Intern. Med.* **147**, 157–160.

Correa, P. (1992). Human gastric carcinogenesis: A multistep and multifactorial process. First American Cancer Society Award Lecture on Cancer Epidemiology and Prevention. *Cancer Res.* **52**, 6735–6740.

Correa, P., and Chen, V. W. (1994). Gastric cancer. *Cancer Surv.* **19/20**, 55–76.

Craddock, V. M. (1992). Aetiology of oesophageal cancer: Some operative factors. *Eur. J. Cancer Prev.* **1**, 89–103.

De Koster, E., Buset, M., Fernandes, E., and Deltenre, M. (1994). *Helicobacter pylori*: The link with gastric cancer. *Eur. J. Cancer Prev.* **3**, 247–257.

Dorant, E., van den Brandt, P., and Goldbohm, R. A. (1994). A prospective cohort study on *Allium* vegetable consumption, garlic supplement use, and the risk of lung carcinoma in the Netherlands. *Cancer Res.* **54**, 6148–6153.

Dwyer, J. (1993). Diet and nutritional strategies for cancer risk reduction. *Cancer* **72**(suppl. 3), 1024–1031.

Eastwood, M. A. (1992). The physiological effect of dietary fiber: An update. *Annu. Rev. Nutr.* **12**, 19–35.

Eichholzer, M., and Gutzwiller, F. (1998). Dietary nitrates, nitrates, and N-nitroso compounds, and cancer risk: A review of the epidemiologic evidence. *Nutr. Rev.* **56**, 95–105.

Farnsworth, N. R., Bingel, A. S., Cordell, G. A., Crane, F. A., and Fong, H. S. (1975). Potential value of plants as sources of new antifertility agents II. *J. Pharm. Sci.* **64**, 717–754.

Felton, J. S., and Gentile, J. M. (1997). Mutagenic/carcinogenic N-substituted aryl compounds. *Mutat. Res.* **376**, 1–276.

Fournier, D. B., Erdman, J. W., Jr., and Gordon, G. B. (1998). Soy, its components, and cancer prevention: A review of the in vitro animal and human data. *Cancer Epidemiol. Biomarkers Prev.* **7**, 1055–1065.

Franceschi, S., Boyle, P., Maisonneuve, P., La Vecchia, C., Burt, A. D., Kerr, D. J., and MacFarlane, G. J. (1993). The epidemiology of thyroid carcinoma. *Crit. Rev. Oncog.* **4**, 25–52.

Freedman, L. S., Clifford, C., and Messina, M. (1990). Analysis of dietary fat, calories, body weight, and the development of mammary tumors in rats and mice: A review. *Cancer Res.* **50**, 5710–5719.

Freudenheim, J. L., Graham, S., Horvath, P. J., Marshall, J. R., Haughey, B. P., and Wilkinson, G. (1990). Risk associated with source of fiber and fiber components in cancer of the colon and rectum. *Cancer Res.* **50**, 3295–3300.

Freudenheim, J. L., Marshall, J. R., Graham, S., Laughlin, R. Vena, J. E., Swanson, M., Ambrosone, C., and Nemoto, T. (1995). Lifetime alcohol consumption and risk of breast cancer. *Nutr. Cancer* **23**, 1–11.

Friedenreich, C. M., and Rohan, T. E. (1995). A review of physical activity and breast cancer. *Epidemiology* **6**, 311–317.

Fuchs, C. S., Giovannucci, E. L., Colditz, G. A., Hunter, D. J., Stampfer, M. J., Rosner, B., Speizer, F. E., and Willett, W. C. (1999). Dietary fiber and the risk of colorectal cancer and adenoma in women. *N. Engl. J. Med.* **340**, 169–176.

Furihata, C., Oka, M., Amin, S., Krzeminiski, J., Weisburger, J. H., Kobayashi, K., and Tatematsu, M. (1996). Effect of 2-chloro-4-methylthiobutanoic acid in a rapid bioassay for gastric carcinogens. *Cancer Lett.* **108**, 129–135.

Gallaher, D. D., Stallings, W. H., Blessing, L. L., Busta, F. F., and Brady, L. J. (1996). Probiotics, cecal microflora, and aberrant crypts in the rat colon. *J. Nutr.* **126**, 1362–1371.

Gann, P. H., Ma, J., Giovannucci, E., Willet, T., Sacks, F. M., Hennekens, C. H., and Stampfer, M. J. (1999). Lower prostate cancer risk in men with elevated plasma lycopene levels: Results of a prospective analysis. *Cancer Res.* **59,** 1225–1230.

Garewal, H. (1995). Antioxidants in oral cancer prevention. *Am J. Clin. Nutr.* **62**:1410–1416S.

Garland, C., Shekelle, R. B., Barrett-Connor, E., Criqui, M. H., Rossof, A. H., and Ogelsby, P. (1985). Dietary vitamin D and calcium and risk of colorectal cancer: A 19-year prospective study in men. *Lancet* **1**, 307–309.

Gibson, G. R., and Roberfroid, M. B. (1995). Dietary modulation of the human colon microbiota: Introducing the concept of prebiotics. *J. Nutr.* **125**, 1401–1412.

Giovannucci, E. (1999). Tomatoes, tomato-based products, lycopene, and cancer: Review of the epidemiologic literature. *J. Natl. Cancer Inst.* **91** 317–331.

Godley, P. A., Campbell, M. K., Gallagher, P., Martinson, F. E. A., Mohler, J. L., and Sandler, R. S. (1996). Biomarkers of essential fatty acid consumption and risk of prostatic carcinoma. *Cancer Epidemiol., Biomarkers. Prev.* **5**, 889–895.

Gold, E. B., and Goldin, S. B. (1998). Epidemiology of and risk factors for pancreatic cancer. *Surg. Oncol. Clin. North Am.* **7**, 67–91.

Greenberg, E. R., Baron, J. A., Tosteson, T. D., Freeman, D. H., Beck, G. J., Bond, J. H., Colacchio, T. S., Coller, J. A., Frankl, H. D., Haile, R. W., Mandel, J. S., Nierenberg, D. W., Rothestein, R., Snover, D. C., Stevens, M. M., Summers, R. W., and Stolk, R. U. (1994). A clinical trial of antioxidant vitamins to prevent colorectal adenoma. *N. Engl. J. Med.* **331**, 141–147.

Greenwald, P., Kelloff, G., Burch-Whitman, C., and Kramer, B. S. (1995). Chemoprevention. *CA Cancer J. Clin.* **45**, 31–49.

Grundy, S. M. (1996). Dietary fat. In *Present Knowledge in Nutrition* (E. E. Ziegler and L. J. Filer, Jr., Eds.), 7th ed., pp.44–57. ILSI Press, Washington, DC.

Gugler, R., Leschik, M., and Dengler, H. J. (1975). Disposition of quercetin in man after single oral and intravenous doses. *Eur. J. Clin. Pharmacol.* **9**, 229–234.

Hansson, L.-E., Nyrθn, O., Bergstr&primem, R., Wolk, A., Lindgren, A., Baron, J., and Adami, H.-O. (1994). Nutrients and gastric cancer risk: A population-based case-control study in Sweden. *Int. J. Cancer* **57**, 638–644.

Hayes, R. B., Ziegler, R. G., Gridley, G., Swanson, C., Greenberg, R. S., Swanson, G. M., Schoenberg, J. B., Silverman, D. T., Brown, L. M., Pottern, L. M., Liff, J., Schwartz, A. G., Fraumeni, J. F., Jr., and Hoover, R. N. (1999). Dietary factors and risk for prostate cancer among blacks and whites in the United States. *Cancer Epidemiol. Biomarkers Prev.* **8**, 25–34.

Hill, M. J. Cereals, cereal fiber, and colorectal cancer risk: A review of the epidemiological literature. (1998). *Eur.J. Cancer Prev.* **7**, S5–10.

Hoffman, E. L. (1937). *Cancer and Diet.* Williams and Wilkins, Baltimore, MD.

Holmberg, L., Baron, J.A., Byers, T., Wolk, A., Ohlander, E-M., Zack, M. And Adami, H-O. (1995). Alcohol intake and breast cancer risk: Effect of exposure from 15 years of age. *Cancer Epidemiol. Biomarkers Prev.* **4**, 843–847.

Howe, G. R. (1994). Dietary fat and breast cancer risks: An epidemiologic perspective. *Cancer* **74**(suppl.), 1078–1084.

Howe, G. R., and Burch, J. D. (1996). Nutrition and pancreatic cancer. *Cancer Causes Control* **7**, 69–82.

Howe, G. R. Hirohata, T., Hislop, T. G., Iscovich, J. M., Yuan, J.-M., Katsouyanni, K., Lubin, F., Marubini, E., Modan, B., Rohan, T., *et al.* (1990). Dietary factors and risk of breast cancer: Combined analysis of 12 case-control studies. *J. Natl. Cancer Inst.* **82**, 561–569.

Howe, G. R., Benito, E., Castelleto, R., Cornθe, J., EstΠve, J., Gallagher, R. P., Iscovich, J. M., Deng-ao, J., Kaaks, R., Kune, G.A., Kune, S., L=Abbθ, K. A., Lee, H. P., Lee, M., Miller, A. B., Peters, R. K., Potter, J. D., Riboli, E., Slattery, M. L., Trichopoulos, D., Tuyns, A., Tzonou, A., Whittemore, A. S., Wu-Williams, A. H., and Shu, Z. (1992). Dietary intake of fiber and decreased risk of cancers of the colon and rectum: Evidence from the combined analysis of 13 case-control studies. *J. Natl. Cancer Inst.* **84**, 1887–1896.

Howson, C. P., Hiyama, T., and Wynder, E. L. (1986). The decline in gastric cancer: Epidemiology of an unplanned triumph. *Epidemiol. Rev.* **8**, 1–27.

Hwang, H., Dwyer, J., and Russell, R. M. (1994). Diet, helicobacter pylori infection, food preservation, and gastric cancer risk: Are there new roles for preventative factors? *Nutr. Rev.* **52**, 75–83.

International Agency for Research on Cancer (1987). IARC Monographs on the Evaluation of the Carcinogenic Risks to Humans: *Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs*, Vols. 1–42, pp. 83–85, Suppl. 7. IARC, Lyon, France.

International Agency for Research on Cancer (1988). IARC Monographs on the Evaluation of the Carcinogenic Risks to Humans: Alcohol Drinking, Vol. 44. IARC, Lyon, France.

International Agency for Research on Cancer (1991). IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Coffee, Tea, Mate, Merthylxanthines and Methylglyoxal. Vol. 51, pp. 41–206. IARC, Lyon, France.

Jacobs, D. R., Jr., Marquart, L., Slavin, J., and Kushi, L. H. (1998). Whole-grain intake and cancer: An expanded review and meta-analysis. *Nutr. Cancer* **30**, 85–96.

Jones, G. M. (1992). Food additives. In *Food Safety*, pp. 239. Eagan Press, St. Paul, MN.

Johnson, I. T. (1998). Antioxidants and anticarcinogens. *Eur. J. Cancer Prev.* **7**(suppl. 2), S55–62.

Kampman, E., Slattery, M. L., Bigler, J., Leppert, M., Samowitz, W., Caan, B. J., and Potter, J. D. (1999). Meat consumption, genetic susceptibility, and colon cancer risk: A United States multicenter case-control study. *Cancer Epidemiol. Biomarkers Prev.* **8**, 15–24.

Katiyar, S., and Mukhtar, H. (1996). Tea in chemoprevention of cancer: Epidemiologic and experimental studies (Review). *Int. J. Oncol.* **8**, 221–238.

Keenan, K. P., Ballam, G. C., Dixit, R., Soper, K. A., Laroque, P., Mattson, B. A., Adams, S. P., and Coleman, J. B. (1997). The effects of diet, over-feeding, and moderate dietary restriction on Sprague-Dawley rat survival, disease, and toxicology. *J. Nutr.* **127**, 851–856S.

Klurfeld, D. M. (1992). Dietary fiber-mediated mechanisms in carcinogenesis. *Cancer Res.* **52**, 2055–2059s.

Kneller, R. W., Guo, W. D., Hsing, A. W., Chen, J. S., Blot, W. J., Li, J. Y., Forman, D., and Fraumeni, J. F., Jr. (1992). Risk factors for stomach cancer in sixty-five Chinese counties. *Cancer Epidemiol. Biomarkers Prev.* **1**, 113–118.

Krey, G., Braissant, O., L=Horset, F., Kalkhoven, E., Perroud, M., Parker, M. G., and Wahli, W. (1997). Fatty acids, eicosanoids, and hypolipidemic agents identified as ligands of peroxisome proliferator-activated receptors by coactivator-dependent receptor ligand assay. *Mol. Endocrinol.* **11**, 779–791

Kritchevsky, D. (1995). The effect of over-and undernutrition on cancer. *Eur. J. Cancer Prev.* **4**, 445–451.

Kune, G. A., and Vitetta, L. (1992). Alcohol consumption and the etiology of colorectal cancer: A review of the scientific evidence from 1957 to 1991. *Nutr. Cancer* **18**, 97–111.

Kurzer, M. S., and Xu, X. (1997). Dietary phytoestrogens. *Annu. Rev. Nutr.* **17**, 353–381.

Lachance, P., and Langseth, L. (1994). The RDA concept: Time for a change? *Nutr. Rev.* **52**, 266–270.

Landis, S. H, Murray, T., Bolden, S., and Wingo, P. A. (1998). Cancer statistics–1998. *CA Cancer J. Clin.* **48**, 26–29.

La Vecchia, C., Ferraroni, M., Franceschi, S., Mezzetti, M., Decarli, A., and Negri, E. (1997). Fibers and breast cancer risk. *Nutr. Cancer* **28**, 264–269.

Layton, D. W., Bogen, K. T.,Knize, M. G., Hatch, F. T., Johnson, V. M., and Felton, J. (1995). Cancer risk of heterocyclic amines in cooked foods: An analysis and implications for research. *Carcinogenesis* **16**, 39–52.

Le Marchand, L., Kolonel, L. N., Wilkens, L. R., Myers, B. C., and Hirohata, T. (1994). Animal fat consumption and prostate cancer: a prospective study in Hawaii. *Epidemiology* **5**, 276–282.

Le Marchand, L., Wilkens, L. R., Kolonel, L. N., Hankin, J. H., and Lyu, L-C. (1997). Associations of sedentary lifestyle, obesity, smoking, alcohol use, and diabetes with the risk of colorectal cancer. *Cancer Res.* **57**, 4787–4794.

Le Marchand, L. L., Yoshizawa, C. N., Kolonel, L. N., Hankin, J. H., and Goodman, M. T. (1989). Vegetable consumption and lung cancer risk: A population-based case-control study in Hawaii. *J. Nat. Cancer Inst.* **81,** 1158–1164.

Lipkin, M. and Newmark, H. (1995). Calcium and the prevention of colon cancer. *J. Cell. Biochem.* **22**(suppl..) 65–73.

Longnecker, M. P., Paganini-Hill, A., and Ross, R. K. (1995). Lifetime alcohol consumption and breast cancer risk among postmenopausal women in Los Angeles. *Cancer Epidemiol. Biomarkers Prev.* **4**, 721–725.

Lyon, J. L., Slattery, M. L., Mahoney, A. W., and Robison, L. M. (1993). Dietary intake as a risk factor for cancer of the exocrine pancreas. *Cancer Epidemiol. Biomarkers Prev.* **2**, 513–518.

Martinez, M. E., and Willett, W. C. (1998) Calcium, vitamin D, and colorectal cancer: A review of the epidemiologic evidence. *Cancer Epidemiol. Biomarkers Prev.* **7**, 163–168.

Martin-Moreno, J. M., Willett, W. C., Gorgojo, L., Banegas, J. R., Rodriguez-Artalejo, F., Fernandez-Rodriguez, J. C., Maisonneuve, P., and Boyle, P. (1994). Dietary fat, olive oil intake, and breast cancer risk. *Int. J. Cancer* **58**, 774–780.

Masoro, E. J. (1991). Caloric restriction and aging in rats. In *The Potential for Nutritional Modulation of Aging Processes* (D. K. Ingram, G. T. Baker, III, and N. W. Shock, Eds.), pp. 123, Food & Nutrition Press, Trumbull, CN.

McLaughlin, J. K., Gridley, G., Block, G., Winn, D. M., Preston- Martin, S., Schoenberg, J. B., and Messina, M. (1995). Modern applications for an ancient bean: Soybeans and the prevention and treatment of chronic disease. *J. Nutri.* **125**, 567–569S.

Mettlin, C. (1997). Clinical oncology update: Prostate cancer: Recent developments in the epidemiology of prostate cancer. *Eur.. J. Cancer* **33**, 340–347.

Micozzi, M. S., and Moon, T. E. (Eds.) (1992). *Nutrition and Cancer Prevention II: Investigating the Role of Macronutrients.* Marcel Dekker, New York.

Miller, A. B., Berrino, F., Hill, M., Pietinen, P., Riboli, E., and Wahrendorf, J. (1994). Diet in the aetiology of cancer: A review. *Eur. J. Cancer* **30**, 207–220.

Mirvish, S. S. (1994). Experimental evidence for inhibition of N-nitroso compound formation as a factor in the negative correlation between vitamin C consumption and the incidence of certain cancers. *Cancer Res.* **54**, 1948–1951.

National Research Council (1996). *Carcinogens and Anticarcinogens in the Human Diet.* National Academy Press, Washington, DC.

Negri, E., Franceschi, S., Parpinel, M., and La Vecchia, C. (1998). Fiber intake and risk of colorectal cancer. *Cancer Epidemiol. Biomarkers Prev.* **7,** 667–671.

Neugut, A. I., Hayek, M., and Howe, G. (1996). Epidemiology of gastric cancer. *Semin. Oncol.* **23**, 281–291.

Nomura, A. M. Y., and Kolonel, L. N. (1991). Prostate cancer: A current perspective. *Epidemiol. Rev.* **13**, 200–227.

Nomura, A. M. Y., Ziegler, R. G., Stemmermann, G. N., Chyou, P.-H., and Craft, N. E. (1997). Serum mirconutrients and upper aerodigestive tract cancer. *Cancer Epidemiol., Biomarkers, Prev.* **6,** 407–412.

Olson, J. A. (1996). Benefits and liabilities of vitamin A and carotenoids. *J. Nutr.* **126**, 1208–1212S.

Omenn, G. S., Goodman, G. E., Thornquist, M. D., Balmes, J., Cullen, M. R., Glass, A., Keogh, J. P., Meyskens, F. L., Jr., Valanis, B., Williams, J. H., Jr., Barnhart, S., Cherniack, M. G., Brodkin, C. A., and Hammar, S. (1996). Risk factors for lung cancer and for intervention effects in CARET, the Beta-Carotene and Retinol Efficacy Trial. *J. Natl. Cancer Inst.* **88**, 1550–1559.

Pariza, M. W., and Boutwell, R. K. (1987). Historical perspective: Calories and energy expenditure in carcinogenesis. *Am. J. Clin. Nutr.* **45**(suppl. 1), 151–156.

Pool-Zobel, B. L., Bub, A., Liegibel, U. M., Treptow-van Lishaut, S., and Rechkemmer, G. (1998). Mechanisms by which vegetable consumption reduces genetic damage in humans. *Cancer Epidemiol. Biomarkers Prev.* **7**, 891–899.

Potter, J. D. (1996). Nutrition and colon cancer. *Cancer Causes Control* **7**, 127–146.

Potter, J. D., Slattery, M. L., Bostick, R. M., and Gapstur, S. M. (1993). Colon cancer: A review of the epidemiology. *Epidemiol. Rev.* **15**, 499–545.

Reddy, B. S. (1996). Dietary fat and colon cancer: Role in cancer prevention. In *Nutrition and Cancer Prevention* (R. R. Watson and S. I. Mufti, Eds.), pp. 105–118. CRC Press, Boca Raton, FL.

Reddy, B. S., Hamid, R., and Rao, C. V. (1997). Effect of dietary oligofructose and inulin on colonic preneoplastic aberrant crypt foci inhibition. *Carcinogenesis* **18**, 1371–1374.

Reinli, K., and Block, G. (1996). Phytoestrogen content of foods: A compendium of literature values. *Nutr. Cancer* **26**, 123–148.

Rolls, B. J., and Hill, J. O. (1998). *Carbohydrates and Weight Management.* ILSI Press, Washington, DC.

Rose, D. P. (1990). Dietary fiber and breast cancer. *Nutr. Cancer* **13**, 1–8.

Rose, D. P., and Connolly, J. M. (1993). Effects of dietary omega-3 fatty acids on human breast cancer growth and metastases in nude mice. *J. Natl. Cancer Inst.* **85**, 1743–1747.

Rosenberg, L., Metzger, L. S., and Palmer, J. R. (1993). Alcohol consumption and risk of breast cancer: A review of the epidemiologic evidence. *Epidemiol. Rev.* **15**, 133–144.

Sardesai, V. M. (1992). Nutritional role of polyunsaturated fatty acids. *J. Nutr. Biochem.* **3**, 154–165.

Schottenfeld, D. (1995). Epidemiology of endometrial neoplasia. *J. Cell. Biochem.* **23**(suppl.), 151–159.

Seitz, H. K., Simanowski, U. A., Garzon, F. T., Rideout, J. M., Peters, T. J., Koch, A., Berger, M. R., Einecke, H., and Maiwald, M. (1990). Possible role of acetaldehyde in ethanol-related rectal cocarcinogenesis in the rat. *Gastroenterology* **98**, 406–413.

Shils, M. D., Olson, J. A., and Shike, M. (Eds.) (1994). *Modern Nutrition in Health and Disease*, 8th ed. Lea & Febiger, Philadelphia.

Singh, J., Hamid, R., and Reddy, B. S. (1997). Dietary fat and colon cancer: Modulation of cyclooxygenase-2 by types and amount of dietary fat during the post-initiation stage of colon carcinogenesis. *Cancer Res.* **57**, 3465–3470.

Sinha R., Chow, W. H., Kulldorf, M., Denobile, J., Butler, J., Garcia-Closas, M., Weil, R., Hoover, R. N., and Rothman, N. (1999). Well-done, grilled red meat increases the risk of colorectal adenomas. *Cancer Res.* **59,** 4320–4324.

Sokol, R. J. (1996). Vitamin E. In *Present Knowledge in Nutrition*, 7th ed. (E. E. Ziegler and L. J. Filer, Jr., Eds.), pp. 130–136. ILSI Press, Washington, DC.

Soler, M., Chatenoud, L., La Vecchia, C., Franceschi, S., and Negri, E. (1998). Diet, alcohol, coffee, and pancreatic cancer: Final results from an Italian study. *Eur. J Cancer Prev.* **7**, 455–460.

Steinmetz, K., and Potter, J. D. (1991). Vegetables, fruit, and cancer: I. Epidemiology. *Cancer Causes Control* **2**, 325–357.

Sugimura, T. (1996). An overview of cancer prevention. *Eur. J. Cancer Prev.* **5**(suppl. 2), 1–8.

Swanson, C. A., Brown, C. C., Brownson, R. C., Alavanja, M. C. (1997). Re: Saturated fat intake and lung cancer among nonsmoking women in Missouri. *J. Natl. Cancer Inst.* **89,** 1724–1725.

Takahashi, M., Kokubo, T., Furukawa, F., Kurokawa, Y., Tatematsu, M., and Hayashi, Y. (1983). Effect of high salt diet on rat gastric carcinogenesis induced by N-methyl-N′-nitro-N-nitrosoguanidine. *Gann* **74**, 28–34.

Takezaki, T., Hirose, K., Inoue, M., Hamajima, N., Kuroishi, T., Nakamura, S., Koshikawa, T., Matsuura, H., and Tajima, K. (1996). Tobacco, alcohol, and dietary factors associated with the risk of oral cancer among Japanese. *Jpn. J. Cancer Res.* **87**, 555–562.

Tannenbaum, A. (1942). The genesis and growth of tumors. II Effects of caloric restriction per se. Cancer Res. 1942;2:460–7.

Tannenbaum, A. (1959). Nutrition and cancer. In *Physiopathology of Cancer* (F. Homburger, Ed.), pp. 517–562. Phiebig, White Plains, NY.

Toma, S., Losardo, P. L., Vincent, M., and Palumbo, R. (1995). Effectiveness of β-carotene in cancer chemoprevention. *Eur. J. Cancer Prev.* **4**, 213–224.

Tominaga, S., and Kuroishi, T. (1997). An ecological study on diet/nutrition and cancer in Japan. *Int. J. Cancer* **10**(suppl.), 2–6.

Trichopoulos, D., Ouranos, D., Day, N. E., Tzonou, A., Manusos, O., Papadimitriou, C., and Trichopoulos, A. (1985). Diet and cancer of the stomach: A case-control study in Greece. *Int. J. Cancer* **36**, 291–297.

Trichopoulou, A., Katsouyanni, K., Stuver, S., Tzala, L., Gnardellis, C., Rimm, E., and Trichopoulos, D. (1995). Consumption of olive oil and specific food groups in relation to breast cancer risk in Greece. *J. Nat. Cancer Inst.* **87**, 110–116.

Trowell, H. (1974). Definitions of fibre. *Lancet* **1**, 503.

Vainio, H., and Rautalahti, M. (1998). An international evaluation of the cancer preventive potential of carotenoids. *Cancer Epidemiol. Biomarkers Prev.* **7**, 725–728.

Vainio, H., and Rautalahti, M. (1999). An international evaluation of the cancer preventive potential of vitamin A. *Cancer Epidemiol., Biomarkers, Prev.* **8**, 107–109.

van Poppel, G. and Goldbohm, R. A. (1995). Epidemiologic evidence for &exists;-carotene and cancer prevention. *Am. J. Clin. Nutr.* **62**, 1393–1402S.

Wattenberg, L. W. (1992). Inhibition of carcinogenesis by minor dietary constituents. *Cancer Res.* **52**(suppl.), 2085–2091s.

Weber, P., Bendich, A., and Schalch, W. (1996). Vitamin C and human health: A review of recent data relevant to human requirements. *Int. J. Vitam. Nutr. Res.* **66**,19–30.

Weisburger, J. H. (1997a). Dietary fat and risk of chronic disease: Mechanistic insights from experimental studies. *J. Am. Diet Assoc.* **97**(suppl.), S16–22.

Weisburger, J. H. (1997b). Tea and health: A historical perspective. *Cancer Lett.* **114**, 315–317.

Weisburger, J. H. (1998a). Chemoprevention of cancer by tea. In *Cancer and Nutrition* (K. N. Prasad and W.C. Cole, Eds.), pp. 167–171. IOS Press, Amsterdam.

Weisburger, J. H. (1998b). Can cancer risks be altered by changing nutritional traditions? *Cancer* **83**, 1278–1281.

Weisburger, J. H. (Ed.) (1998c). International symposium on lycopene and tomato products in disease prevention: An introduction. *Proc. Soc. Exp. Biol. Med.* **218**, 93–94.

Weisburger, J. H., Dolan, L., Pittman, B. (1998) Inhibition of PhIP mutagenicity by caffeine, lycopene, daidzein, and genistein. *Mutat. Res.* **416**, 125–128.

Weisburger, J. H., and Williams, G. M. (1995). Causes of cancer. In *American Cancer Society Textbook of Clinical Oncology* (G. P. Murphy, W. Lawrence, Jr., and R. E. Lenhard, Jr., Eds.), pp. 10–39. American Cancer Society, Atlanta, GA.

Welsch, C. W. (1992). Relationship between dietary fat and experimental mammary tumorigenesis: A review and critique. *Cancer Res.* **52**(suppl. 7), 2040–2048s.

White, E., Shannon, J. S., and Patterson, R. E. (1997). Relationship between vitamin and calcium supplement use and colon cancer. *Cancer Epidemiol. Biomarkers and Prev.* **6**, 769–774.

Whitney, E. N., and Hamilton, E. M. N. (1981). *Understanding Nutrition*, 2nd ed. West Publishing, St. Paul, MN.

Whysner, J., and Williams, G. M. (1996). Saccharin mechanistic data and risk assessment: Urine composition, enhanced cell proliferation, and tumor promotion. *Pharmacol. Ther.* **71**, 225–251.

Willett, W. C. (1994). Diet and health: What should we eat? *Science* **264**, 532–537.

Willett, W. C., and Hunter, D. J. (1994). Vitamin A and cancers of the breast, large bowel, and prostate: Epidemiologic evidence. *Nutr. Rev.* **52**, S53–59.

Williams, C. L. (1995a). A summary of conference recommendations on dietary fiber in childhood. *Pediatrics* **96**, 1023–1028.

Williams, C. L. (1995b). Importance of dietary fiber in childhood. *J. Am. Diet. Assoc.* **95**, 1140–1146.

Williams, C. L. (1996). Nutrition in childhood: A key component of primary cancer prevention. In *Nutrition and Cancer Prevention* (R. R.Watson and S. I. Mufti, Eds.), pp. 25–50. CRC Press, Boca Raton, FL.

Williams, C. L., and Bollella, M.(1995). Is a high fiber diet safe for children? *Pediatrics* **96**, 1014–1019.

Williams, C. L., Bollella, M., and Williams, G. M. (1993). Cancer prevention beginning in childhood. In *Cancer Prevention* (V. T. DeVita, Jr., S. Hollman, and S. A. Rosenberg, Eds.), pp. 1–13. J. B. Lippincott Co., Philadelphia, PA.

Williams, C. L., Bollella, M., and Wynder, E. (1995). A new recommendation for dietary fiber in childhood. *Pediatrics* **96**, 985–988.

Williams, G. M. (1993a). Food: its role in the etiology of cancer. In *Food and Cancer Prevention: Chemical and Biological Aspects* (K. W. Waldron, I. T. Johnsen, and G. R. Genwick, Eds.), pp. 3–11. The Royal Society of Chemistry, Cambridge, U.K.

Williams, G. M. (1993b). Inhibition of chemical-induced experimental cancer by synthetic phenolic antioxidants. In *Antioxidants: Chemical Physiological, Nutritional and Toxicological Aspects* (G. M. Williams, H. Sies, G. T. Baker III, C. J. H. Erdman, Jr., Eds.), pp. 303–308. Princeton Scientific Press, Princeton, NJ.

Williams, G. M. (1994). Interventive prophylaxis of liver cancer. *Eur. J. Cancer Prev.* **3**, 89–99.

Williams, G. M., and Weisburger, J. H. (1991). Chemical carcinogenesis. In *Casarett and Doull's Toxicology: The Basic Sciences of Poisons,* 4th ed. (M. O. Amdur, J. Doull, and C. D. Klaassen, Eds.), pp. 127–200. Pergamon Press, New York.

Williams, G. M., and Wynder, E. L. (1996). Diet and cancer: A synopsis of causes and prevention strategies. In *Nutrition and Cancer Prevention* (R. R. Watson, and S. I. Mufti, Eds.), pp. 1–12. CRC Press, Boca Raton, FL.

Williams, W. R. (1908). *The Natural History of Cancer.* William Wood, New York.

Williamson, G., Faulkner, K., and Plumb, G. W. (1998). Glucosinolates and phenolics as antioxidants from plants foods. *Eur. J. Cancer Prev.* **7**, 17–21.

Wolk, A., Gridley, G., Niwa, S., Lindblad, P., McCredie, M., Mellemgaard, A., Mandel, J. S., Wahrendorf, J., McLaughlin, J. K., and Adami, H.-O. (1996). International renal cell cancer study: VII. Role of diet. *Int. J. Cancer* **65**, 67–73.

World Cancer Research Fund (1997). *Food, Nutrition and the Prevention of Cancer: A Global Perspective.* American Institute for Cancer Research, Washington, DC.

Wu, A., Pike, P. C., and Stram, D. O. (1999). Meta-analysis: Dietary fat intake, serum estrogen levels, and the risk of breast cancer. *J. Natl. Cancer Inst.*, **91,** 524–534.

Wynder, E. L., Weisburger, J. H., and Ng, S. K. (1992). Nutrition: The need to define "optimal" intake as a basis for public policy decisions. *Am. J. Public Health* **82**, 346–350.

Wynder, E. L., and Williams, G. M. (1993). Metabolic overload and carcinogenesis from the viewpoint of epidemiology. In *Chemical Carcinogenesis: The Relevance of Mechanistic Understanding in Toxicological Evaluations* (A. Somogyi, K. E. Appel, and A. Katenkamp, Eds.), pp. 17–24. MMV Medizin Verlag GmbH, Mηnchen.

Yang, C. S., and Wang, Z.-Y. (1993). Tea and cancer. *J. Natl. Cancer Inst.* **85**, 1038–1049.

Zhang, S., Hunter, D. J., Forman, M. R., Rosner, B. A., Speizer, F. E., Colditz, G. A., Manson, J. E., Hankinson, S. E., and Willett, W. C. (1999). Dietary Carotenoids and Vitamins A, C, and E and risk of breast cancer. *J. Natl. Cancer Inst.* **91,** 547–556.

Zumbé, A. (1998). Polyphenols in cocoa: are there health benefits? *BNF Nutr. Bull.* **23**, 94–102