Table 4-8 (continued)

First Author/ Year	Location	Comments
Breast (continued)		
Kelsey 1981	U.S.	Increased risk with BW in postmenopausal women. Decreased risk in premenopausal women.
Brisson 1984	U.S.	Increased risk with BW in pre- and postmenopausal women; inverse association with height.
Kidney		
Wynder 1974	U.S.	Greater proportion cases with RBW > 125% in females only.
McLaughlin 1984	U.S.	Increased risk with BMI in females. Positive association for weight gain since age 20 in females.
Maclure 1985 (abstr)	U.S.	Increased risk with BMI in men and women.
Goodman 1986	U.S.	Increased risk with BMI in men and women.
Asal 1985 (abstr)	U.S.	Increased risk with BMI in men and women.
Yu 1986	U.S.	Increased risk with BMI in men and women independent of tobacco and other risk factors.
Endometrium		
Kelsey 1982	U.S.	Increased risk with BW and similar trend for BMI (not presented by authors).
Henderson 1983	U.S.	Increased risk with BW and similar trends for BMI and BW at age 20.
La Vecchia 1984	Italy	Increased risk with BMI greater for premenopausal than for postmenopausal women.

Table 4-8 (continued)

First Author/ Year	Location	Comments
Prostate		
Wynder 1971	U.S.	No significant difference in RBW between cases and controls with no significant difference in height.
Colorectal		
Wynder 1969	Japan	No significant difference in RBW between cases and controls.
Thyroid		
McTiernan 1985 (abstr)	U.S.	Increased risk with BW in > = 60 vs. < = 52 kg. Only women studied.
Meningioma		
Bellur 1983	U.S.	Increased risk for "obese" women. No significant difference among men.

Key: BW = body weight.
BMI = body mass index.
RBW = relative body weight.
P values for test for trend, unless otherwise indicated.

Source: Adapted from Albanes 1987.

smokers but have a lower cancer risk) showed a relationship between relative body weight and cancer death that was nearly linear (Lew and Garfinkel 1979). In the United States, individuals greater than 40 percent overweight have mortality ratios (observed cancer deaths divided by expected cancer deaths) higher than average-weight individuals by 33 percent for men and 55 percent for women (Garfinkel 1985). In men, this relationship was statistically significant for cancer of the colon, rectum, and prostate, and in women, for cancer of the breast, uterus (cervix and endometrium), ovary, and gallbladder.

Animal Studies

Restriction of caloric intake reduces the incidence of many different cancers and increases the lifespan of laboratory animals (Tannenbaum 1940a; Kritchevsky and Klurfeld 1987). Some of these suggest that the greatest reduction in cancer incidence is associated with lifelong restriction of

calories, but caloric restriction begun in adulthood may also have a protective effect (Weindruch and Walford 1982).

Total caloric intake as well as calories derived from fat affect cancer risk, but their relative importance may vary for different tumor types (Kritchevsky, Weber, and Klurfeld 1984). One study that has attempted to separate the effects of calories from those of fat suggested that tumor incidence in rats depends on energy intake, energy retention, and body size rather than on percent of fat calories in the diet (Boissonneault, Elson, and Pariza 1986).

Biochemical Mechanisms

While no unifying principle to explain the relationship has emerged, current investigations in animals support the idea that overnutrition increases cancer risk (Pariza and Boutwell 1987). One hypothesis is that chemical carcinogens may be stored in body fat for mobilization and transport to target tissues. A second hypothesis is that the supply of available energy is one factor that controls cell growth (Pardee et al. 1978; Scott, Wille, and Wier 1984), and an excess of available energy may increase cell multiplication and affect the promotion phase of carcinogenesis. Excess energy could also shorten the latent period. A third hypothesis involves the influences of female hormones on breast, ovarian, and uterine cancers, with metabolism of hormones in adipose tissue possibly playing a role in tumor formation and growth. Androstenedione from the adrenal gland can be converted to estrogen in adipose tissue and may stimulate cell division in the target organs of obese individuals (Siiteri 1987). Thus, although animal studies suggest that caloric restriction might reduce cancer incidence, the results of human studies are not wholly consistent (see Table 4-8). To resolve these inconsistencies, additional studies are needed to separate the individual effects of calories, fat, and obesity (Willett 1987).

Role of Dietary Fiber in Cancer

Dietary fiber includes components of plant materials that, when eaten, resist the action of human digestive enzymes. Dietary fiber has diverse chemical constituents, including carbohydrate and carbohydrate-like cellulose, hemicelluloses, lignin, gums, and pectins. Major food sources of fiber are fruits, vegetables, and whole grain cereals.

In some studies, particularly correlation studies, consumption of high-fiber foods has been correlated with lower risk of colon cancer. An important

issue in human studies is the lack of information about the specific components of dietary fiber and how they may affect cancer risk. Although rodent studies have provided conflicting results, they do suggest that the type of fiber is important. In those studies that showed a protective effect, wheat bran, a source of water-insoluble fiber, was more consistently associated with lower risk of colon cancer than other fiber sources (Pilch 1987).

Human Epidemiologic Studies

The results from 44 epidemiologic studies conducted between 1973 and 1987 are summarized in Table 4-9. Numerous correlation studies have suggested a protective effect of dietary fiber against colon cancer (Burkitt 1980; Reddy 1982; Greenwald, Lanza, and Eddy 1987). Of the 24 correlation studies, 21 identified an inverse association of dietary fiber, fiber-rich diets, or other measures of fiber consumption with occurrence of colon cancer; 3 showed no association; and none reported a positive association. One international study that found an inverse association with total dietary fiber also found a protective effect of cereal fiber, even after adjustment for intake of fat or meat (McKeown-Eyssen and Bright-See 1985).

In some studies, correlations with other nutrients were also observed. Thus, while patterns of eating foods high in fiber show good correlation with low colon cancer rates, other dietary components might also be influencing this association. It must also be noted that international correlation studies (seven studies) tend to derive their food data from similar sources.

Several epidemiologic studies that include biochemical markers have correlated cancer rates to measures of stool weights, fecal bile acids, enzymes from colonic bacteria, and fecal mutagens. Comparison of rural Finns (who have low rates of colon cancer) to their urban counterparts shows that intake of calories and fat is similar for both groups, but the rural Finns have a higher intake of dietary fiber, a greater stool weight, and a lower level of fecal bile acids than urban Finns (Englyst et al. 1982; Cummings and Branch 1982; Jensen, MacLennan, and Wahrendorf 1982; Bingham et al. 1982).

The importance of these observations derives in part from the fact that secondary bile acids, formed by bacterial degradation of primary bile acids in the intestine, have been shown to promote tumors in animals (Wynder and Reddy 1983), may be mutagenic (Wilpart et al. 1983), and are directly correlated with population incidence of colon cancer (Hill 1983). Fecal mutagens are also correlated with the incidence of colon cancer in popula-

Table 4-9
Summary of Epidemiologic Studies Examining Dietary Fiber and Colon Cancer

Authors	Year	Fiber	Cereals	Vege-tables	High Fiber/ Low Fat
International Correlation Studies					
Drasar & Irving	1973	0			
Irving & Drasar	1973		−(a)		
Armstrong & Doll	1975		−(a)		
Howell	1975		−	−	
Knox	1977		−	−	
Liu et al.	1979	−(a)			
McKeown-Eyssen & Bright-See	1985	−			
Within-Country Correlation Studies					
Malhotra	1977	−(b)			
Lyon & Sorenson	1978	0			
Enstrom	1980			−(b)	
Rozen et al.	1981	−			
Maisto & Bremner	1981	−(b)			
Jensen	1983	−(b)		−	
Bingham et al.	1985	−			
Metabolic Correlation Studies					
MacLennan et al.	1978	−	−		
Reddy et al.	1978		−		
Reddy et al.	1980	−			
Jensen et al.	1982	−	−		
Reddy et al.	1983	−			
Nair et al.	1984	−			
Walker et al.	1986	0			
Time Trend Correlation Studies					
McMichael et al.	1979	−(b)			
Helms et al.	1982	−			
Powles & Williams	1984	−	−(a)		

Table 4-9 (continued)

Authors	Year	Fiber	Cereals	Vege-tables	High Fiber/ Low Fat
Case-Control Studies					
Haenszel et al.	1973			+	
Bjelke	1974a			−	
Bjelke	1974b			−	
Phillips	1975			−(b)	
Modan et al.	1975	−			
Graham et al.	1978			−	
Dales et al.	1978				−
Moskowitz et al.	1979	0			
Haenszel et al.	1980			−	
Hunter et al.	1980	−(b)			
Jain et al.	1980	0			
Martinez et al.	1981	+	+		
Manousos et al.	1983			−	
Pickle et al.	1984	0			
Potter & McMichael	1986	+(a)	+(a)		
Tuyns	1986			−	
Macquart-Moulin	1986	−(a)		−	
Lyon et al.	1987	−(b)			
Kune et al.	1987	−		−	
Cohort Studies					
Hirayama	1981			−	

Key: 0 = No association.
− = Inverse association (decreased risk).
+ = Direct association (increased risk).
(a) = Adjustment for other food components removes the association.
(b) = No test for significance or not statistically significant.

tions (Wilkins and Van Tassell 1983), although no such correlations have been observed for individuals (Correa 1981). Recently, fecal mutagens have been shown to be modulated by dietary fiber (Reddy et al. 1987). In addition, fermentation of fiber in the colon by intestinal bacteria results in the release of short-chain fatty acids, which may directly influence colonic mucosal cells (Reddy 1982). Further research is needed to elucidate the role of fecal mutagens in colon cancer and the influence of various dietary fibers (Pilch 1987).

Additional support for generating the fiber/cancer hypothesis comes from time-trend correlation studies. Long-term trends in colon cancer for several population groups also offer insights into the role of dietary fiber. In

Denmark, the decrease in dietary fiber consumption from 1927 to 1977 has been correlated to the rise in prevalence of colon cancer (Helms et al. 1982). In seven other countries, changes in flour milling practices during World War II led to increased consumption of total fiber, which correlated with a reduced mortality of colon cancer in those countries 15 years later (Powles and Williams 1984). Other wartime lifestyle changes, such as decreased fat or meat consumption, however, could have also influenced mortality.

To date, 19 case-control studies have assessed the role of fiber-containing foods in colon cancer: 3 of these studies found no effect (Moskowitz et al. 1979; Jain et al. 1980; Pickle et al. 1984), 3 found an increased risk (Haenszel et al. 1973; Martinez et al. 1981; Potter and McMichael 1986), and 13 observed a protective effect of fiber-containing foods, especially vegetables. Protective effects have been found in two case-control studies that examined the relative risk for a high-fat, low-fiber diet (Dales et al. 1978; Manousos et al. 1983). Overall, case-control studies present mixed results. Some show fiber and fiber-containing foods to be protective; others do not.

Animal Studies

Animal studies of dietary fiber and colon cancer have provided inconsistent results due to a number of factors, including differences in the nature of the carcinogen used, variations in composition of the diet, qualitative and quantitative differences in the fibers fed, animal strain, or duration of the experiment (Reddy 1986; Pilch 1987). In the past decade, a number of studies have been conducted on laboratory rats fed diets of various fiber sources and levels and exposed to certain known colonic carcinogens: DMH, AOM, DMAB, and methylnitrosurea (MNU). When wheat bran was used as the source of dietary fiber, a protective effect was seen in the majority (Reddy 1982; Barbolt and Abraham 1978) but not all studies (Bauer et al. 1979; Jacobs 1983). A protective effect against colon cancer was found in studies of chemical carcinogens requiring microsomal activation (DMH, AOM, DMAB) but not in one study with MNU, a direct-acting carcinogen. Other studies reported were less suggestive of protection. Although two-thirds of studies showed that dietary cellulose was protective for rats exposed to DMH and AOM, no effect was observed for the rest. Studies of the effect of corn bran, rice bran, oat bran, pectin, and guar gum must be considered indeterminant, with some showing a protective effect, more showing an enhancing effect, and others showing no effect (Pilch 1987). The relevance of these animal models to human cancer needs to be determined.

Biochemical Mechanisms

The means by which fiber may exert its protective action are not understood. Several possibilities have been advanced: Fiber may act to reduce transit time in the bowel and therefore decrease the time for exposure to potential carcinogens; through its hydrophilic nature, it can dilute the concentration of carcinogens in the colon; it can affect the production of bile acids and other potential carcinogens in the stool; it can alter the nature of fecal bile acids by virtue of its influence on the composition and metabolic activity of fecal flora; and it can reduce colonic pH by increasing fermentation and short-chain fatty acid production (NRC 1982; Eastwood, McKay, and Brydon 1986).

Limited information is available on the types of dietary fiber that might protect against cancer. Research will have to define the importance of various fiber compounds relative to the risk for specific cancers. The term fiber embraces a broad range of food components whose primary commonality is their relative indigestibility. Different types of fiber have very different qualities. Some are classified as soluble, others insoluble. Some, but not all, appear to affect gastric emptying. Some affect absorption of certain nutrients, others do not. Animal studies suggest that different types of fiber work differently with respect to the occurrence of colon cancer. As noted earlier, wheat bran, which decreases gastrointestinal transit time and increases stool weight, appears to more consistently reduce the frequency of colon tumors in animals than other types of fiber (Pilch 1987). However, until better methods for analyzing the fiber content of foods are developed, the influence of fiber components such as pentosan fractions (Bingham et al. 1979), uronic acids (pectins), or cellulose (Bingham, Williams, and Cummings 1985) must be considered uncertain.

In humans, a sudden change from a low-fiber to a high-fiber diet may provoke symptoms of gastrointestinal distress, although effects are not generally seen with gradual increases. The most frequently suggested adverse effect of high fiber intake is mineral imbalance. While the evidence is mixed, a recent review suggested that consumption of diets containing about 20 to 25 g of insoluble fiber from foods per day does not appear to pose a problem relative to mineral availability (Pilch 1987). This amount translates to approximately 30 to 35 g of total dietary fiber from a mixed adult diet and is consistent with current recommendations of the National Cancer Institute (20 to 30 g daily from a variety of food sources, including vegetables, fruits, and whole grain cereals).

Role of Vitamin A and Carotenoids in Cancer

A large body of evidence suggests that foods high in vitamin A and carotenoids are protective against a variety of epithelial cancers (Mettlin 1984; Kummet, Moon, and Meyskens 1983; Bertram, Kolonel, and Meyskens 1987; Palgi 1984).

Vitamin A in foods occurs in two forms: (1) preformed vitamin A (retinol and retinol esters) from animal foods and (2) provitamin A (carotenoids that the body can convert to vitamin A) from plant foods. Hundreds of other carotenoid compounds in fruits and vegetables seem to have no vitamin A activity. Beta-carotene-containing foods have been extensively studied in cancer epidemiology (Peto et al. 1981). Although beta-carotene is most efficiently converted (Linder 1985), it still has only one-sixth the biologic activity of retinol. Many reports on the effects of vitamin A do not specify whether they are studying preformed vitamin A, carotenoids in general, retinoid analogs of vitamin A, or beta-carotene alone (NRC 1982). This chapter uses the term vitamin A to include all of the above unless otherwise specified.

Epidemiologic studies have used food intake records to analyze the intake of beta-carotene, carotenoids, and retinol, or a "vitamin A index" that combines these. A methodological difficulty is that foods such as green and orange-yellow vegetables may contain protective factors in addition to carotenoids (Mettlin 1984). Other complications are presented because inverse correlations between blood levels of beta-carotene and retinol and risk for cancer have been identified in some but not all studies (Willett and MacMahon 1984a). Future studies that better distinguish the individual effects of beta-carotene, carotenoids, retinol, and other food components will require improved dietary assessment methods (Russell-Briefel, Caggiula, and Kuller 1985).

Human Epidemiologic Studies

Low levels of vitamin A (or retinol) in blood have been associated with an increased risk for cancer in some (Wald, Idle, and Boreham 1980; Kark et al. 1981) but not all (Wald et al. 1984; Willett et al. 1984; Nomura et al. 1985; Salonen et al. 1985) studies. Low levels of beta-carotene in stored blood also have been associated with an increased risk for cancer in some (Nomura et al. 1985; Stahelin et al. 1984) but not all (Willett et al. 1984; Menkes and Comstock 1984) studies. There are problems, however, in relating blood levels to cancer risk. Blood retinol remains unchanged across a wide range of dietary intakes because of homeostatic mechanisms.

Thus, increased vitamin A is unlikely to result in increased serum retinol, except during vitamin A depletion. Consequently, the association between serum retinol and cancer may be due to factors that regulate serum retinol rather than to dietary vitamin A itself. In contrast, serum carotenoids may better reflect dietary carotenoids, and the relationship between dietary carotenoids (or the foods that contain them) and cancer may be more direct than that between serum retinol and cancer. A major weakness of these studies is that blood levels of vitamin A or carotenoids observed at the time of diagnosis may be different from those present when the disease began.

One prospective cohort study on the older population in Massachusetts has shown that the risk for all cancers decreases with increasing intake of carotenoid-containing vegetables (Colditz et al. 1985). Foods containing vitamin A may be protective against cancer of the oropharynx (Ibrahim, Jafarey, and Zuberi 1977), larynx (Graham et al. 1981), breast (Graham et al. 1982), stomach (Stehr et al. 1985), cervix (La Vecchia et al. 1984), colon (Modan, Cuckle, and Lubin 1981), and bladder (Mettlin, Graham, and Swanson 1979). Results for cancer of the prostate have been mixed, however, with one study showing a protective effect (Schuman et al. 1982), two studies showing the opposite (Graham et al. 1983; Heshmat et al. 1985), and one showing no effect (Whelan, Walker, and Kelleher 1983).

Lung Cancer. The strongest evidence for the role of vitamin A in prevention of human cancer comes from epidemiologic studies that correlate consumption of carotenoid-containing vegetables or foods with a high vitamin A index to protection against cancer of the lung (Shekelle et al. 1981; Kvale, Bjelke, and Gart 1983). These studies are summarized in Table 4-10. The Western Electric Study of 1,984 middle-aged men, for example, found a protective effect with provitamin A (beta-carotene) but not preformed vitamin A (Shekelle et al. 1981). A case-control study of lung cancer in white males in New Jersey showed a 30 percent greater risk of cancer for men in the lowest quartile of carotenoid intake but no increased risk for a low consumption of retinol or total vitamin A intake (Ziegler et al. 1986). The Western New York Diet Study showed a protective effect for both total vitamin A and vitamin A from fruits and vegetables in men but not in women (Byers et al. 1987).

An important question in each of these studies is whether the protective effects attributed to vitamin A activity, as discussed above, are truly attributable to vitamin A or whether they are due to some other factor that may be present in the foods. For example, epidemiologic studies have shown an inverse association between the consumption of cruciferous vegetables such as cabbage, broccoli, Brussels sprouts, or cauliflower and

Table 4-10
Dietary Vitamin A and Lung Cancer Risk: A Summary of Previous Studies

Reference (location)	No. of Cases: Controls or Cohort Size	Sex	No. of Foods	Nutrient	Nutrient Level	Findings (Approximate % of Study Group)	Relative Risk
Case-Control Studies							
MacLennan et al. 1978 (Singapore)	233:300	Males and females	100	Green, leafy vegetables	Low	(NP)[a]	2.2
					High	(NP)	1.0
Mettlin et al. 1979 (New York)	292:801	Males	33	Vitamin A	Low	(49)	1.7
					Medium	(27)	1.5
					High	(24)	1.0
Gregor et al. 1980 (England)	78:110	Males	10	Vitamin A	Low	(32)	2.5
					Medium	(46)	2.8
					High	(22)	1.0
Hinds et al. 1984 (Hawaii)	364:627	Males and females	85	Carotene	Lowest 1	(25)	1.6
					2	(25)	1.2
					3	(25)	1.1
					Highest 4	(25)	1.0
Ziegler et al. 1986 (New Jersey)	763:900	Males	44	Carotene	Low	(25)	1.3
					Medium	(50)	1.3
					High	(25)	1.0
Samet et al. 1985 (New Mexico)	342:546 (Anglos only)	Males and females	55	Carotene	Low	(33)	1.5
					Medium	(33)	1.5
					High	(33)	1.0

Table 4-10 (continued)

Wu et al. 1985 (Los Angeles)							
Adenocarcinoma	149:149	Females	21	Carotene	Lowest 1	(25)	2.5
					2	(25)	1.3
					3	(25)	0.8
					Highest 4	(25)	1.0
Squamous cell	71:71	Females	21	Carotene	Low	(50)	1.5
					High	(50)	1.0
Byers et al. 1987 (New York)	450:902	Males and females	129	Fat, vits. A, C, E, fiber, protein	Lowest 1	(25)	1.8
					2	(25)	1.8
					3	(25)	1.0
					Highest 4	(25)	1.0 (fruits/vegs.)
Prospective Studies							
Bjelke 1975 (Norway)	8,278	Males	50	Vitamin A	Low	(32)	2.6
					High	(68)	1.0
Hirayama 1979 (Japan)	265,118	Males and females	1	Green-yellow vegetables	Low[b]	(NP)	1.8
					High[b]	(NP)	1.0
Shekelle et al. 1981 (Chicago)	3,102	Males	26	Carotene	Lowest 1	(25)	7.2
					2	(25)	5.5
					3	(25)	3.0
					Highest 4	(25)	1.0
Kvale et al. 1983 (Norway)	16,713	Males and females	50	Vitamin A	Low	(35)	1.4
					Medium	(29)	1.2
					High	(36)	1.0

[a]NP = Not presented.
[b]For Hirayama, low = not daily; high = daily.

Source: Byers, T.E.; Graham, S.; Haughey, B.P.; Marshall, J.R.; and Swanson, M.K. 1987. Diet and lung cancer risk: findings from the Western New York Diet Study. *American Journal of Epidemiology* 125:351–63. Reprinted with permission.

cancers of the alimentary tract (Hirayama 1977; Haenszel et al. 1976) and large bowel (Graham et al. 1978). A study of lung cancer among New Jersey white males showed a protective effect for fruits and vegetables that was greatest for dark yellow-orange and green vegetables, but no statistically significant effect for retinol, carotenoids, or vitamin A activity (Zeigler et al. 1986). The protective effect could have been due to unmeasured carotenoids, vitamin C, indoles, or other unknown components present in these foods (Wattenberg and Loub 1978; NRC 1982). The lack of association for vitamin A or carotenoids might also be due to problems in calculating vitamin A and carotenoid intake from food composition tables based on dietary records (Beecher and Khachik 1984).

Animal Studies

Vitamin A and synthetic retinoids protect against epithelial cancers of the skin, lung, bladder, and breast in animals (Sporn 1980). High doses suppress induction of cancers of the cervix, vagina, colon, skin, forestomach, tracheobronchi, pancreas, and liver (Welsch, Zile, and Cullum 1986). Retinoids have also been shown to reverse the effects of carcinogens in mouse prostate organ cultures (Lasnitzki and Goodman 1974). Although beta-carotene is protective against skin cancer in animals, it has not received as much attention as vitamin A or retinoids because beta-carotene is poorly absorbed in animals. Synthetic analogs may have greater effects, greater site specificity, and less toxicity than natural vitamin A (Sporn and Roberts 1984).

Biochemical Mechanisms

Because retinoids are required for normal cell differentiation, their deficiency leads to improper differentiation of stem cells in epithelial tissue. In animals, retinoids may inhibit initiation and promotion stages of carcinogenesis (Welsch, Zile, and Cullum 1986). Retinoids may also have a role in reversing cancerous changes, as has been demonstrated in mouse prostate organ cultures (Sporn 1980).

Antioxidant chemicals are thought to protect against certain promoters of carcinogenesis (Ames 1983). Foods containing vitamin A have been shown to protect against the formation of oxygen radicals and lipid peroxidation (Welsch, Zile, and Cullum 1986), and beta-carotene is a very efficient neutralizer of oxygen radicals (Foote 1976). Vitamin A, along with vitamin C, vitamin E, and selenium, may neutralize peroxidation effects and minimize carcinogenesis (Ames 1983), although these hypotheses remain to be confirmed.

Clinical Trials

Recurrence of urinary bladder cancer has been shown to decrease by about half with synthetic retinoid treatment in two clinical trials (Studer et al. 1984; Alftlan et al. 1983). Micronucleus formation, a marker for cellular genetic damage, has been reversed by beta-carotene treatment of people who chew betel nuts and tobacco (Stich et al. 1984). Synthetic retinoid treatment causes regression of bronchial dysplasia (Gouveia et al. 1982). Clinical trials are now in progress to determine the efficacy of retinoids in the prevention and treatment of cervical cancer, malignant melanoma, and other cancers (Meyskens 1982). The National Cancer Institute is funding a number of trials (Table 4-11) to determine the effects of beta-carotene and other antioxidant nutrients on several cancer types. These will produce results in the early 1990's.

Large amounts of retinoids in the blood or tissues, however, can be toxic and may cause birth defects (Kamm 1982) and adverse effects on skin, liver, and neurologic tissue (Olson 1983). Excessive intake of preformed vitamin A or retinoid supplements should be avoided, especially by pregnant women. However, increased intake of carotenoids from foods alone is unlikely to have any adverse effects, other than skin discoloration at very large intakes.

Role of Alcohol in Cancer

Reviews of experimental and epidemiologic data suggest an association between alcohol consumption and human cancer that is strongest for certain head and neck cancers (Tuyns 1982; NRC 1982). Alcohol intake and smoking act synergistically to increase the risk for cancer of the mouth, larynx, and esophagus (Broitman, Vitale, and Gottlieb 1983). Although alcohol has an effect independent of smoking in increasing cancer risk, it remains uncertain whether the responsible agent is alcohol itself or any of the more than 400 congeners (other chemicals) identified in alcoholic beverages (Darby 1982). Consumption of excess alcohol is often accompanied by poor eating habits, but the effects of alcohol and nutrition can be distinguished (see chapter on alcohol), and poor nutritional intake and alcohol intake appear to have separate and multiplicative effects on the risks of esophageal cancer (Ziegler et al. 1981). Chronic alcoholism, particularly in the marginally nourished individual, can deplete various essential nutrients (Vitale, Broitman, and Gottlieb 1981). As discussed in the chapter on infections and immunity, the nutritional deficiencies produced in alcoholics could be associated with impaired immune function, permitting increased carcinogenesis (Watson 1984).

Table 4-11
NCI-Sponsored Prevention Clinical Trials Related to Vitamin A

Investigator/Cancer Site/Agent	Population Under Study
Hennekens/all sites/beta-carotene, aspirin	U.S. male physicians, 40–84 years old. No evidence of cancer, heart disease, or stroke.
Greenberg/skin/beta-carotene	Males and females less than 85 years of age, basal or squamous cell carcinoma within past year.
Luande/skin/beta-carotene	African albinos with epidermal atrophy, dermal hypertrophy, or stage III solar keratoses.
Bowen/colon/beta-carotene	Males and females with prior adenomatous colonic polyp.
Kuller/lung/beta-carotene	Males, 55–70 years old, moderate to heavy cigarette smokers.
Albanes/lung/beta-carotene, alpha-tocopherol	Finnish males, 50–69 years old, cigarette smokers.
Safai/skin/beta-carotene, vitamins C and E	Males and females, 40–80 years old, 2 or more prior basal cell carcinomas.
Greenberg/colon/beta-carotene, vitamins C and E	Males and females, less than 75 years old, prior neoplastic polyp.
Moon/skin/retinol	Males and females, 21–85 years old, more than 10 prior actinic keratoses.
Tangrea, Peck/skin/13-*cis* retinoic acid	Males and females, 40–75 years old, 2 or more prior basal cell carcinomas.
Meyskens/skin/retinol, 13-*cis* retinoic acid	Males and females, 40–85 years old, 8 or more prior basal cell or squamous cell carcinomas.
Taylor/esophagus/beta-carotene	Males and females, 40–69 years old, severe esophageal dysplasia, Linxian, China.
Taylor/esophagus/beta-carotene, multiple vitamins and/or minerals	Males and females, 40–69 years old, general population, Linxian, China.
Omenn/lung/retinol, beta-carotene	Males and females, minimum age 45 years, at least 20 years since first exposure to asbestos, diagnosis of asbestosis.

Table 4-11 (continued)

Investigator/Cancer Site/Agent	Population Under Study
Goodman/lung/retinol, beta-carotene	Males and females, 50–67 years old, smoking history of 20 pack years or greater, current smokers or those who have quit smoking less than 6 years previously.
McLarty/lung/retinol, beta-carotene	Males and postmenopausal females, former asbestos workers verified by the Tyler Asbestos Workers Program, University of Texas Health Center patients with moderate or severe sputum cytology atypia.
Schatzkin/lung/beta-carotene, retinol, vitamin E, selenium	Tin miners active and retired, more than 40 years of age, at least 10 years of underground experience.
Surwit/cervix/*trans*-retinoic acid, retinyl acetate	18–45 years old, moderate or severe cervical dysplasia.

An international comparison shows a correlation between intake of beer and the incidence of colorectal cancer (Vitale, Broitman, and Gottlieb 1981). A strong association between beer intake and rectal cancer and a weak association between wine or whiskey and lung cancer have been found in a prospective cohort study of Japanese men in Hawaii (Pollack et al. 1984). These associations were seen only at high intakes, and no increased risk was observed at moderate intakes. Case-control studies have failed to show a consistent relationship between alcohol and colon or rectal cancers, possibly due to confounding variables, including contaminants in alcoholic beverages. An increased incidence of liver cancer among alcoholic patients appears to be due to increased exposure to hepatitis B virus rather than to alcohol itself (Brechot et al. 1982).

Although it is difficult to determine true levels of alcohol consumption, women with breast cancer are reported to consume more alcohol than controls (Williams and Horm 1977). A slightly greater risk for breast cancer in women has been associated with intake of as few as three alcoholic drinks per week (Schatzkin et al. 1987). Another recent study found increased risk associated with an average of one drink per day in a cohort of 89,538 U.S. women (Willett et al. 1987). Results of other analytical studies are inconsistent.

Although the associations observed between alcohol and oral, esophageal, and laryngeal cancers may be due in part to smoking, appropriate study designs and analyses have demonstrated independent effects of alcohol (Misslbeck and Campbell 1986). If the consumption of alcoholic beverages is reduced, a sizeable decrease in the incidence of cancers of the buccal cavity, pharynx, larynx, and esophagus should be possible (Tuyns 1982).

Role of Other Dietary Constituents in Cancer

Vitamin C

Vitamin C functions as a chemical-reducing agent and antioxidant. It is synthesized in adequate amounts by most animals but not by some primates, fish, guinea pigs, and humans (Linder 1985).

Human studies have shown a protective association between foods that contain vitamin C and cancers of the esophagus (Aoki et al. 1982; Ackerman, Weinstein, and Kaplan 1978), stomach (Graham, Schotz, and Martino 1972; Higginson 1967; Kolonel, Nomura, et al. 1981), and cervix (Wassertheil-Smoller et al. 1981). Small-scale studies have indicated that colonic polyps regress (DeCosse et al. 1975) or decrease in area (Bussey et al. 1982) with vitamin C therapy. Recurrence of colonic polyps after polypectomy was reduced among patients in the treatment group of a study with 200 subjects (McKeown-Eyssen et al. 1987). Supplements of vitamins C and E have been shown to reduce the formation of mutagens in the feces in one study (Dion et al. 1982) but not in another (Wilkins, Lederman, and Van Tassell 1981). While many studies support a role of vitamin C in reducing cancer risk (Block and Menkes 1988), no wholly consistent picture of the role of vitamin C in human cancer has been defined.

Experimental animal studies have found that animals given both precursors of carcinogenic nitrosamines and vitamin C develop fewer tumors than animals given these precursors alone (Mirvish et al. 1976). Vitamin C protects hamster lung cultures from the mutagenic effects of tobacco smoke (Leuchtenberger and Leuchtenberger 1977) and has been shown to reduce bladder tumors induced by one carcinogen (Pipkin et al. 1969) but not by another (Soloway et al. 1975).

Biochemical studies suggest that vitamin C blocks the formation of carcinogenic nitrosamines from nitrates and nitrites within the digestive tract (Weisburger et al. 1980; Mirvish et al. 1975) and prevents oxidation of certain chemicals to active carcinogenic forms (Pipkin et al. 1969).

Because most studies demonstrating a beneficial effect of vitamin C have not quantified its actual intake levels, associations between vitamin C and cancer prevention are subject to the same difficulties as those discussed for vitamin A. Amounts of vitamin C in excess of the Recommended Dietary Allowances (RDA's) may cause rare adverse effects, including gastrointestinal disturbances, iron overload in susceptible individuals, altered metabolism of certain drugs, precipitation of calcium oxalate kidney stones, altered absorption (both positive and negative) of several minerals, and interference with several laboratory tests (Sestili 1983). Despite limitations in data, the American Cancer Society guidelines recommend "foods rich in vitamins A and C" (ACS 1984), and the National Cancer Institute suggests eating a variety of fruits and vegetables, thus ensuring an adequate supply of vitamin C (Butrum, Clifford, and Lanza 1988). There is no adequate evidence that larger amounts of vitamin C provide any additional benefits.

Vitamin E

Studies on vitamin E and the development of cancer are complicated by its instability in stored blood serum, its wide prevalence in the food supply, and its multiple chemical forms. Perhaps because of these problems, there are relatively few studies on the role of vitamin E and cancer, but the role of vitamin E as an antioxidant justifies its further consideration as a potential preventive agent in cancer control (Willett and MacMahon 1984a).

In human studies, no relationship has been found between vitamin E levels and the risk for cancer when incidence rates at all sites are combined in either prospective (Willett et al. 1984; Stahelin et al. 1984) or case-control analyses (Salonen et al. 1985; Nomura et al. 1985). In one case-control analysis of prospective data, serum vitamin E had no statistically significant independent association with cancer mortality, but low vitamin E enhanced an independent risk observed for low serum selenium levels (Salonen et al. 1985). A protective effect of serum vitamin E against cancer of the breast has been found in one (Wald et al. 1984) but not a second (Willett et al. 1984) study. In the positive study, an increased risk was associated only with the lowest 20 percent of serum vitamin E levels. Low vitamin E levels have also been correlated with an increased risk for lung cancer (Menkes and Comstock 1984) and intestinal cancer (Gey, Brubacher, and Stahelin 1987), but a recent study found no such association with ovarian cancer (Heinonen, Koskinen, and Tuimala 1985).

Variable results have also been observed in experimental animal studies. Vitamin E was protective in carcinogen-induced tumor systems (Shamberger and Rudolph 1966; Bonmasser, Dallavalle, and Guiliani 1968) or

when administered as a dietary supplement (Haber and Wissler 1962), but other studies have not observed this effect (Cook and McNamara 1980; Epstein et al. 1967). A recent review states that the animal evidence is inconsistent but suggests a protective effect of vitamin E in carcinogen-induced tumor systems (Newberne and Suphakarn 1983).

Biochemical studies indicate that vitamin E functions as a lipid-soluble antioxidant and free radical scavenger. Thus, the protective role tentatively assigned to both carotenoids and vitamin C may also apply to vitamin E and its derivatives. Vitamin E, like vitamin C, blocks the *in vitro* formation of nitrosamines. The fact that vitamin E is lipid soluble permits this action in a lipid environment, as opposed to the water-soluble vitamin C. Knowledge of carcinogenic mechanisms from experimental and animal studies justifies further exploration of the vitamin E and cancer prevention hypothesis. Some concern has been expressed that reduced fat intake would compromise availability of this fat-soluble vitamin, but it has been estimated that a reduction in fat intake to 20 to 25 percent of daily calories should not result in adverse effects from lowered vitamin E or other fat-soluble vitamin intake (Judd, Kelsay, and Mertz 1983).

Selenium

Selenium is present in animal and plant foods as selenate, selenocystine, selenomethionine, and other yet unidentified forms. A suggested daily dietary intake for selenium has been established by extrapolation from animal studies, but the range of 50 to 200 μg per person (NRC 1980) does not imply greater benefit at the upper limit (Diplock 1987). Well over 90 percent of selenium intake is from cereal grains, fish, meat, and poultry (Lo and Sandi 1980).

The average per capita consumption of dietary selenium in 27 countries was inversely correlated with total cancer mortality as well as deaths from leukemia and cancers of the colon, rectum, breast, ovary, and lung (Schrauzer, White, and Schneider 1977). Inverse correlations between local soil and crop levels of selenium and regional cancer incidence in the United States (Shamberger and Willis 1971) and between the average blood selenium concentration of residents in different regions of the United States and the incidence of cancer of the breast, colon, rectum, and lung in these regions (Schrauzer, White, and Schneider 1977) have been reported. These studies must be interpreted cautiously due to the mobility of both food supply and population.

In several case-control studies, persons with cancer had lower blood selenium levels than controls (Shamberger et al. 1973; McConnell et al. 1980). These studies must also be interpreted cautiously because these low levels of blood selenium may be a consequence of illness rather than its cause (Helzlsouer 1983).

Prospective studies can show whether low serum levels precede cancer. One prospective study showed that risk for cancer was increased in a group with low serum levels of selenium and vitamins A and E (Willett et al. 1983). Two other prospective studies in Finland, where selenium intake is half that of the United States, found an increased risk for cancer at all sites among the population with low serum levels of selenium (Salonen et al. 1984; Salonen et al. 1985). All three of these prospective studies as well as a subsequent case-control study (Kok et al. 1987) support the hypothesis that serum selenium is a risk factor for cancer death in men but not in women. These studies are summarized in Table 4-12.

Selenium inhibits neoplastic transformation in a variety of epithelial organs in animals (Medina 1985). Studies have demonstrated protective effects against cancer of the liver (Daoud and Griffin 1978), breast (Ip 1981), colon (Jacobs, Matney, and Griffin 1977), and skin (Shamberger 1970) from selenite, selenate, or organic selenium. However, the dose giving this protective effect in most experiments is similar to the dose that may be toxic with long-term administration (Helzlsouer 1983).

Selenium is among the most toxic essential elements (Longnecker et al. 1987). Its effects in humans have been mostly limited to occupational hazards (Buell 1973), but toxic effects have been reported among individuals consuming excessive selenium supplements (CDC 1984). Selenium is present in the active site of glutathione peroxidase, an enzyme that helps to prevent perioxidative damage to the cells. Although the molecular basis for the function of selenium as an inhibitor of neoplastic transformation is not understood, its enzymatic role may explain this relationship. The documented toxicity and the narrow range of safe levels of intake of this nutrient suggest that recommendations for increasing dietary intakes are not warranted.

Protein

An association between protein consumption, especially animal protein, and the incidence of certain cancers has been observed in several human epidemiologic studies. However, the association of cancer and protein intake is confounded by a high correlation of protein intake to many other

Findings	Cancer Site	No. of Studies Showing the Association	No. of Studies Not Showing the Association	Specific Nature of the Association
		Correlation Studies		
Inverse relationship between cancer rates and selenium exposure	General	4		Selenium in forage crops
			1	Selenium in forage crops; association a direct one for some sites
		1		Selenium in soil and water
		1		Dietary selenium intake
		2		Blood selenium levels
	Colon-rectum		1	Selenium in water; association a direct one
		Case-Control Studies		
Lower blood selenium levels in cases than in controls	General	1		Gastrointestinal tract cancers and Hodgkin's disease
		2	1	Carcinoma only
	Leukemias & Lymphomas	1		Chronic lymphocytic leukemia only
			3	
	Mouth & Pharynx		1	Plasma selenium increased in cases, but RBC selenium and glutathione peroxidase levels decreased
	Breast	1		
	Skin	1		Both basal and squamous cell types
		Cohort Studies		
Lower prediagnostic serum selenium levels in cases than in noncases	General	3		Association especially evident in males and smokers

Source: Adapted from Bertram, Kolonel, and Meyskens 1987.

nutrients, including fat. Thus, it has not been possible to define an independent effect for protein (Kolonel and Le Marchand 1986; Palmer 1986). In one international correlational study, for example, a positive association was observed between total protein and animal protein and breast, colon, prostate, renal, and endometrial cancers (Armstrong and Doll 1975). Similarly, a migrant study indicated an association between meat consumption and cancer of the breast and colon (Kolonel 1987). In a recent case-control study of breast cancer, the greatest positive association was with a high-protein, high-fat, and low-fiber diet, but when these three dietary components were assessed independently, fat had the strongest association (Lubin, Wax, and Modan 1986). A positive association between protein and colon cancer has been found in another study, but again, the association with fat was stronger (Jain et al. 1980). In an Australian case-control study on large bowel cancer, the highest risk was assigned to a high-protein, high-energy, low-fiber diet (Potter and McMichael 1986). Studies have also found an association between breast cancer and meat intake (Lubin et al. 1981) and an association of meat, especially beef, with large bowel cancer among Japanese (Haenszel et al. 1973), although a subsequent study found a lower risk for all cancers among Japanese who consumed a higher daily intake of meat (Hirayama 1981).

In animal studies, an excessive intake of protein is not consistently associated with an increased incidence of tumors at most sites. When animals were fed *ad libitum* diets with a protein content ranging from 10 to 51 percent of calories, the total incidence of tumors was not affected (Ross and Bras 1973; Tannenbaum and Silverstone 1949), although certain tumors such as bladder papillomas and mammary tumors are enhanced by increased protein intake (NRC 1982). These same studies reported that high-protein diets in early life increased the incidence of tumors (Ross and Bras 1973). Because very low-protein diets have a suboptimal nutritional value, the decreased tumor risk at very low intake is not relevant for guidelines for human diets.

Salt-Pickled, Salt-Cured, and Smoked Foods

Methods of storage and preparation of foods vary widely in different parts of the world, and these differences may contribute to the large international variation in some types of cancer. Smoked and charred foods acquire polycyclic aromatic hydrocarbons (PAH's), some of which are known to be carcinogenic in animals (Chu and Malmgren 1965; Ames 1983). These and other potential carcinogenic agents may be formed within foods during cooking in amounts that may be related to the temperature and duration of cooking at very high temperatures (Lijinsky and Shubik 1964; Lijinsky and Ross 1967; Weisburger, Horn, and Barnes 1983). For example, high temper-

ature grilling and broiling with open flames produces carcinogenic PAH's on the charred surface of foods (Sugimura 1982). Burning amino acids with sugars during cooking results in a variety of mutagenic chemicals, some of which may be carcinogenic (Pourie et al. 1981). Salt-cured and salt-pickled foods contain nitrates and nitrites that can form carcinogenic nitrosamines in the mouth and stomach (Weisburger, Barnes, and Czerniak 1986). Salt-cured and salt-pickled foods have been linked to gastric cancer, possibly because of effects of salt on gastric mucosa (Joossens and Geboers 1985) or conversion of nitrates to carcinogenic nitrosamines (Weisburger, Barnes, and Czerniak 1986). Except for a few instances, however, potential causative agents have not been identified in cured, pickled, or smoked foods (Palmer and Bakshi 1983).

International epidemiologic evidence suggests that populations consuming diets high in salt-cured, salt-pickled, and smoked foods have a higher incidence of stomach and esophageal cancers. Stomach cancer has been linked to pickled vegetables in Japan (Haenszel et al. 1972), salted fish in Norway (Bjelke 1978), and smoked trout and mutton in northwestern Iceland (Dungal 1961). Nitrates, nitrites, and N-nitroso compounds in food and water (Weisburger, Barnes, and Czerniak 1986) and salted foods (Geboers, Joossens, and Kesteloot 1985) have been associated with gastric cancer in several epidemiologic studies. Salt-pickled and salt-cured foods have been associated with an increased risk for cancers of the nasopharynx (Sasco, Hubert, and De The 1985) and esophagus (Tuyns, Riboli, and Doornbos 1985). Esophageal cancer in China has been linked to the consumption of pickled vegetables and nitroso compounds (Yang 1980). Most international epidemiologic studies have linked smoked foods to gastric or esophageal cancers (Bjelke 1978).

Esophageal (Tuyns, Riboli, and Doornbos 1985) and stomach cancers (Geboers, Joossens, and Kesteloot 1985) have been associated with poor nutrition. In fact, almost all diet and stomach cancer studies have found a protective effect of vegetable and fruit intake (Cordle 1986), and even the *in vitro* formation of N-nitroso compounds can be minimized by antioxidants such as vitamins E and C (Weisburger, Barnes, and Czerniak 1986).

Nevertheless, the impact of risks from salt-cured, salt-pickled, and smoked foods in the U.S. diet appear to be small, because rates of stomach and esophageal cancers are low compared with those in other parts of the world and because consumption of smoked, salt-cured, and salt-pickled foods generally is not high.

Food and Color Additives

The FDA approves (or disapproves) all new food and color additives after detailed review of the safety, purpose, and anticipated exposure. The FDA also monitors the food supply for chemical contaminants such as pesticides, environmental contaminants, and heavy metals through the annual Total Diet Study, which has been conducted since the mid-1960's (NRC 1982). Before substances are approved for marketing, they are evaluated for safety on the basis of experimental studies in animals and relevant clinical studies demonstrating their suitability for their intended use. After marketing, if new evidence on the safety of the substance is brought to light, such evidence is reviewed in depth to determine if there should be a change in the regulatory status of the substance. This process should protect the U.S. population against the presence of added substances in the food supply that could involve a risk to health, including cancer.

Implications for Public Health Policy

Dietary Guidance

General Public

The dietary factors evaluated for the possible relationship to cancer risk are fat, calories, fiber, foods high in vitamin A and carotenoids, and alcohol. Roles for vitamin C, vitamin E, selenium, protein, and salt-cured, salt-pickled, and smoked foods have been proposed.

Studies of carcinogen-induced tumorigenesis in experimental animals and international epidemiologic comparisons have provided substantial but not conclusive evidence that dietary fat increases the risk for cancers of the breast, colon, rectum, endometrium, and prostate. The results of epidemiologic investigations within more homogeneous population groups, however, are inconsistent. Because fat contains more than twice the calories per given quantity of protein or carbohydrate, high-fat diets are generally high in calories. Despite such complications, the animal and international epidemiologic data suggest that a decrease in fat consumption by the general public from the current 37 percent of total caloric intake might reduce the risk for certain cancers.

Results from animal and human studies of obesity and cancer are not wholly consistent, perhaps because of the difficulty of separating the effects of calories, fat, and body weight. Furthermore, the level of caloric restriction that seems effective in preventing cancer in most animal studies

is at a food intake level not advisable for most humans. Consistent with other health recommendations, maintenance of desirable weight is recommended and may potentially decrease the risk of breast, colon, prostate, and endometrial cancers.

Correlational epidemiologic studies suggest an association between diets low in fiber and increased risk for colon cancer, while results from case-control studies are mixed. Studies in experimental animals indicate that further research is needed on the effects of different types of fiber. While inconclusive, evidence suggests that an overall increase in intake of foods high in fiber might decrease the risk for colorectal cancer. Despite the need for additional evidence, this recommendation is consistent with guidance for reducing gastrointestinal disease.

Likewise, epidemiologic studies provide suggestive evidence that consumption of foods containing carotenoids, including the beta-carotene precursor of vitamin A, protects against development of epithelial cell cancers such as those of the oral cavity, bladder, or lung. These studies have generally shown lower rates of cancer among individuals consuming the highest overall levels of vitamin A, carotenoids, or fruits and vegetables. These studies have not distinguished the specific form of vitamin A associated with protection, nor have they ruled out the possibility of protection from as yet unidentified components of fruits and vegetables. Until the results of clinical trials examining these relationships become available, an increase in consumption of fruits and vegetables might benefit persons who now consume below-average amounts of these foods. There is no evidence that vitamin A in amounts greater than the RDA is beneficial.

Despite some difficulties in distinguishing the cancer-producing effects of excessive alcohol intake from those of cigarette smoking, evidence suggests that a reduction in alcohol intake among the portion of a population that drinks most heavily would help to reduce the prevalence of cancers of the mouth, esophagus, pharynx, and perhaps other sites.

Excessive selenium intake is toxic. This fact and limitations in information about selenium intake in the general population suggest that selenium intake should not be increased above levels now in the average diet.

Although some epidemiologic studies suggest an association between dietary protein and cancer incidence, these studies are limited and not consistently supported by animal evidence. Thus, the evidence does not justify a recommendation to the general public to decrease protein on the basis of its relationship to cancer.