Chapter 4

Cancer

One should eat and drink in moderation (not in excess, not at a rapid rate, foods not too hot and not overly hard), maintain an even temperament, eat a good diet and Ye Ge (esophageal cancer) will not develop.
Ancient Chinese aphorism of Yan,
quoted in O'Connor and Campbell (1986)

Introduction

Cancer, the second leading cause of death in the United States, is a group of conditions of uncontrolled growth of cells originating from almost any tissue of the body. The fundamental basis of cancer has been explained as follows: "Every minute 10 million cells divide in the human body. Usually, they divide in the right way and at the right time, governed by a complex set of controls that have yet to be fully elucidated. When those controls fail, cancer may arise. The carefully ordered pattern of cell growth, division, and differentiation is lost" (Bishop 1984). This chapter reviews the scientific evidence for the role of dietary factors in these processes.

Historical Perspective

Although diet has been suspected as a cause of cancer since the disease was recognized in the 1st century (Armstrong and Mann 1985), empirical evidence was not reported until the early 20th century (Van Alstyne and Beebe 1913). The current era of research grows out of studies that were reported more than 50 years ago. In one of the earliest investigations, dietary information obtained from 462 cancer patients suggested protective effects of whole meal bread, cruciferous vegetables, and fresh milk (Stocks and Kay 1933). Records from insurance companies suggested that overweight people were at higher risk for cancer than normal or underweight people (Tannenbaum 1940b).

This finding stimulated a series of animal experiments that demonstrated a lower incidence of skin tumors, mammary tumors, sarcomas, hepatomas, lung adenomas, and pituitary adenomas in severely underfed animals

(Tannenbaum 1940a; Tannenbaum and Silverstone 1957). Early rodent studies showed that high-fat diets favored development of mammary tumors (Silverstone and Tannenbaum 1950) and that vitamin A deficiency was associated with gastric papillomas (Fujimaki 1926). These and other early studies of diet and cancer causation have been reviewed (Armstrong and Mann 1985; Carroll and Khor 1975).

Although research on the effects of dietary modification on induction of cancer in rodents continued, there was little attempt to relate the results of this research to humans. Interest in the role of nutrition in human carcinogenesis renewed in the 1960's when a report from the World Health Organization examined lifestyle and environmental factors associated with cancer risk and concluded "that the majority of human cancer is potentially preventable" (WHO 1964). Since then, epidemiologic and experimental research on the relationship between diet, nutrition, and cancer has expanded rapidly. In 1980, the National Cancer Institute commissioned the National Academy of Sciences (NAS) to review available information, develop dietary recommendations for public distribution, and develop recommendations for further research on diet, nutrition, and cancer (NRC 1982). This chapter reviews the evidence available at the time the recommendations of the NAS report were developed as well as findings since that time.

Significance for Public Health

Cancer accounted for 22 percent of all deaths in the United States in 1984. It has been estimated that 965,000 new cases of cancer were diagnosed and 483,000 people died of cancer in the United States in 1987 (Silverberg and Lubera 1987). An American born in 1985 has an approximately 30 percent chance of eventually dying of cancer (Seidman et al. 1985). Although the annual number of cancer cases has been steadily increasing as the population grows, the age-adjusted total cancer incidence and mortality rates for sites other than respiratory tract (cancers that are primarily due to cigarette smoking) have as a whole remained stable during the past 30 to 40 years (NRC 1982).

Incidence and mortality rates for cancer are significantly higher in black than in white Americans or members of other minority groups. This difference is especially pronounced in males. Blacks also have the lowest survival rates for cancers at most sites. These differences in cancer experience are more readily explained by social and environmental factors than by biologic differences. Although their cancer rates vary greatly according to

disease site and specific tribal group, Native Americans have the lowest overall cancer rates among the U.S. population (DHHS 1985).

The costs of this illness can be divided into those that are economic (direct and indirect) and psychosocial (Hodgson and Meiners 1982). The direct costs of cancer treatment in the United States were estimated to be $22 billion and the indirect costs $50 billion in 1985 (Sondik et al. 1987). Thus, successful strategies to prevent cancer could have an enormous public health impact on the saving of both lives and dollars.

Cancer may arise in any organ in the body, but tumors of the lung, colon and rectum, breast, skin, and prostate occur most frequently. Cancers of 10 sites—lung, colon-rectum, breast, prostate, pancreas, leukemias, stomach, ovary, bladder, and liver-biliary cancers—account for more than 73 percent of all cancer deaths in the United States (Silverberg and Lubera 1987) and are variably associated with dietary factors. Although the exact proportion is unknown, several researchers have attempted to provide quantitative estimates of the percentage of cancer in the United States attributable at least in part to diet. One group estimated the proportion of cancer deaths attributed to diet to be 40 percent in men and 60 percent in women (Wynder and Gori 1977), and another estimated it to be 35 percent overall, with a range of 10 to 70 percent (Doll and Peto 1981) (Table 4-1).

Scientific Background

Lifestyle Factors and Cancer Risk

In searching for the causes of cancer, considerable effort has been devoted to studying both environmental and genetic factors on the incidence of cancer. In the course of this research, it has become clear that many cancers have external causes and, in principle, should therefore be preventable. These conclusions are supported by several lines of evidence.

Comparisons of Incidence Rates Between Populations. Incidence rates of specific cancers differ as much as 100-fold among populations. These variations are illustrated in Figure 4-1 for several types of cancer. Because the incidence of cancer increases with age, rates are age adjusted for comparison of populations with different age structures. Different groups within the same country may also have distinctly different cancer incidence rates. For example, a comparison of Mormons versus non-Mormons in Utah in 1967–1975 demonstrated overall cancer rates that were 28 percent greater in the non-Mormons even after all smoking-associated cancers were eliminated (Lyon, Gardner, and West 1980). Environmental and social factors, including diet and nutrition, have been implicated as partial causes of this variation.

Table 4-1
Proportions of Cancer Deaths Attributed to Various Factors[a]

Factor or Class of Factors	Percent of All Cancer Deaths: Best Estimate	Percent of All Cancer Deaths: Range of Acceptable Estimates
Tobacco	30	25–40
Alcohol	3	2–4
Diet	35	10–70
Food additives	1	(−5[b])–2
Reproductive and sexual behavior	7	1–13
Occupation	4	2–8
Pollution	2	1–5
Industrial products	1	1–2
Medicines and medical procedures	1	0.5–3
Geophysical factors	3	2–4
Infection	10?	1–?
Unknown	?	?

[a]It should be understood that these figures are speculative, and there is considerable uncertainty associated with them.
[b]Some factors (e.g., food fortification) may be protective.

Source: Doll and Peto 1981.

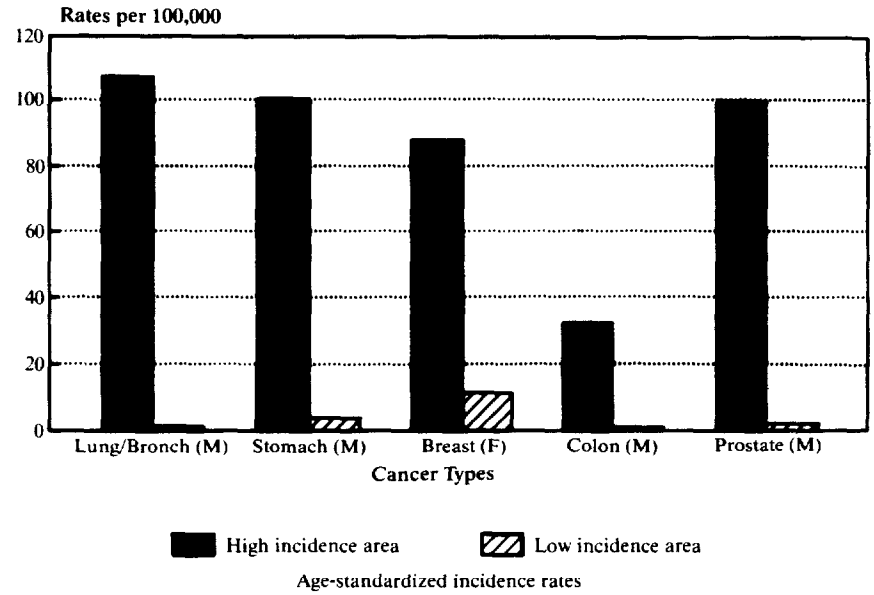

Figure 4-1. Range of incidence rates (international comparisons).

Source: Adapted from Howe 1986.

Variation in Rates Within a Population Over Time. Changes in cancer rates in a stable population must be due to environmental rather than genetic causes, but it is not always easy to distinguish between actual changes in rates and those due to improvements in screening, diagnosing, and treating as well as identifying cancer as a cause of death. Table 4-2 demonstrates rate changes over time for stomach and lung cancer mortality, two cancers for which death records are fairly reliable and survival is relatively short. These data indicate that the rate of stomach cancer mortality in the United States declined by 61 percent from 1950–51 to 1975—the reasons for this decline have not been established (Silverberg and Lubera 1987)—while the rate of lung cancer increased 148 percent. The increase in rate of lung cancer mortality is due primarily to increases in cigarette smoking.

Migrant Studies. Studies of migrants offer clear support for the roles of life style and environment in cancer etiology because such populations have "unwittingly performed etiological experiments on a large scale by migration from one environment to another" (Steiner 1954). Table 4-3 compares cancer incidence rates among Filipinos in the Philippines (Manila), migrants to Hawaii, and Hawaiian Caucasians and indicates a migration-related decrease in cancers of the stomach, liver, and cervix, as well as an

Table 4-2
International Changes Since 1950 in Death Certification Rates for Cancers of Stomach and Lung

Country	Period	Stomach	Lung
Australia	1950-51 to 1975	−53	+146
Austria	1952-53 to 1976	−53	−8
Chile	1950-51 to 1975	−56	+38
Denmark	1952-53 to 1976	−62	+87
England and Wales	1950-51 to 1975	−49	+33
West Germany	1952-53 to 1975	−50	+36
Ireland	1950-51 to 1975	−54	+177
Israel	1950-51 to 1975	−49	+58
Japan	1950-51 to 1976	−37	+408
The Netherlands	1950-51 to 1976	−60	+89
New Zealand	1950-51 to 1975	−54	+137
Norway	1952-53 to 1975	−59	+118
Scotland	1950-51 to 1975	−46	+44
Switzerland	1952-53 to 1976	−64	+72
United States	1950-51 to 1975	−61	+148

Average of male and female rates at ages 35 to 64, standardized for age.

Source: Doll and Peto 1981.

Table 4-3
Cancer Incidence Rates in the Philippines and Among Filipinos and Caucasians in Hawaii

Cancer Site	Philippines	Hawaii		
	Manila 1977	Filipinos 1962–65	Filipinos 1978–81	Caucasians 1978–81
Males				
Stomach	10	7.1	6.6	14.8
Colon	5	14.3	18.8	33.6
Rectum	6	12.4	16.2	17.5
Liver	20	7.5	4.1	5.6
Lung	29	15.9	27.3	75.3
Thyroid	2	5.0	5.6	1.0[a]
Prostate	8	14.0	33.4	69.0
Females				
Colon	4	6.4	11.6	26.7
Lung	9	17.3	16.3	36.4
Thyroid	5	22.4	17.4	6.3
Breast	31	18.2	36.2	92.9
Cervix	16	16.6	7.5	10.2

Average annual incidence per 100,000 population, age-adjusted to the World Population Standard.

[a]Rate is based on fewer than 10 cases.

Source: Adapted from Kolonel, Hankin, and Nomura 1986.

increase in cancers of the colon, thyroid, prostate, and breast. Similar trends have been noted for Japanese migrants (Doll and Peto 1981). Although migrant studies suffer from variations in the source and quality of data, these studies do imply that environmental conditions, rather than genetics, are responsible for the changing incidence patterns (Modan 1980; Haenszel 1982).

Carcinogenic Agents. Identification of carcinogenic agents through animal assays may suggest sources of exposure through contamination of food or water supplies. However, because of continuous monitoring of the food supply and regulatory requirements that prevent the addition of or minimize the concentration of food contaminants that have carcinogenic potential, this possible source of cancer risk has a nondetectable impact on cancer incidence in the United States.

Concepts of Carcinogenesis

The complex process of cancer development can work through multiple paths. Figure 4-2 illustrates a current view of the steps that lead to cancer.

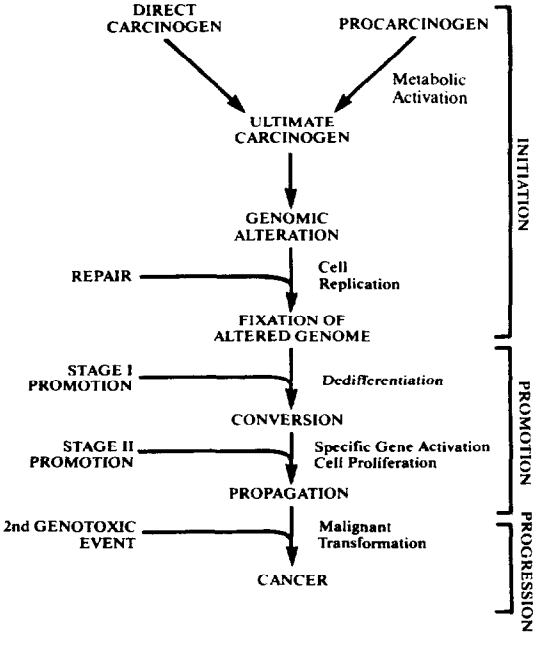

Figure 4-2. Carcinogenesis.

Initiation of carcinogenesis alters the genetic information (i.e., DNA) of the cell. Promotion then leads to expression of genetic changes as malignancy, which involves loss of control over cellular proliferation. According to this model, both events are required for malignant transformation, and they must occur in this order. Many factors, including dietary factors, may enhance or inhibit this process at certain stages. Recent advances in molecular biology have revealed the presence of cancer-inducing genes (oncogenes) within cells that can be activated under specific environmental conditions (Bishop 1987). Current knowledge of initiation, promotion, and regulation of oncogene expression is consistent with suggestions that most cancers have external causes and therefore are likely preventable.

Carcinogenesis is complete when cells become neoplastic and are independent of normal biologic controls. These tumor cells grow in number during a silent interval, which may last 5 years or more, sometimes much more, before a tumor can be detected clinically. This long latent period makes it difficult to establish the time of onset of carcinogenesis and requires that studies of dietary effects on cancer estimate dietary intake for times up to 20 or more years before diagnosis.

Diet and Carcinogenesis

Several mechanisms have been proposed to account for observed associations between diet, digestive processes, and cancer. These include:

- Carcinogens in food that are present naturally, that are inadvertent contaminants, or that form as products of cooking or preservation.
- Diet-induced metabolic activation or deactivation of carcinogens (Miller and Miller 1976). For example, formation of oxygen radicals and lipid peroxidation products can be retarded or blocked by normal enzymatic processes or by the selenium or beta-carotene present in food (Ames 1983).
- Biologic formation of carcinogens *in vivo*, as with conversion of bile acids to tumor-promoting chemicals by normal colonic bacteria (Hill et al. 1971). The bacteria that accomplish this conversion may be affected by diet.
- Enhancement (e.g., by fats) or inhibition (e.g., by vitamin A) of promotion (Doll and Peto 1981).
- Nutrient imbalance may impair immunity (Beisel 1984) and thus may influence early rejection of malignant cells or the ability of cells to repair damaged DNA (Wood and Watson 1984). This topic has been reviewed extensively (Good 1981; Gershwin, Beach, and Hurley 1985; Watson 1984).

Nutritional Support With Cancer Treatment

Severe losses of weight, digestive and absorptive ability, and cellular immune competence are frequent consequences of cancer, and cancer patients may exhibit classic signs of extreme malnutrition. This cachexia of cancer has been attributed to reduced food intake due to anorexia, which may be compounded by disorders of taste and smell; to gastrointestinal malfunction caused by radiation, chemotherapy, or surgical therapy (Brennan and Copeland 1981); and to metabolic abnormalities induced by the tumor itself (Anonymous 1984).

The observation that some cancer patients show marked weight loss has led to the idea that correction of malnutrition by diet or by tube or intravenous feeding might improve the tolerance of patients to therapy as well as improve the quality and length of life. Despite some inconsistencies in results, numerous studies have demonstrated the ability of nutritional support to restore body weight and other indices of nutritional status, functional ability, and feelings of well-being in cachectic cancer patients (Brennan 1981). On the other hand, although some studies have demon-

strated improved ability of well-nourished patients to withstand therapy with radiation (McArdle, Laplante, and Freeman 1986), many others have not (Donaldson 1984). Most prospective clinical trials to determine the effects of nutritional support on the survival of cancer patients have also failed to demonstrate an improvement (Koretz 1984).

Suggestions that macrobiotic diets, high doses of vitamins, minerals, and other nutritional supplements or other unorthodox nutritional methods might cure cancer or delay its course have not been supported by controlled scientific investigations (ACS 1984; Herbert 1986). The use of high-dose (10 g/day) vitamin C, for example, has been used in attempts to prolong the quality of life and the lifespan of terminally ill cancer patients (Cameron and Pauling 1978), but controlled studies have found no difference in outcome among patients taking vitamin C or placebos (Creagan et al. 1979; Moertel et al. 1985).

Methodological Issues

Different types of studies provide different types of information, and no studies are without limitations. An important consideration in reaching conclusions is consistency of data. The conclusions reached must be based on the relevance, quality, and the degree of concordance between the epidemiologic data and laboratory evidence, as applicable.

Interpretation of the associations between diet and cancer depends upon a critical evaluation of the study design and methods of analysis used to reach conclusions. The following types of investigations have yielded important information about diet-cancer relationships.

Epidemiologic Studies. Much of the evidence on diet and cancer risk derives from epidemiology, "the study of the distribution and determinants of health-related states and events in populations, and the application of this study to control of health problems" (Last 1983). Epidemiology is a relatively young science that has contributed to the expansion of knowledge and improvement of public health (Feinstein 1987). Epidemiologic studies are generally classified as correlation (ecologic), case-control (retrospective), and cohort (retrospective or prospective) studies (for reviews see NRC 1982; Byers and Funch 1984). Case-control and cohort studies tend to be stronger scientifically than ecologic studies because they use data from individuals, rather than population averages, to reach their conclusions. However, they sometimes are limited by narrow ranges of variation in exposure (e.g., to food groups or nutrients), which reduces the opportunity to see a potentially true biologic association. The ability to

detect a meaningful level of association is determined by the range of exposure as well as the size of the sample studied (Self et al. 1988).

Ecologic Studies. These studies permit analysis of a variety of diets, especially in international comparisons, that might not be observable in case-control or cohort studies. They can also assess changes over long periods of time. In such studies, cancer rates among various populations can be correlated with data on food disappearance, dietary surveys, or blood chemistries. This type of study is most useful for generating hypotheses about dietary factors related to cancer risk. An example is the high correlation between dietary fat intake and death rate from breast cancer illustrated in Figure 4-3. Ecologic studies can also relate metabolic or biochemical changes in circulating hormones or fecal bile acids, for example, to dietary intake and cancer incidence (Reddy et al. 1980). Such comparisons usually rely on average population data rather than on individual measures, and they tend to focus on cancer mortality rather than on incidence. Their most serious weakness is the potential for an "ecologic fallacy," which means that populations may differ with respect to two associated variables (e.g., dietary fat, colon cancer) but that the individuals who get the disease (i.e., colon cancer) may not necessarily be the ones who had the exposure (e.g., high fat); variables other than the one of interest, such as obesity, or caloric intake, may account for the observed difference in disease incidence or mortality (Last 1983). Despite such limitations, ecologic studies allow multiple comparisons and correlations that permit relatively inexpensive rapid generation and examination of hypotheses regarding the causes of disease (DHHS 1982).

Case-Control Studies. Case-control studies begin with selection of individuals who have the disease of interest (the cases) and compare their present or past exposure to potential risk factors to that of persons without the disease (the controls). The greater the proportion of cases exposed to a factor, the stronger is the hypothesis that the factor increases disease risk. Increased risk is often expressed as a relative odds, or odds ratio, which for uncommon diseases like cancer expresses the risk of disease in persons exposed to the factor as a ratio or multiple of the risk in persons not exposed. An important component of the study design is that cases and controls should be drawn from the same population so that the potential contribution of confounding variables can be minimized. Case-control studies are advantageous for studying rare cancers with long latent periods because they require relatively few subjects and can be used to assess multiple hypotheses for causation. However, they can be affected by uncertainties regarding the representativeness of both cases and controls and the validity of dietary measures. Statistical significance of such rela

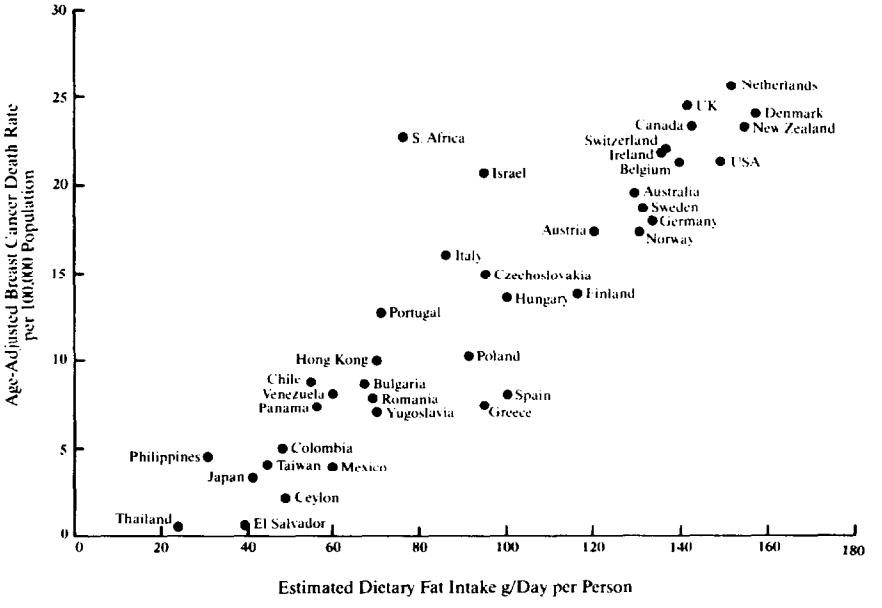

Figure 4-3. Dietary fat intake in relation to breast cancer-related death rate.

Source: Carroll, K.K., and Khor, H.T. 1975. Dietary fat in relation to tumorigenesis. *Progress in Biochemical Pharmacology* 10:308-53. Reprinted with permission from S. Karger AG, Basel.

tionships, however, does not guarantee a causal association, nor does lack of statistical significance necessarily indicate a noncausal association (Schlesselman 1982). Case-control studies may fail to confirm strong associations observed in correlation studies of diet and disease. Whether this is caused by the better control of confounding variables, by the inability of studies on individuals to make sufficiently valid measurements of diets, by insufficient variation of diets within a single population, or by a combination of these or other factors needs to be evaluated.

Several potential constraints must be addressed for a case-control study to identify a relationship between a dietary pattern and a disease outcome. If, for example, a population is homogeneous in intake of a food or nutrient, or if amounts ingested by most members of the population are insufficient to observe an effect, one may find little difference in exposure between cases and controls, even for dietary factors that show associations in other studies. Case-control studies also depend on the sensitivity of the dietary questionnaire or other instrument of measure. Cancer itself, or another

preexisting condition, may lead to dietary changes and result in spurious associations because the measured exposure at the time of disease onset may be quite different from the exposure at the time the case is found.

Cohort Studies. Cohort studies solve some of these problems by comparing groups that have and do not have the dietary patterns of interest. The main difference in concept between cohort and case-control studies is that in cohort studies, subjects were selected on the basis of exposure versus nonexposure, while subjects are selected for case-control studies on the basis of disease versus nondisease. Because prospective cohort studies assess the risk of disease after a given exposure, they require more time and resources than case-control studies. In such studies, there is no need to attempt retrospective measures of diet and, therefore, less concern about the possibility of biased recall. When the relationship of dietary exposure to subsequent cancer risk is to be studied, a very large group must be followed for many years because of the long latency period for a sufficient number of incident cases to be collected. In such studies, a sufficient exposure difference must also exist between the two groups for a potential effect to be noticed, and diligent surveillance is required to ensure that no cases of cancer are missed. The advantages of cohort studies are that exposure is known at a given point in time, greater control over measurement techniques is afforded, and exposure is known to occur before the onset of disease. While good cohort studies can provide stronger scientific information than case-control studies, they still suffer from the potential limited range of dietary exposure and require many years for completion.

Clinical Intervention Trials. Clinical trials provide the strongest research design to test whether an intervention will have the hypothesized effect. A specificity not possible in epidemiologic studies derives from the prospective nature and use of random assignment to a treatment (such as a diet) in clinical trials. These trials may show whether animal studies are applicable to people and whether people will adhere to the intervention for the duration of the trial (Greenwald, Sondik, and Lynch 1986). In clinical trials, a prospective cohort is randomly assigned to an intervention or to a control group—for example, assigning women at increased risk for breast cancer to either a customary diet or a long-term intervention program to lower dietary fat to less than 20 percent of daily calories. To achieve the statistical power necessary to reach solid conclusions in the face of diseases of multiple etiologies and widespread risk factor exposure may require trials involving many thousands of participants and many millions of dollars. On the other hand, the expense and effort are warranted if the results can be expected to benefit a large share of the population.

To facilitate the conduct of these clinical trials, methodological improvements are needed. Present methods to determine the relationship between diet and cancer risk require long waiting periods to identify end points. The lack of sensitive and specific markers of carcinogenesis makes nutrient and chemoprevention trials difficult, although advances in molecular biology may improve this situation (Perera 1987). Finally, ethical issues may be important in such trials—for example, withholding an intervention that might benefit a group on one or several dimensions—and have been reviewed recently (Freedman 1987).

Animal Studies. Animal studies offer the advantage of confined populations and closer control of experimental variables, and they provide invaluable opportunities to study the mechanisms that underlie the relationship of diet and cancer. The use of very high levels of a specific nutrient or food type (e.g., vitamin C or wheat bran) to maximize efficiency and minimize costs in these studies complicates extrapolation of results to humans. An important weakness is that virtually all animal studies test single, genetically uniform (inbred) strains of one or two nonhuman species under highly uniform conditions of diet, temperature, stress, exposure to infectious diseases, etc., so that there are often serious constraints in generalization of results to a highly variable human population. However, animal studies may complement human studies, and these two basic approaches should be used in conjunction when possible (NRC 1982).

Association and Causation. When an epidemiologic study shows an association between a dietary factor and the risk of a specific cancer, other studies may not necessarily show the same degree of association because of variations in research design, length of observation, relevant nondietary exposures, variation in human response, or chance associations. To demonstrate a true association, it is necessary to rule out spurious correlations due to artifacts or biases (problems of validity) that stem from systematic errors in design or analysis (Lilienfeld and Lilienfeld 1980; Sackett 1979). Even statistical associations between diet and disease do not guarantee that a specific factor causes the disease; noncausal (confounding) associations may exist (Miettinen and Cook 1981). Statistical methods to identify problems of bias and confounding can strengthen the interpretation of study results (Kleinbaum, Kupper, and Morgenstern 1982) but cannot solve all of the problems encountered in interpreting results and in isolating "true" effects.

Dietary Interactions. Complex interrelationships and interactions among nutrients are often not appropriately considered. For example, dietary fats supply more than twice the calories per gram as protein or carbohydrates.

Although fat consumption would be expected to correlate with caloric intake, few studies of the role of fat in colorectal cancer have taken this into account. Distinctions between tightly linked nutrients may not always be possible. Methods to control highly correlated variables, however, can result in difficulty in interpreting results because control for the effect of the confounding variable may also remove variance due to the "true" effect. Thus, the statistical instability of highly correlated variables often makes use and interpretation of multivariance analysis difficult if not impossible (Pilch 1987).

Another type of interaction of nutrients and food components can result in a synergistic effect, an effect greater than that expected from the sum of the individual effects. The synergy between asbestos exposure and smoking in causing lung cancer is a well-known example of a synergistic effect. It is also possible to have factors that counterbalance each other. Nutrient synergies in cancer etiology are not as well established, but a recent study correlating cancer with low serum levels of selenium and alpha-tocopherol (vitamin E) is illustrative. While the relative risk for cancer was 5.8 for low selenium level and 1.6 for low alpha-tocopherol level, the interactive risk was 11.4 for both occurring together (Salonen et al. 1985).

Detailed food diaries, the usual instruments for assessing diet (Sorenson 1982), are generally recorded only for days or weeks, whereas dietary histories over several years may be most pertinent (Byers and Graham 1984). More recent dietary survey instruments may improve the validity and efficiency of dietary assessment (Byers and Graham 1984; Willett and MacMahon 1984a, 1984b).

These methodological problems, the limited understanding of cancer at the molecular level, the variety of foods, and the complexity of the composition of foods in the diet have hindered our understanding of the relationship among diet, nutrition, and cancer. Despite uncertainties, evidence supports a role for several dietary components in prevention or causation of specific cancers. The most important of these reported associations are summarized in Table 4-4 and discussed further below.

Dietary Guidelines for Cancer Prevention

Dietary changes beyond the minimum intakes required for preventing nutritional deficiencies may decrease an individual's risk for cancer (EOC-CPS 1986). Translation of research results into dietary guidelines has always been controversial, but in 1979 the Director of the National Cancer Institute proposed a series of recommendations (Upton 1979). Also in

Table 4-4
Reported Relationship Between Selected Dietary Components and Cancer

Selected cancer sites in descending order of incidence (Age-adjusted incidence, SEER, 1984)		Fat	Body Weight and Calories	Fiber	Fruits and Vegetables	Alcohol	Smoked, Salted, and Pickled Foods
Lung	(55)[a]				−	+[b]	
Breast	(51)	+	+		−	+	
Colon	(36)	+	+	−	−		
Prostate	(34)	+	+		−		
Bladder	(16)				−		
Rectum	(15)	+				+	
Endometrium	(13)	+	+				
Oral Cavity	(11)				−	+	
Stomach	(8)				−		+
Kidney	(8)		+				
Cervix	(5)		+		−		
Thyroid	(4)		+				
Esophagus	(4)					+	+

Key: + = Positive association; increased intake with increased cancer.
− = Negative association; increased intake with decreased cancer.

[a]Rate per 100,000 population, age-adjusted incidence from United States, 1984, Sondik et al. 1987.
[b]Synergistic with smoking.

1980, the National Cancer Institute commissioned the NAS to conduct a comprehensive review of research findings on diet, nutrition, and cancer to use as a basis for development of dietary guidelines and recommendations for future investigation (NRC 1982). The most recent dietary guidelines from the National Cancer Institute (Butrum, Clifford, and Lanza 1988) are listed in Table 4-5.

As shown in Table 4-6 and discussed in the introductory chapter, dietary guidelines have been issued by the National Cancer Institute, the American Cancer Society, the Federal Government (USDA and DHHS), and the American Heart Association. They tend to be similar in making general recommendations about maintenance of desirable weight, the importance of a variety of wholesome foods, reduction of fat, adequate levels of fiber, and, at most, moderate levels of alcohol intake. They vary, however, in the development of quantitative guidelines and in the rationale used to indicate a link between dietary intake and the risk for various diseases.

Key Scientific Issues

- Role of Dietary Fats in Cancer
- Role of Calories and Body Weight in Cancer
- Role of Dietary Fiber in Cancer
- Role of Vitamin A and Carotenoids in Cancer
- Role of Alcohol in Cancer
- Role of Other Dietary Constituents in Cancer

Table 4-5
National Cancer Institute
Dietary Guidelines

1. Reduce fat intake to 30 percent or less of calories.
2. Increase fiber intake to 20 to 30 grams daily, with an upper limit of 35 grams.
3. Include a variety of vegetables and fruits in the daily diet.
4. Avoid obesity.
5. Consume alcoholic beverages in moderation, if at all.
6. Minimize consumption of salt-cured, salt-pickled, and smoked foods.

Source: Butrum, Clifford, and Lanza 1988.

Table 4-6
Comparison of Dietary Guidelines for the American Public

	Fat	Fiber	Fruits and Vegetables	Obesity	Alcohol	Salt
NCI Dietary Guidelines Butrum et al. 1988	Reduce fat intake to 30% or less of calories	Increase fiber intake to 20 to 30 g, not to exceed 35 g	Include a variety of fruits and vegetables in the daily diet	Avoid obesity	Consume alcoholic beverages in moderation, if at all	Minimize consumption of salt-cured, salt-pickled, and smoked foods
American Cancer Society 1985	Cut down total fat intake	Eat more high-fiber foods	Include foods rich in vitamins A and C; include cruciferous vegetables	Avoid obesity	Keep alcohol consumption moderate if you do drink	Keep consumption of salt-cured, smoked, and nitrite-cured foods moderate
USDA/DHHS 1985 *Dietary Guidelines for Americans*	Avoid too much fat, saturated fat, and cholesterol	Eat foods with adequate starch and fiber	Eat a variety of foods	Maintain desirable body weight	If you drink alcoholic beverages, do so in moderation	Avoid too much sodium
American Heart Association 1985	Total fat, 30% or less of calories; saturated fat, 10% of calories; cholesterol, 100 mg/1,000 calories—not 300 mg/day	Include breads, cereals, pasta, and starchy vegetables containing natural complex carbohydrates	Include at least 3 servings/day of fruits and 3 servings/day of vegetables	Achieve and maintain desirable weight	If you drink, do so in moderation	Limit salt intake

Source: Butrum, Clifford, and Lanza 1988.

Role of Dietary Fats in Cancer

Despite some inconsistencies in the data relating dietary fat to cancer causation, animal studies show an effect on carcinogenesis and support a cancer-promoting role, and international epidemiologic studies have suggested that differences in dietary fat intake may provide a meaningful key to prevention of cancer. For example, substantial epidemiologic and animal evidence supports a relationship between dietary fat and the incidence of both breast cancer (Kakar and Henderson 1985) and colon cancer (Kolonel and Le Marchand 1986). Indeed, a comparison of populations indicates that death rates for cancers of the breast, colon, and prostate are directly proportional to estimated dietary fat intakes (Wynder et al. 1981; Rose 1986). Other cancers that have been related to fat intake are those of the rectum (Armstrong and Doll 1975), ovaries (Rose, Boyar, and Wynder 1986), and endometrium (Mahboubi, Eyler, and Wynder 1982). Considerable uncertainties remain to be resolved about these relationships. For example, the effects of different types of dietary fat (i.e., saturated vs. unsaturated; animal vs. plant origin) have not been separated in most human studies. But the weights of the studies to date are strongly suggestive of the role for dietary fat in the etiology of some types of cancer.

Human Epidemiologic Studies

The risk for breast cancer is correlated with total fat consumption in comparisons of countries (Armstrong and Doll 1975; Gray, Pike, and Henderson 1979; Rose, Boyar, and Wynder 1986), districts in Japan (Hirayama 1977), and ethnic groups in Hawaii (Kolonel, Hankin, et al. 1981). The risk for cancers of the colon and prostate is also correlated with total fat consumption in international comparisons (Armstrong and Doll 1975; Knox 1977; Liu et al. 1979). A worldwide correlation between breast and colon cancer mortality and total fat consumption has been demonstrated (Carroll and Khor 1975) and is illustrated for breast cancer death rates in Figure 4-3.

Although further epidemiologic study is needed to verify the association between diet and breast cancer and to elucidate its biologic basis, the consistency of the evidence derived from the epidemiologic and animal studies suggests that the association may be causal (Miller 1986). Table 4-7 summarizes certain key (although limited) dimensions of the human epidemiologic studies of diet and breast cancer. Correlation studies show the strongest associations. Migrant studies often show that people who move to a country with a higher incidence of breast cancer than their native country tend to acquire the dietary habits of their new country of residence

and may experience a cancer incidence that changes with the change in dietary fat (Kolonel, Nomura, et al. 1981; Gori 1979). Case-control and cohort studies relate the risk for breast cancer to total fat consumption in some (Miller et al. 1978; Lubin, Wax, and Modan 1986) but not all (Graham et al. 1982; Willett et al. 1987) studies. While methodological problems may have obscured a true risk association in these negative studies (Willett et al. 1987; Hebert and Wynder 1987; Self et al. 1988), they reinforce the need for cautious interpretation and additional study of diet and breast cancer risk.

A Canadian case-control study has related an elevated risk for colon cancer with an increased intake of calories, total fat, and saturated fat (Jain et al. 1980). Fat consumption has been associated with colon cancer in American blacks (Dales et al. 1978) and in Americans of Bohemian ancestry in Nebraska (Pickle et al. 1984). Other studies have demonstrated no excess risk for colon cancer, and a recent review has found the evidence to be inconclusive (Kolonel 1987).

Some studies show associations between breast or colon cancer and meat intake that are similar to those with fat intake (McKeown-Eyssen and Bright-See 1985; Armstrong and Doll 1975; Lubin et al. 1981). At present, these data do not establish meat and other animal protein intake as risk factors independent of fat intake (Kolonel and Le Marchand 1986). In postmenopausal breast cancer, the association of dietary fat may be related to a higher intake of total calories during a high-fat diet, to obesity, or to a lower intake of foods that provide protective micronutrients (Willett 1987). In colon cancer, if various hypotheses hold true, the carcinogenesis-enhancing effects of dietary fat may interact with the possibly protective effects of dietary fiber (Jensen, MacLennan, and Wahrendorf 1982).

The effect of dietary cholesterol on cancer incidence is difficult to determine both because of the strong correlation of cholesterol with animal fat, and therefore with protein intake, and because blood cholesterol levels reflect more than *dietary* cholesterol levels. In one study, the correlation with colon cancer incidence was stronger for dietary cholesterol than for dietary fat (Liu et al. 1979). On the other hand, some studies that have examined blood cholesterol correlations and cancer suggest that very low blood cholesterol levels may be a risk factor for cancer (McMichael et al. 1984). Much more work is needed before firm conclusions can be drawn about the relationship of either dietary or blood cholesterol levels to cancer.

Table 4-7
Summary of Epidemiologic Studies Examining Dietary Fat and Breast Cancer

Author(s)	Total Fat	Animal Fat	Meat	Eggs	Vegetable Fat
International Correlation					
Lea 1966	+(a)				
Carroll et al. 1968	+				
Hems 1970	+				
Drasar & Irving 1973	+	+	+(b)	+	
Armstrong & Doll 1975	+		+(c)		
Carroll & Khor 1975	+				
Hems 1978	+				
Gray et al. 1979	+		+(b)		
Carroll 1980	+	+			0
Rose et al. 1986	+	+	+(d)		0
Within-Country Correlation					
Hirayama 1977	+				
Enig et al. 1978	+	−			+
Nomura et al. 1978			+		+
Gaskill et al. 1979		+(e)		−	
Ingram 1981	+		+		
Kolonel et al. 1981	+	+	+(b)		
Kinlen 1982			0		
Case-Control Studies					
Phillips 1975					+(d)
Miller et al. 1978	+				
Lubin et al. 1981			+(g)		
Graham et al. 1982	0				
Talamini et al. 1984		+(h)	0		
Nomura et al. 1985	0				
Le et al. 1986		+/−(i)			
Hislop et al. 1986		+/−(j)	+(b)		
Katsouyanni et al. 1986	0(a)				
Lubin et al. 1986	+		+(b)		
Hirohata et al. 1987	0		0(b)		

Table 4-7 (continued)

Author(s)	Total Fat	Animal Fat	Meat	Eggs	Vegetable Fat
Cohort Studies					
Hirayama 1978			+		
Phillips & Snowden 1983			0		
Willett et al. 1987	0				
Jones et al. 1987	0				

Key: (a) = Fats and oils.
(b) = Animal protein.
(c) = Meat and animal protein.
(d) = Meat, milk, and animal protein.
(e) = Milk.
(f) = Fried potatoes.
(g) = Beef and pork.
(h) = Dairy products.
(i) = Positive for cheese and fat in milk. Negative for yogurt. No association for butter.
(j) = Positive for gravy, beef, and pork. Negative for fish.

Animal Studies

Animals fed a high-fat diet often have higher rates of carcinogen-induced cancers of the breast, colon, and pancreas than those fed low-fat diets (Carroll 1986). Animal studies that indicate that dietary fat could influence carcinogenesis date back more than half a century (Watson and Mellanby 1930), with experiments indicating that the incidence of skin tumors on coal-tar-treated mice could be increased by more than 70 percent by feeding them diets higher in saturated fat. Investigators studying mammary tumors in mice found that the later a high-fat diet was begun, the lower the incidence of tumors; that tumors occurred more frequently in obese mice (Tannenbaum and Silverstone 1957); and that fat restriction inhibited mammary tumorigenesis in normal mice (Tannenbaum 1942). Rats fed a low-fat diet (2 percent linoleic acid) were noted to have markedly lower rates of chemically induced (7,12-dimethylbenz[a]anthracene (DMBA)) mammary tumors than those fed high polyunsaturated (20 percent corn oil) or saturated (18 percent coconut oil, 2 percent linoleic acid) fats (McCay et al. 1980).

Various animal studies have also associated intestinal tumors with higher levels of dietary fat. Rats fed 35 percent of total calories as beef fat were

noted to develop both more intestinal tumors and more metastases in response to azoxymethane (AOM) than rats fed normal chow (Nigro et al. 1975). Rats given 1,2-dimethylhydrazine (DMH) for tumor induction were noted to have more large bowel tumors on 30 percent lard diets than on low-fat standard diets (Bansal, Rhoads, and Bansal 1978). The role of fat as a tumor promoter, rather than inducer, is suggested by studies such as one indicating that, relative to a 5 percent beef fat diet, a diet of 30 percent beef fat increased the rate of intestinal tumors only when fed to rats after AOM administration (Bull et al. 1979).

Some studies suggest that polyunsaturated fat has the greatest tumor-enhancing effect for mammary (Cohen 1986), pancreatic (Birt and Roebuck 1986), and colon (Reddy 1986) cancers. High intakes of oleic (monounsaturated) and linoleic (polyunsaturated) acids correlate with increased mammary tumor incidence (Chan, Ferguson, and Dao 1983). In contrast, highly unsaturated omega-3 fatty acids derived from fish oils may protect against cancer (Braden and Carroll 1984), reduce tumor growth rates (Karmali, Marsh, and Fuchs 1984), and minimize the incidence of tumors promoted by high amounts of dietary corn oil (Ip, Ip, and Sylvester 1986). Hypotheses regarding types of fat and cancer risk require additional study.

Biochemical Mechanisms

Although dietary fat generally exerts its maximum effect when fed after carcinogen administration, it appears that sufficient duration of exposure to high dietary fat levels before carcinogen administration might affect tumor initiation as well; such an effect has been demonstrated for rat mammary carcinogenesis (Dao and Chan 1983).

The effect of dietary fat may be direct or indirect (Cohen 1986). Fat directly affects many cellular functions, including cell membrane fluidity, prostaglandin metabolism, and synthesis of potentially mutagenic lipid peroxide radicals (Welsch 1987). Direct effects also include changes in hormone receptors (which might promote hormonally mediated tumor growth), cell growth characteristics, and various intracellular chemicals. Fat-induced changes in bile acid composition in the colon may promote bacterial conversion of bile acids to tumor-promoting substances or may directly damage the colonic mucosa (Kritchevsky 1982; Goldin 1986).

Role of Calories and Body Weight in Cancer

Animal studies and a few epidemiologic investigations support the hypothesis that total caloric intake affects the risk of cancer. Some animal studies compared normal controls with animals on diets severely restricted in calories; others have compared normal and obese animals (Stunkard 1983). Because accurate measures of caloric intake over long periods of time are difficult, human studies usually focus on indirect measures such as body weight, relative body weight, or body weight indices that are presumed to correlate with increased caloric intake. Complicating these studies is the question of energy expenditure in maintaining caloric balance. The relationship between caloric intake, body weight, and cancer was the subject of a recent review (Albanes 1987) and a symposium (Pariza and Simopoulos 1987). This symposium also contains several studies on the association of exercise to cancer prevention.

Human Epidemiologic Studies

In international studies, a correlation between total per capita calories and cancers of the breast, colon, rectum, uterus, and kidney has been reported (Armstrong and Doll 1975). Case-control studies have found positive associations between energy intake and breast cancer (Miller et al. 1978) and energy intake and colorectal cancer (Jain et al. 1980; Lyon et al. 1987).

A positive association between increased body weight or body mass index and an increased risk for cancer has been observed for several cancers, including breast (de Waard and Baanders-van Halewijn 1974; Hirayama 1978; Mirra, Cole, and MacMahon 1971), kidney (Goodman, Morgenstern, and Wynder 1986), endometrium (La Vecchia et al. 1984), and prostate (Snowdon, Phillips, and Choi 1984). Other studies report no effect of body weight on increased risk for cancers of the breast (Adami et al. 1977; Soini 1977), colon (Wynder et al. 1969), and prostate (Greenwald et al. 1974). Table 4-8 summarizes some of these and other retrospective human studies of cancer and body weight.

In a large cohort study conducted by the American Cancer Society, the lowest overall cancer mortality was observed in men whose body weights ranged from 10 percent below to 20 percent above the average for their age and height. The lowest risk overall for women was seen in those whose weights ranged from 20 percent below to 10 percent above the average for their age and height. Nonsmoking males (who usually weigh more than

Table 4-8
Retrospective Human Studies Relating Body Weight and Cancer

First Author/ Year	Location	Comments
Breast		
de Waard 1964	The Netherlands	No statistical tests presented; 30% increased risk for obesity, and 60% increased risk for obesity plus hypertension; opposite trend in premenstrual women.
Valaoras 1969	Greece	Positive association with height, BW, and BMI.
Mirra 1971	Brazil	Associations observed among women 50 years old only; positive association with height, BW, and BMI.
Lin 1971	Taiwan	Increased effect among women 50 years old; no effect for height; positive effect for weight.
Adami 1977	Sweden	Nonsignificant case-control differences in mean BW and BMI in postmenopausal women. Opposite trend in premenopausal women also not significant; no effect for height; used measured BW for cases, self-reported BW for controls.
Soini 1977	Finland	Nonsignificant case-control differences for BW or BMI. Nonsignificant positive association with height; limited age range (41–60 years), and no analysis by menopausal status.
Hirayama 1978	Japan	Increased risk for postmenopausal women greater than for premenopausal. Independent positive associations for both BW and height.
Choi 1978	Canada	Increased BW in postmenopausal cases. Decreased BW in premenopausal cases. Postmenopausal cases also taller.
Paffenbarger 1980	U.S.	Increased risk with BMI in postmenopausal women. Decreased risk in premenopausal women. Increased height in premenopausal cases.