3. Factors Associated With Cancer

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3. Factors Associated With Cancer

A select committee of the World Health Organization (WHO) broadly defined environmentally caused cancers as those in which extrinsic factors are responsible (364):

> These include all environmental carcinogens (whether identified or not) as well as "modifying factors" that favor neoplasia of apparently intrinsic origin (e. g., hormonal imbalances, dietary deficiencies, and metabolic defects).

This overarching picture of "environment" contrasts sharply with the more usual use of the word "environment ." Common usage is restricted to what is seen as the purview of the Environmental Protection Agency (EPA): air, water, and soil.

The WHO committee expressed its belief that "the majority of cancers are caused by, or their causation modified by extrinsic factors" (364). This view represents a general consensus among cancer researchers, and lays the foundation for the theory that the majority of cancers are preventable. Individuals have gone further than the WHO committee, and have used figures of 60 to 90 percent for the proportion of cancers that are potentially preventable (31,115,164, 165,166,368). These and other estimates have been erroneously cited as if they referred only to man-caused pollution or even more narrowly, only to manmade chemicals, in the "environment. " In this report, "environment" is used to describe the gamut of exposures and behaviors that are associated with cancer.

GENETICS AND ENVIRONMENT

Environment, as used in this assessment, excludes genetic factors. Genetic makeup does, however, play a role in determining the probability of an individual developing cancer. Knudson ***(201)*** classifies all individuals as falling into four groups, according to the participation of heredity and environment in the possible development of cancer:

1. genetic predisposition to cancer even in the absence of environmental variation;
2. predisposition imposed by environmental variation in the absence of genetic variation;
3. predisposition imposed by both genetic and environmental factors; and
4. neither genetic nor environmental predisposition.

The first category represents individuals with a genetic defect who have an extremely high probability of developing one or more particular cancers, regardless of environmental factors. Retinoblastoma, a malignancy of the retina, is a childhood cancer which develops in about 95 percent of those with the genetic predisposition. Several other childhood tumors—neuroblastoma and Wilms' tumor of the kidney—fall into this category. In adults, polyposis of the colon, an inherited condition, often leads to colon cancer; another hereditary syndrome is characterized by high susceptibility to cancers of the colon and endometrium, and other inherited conditions are associated with other cancer sites. Fortunately, these conditions are relatively rare and are involved in probably 1 to 2 percent of all cancer. Categories 2 and 4 represent cancers which are not dependent on genetic susceptibility.

A well-understood example of the third category is xeroderma pigmentosum, a genetic condition involving a defect in deoxyribonucleic acid (DNA) repair mechanisms. *Affected individuals* exposed to ultraviolet light, a component of sunlight, develop skin tumors, as well as other skin abnormalities and some internal

tumors. However, if sunlight is avoided entirely, these individuals will not develop tumors. Both environmental and hereditary predisposing factors must be present for clinical manifestation of the disease.

Xeroderma pigmentosum is rare, but the occurrence of many common cancers have a genetic component as well. One of potentially large importance is an apparent relationship between genetically controlled responses to cigarette smoke carcinogens (197) and the probability of developing lung cancer.

Daughters of breast cancer patients have a higher risk of developing breast cancer than women without this family history, though many other factors affect the probability of the cancer occurring. Individuals with deeply pigmented skin have a lower risk of skin cancer induced by sunlight. (The above discussion draws heavily on Knudson (201).)

MULTISTAGE DEVELOPMENT OF CANCER

Cancer epidemiology and experimental carcinogenesis have established that the carcinogenic process is multifactor in its causation and multistage in its development (302).

Multifactored causality means that several agents, environmental and genetic, may be involved in cancer occurrence. The multistep development of cancer is pictured as involving at least two steps which must occur in sequence in the cell that is eventually to develop into a tumor. The two steps are generally called "initiation" and "promotion," and more general terms are "early" and "late" events.

Some substances, "complete carcinogens, " function both as initiators and promoters. Other substances are known to behave only as either initiators or promoters.

Initiation is seen as occurring in response to an external stimulus and produces a cell that is "latently premalignant" (302). The initiation event is generally thought to be a mutational change in the cell's genetic material, but the change is unexpressed and causes no detectable change in the cell's growth pattern. Initiated cells can remain as such for at least a large segment of the animal's life without being removed, destroyed, or otherwise harmed in any measurable way (116).

In laboratory experiments, exposure of an initiated cell to another substance, a promoter, converts the cell to an "irreversible malignancy" (302). Promoters convert only initiated cells to tumor cells and have no lasting effect on noninitiated cells. The long latency period between exposure to carcinogens and the manifestation of disease may represent the time necessary for the occurrence of a promotional event.

The importance of initiation and promotion (or early and late events in carcinogenicity) in humans is that interference in either one might reduce cancer's toll. Radman and Kinsella (302) draw attention to the possibility of identifying substances which can inhibit the activities of either initiators or promoters.

SHARED RESPONSIBILITY

Attribution of the risk of cancer to specific, single causes is the exception rather than the rule. Genetic factors affecting individual susceptibility are frequently part of the interaction. Of more relevance to this assessment are environmental agents which interact with each other to produce carcinogenic effects.

There is clear evidence that smoking acts synergistically with some other factors. Synergism in this context means that the number of cancers resulting from exposure to two agents is greater than the sum of cancers that would be expected from the two exposures individually. Smoking interacts with ionizing radiation to

produce cancer of the lung; and with alcohol to produce cancer of the esophagus. One of the best known synergisms is the interaction of tobacco and asbestos.

Asbestos and Smoking

In 1979, the Surgeon General stated (286):

> Asbestos provides one of the most dramatic examples of adverse health effects resulting from interaction between the smoking of tobacco products and an agent used in the workplace.

Exposure to asbestos is one of the most extensively studied occupational health hazards, and one which continues to attract the efforts of epidemiologists, in part because of its interaction with smoking, Indisputable evidence links asbestos to lung cancers and to rare cancer types, mesotheliomas of the pleura and the peritoneum. Smokers exposed to asbestos, especially those exposed at high levels, have a much greater probability of developing lung cancers than either smokers not exposed to asbestos, or nonsmokers exposed to asbestos. Rates for mesotheliomas, on the other hand, are similar for smokers and nonsmokers exposed to asbestos.

Hammond, Selikoff, and Seidman (156) have analyzed mortality data from a large group of U.S. male asbestos insulation workers. Computations were carried out comparing the insulation workers to a control group of males from a large cohort assembled by the American Cancer Society (ACS). Table 10 presents the results of the analysis, supporting the existence of strong synergism between smoking and exposure to asbestos in the production of lung cancer. As the authors explain, if the two exposures were acting independently in this cohort, one would predict the following (156):

> . . . the lung cancer death rate of asbestos workers with a history of cigarette smoking should be very close to the sum of the following three numbers: ***11.3*** (the rate for the "no,no" group), 47.1 (the mortality difference for the "yes, no" group), and 111.3 (the mortality difference for the "no, yes" group). The sum comes to **169.7** lung cancer deaths per 100,000 man-years . . . . In contrast, the observed lung cancer death rate of the "yes, yes" group was **601.6** per 100,000 man-years. The difference **(601.6 – 169.)7 = 431.9** lung cancer deaths per 100,000 man-years, was presumably due to a synergistic effect in men with both of the two types of exposure . . , .

Another measure, in addition to the mortality difference, is the mortality ratio, which in this case is the lung cancer death rate in each of the four exposure groups, divided by the lung cancer death rate in the group of nonsmokers who were not exposed to asbestos (group 1). The mortality ratio for exposure to both agents, 53.24, is much higher than would be expected from the additive effects of cigarette smoking alone (mortality ratio = 10.85) and asbestos exposure alone (mortality ratio = 5.17). The effects appear to be multiplicative.

Attribution of Risk

In the case of smoking and asbestos, and in other cases where two or a variety of factors interact to produce some cases of cancers, the disease may be prevented by interventions in any of the factors. Shared responsibility, however, complicates the attribution of risk to a

Table 10.—Age-Standardized Lung Cancer Death Rates[a] for Cigarette Smoking and/or Occupational Exposure to Asbestos Dust Compared With No Smoking and No Occupational Exposure to Asbestos Dust

Group	Exposure to asbestos?	History of cigarette smoking	Death rate	Mortality difference	Mortality ratio
Control	No	No	11.3	0.0	1.00
Asbestos workers	Yes	No	58.4	+ 47.1	5.17
Control	No	Yes	122.6	+ 111.3	10.85
Asbestos workers	Yes	Yes	601.6	+ 590.3	53.24

[a]Rate per 100000 m_{st}. years standardized for age on the distribution of the man-years of all the asbestos workers. Number Of lung cancer deaths based on death certificate information.

SOURCE: Hammond, Selikoff, and Seidman (156)

particular factor. Adding up the numbers of cases that might be prevented by various individual measures taken separately may produce a total number of "preventable" cancers larger than the number that actually occurs. An example of this concept, presented in table 11, is based on Lloyd's (214) analysis of the asbestos insulation worker mortality data described above. He estimated the percentage reduction in lung cancer mortality that would accrue by eliminating smoking cigarettes alone to be 88.5 percent, and by eliminating exposure to asbestos alone to be 79.6 percent. By eliminating both exposures, the total reduction would be 97.8 percent, and not the sum of the individual reductions, which would amount to a whopping 168.1 percent. The multifactorial nature of cancer means that it is impossible a present a neat balance sheet adding up to 100 percent that indicates the proportion of all cancers that can be attributed to factors X, Y, and Z.

Table 1 1.—Estimates of Percentage Reduction in Lung Cancer Mortality in Asbestos Workers by Elimination of Exposure to Cigarettes and to Asbestos

Status	Percentage reduction from current rate
Current	0.0
Eliminate smoking only	88.5
Eliminate asbestos only	79.6
Eliminate smoking and asbestos	97.8

SOURCE: Lloyd (214).

ESTIMATES OF THE AMOUNTS OF CANCER ASSOCIATED WITH ENVIRONMENTAL FACTORS

Diverse methods have been used to produce estimates of the amounts of cancer associated with various exposures and behaviors. The methods are variously described as ranging from "seat of the pants, " to "top of the head," to figures based on more quantified inputs. Evidence for associations between various "factors" and cancer ranges from very strong to very weak. There is no relationship between the strength of the association and the estimated magnitude of the amount of cancer associated with a factor. For instance, the strongest associations include those 'between smoking tobacco and respiratory cancers, between asbestos and cancer of the lung and other sites, and between ionizing radiation and cancer at many sites. While each of the three associations is strong, the percentage of cancer associated with each is different. Smoking is associated with more than 20 percent of cancer, asbestos with between 3 and 18 percent, and natural background radiation, with less than 1 to 3 percent.

The importance of a factor, as measured by the magnitude of the proportion of cancer with which it is associated, is one starting point for deciding on the development of preventive strategies. However, a large proportion, by itself does not give any indication of the practicality or availability of strategies. If all factors were equally well understood, and preventive strategies equally available, one would choose to go for big reductions. Under real conditions, strategies that can be implemented receive preference.

Most numerical estimates of associations are based on cancers occurring today or in the last few years. Therefore, they are not predictors of carcinogenic activity today, but reflections of carcinogenic activity in the past, possibly 20 to 50 years ago. A few authors have attempted to relate today's carcinogenic risk to future cancers and these are also cited.

All factors discussed here have not been" investigated equally in the scientific community, either because of perceived differences in relative importance, or because of difficulty in obtaining meaningful results. Therefore, it has not been possible for "equal" evidence to be presented for each factor in this assessment. Evidence for carcinogenicity in humans from good epidemiologic studies is given more weight than are animal data.

The remainder of this chapter discusses what is known about the contributions of the following factors to cancer incidence and mortality: tobacco, alcohol, diet, occupation, pollution, consumer products, medical drugs and radiation, sexual development, reproductive patterns and sexual practices, natural radiation, infection, and other or unknown associations. Current thinking, with some historical background, is presented for the major elements of each factor, and attempts are made to mention studies giving quantified estimates of the importance of various factors. [1]

I Discussion of the factors draws heavily on a contract report by Sir Richard Doll and Richard Pete, who were charged with reviewing existing literature about the quantified estimates of cancer causation. They also made their own estimates, which are cited in this assessment. Doll and Pete's report, in its entirety, is published in the *Journal of National Cancer Institute (93).*

The categories used are not necessarily "natural" assemblages, nor are they the only possible groupings of the components. The discussion of each factor includes a description of important inclusions and exclusions. For instance, the "diet" section looks at all "foodstuffs," including naturally occurring and added contaminants. Drinking water, which is discussed under "pollution, " and "alcohol," which is treated as a factor unto itself, are excluded from diet.

All of the estimates considered in preparing the following discussion of factors are listed in table 19, at the end of this chapter. Only "best estimates, " either point estimates or intervals, as presented by each author are included in the table. The primary references should be consulted for acceptable ranges and/or confidence limits, exact data sources and methods, and caveats.

TOBACCO

Diseases related to the smoking of tobacco include lung cancer and cancer at other sites, coronary heart disease and stroke, chronic bronchitis and emphysema, and many other diseases, including peptic ulcers (157). Tobacco smoking "is the single most important preventable environmental factor contributing to illness, disability, and death in the United States" (286). WHO (365) states:

> Smoking-related diseases are such important causes of disability and premature death in developing countries that the control of cigarette smoking could do more to improve health and prolong life in these countries than any single action in the whole field of preventive medicine.

The harmful effects of tobacco are greater when it is smoked as cigarettes than when consumed in other forms. This may be because acid cigarette smoke is less irritating than the alkaline smoke from pipes and cigars and, therefore, more easily inhaled. However, tobacco consumption in any form appears to be accompanied by adverse effects, most recently demonstrated in a study showing that long-time snuff dippers experience a highly increased risk of oral cancer (363).

Tobacco is known to contribute more heavily to the number of cancer deaths than any other single substance.. The relationship of cigarette smoking and cancer was first suggested in the 1920's. During the 1950's, results from many epidemiologic studies confirmed this association (287). Many carcinogens have been identified in cigarette smoke, and the differences consistently observed between rates of lung cancer among regular cigarette smokers and lifetime nonsmokers is so extreme that it is not likely to be an artifact of the epidemiologic method (287):

> The 1964 Surgeon General's Report reached the following conclusion: 'Cigarette smoking is causally related to lung cancer in men . . . The data for women, though less extensive, point in the same direction. '

Today, cigarette smoking is regarded as the major cause of lung cancer in both males and females and is largely responsible for the recent rapid rise in female lung cancer rates. The 1980 Surgeon General's report, The ***Health*** *Consequences of Smoking For Women,* states (287):

> . . . the first signs of an epidemic of smoking-related disease among women are now appearing.

It has been predicted that by the early 1980's, the age-adjusted female lung cancer death rate will surpass the breast cancer rate, which is today's leading cause of cancer death in women. The Surgeon General's 1980 report estimates (287):

> . . . smoking will contribute to 43 percent of the male and 18 percent of the female newly diagnosed cancer cases in the United States in 1980 and to 51 percent of the male and 26 percent of the female cancer deaths.

The principal impact of tobacco smoking is on the incidence of cancer of the lung although cancer at many other body sites, including larynx, oral cavity, esophagus, urinary bladder, kidney, and pancreas are also associated (287). By late middle age, the risk of developing lung cancer is more than 10 to 15 times greater in cigarette smokers than in lifelong nonsmokers (152). Present evidence indicates that the effect of smoking on the development of lung cancer is affected by number of years smoked, age when smoking began, the number of cigarettes smoked per day, the degree of inhalation, and the composition of the cigarette.

Studies have shown that discontinuing smoking decreases the risk of developing lung cancer. Ten to fifteen years following cessation of smoking, an ex-smoker's risk of dying of lung cancer decreases to a level only about two times higher than the risk for lifelong nonsmokers (286). This phenomenon is nicely illustrated by data in table 12 from an epidemiologic study of British doctors (92).

Higginson and Muir (166) attributed 30 percent of male and 7 percent of female cancers from 1968 through 1972 in the Birmingham and West Midland region of England to tobacco. They specifically ascribed 80 to 85 percent of lung cancers to smoking. Wynder and Gori (368) estimated that 28 percent of male and 8 percent of female 1976 cancer deaths in the United States can be attributed to smoking. Their estimate is based on calculating the percent difference between U.S. mortality rates and the lowest reported worldwide mortality rates for each site and by considering specific case-control studies.

Table 12.—Lung Cancer Mortality Ratios in Ex.Cigarette Smokers, by Number of Years Stopped Smoking

Years stopped smoking	Mortality ratio
Still smoking	15.8
1-4	"16.@
5-9	5.9
10-14	5.3
15+	2.0
Nonsmokers	1.0

[a]The higher mortality ratios observed in the 1-4 year Category after quitting compared to those continuing smoking is believed to be due 10 those individuals who quit smoking because of illness,

SOURCE: Doll and Peto (93).

Enstrom (100) reported:

> If all Americans did not smoke, the mortality reduction that would occur has been estimated to be 80,000 lung cancer deaths plus **22,000 other cancer deaths of the "1978 total of 390,000 cancer deaths—a** reduction of **26** percent.

Data from a representative sample of nonsmokers derived from a 1966–68 National Mortality Survey indicated that this group had a total cancer rate which was 24 percent less than that of all U.S. whites (100).

Numerous estimates have been made of the contribution of tobacco to the overall cancer rate. Most have taken advantage of concurrent epidemiologic cohort studies, in which large numbers of people are queried about their smoking habits at the initiation of the study and then followed to determine their causes of deaths. The largest such study involved 1 million Americans who were self-identified as smokers or nonsmokers in 1959 and whose subsequent mortality was monitored by ACS. The magnitude of the excess risk observed for women in the ACS population was less than for men. The difference is thought to be due to women having smoked fewer cigarettes per day, inhaling less deeply, and being more likely to smoke cigarettes with reduced tar and nicotine (153). In addition, women are less frequently exposed to occupational hazards, including those that may act additively or synergistically with tobacco to cause cancer.

Several researchers have evaluated data from the ACS study population. Doll and Peto (93)

computed mortality rates from the ACS study group and estimated that between 25 and 40 percent of 1978 American cancer deaths, with a best estimate of 30 percent (94,782 or 43 percent male; 27,266 or 15 percent female), could be attributed to tobacco smoking. Their computation method assumes that the male and female age-specific cancer death rates observed among the ACS nonsmokers, between 1960 and 1972, would have applied to the entire country had no one smoked.

Hammond and Seidman (155) estimated that from 25 to 35 percent of cancer mortality in the U.S. male population and 5 to 10 percent in the female population are "mainly due to smoking of tobacco products and cigarettes. " Enstrom (100) calculated a 38-percent reduction in the total cancer rate in the "never smoked regularly" group as compared with all U.S. whites. These estimates from ACS data do not greatly differ and the reported differences can be explained by the different methodological approaches and assumptions used. Hammond and Seidman (155) assumed that the age-specific distribution of smoking habits in the ACS group was similar to the country as a whole and relied on mortality rates computed for individuals classified as smokers in 1959, many of whom are known to have quit the habit by 1967. In the approach taken by Doll and Peto (93), it was unnecessary to speculate on the smoking habits of the general population and instead of using mortality rates for smokers, they relied on cancer rates in the nonsmoking group. The specifics of Enstrom's (100) calculations were not given.

Data derived from a unique study cohort such as the ACS population are not free of bias, but the risks estimated from the study are comparable with those found in a study of U.S. veterans. Rogot and Murray (312) reported mortality ratios for cigarette smokers versus nonsmokers and ex-cigarette smokers versus nonsmokers in a cohort of 250,000 American World War I veterans. After a 16-year followup period, lung cancer deaths occurred 11.3 times more frequently among smokers; laryngeal cancer 11.5 times, buccal cavity cancer, 4.2 times; pancreas and bladder cancer, approximately 2 times; and deaths from cancer at all other sites 1.38 times more often (see table 13). Studies from Great Britain (94,192) and other countries (286,287) show similar elevated cancer death rates among smokers.

Many of these estimates have been criticized for overstating the impact of tobacco on cancer. Objections are expressed because the studies measured mortality rather than incidence, and because they did not take into account improvements in survival, changes in smoking habits, and changes in cigarette composition. None of the estimates attempt to account for any effects of "passive smoking" and it is only recently that evidence of a carcinogenic effect

Table 13.–Mortality in a Population of U.S. Veterans Classified as Smokers Compared to Mortality Expected for Nonsmokers

Cause of death (7th Revision International Classification of Disease)	Cigarette smokers			Ex-cigarette smokers[a]		
	Observed deaths	Expected deaths	O - E[b]	Observed deaths	Expected deaths	O - E[b]
All cancers (140-207)	7,608	3,590'	2.12	2,816	2,025[c]	1.39
Cancer of buccal cavity (140-144)	110	26	4.22	24	14	1.67
Cancer of pancreas (157)	459	256	1.79	170	145	1.17
Cancer of larynx (161)	94	8	11.49	22	5	4.78
Cancer of lung and bronchus (162.1, 162.8, 163)	2,609	231	11.28	517	130	3.97
Cancer of bladder and other urinary organs (181)	326	151	2.16	126	90	1.41
All other cancers	4,010	2,916	1.38	1,957	1,642	1.19

[a]Only ex.cigarette smokers who stopped smoking cigarettes for reasons other than physicians' orders.
[b]O + E values are based on expected numbers to two decimal places.
[c]Values d. not exactly total due to rounding.

SOURCE Rogot and Murray (312)

from such exposure has been documented. Hirayama (167) reported an approximately twofold increased risk of developing lung cancer among nonsmoking wives of cigarette smokers. The effects may even be greater; a fourfold excess was estimated by Doll and Peto (93), who considered lifelong exposure, as would be the case with children.

A more precise estimate of the proportion of cancer associated with tobacco smoking requires a more exhaustive study of lung cancer. Such an effort might be desirable because of the importance of lung cancer to overall cancer rates. As American lung cancer death rates continue to rise, the estimate of the percentage of cancer deaths caused by tobacco will likewise increase. The future course of lung cancer rates depends largely on patterns of cigarette consumption and possibly on changes in tar and nicotine yields. The latter point may be particularly important in light of the large numbers of smokers who have switched to lower tar and nicotine cigarettes.

There is some evidence to indicate that low-tar/nicotine cigarettes may have a lesser carcinogenic risk (6,153,157,287). The tar and nicotine yield is believed to be a function both of the tar/nicotine content of the tobacco and the number of puffs taken (202). Therefore, a reduced risk is dependent on the smoker's behavior as well as the cigarette itself. The decreased risk from a "less hazardous" cigarette may be somewhat offset by an increase in the number of cigarettes smoked. Reports indicate that with the increased production of low-tar/nicotine cigarettes, there has been an increase in the number of cigarettes consumed per current smoker (286). It is also unknown whether chemicals newly added to cigarettes and changes in the composition of the gaseous phase will have health consequences.

The extent to which the increase in male and female lung cancer rates over the last few decades can be accounted for by tobacco is debated. Doll and Peto (93) argue that the increase within the last century can almost totally be explained by cigarette smoking, while others, Schneiderman (321) and the Toxic Substances Strategy Committee (345) included, contend that additional factors are responsible. (For a more complete discussion, see ch. 2.)

Examination of cigarette-consumption patterns in this country leads to speculations about future cancer statistics at tobacco-related sites. The proportion of adult men smoking cigarettes has declined from 51 to 37 percent during the period 1965 to 1978 (287). There has also been a slowdown in the rate of initiation of smoking among adolescent males. The decreases began at the time of release of the first Surgeon General's report in 1964, and the widespread discussion of the dangers of smoking that followed (287). This information demonstrates that worthwhile decreases in cigarette consumption can take place even without radical Government intervention, chiefly by increasing public awareness of the hazards of smoking. The proportion of adult women who smoke remained virtually constant at around 32 percent between 1965 and 1976, and has since started declining slightly. Unfortunately, the rate of smoking initiation among young women has not declined (287).

Changes in smoking habits that should lower risks are believed to have already influenced lung cancer rates. The rate of increase in lung cancer among men under 65 years of age has slowed during the last decade (see table 8 and fig. 10). Recent female mortality statistics are also promising, for they indicate that female lung cancer rates in the 30- to 49-year age group are steady or decreasing. There is reason to hope that with continued reductions in exposure to the harmful components of cigarettes, the decreases will follow through to older age groups.

Public health laws exclude tobacco from regulatory action because smoking tobacco is viewed as a personal decision, and one in which Congress has decided not to intervene. The Government limits its responsibility to informing smokers and potential smokers of the hazards of cigarettes, conducting behavioral studies on ways of affecting smoking habits, and supporting research on low-tar/nicotine cigarettes.

ALCOHOL

Alcohol is considered next because of the interaction between tobacco smoking and alcohol-related cancers. The National Institute on Alcohol Abuse and Alcoholism (NIAAA) (257) estimated that approximately one-third of adult Americans drink alcoholic beverages at least once a week and another third do not drink so regularly but drink primarily on special occasions. In addition, NIAAA estimated that there are 9.3 to 10 million "problem drinkers, " including alcoholics, in the adult population. Alcohol consumption is influenced by numerous personal characteristics including sex, age, education, socioeconomic status, occupation, residence, ethnicity, and religious affiliation.

Alcohol's association with cancer was first suspected around the turn of the century. Today, as is the case with tobacco, there is indisputable evidence that alcohol consumption increases the risk of developing cancer at various body sites. The 1978 Department of Health, Education, and Welfare (DHEW) report, *Alcohol and Health* (257), states:

> In comparison to the general population, heavy consumers of alcohol always show a marked excess of mortality from cancers of the mouth and pharynx, larynx, esophagus, liver, and lung. In the United States, these cancers range from 6.1 to 27.9 percent of the total incidence of all cancer recorded in those locations where there are cancer registries.

Epidemiologic studies have demonstrated that cancers are more common in men employed in trades that encourage the consumption of large amounts of alcohol. A recent study showed that Danish brewery workers have a higher risk of developing cancer then the general population (193). Clinical evidence suggests that consumption of alcohol at levels sufficient to cause cirrhosis of the liver also increases the incidence of liver cancer (257).

Researchers have tried to determine whether the association between alcoholic drink and cancer is due to the alcohol itself or to other chemicals found in spirits, wines, and beers (348). Pure grain alcohol (ethanol) has not been shown to be carcinogenic in animal bioassays (93,277); however, both pure ethanol and methanol, a contaminant of many alcoholic beverages, are mutagenic in bacteria (160,277). Additionally, many alcoholic drinks are found to be mutagenic. The resuIts from such experiments do not yet lead to firm conclusions, but it may be that components of alcoholic beverages as well as alcohol itself are related to increased cancer risk. Some evidence suggests that the risk of cancer is greatest when alcohol is consumed as spirits and that the apple-based drinks consumed in Northwest France are particularly harmful (93). However, the carcinogenic effect of alcoholic beverages is largely independent of the form in which it is drunk. In addition to a direct effect, alcohol may also exert a carcinogenic effect by facilitating contact between extrinsic carcinogenic chemicals and the contents of the stem cells that line the upper digestive tract and larynx.

Epidemiologic evidence supports the view that excessive alcohol consumption increases the risk of developing cancers of the mouth (excluding lip), larynx, and esophagus and that alcohol acts additively and even synergistically with tobacco in the pathogenesis of cancers of the upper digestive tract (257,367).

Most estimates of the percentage of cancer associated with alcohol fall in the 3- to 5-percent range. From data presented by Schottenfeld (233), alcohol appears to be associated with 4 to 5 percent of 1978 U.S. cancer deaths; Wynder and Gori (368) estimated 4 percent male and 1 percent female 1976 U.S. cancer incidence; and Higginson and Muir (166) estimated 5 percent male and 3 percent female 1968–1972 cancers in the Birmingham and West Midland region of England.

Rothman (313) (see table 14) and Doll and Peto (93) estimated that 3 percent of U.S. cancer mortality is related to alcohol. Rothman's calculations are based on attributing a proportion of 1974 cancer deaths at each alcohol-related body site to alcohol consumption. Doll

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Table 14.—Praportion of Cancer Deaths Attributable to Alcohol Consumption by Site and Sex

	Males			Females		
Body site	Number of deaths[a] from cancer	Percent ascribed[b] to alcohol	Number of deaths ascribed to alcohol	Number of deaths[a] from cancer	Percent ascribed[b] to alcohol	Number of deaths ascribed to alcohol
Buccal cavity and pharynx . . .	5,686	50	2,843	2,282	40	913
Esophagus . .	4,917	75	3,688	1,735	75	1,301
Liver.	1,600	30	480	865	30	260
Larynx	2,826	50	1,413	436	40	174
Total.	15,029		8,424	5,318		2,648
Total cancer deaths	**199,194**	**4.2**		**166,338**	**1.6**	

[a] In 1974
[b] Proportion of alcohol. caused cancer at each site from (313).

SOURCE: Adapted from Rothrnan (313).

and Peto assume that cancers at sites related to alcohol consumption account for 7 percent of all cancer deaths in men and 3 percent in women. They attribute to alcohol about two-thirds of these cancer deaths in men, about one-third in women, plus a small proportion of the liver cancer deaths (which constitute less than 1 percent of all cancer deaths) and derive overall estimates for the combined sexes of 3 percent (range: 2 to 4 percent:). It should be emphasized that most of the cancer risk posed by alcohol consumption is also related to cigarette smoking. Therefore, most of the cancer deaths caused by alcohol would be avoided in the absence of smoking even if alcohol consumption remained unchanged.

Table 15 shows annual incidence rates for alcohol-related cancer sites for several regions in the United States where cancer registries exist (348). Among the white population, the proportion of total cancer incidence associated with

Table 15.—Age-Adjusted Annual incidence Rates for Selected Cancer Sites in Various Population Groups in the United States

Place	Population	Tongue	Mouth	Oropharynx	Hypopharynx	Esophagus	Liver	Larynx	Total for the 7 cancer sites	Proportion 01 all cancers (O/.)
California:										
Alameda	White	3.0	3.7	2.2	1.1	3.6	2.2	7.9	23.7	8.5
	Black	2.2	4.1	2.2	1.5	13.2	4.3	12.9	40.4	12.3
Bay Area	White	3.2	4.2	2.6	1.5	**4.0**	2.8	7.5	25.8	13.6
	Black	2.1	4.8	3.3	1.5	**15.2**	4.2	11.8	42.9	12.5
Connecticut		2.8	4.3	2.1	1.5	5.7	**2.0**	7.8	26.2	9.2
Iowa		1.4	2.6	1.1	1.2	**3.0**	1.6	5.8	16.7	6.7
Detroit	White	2.7	3.3	**2.0**	1.2	**4.0**	2.6	7.5	23.3	&7
	Black	3.3	3.3	**2.1**	1.1	**14.1**	4.5	7.7	36.1	11.3
New Mexico	Spanish	**0.4**	**0.7**	**0.4**	**0.2**	2.2	**3.0**	2.7	9.6	6.1
	Other white	2.2	**2.8**	**1.4**	**3.0**	**3.0**	**3.1**	5.8	18.6	6.7
New York State		2.2	3.2	1.3	0.8	4.5	1.9	5.9	19.8	**8.0**
Puerto Rico		7.5	7.8	4.3	4.4	14.8	3.3	6.4	48.5	27.9
Utah		2.1	2.5	**0.9**	**0.4**	1.8	**0.9**	4.4	**13.0**	6.1

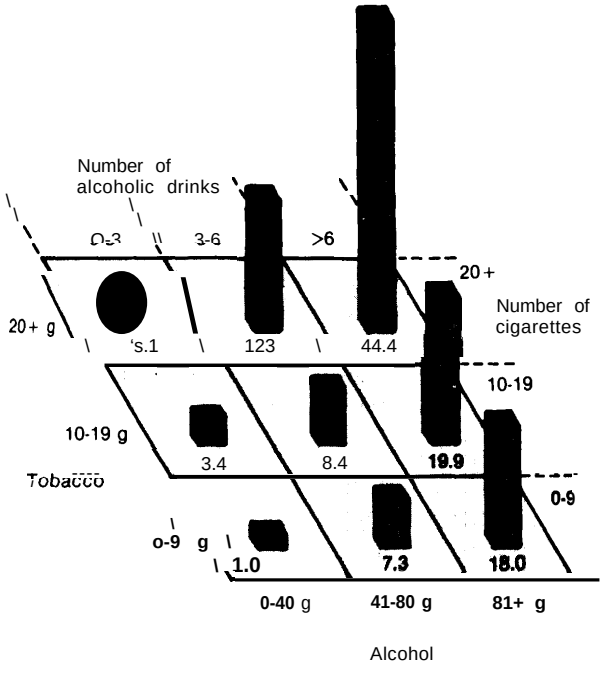
SOURCE: Tuyns (348)

alcohol varies from 6.1 to 9.1 percent but reaches 11.3 to 12.5 percent among blacks. The highest proportion, 27.9 percent, is found among people living in Puerto Rico. It should be noted that these data refer only to those cancers for which an obvious association with alcohol consumption has been demonstrated.

Estimating the proportion of cancer attributable to alcohol alone is hindered by the difficulty of obtaining accurate data on the amount of alcohol consumed. Results of studies must also be interpreted with caution in view of the fact that individuals who do not drink are often distinguished by behavioral characteristics very different from those seen in drinkers, many of which may affect cancer incidence.

Figure 18 depicts the relative risk of developing esophageal cancer in relation to different

Figure 18.—Relative Risks of Esophageal Cancer in Relation to the Daily Consumption of Alcohol and Tobacco



Note: The risk is 44.4 times greater for individuals consuming 20 g or more of tobacco and 80 g or more of alcohol per day (upper right block) than for individuals consuming little or none of either drug (lower left block). One ounce of ethyl alcohol is approximately 23.4 grams, thus 40 grams is 1.7 oz. or approximately equivalent to 3 drinks.

SOURCE National Institute on Alcohol Abuse and Alcoholism (257)

smoking and drinking habits. The risk of the nonsmoker developing cancer from the consumption of even very large amounts of alcohol is small.

Feldman et al. (118) found that the risk of head and neck cancer was 6 to 15 times greater in heavy drinkers who smoked than in nondrinkers and nonsmokers. Nonsmoking drinkers had a "slightly" higher risk (around 1.5) than total abstainers while nondrinking or light drinking smokers had 2 to 4 times the risk.

Breslow and Enstrom (32) correlated average annual age-adjusted cancer mortality rates for the period 1950-1967 with per capita consumption of cigarettes, spirits, wine, and beer as estimated from 1976 tax receipts in 41 States. As expected, respiratory cancers were related to cigarette consumption. They also found a correlation between consumption of spirits and certain cancers of the upper alimentary tract. In addition, cancers of the stomach, large intestine, kidney, bladder (for men), and breast (for women), were correlated with spirits consumption. The strongest correlation was found between rectal cancer and beer consumption. This finding was also observed in a separate analysis involving 24 countries.

A retrospective study of male veterans by Rothman and Keller (315) demonstrated individual effects for smoking and drinking and synergistic effects for cancers of the mouth and pharynx. Both they and Schottenfeld (323) calculated that 76 percent of cancers at alcohol and tobacco-related sites, which represents 36 percent of total male cancer mortality, could be eliminated if drinking and smoking were avoided.

Examining trends of alcohol consumption permits some speculation about future cancer rates. Quantitative estimates cannot be made, but several factors highlighted in the *Third Special Report to the U.S. Congress on Alcohol and Health (257)* indicate that alcohol will increase in importance as a carcinogenic factor:

- Increased availability of alcoholic beverages has occurred as a result of the lowering of the drinking age in several States, a trend to longer hours of sales, and an increase in

the number of retail outlets. (Recently, several States have raised drinking ages.)

- Around 1960, total per capita sales of absolute ethanol began to rise significantly registering a 30-percent gain between 1961 and 1971. Since 1971, there has been virtually no change in per capita sales. The effect of the overall increase may not yet have fully manifested itself in cancer rates.
- There is particular concern over increased alcohol consumption in youths. This is heightened by the observation that early drinking behavior predicts drinking habits in later life.
- The proportion of high school students who reported ever having been drunk increased dramatically from 19 percent before **1966** to **4.5** percent between 1966 and 1975. The proportion reporting being intoxicated at least once a month rose from 10 percent before 1966 to 19 percent between 1966 and 1975.

The importance of alcohol as a health hazard is not limited to its association with a relatively small percentage of cancer. Estimates of the annual number of deaths related to alcohol range from 37,000 to 205,000. Cirrhosis of the liver, the seventh leading cause of death in the United States, was responsible for 30,066 deaths in 1978. As an contributory cause of homicides, suicides, and accidents, alcohol's toll is even greater. The Institute of Medicine (178) recently completed a study of alcoholism and related problems and indicated several opportunities for research. These included further research on alcohol metabolism, development of appropriate animal models, and further efforts through epidemiologic studies to explore the link between alcohol and its adverse health consequences.

DIET

Introduction

Studying the relationship of diet and health is a continued source of frustration and excitement. Food affects all body functions and comes into direct contact with the digestive system and indirect contact with all other organs. Cancer rates for digestive sites vary considerably around the world and have prompted studies of diet's role in cancer causation.

As discussed here, diet encompasses those items ingested as food, including substances added to food, those produced during normal cooking, storage, and digestion, but excluding drinking water and alcohol (discussed in this chapter under *Air and* **Water** *Pollution* and *Alcohol,* respectively).

The amounts and balance of the major components of diet are generally believed to be responsible for the lion's share of diet-related cancers. Deficiencies or excesses of microelements, and the presence of additives or contaminants, are probably less important. The various means by which diet may influence the development of cancer are listed in table 16. Diet also plays a role in the treatment of cancer illustrating the pervasive role of diet with respect to all aspects of the disease.

Unfortunately, dietary studies **are** plagued with methodological problems and conflicting evidence exists for almost every specific question that has been investigated. The overall association of cancer with diet exists but there is no reliable indication of exactly what dietary changes would be of major importance in reducing cancer incidence and mortality.

The strongest positive associations identified through correlations of dietary patterns and cancer rates are those between total fat intake, particularly animal fat consumption and cancers of the breast and endometrium; and between total protein intake and cancer of the colon. The most dramatic change observed in a diet-related cancer site has been the reduction in incidence and mortality from stomach cancer. In the United States, the 1950 age-adjusted mortality rate from stomach cancer was 24.4/100,000 for males and 13.1/100,000 for females

Table 16.—Some Currently Attractive Hypothetical or Actual Ways in Which Diet May Affect the Incidence of Cancer

Possible ways or means	Example[a]
Ingest ion of powerful, direct-acting carcinogens or t heir precursors	Carcinogens in natural foodstuffs (plant products) Carcinogens produced in cooking Carcinogens produced in stored food by microorganisms (bacterial and fungal)
Affecting the formation of carcinogens in t he body	Providing substrates for the formation of carcinogens in the body (e.g., nit rites, nitrates, secondary amines) Altering intake or excretion of cholesterol and bile acids (and hence the production of carcinogenic metabolizes in the bowel) Altering the bacterial flora of the bowel (and hence the capacity to form carcinogenic metabolizes)
Affecting transport, activation, or deactivation of carcinogens	Altering concentration in, or duration of contract with, feces Altering transport of carcinogens to stem cells Induction or inhibition of enzymes (which affect carcinogen metabolism or catabolism) Deactivation, or prevention of formation, of short-lived intracellular species (e.g., by use of selenium, vitamin E, or otherwise trapping free radicals; by use of b-carotene or otherwise quenching singlet oxygen; by use of other antioxidant)
Affecting "promotion" of cells (that are already initiated)[b]	Vitamin A deficiency (clinical or subclinical) Retinol [Binding Protein] (hormonal and other factors determine blood RBP, though vitamin A intake may not affect it much) Otherwise affecting stemcell differentiation (carotenoids? determinants of lipid "profile"?)
Overnutrition	Age at menarche Adipose-t issue-derived estrogens Other effects

aThere may be considerable overlap between many of the entries in this table
bOr, more generally, affecting th, probability that a partially transformed stem cell will become fully transformed and will proliferate successfully Into Cancer

SOURCE Doll and Peto (93)

while in 1977 the rate was 8.8/100,000 for males and 4.0/100,000 for females. This decrease has occurred in many other countries, including those with high initial rates, such as Japan and Iceland, and those with lower initial rates, such as Canada and New Zealand. The factors believed to have contributed to these decreases include: reduction in use of salt and pickling, lower consumption of smoked foods, and increased use of refrigeration, increased consumption of milk, green vegetables, fruit, and antioxidants (237).

In general, as a result of increased intake of calories, proteins, and certain other nutrients, Americans have been growing taller and reaching sexual maturation earlier. A great improvement in the Nation's health has resulted from this change, but increased risk for certain cancer sites may accompany the improvement. For example, earlier sexual maturation in women is associated with higher risk of breast cancer later in life, though as yet, no increases in breast cancer has been attributed directly to improved nutrition (see Sexual *Development, Reproductive Patterns, and Sexual Practices* for a more complete discussion of this topic).

Many estimates of the importance of diet to cancer have been put forth. Doll and Peto (93) estimated that altering dietary practices may reduce cancer by as much as 35 percent (stomach and large bowel cancer by 90 percent; endometrium, gallbladder, pancreas, and breast by 50 percent; lung, larynx, bladder, cervix, mouth, pharynx, and esophagus by 20 percent; others by 10 percent). The great uncertainty of this estimate is indicated by the range of 10 to **70** percent which they attach to their estimate. Wynder and Gori (368) estimate, by calculating

the percent difference between U.S. mortality rates and the lowest rates reported worldwide and by considering specific case-control studies, that an even larger proportion of cancer, approximately 40 percent in males and 60 percent in females, could be attributable to diet.

In testimony before the Subcommittee on Nutrition of the Senate Committee on Agriculture, Nutrition, and Forestry, Dr. Arthur Upton (353), then-Director of the National Cancer Institute (NCI), succinctly discussed the extent of involvement of diet and cancer when he stated:

> Despite the impression that cancers are linked with dietary patterns and the inability to pinpoint specific dietary carcinogens, scientists generally agree that factors in diet and nutrition-including drinking water contaminants—appear to be related to a large number of human cancers, perhaps approaching 50 percent.

Dietary Intake

Fat/Meat Intake

Examination of cancer rates in different countries show positive correlations between colon cancer and consumption of meat and animal protein and between cancer of the breast and endometrium with total fat consumption (17). These cancers are common in the United States, Canada, and Western Europe and rarer throughout the developing world.

The most widely held theory is that fat in the diet has a promotional effect on the development of cancer. One suggested mechanism is that fats affect hormone levels. Several cancers, including breast, ovarian, and endometrial are, in turn, influenced by hormones. This association of dietary fat with higher cancer rates is, however, not found uniformly. Breast and colorectal cancers are not uncommon among vegetarians, and the observed incidence in Seventh Day Adventists who are largely vegetarian, is matched by the same incidence in Mormons who eat meat (293). This finding and the fact that meat intake among Mormons is not markedly lower than among the general population is often cited as a rebuttal to the meat/fat cancer causation hypothesis. These interpretations should be viewed cautiously for the studies may not have been adequate to reflect any promotional effect in these low risk groups who are less exposed to many other types of carcinogenic stimuli, such as, cigarettes and alcohol, than is the general population. Additional studies in this area are needed.

More and more, studies have focused on specific types of fat. Evidence suggests that diets with a high ratio of polyunsaturated fats (mainly of vegetable origin) to saturated fats (mainly of animal origin) may increase the risk of cancer. Paradoxically, this type of diet is recommended to lower the risk of heart disease. Results from epidemiological studies (98,290) and animal trials (53,305) have been inconsistent and confusing, and have shown different effects on different cancer sites. In rats, polyunsaturated fats need be only a small proportion of a total high fat intake to promote breast tumor incidence. If the animal model is applicable to humans, virtually all high-fat diets will exert a promotional effect (52).

Serum cholesterol has been investigated in many studies as a risk factor for various cancers. Serum levels are directly affected by intake of cholesterol and fat. A diet with a low saturated fat to polyunsaturated fat ratio decreases the amount of ingested cholesterol that will appear in the serum. The discovery that the stools of colorectal cancer patients contain an abnormally high proportion of acid steroids, derived from bile salts, and cholesterol, supports the hypothesis that certain types of fat play a role in the production of colorectal cancer.

A recent epidemiologic study found an association between high-density lipoproteins and cancer risk (199). On the other hand, in a prospective epidemiologic study of heart disease in Framingham, Mass., serum cholesterol levels were inversely associated with the incidence of colon cancer and other sites in men. Men with the lowest serum cholesterol levels experienced a colon cancer rate which was three times higher than men with the higher cholesterol levels (361). A similar negative association was reported in data from the Paris Prospective Study of Coronary Heart Disease (45).

The hypothesis that dietary cholesterol plays a direct role in the production of colon cancer is supported by some animal studies. For instance, the addition of cholesterol to the diet of rats on a cholesterol-free liquid diet, had a promotional effect and cholesterol enhanced the carcinogenic effect of a known carcinogen (1,2 dimethylhydrazine).

Fiber Intake

Burkitt (40) observed that several intestinal diseases that are common in developed countries are rare in rural Africa where unprocessed food is consumed, and the stools tend to be soft, bulky, and frequent. It is suggested that dietary fiber may reduce colorectal cancer by decreasing the time stools remain in the bowel, by increasing bulk (thereby decreasing the concentration of carcinogens in stool), or by perhaps altering the distribution of bacteria, some of which may produce or destroy carcinogenic metabolizes.

The effects of fiber on cancer incidence have attracted much interest but remain problematical. As in the case of fats, dietary fiber is a term which covers a multitude of different substances, each of which may have different influences on carcinogenesis. The methods by which types of fiber are chemically characterized are still in a primitive state, and analyses of the composition of dietary fiber in many foods is lacking. Despite the drawbacks, some associations have emerged. A close inverse correlation has been found between the pentose fiber content of the diet and mortality from colon cancer in part of the United Kingdom (93). No correlation was shown with any other fiber types, or with dietary fiber as a whole.

Elements and Vitamins

Several metals and vitamins are linked with cancer development. They can either act as carcinogens themselves or they may biologically compete with other dietary constituents to enhance or suppress a cancerous response.

An iron-deficient syndrome was shown to be associated with a high risk of developing cancers of the pharyngeal and esophageal mucosa in northern Scandinavia. The incidence of gastric cancer is found to be 4 to 5 times higher in countries where iron deficiency is prevalent than in the United States (356).

Selenium, an effective antioxidant, is often found at higher levels in plants, milk, or human blood in sections of the United States with low cancer rates. Selenium deficiency in rats consistently increases the carcinogenic effect of known chemical carcinogens, particularly in animals fed on high polyunsaturated fat diets (190). Supplementation with selenium above dietary requirements decreases tumor yield in animals on both low- and high-polyunsaturated fat diets (188).

Stocks and Davies (24) found that a high zinc-copper ratio in soils was associated with elevated rates of human stomach cancer while Strain et al. (24) reported an association of elevated cancer rates with low zinc-copper ratios. Marginal zinc deficiency is associated with increased esophageal cancer in animals (122) and esophageal cancer patients had lower levels of zinc in their blood, hair, and tumor tissue than controls in a study of Chinese men (211). Zinc deficiency may interact synergistically with alcohol to enhance esophageal carcinogenesis (135).

The overall relationship between cancer and vitamins is not well understood. Vitamin C has been shown to reduce carcinogen formation in experimental animals (359), and this activity may be important in reducing cancer occurrence. Vitamin A (retinol) has been more exhaustively studied than any other vitamin (for review see 292) and it has been suggested that vitamin A, or, more particularly, its vegetable precursor, beta-carotene, may decrease the susceptibility of a variety of epithelial tissues to the development of cancer. Retinol (or its analogs retinoic acid and various retinoids) has been repeatedly demonstrated to diminish the risk of experimentally induced cancer in laboratory animals (93). These results are particularly intriguing because the protective effect is observed even when these substances are fed long after the animal is treated with an initiating carcinogen, and the vitamin and its analogs appear to be effective at a wide variety of sites.

People with a history of consuming above average amounts of provitamin A (beta-carotene) have a slightly lower incidence of several different types of cancer than people who give a history of consuming less. Beta-carotene is found in carrots, green leafy vegetables and in red palm oil which is used for cooking in many tropical countries. Further epidemiologic studies are now in progress in areas where red palm oil is habitually used. The role of beta-carotene in cancer prevention is still uncertain and this particular hypothesis has been mentioned to illustrate the potential importance of diet.

Local deficiency of folate (a B-complex vitamin) has been demonstrated in the abnormal cervical tissue of some women taking oral contraceptives. The observed abnormalities are often precursors of cervical cancer. Supplementation with folic acid in these women can reverse the abnormality and appears to prevent progression to carcinoma (41). Deficiencies of lipotropes (choline, methionine, and folic acid) increased the susceptibility of animals to a variety of environment carcinogens in several studies (311).

Dietary Balance

Studies in laboratory animals have shown that altering gross aspects of diet can have substantial impact on the risk of an animal developing cancer. Jose (195) reviewed several reports which demonstrate that restricting calorie intake without modifying the proportion of the individual constituents reduces the incidence of spontaneous tumors and of a variety of cancers produced by exposure to known carcinogens. Not only did calorie restriction result in decreased incidence of tumors, but it also delayed the time of appearance of tumors, and when tumors appeared, they grew and metastasized more slowly. The life spans of animals on restricted diets were often increased up to 50 percent compared to normally fed controls. However, decreased calorie intake, when accompanied by inadequate protein intake makes laboratory animals more susceptible to many environmental carcinogens (47).

A suspected association between obesity and the risk of cancer was strengthened in an epidemiologic study conducted by ACS which followed 750,000 people from 1959 to 1972 (207). Overall cancer mortality was found elevated for those individuals who were more than 40 percent heavier than average. Mortality from cancers of the colon and rectum were increased among men while mortality from cancers of the gallbladder and biliary passages, breast, cervix, endometrium, and ovary were increased among women. The meaning to be attached to the results is not entirely clear since weight is associated with a variety of social and behavioral characteristics that affect the risk of cancer in other ways, including smoking habits and socioeconomic status. Another concern is that diagnosing cancers may be more difficult in obese individuals, and cancers may generally be more advanced when they are detected.

In addition to the quantity and composition of food, the timing of intake has also been shown to be important. For example, Roe and Tucker (cited in 93) randomized mice with a high spontaneous incidence of mammary tumors, between continuous feeding, in which the mice were fed 6 g of food each day, which they consumed in frequent small amounts, and intermittent feeding, in which food was limited to 5 g per day which was eaten at once. No clear difference in longevity was observed, but nonfatal spontaneous mammary tumors arose in 64 percent of the continuously fed mice and in only 8 percent of those fed intermittently.

Immune function in both humans and animals can be severely compromised by deficiencies of certain dietary nutrients—in particular, protein, methionine, choline, folate, vitamin B_{12}, vitamin A, zinc, and pyridoxine (147). Deficiencies in certain of these nutrients, with a concomitant depression of immune system function have been demonstrated in animals and are suspected of increasing the susceptibility of developing certain cancers (356).

Naturally Occurring Carcinogens and Precursors

Along with the major components, thousands of chemical substances occur in small quantities in foods. Most naturally occurring carcinogens

and mutagens are of plant origin, but an important class, nitrates and nitrites, occurs in both plants and animals.

Nitrates and Nitrites

Nitrate and nitrite salts naturally occur in vegetables, fish, and meat, are added to food for their preservative properties (see *Additives* p. 82), and are present in pesticide and drug residues in food (127). They react with other chemicals in the body to produce N-nitrosamines and N-nitrosamides. N-nitrosamines are among the most powerful chemical carcinogens in laboratory animals, producing tumors at a variety of sites including liver, kidney, lungs, esophagus, bladder, pancreas, trachea, nasal cavities, and peripheral nervous system (221). Experimentally, vitamin C has been shown to inhibit the formation of nitrosamines (359).

Epidemiological evidence linking nitrites and nitrates to cancer is fragmentary. Evidence for a relationship between gastric cancer and the nitrite content of the diet is not wholly consistent. It is notable that vegetables, which are usually the main source of dietary nitrates, appear to protect against the development of the disease, possibly because of their vitamin C content (93). On present knowledge, the possible contribution of dietary nitrates and secondary amines to the production of cancer is uncertain.

Other Substances

Cycasin in the cycad nut, safrole in sassafras, pyrrolizidine alkaloids in some plants, and extracts of coltsfoot and bracken fern are a few naturally occurring compounds which exhibit carcinogenic properties in animals. Only bracken fern has been demonstrated to cause cancer in man. Bracken fern is commonly eaten in Japan, and Japanese who eat it daily have three times the risk of developing cancer of the esophagus as Japanese who do not eat it at all (93). It has been postulated that the high bowel cancer rates in Scotland may be due to the ingestion of cattle fed on bracken fern or the leaching of the carcinogenic components into water or food (24). Range-fed cattle and sheep may pass pyrrolizidine alkaloids along to humans in their meat and milk (215).

Certain plant-derived preparations are associated with cancer. Extracts of some plants used to make herbal infusions, for use as home remedies, tonics or beverages, are carcinogenic in animals, and their tannin-containing fractions are particularly active. Some population groups who use these products have high rates of esophageal cancer, suggesting an association (297). Perhaps of greater concern, because of its widespread use, coffee has been associated with human bladder (24) and pancreatic cancer (220), but whether the associations are causal is not yet known. Studies in animal cell cultures have shown caffeine, a constituent of both coffee and tea, to potentate the effect of carcinogenic substances **(96).**

Mutagenic substances have also been identified in cruciferous plants (cabbage, broccoli, etc.), from cereal grains, and some grazing range plants in the Southwestern United States (MacGregor, 1980). Other not-yet-identified carcinogens and mutagens may occur naturally in food, but on present evidence, naturally occurring carcinogens are not regarded as an important cause of cancer in the United States (93).

Carcinogens and Precursors Produced by Cooking

Another possible source of carcinogens is their production in cooking. Humans are the only animals that cook their food, and it has been known for many years that carcinogenic chemicals such as benzo(a)pyrene (B(a)P) and other polycyclic hydrocarbons are produced when meat or fish is broiled or smoked or when food is fried in fat which has been used repeatedly, Sugimura et al. (336) demonstrated that broiling also produces powerful mutagens that cannot be accounted for by the production of B(a)P alone. Few people eat more broiled foods than Americans and while the declining stomach cancer rate provides some assurance that cancer at that site is not related to broiled food, the possibility remains that colorectal cancer, which has not decreased materially, might be related, Recent

evidence has shown that mutagens can in fact be produced by cooking at relatively low temperatures (100-200C) (93).

Contaminants

Natural Contaminants

A less obvious source of carcinogenic activity and one that was overlooked altogether until the early 1960's, is the production of carcinogens by micro-organisms in stored food. Aflatoxin, a product of the fungus *Aspergillus* flavus, is the most powerful liver carcinogen known for some animal species. In addition, human liver cells contain the enzymes necessary to produce the metabolic products that appear to be responsible for its activity. l-here is evidence for believing that aflatoxin is a major factor in the production of liver cancer in certain tropical countries where it is a contaminant of carbohydrate foods, particularly grains and nuts. The incidence rates of primary liver cancer in different parts of Africa are approximately proportional to the amount of aflatoxin in the diet (212).

Liver cancer occurs more commonly in people who are chronically infected with hepatitis B virus and it seems probable that where aflatoxin is present in the diet, both aflatoxin and hepatitis B virus contribute to the risk of liver cancer, each multiplying the other's effects.

In the United States, primary cancer of the liver is a rare disease accounting for less than 1 percent of cancer deaths (2,796 deaths in 1978). The amount of aflatoxin in the American diet is small and is only one among several other possible causes of liver cancer. In the American context, the chief importance of the discovery of the dangers of aflatoxin is that it raises the possibility that other as yet unrecognized mycotoxins in food may be carcinogenic. Recently, there has been some evidence to suggest that a fungus may contribute to the high incidence of esophageal cancer in parts of China by increasing the nitrite content of contaminated food (209).

Environmental Contaminants

In late 1979, OTA (284) examined both regulatory approaches and monitoring strategies for coping with contaminated food. A wide variety of industrial products ranging from heavy metals and pesticide residues, to substances that leach out of packaging, such as polyinyl chloride, can pollute food. Organic compounds are felt to pose the greatest potential for environmental food contamination based on the number, volume, and toxicity of organics manufactured in the United States.

Polycyclic aromatic hydrocarbons (PAH) are found widely in all types of foods, sometimes at the same level which can be present in charcoal-broiled meats and smoked ham, i.e., up to 15 ug B(a)P/kg net weight. Some shellfish and finfish from polluted waters have been reported to contain up to 1,000 ug B(a) P/kg. The importance of ingested B(a)P in cancer induction is uncertain. Epidemiologically, no relationship has been established, and when cancer is produced experimentally in laboratory animals, it either affects an organ not represented in man or occurs by a mechanism that does not appear relevant (93).

Some chlorinated hydrocarbons that were used as pesticides (e.g., DDT, aldrin, dieldrin) produce liver tumors (hepatomas) in mice, and some have been shown to be carcinogenic in other species. These compounds accumulate in human fat, but no increase in liver tumors appears to have accompanied their introduction and use. However, the latent period is not known, and the possibility exists that effects may be seen some years from now. Pesticide residues in the form of secondary amines may constitute a hazard if the formation of nitrosamines in the stomach proves to be a cause of cancer in man.

Many other chemicals fall into this category of environmental contaminants. The extent to which these have contributed to the production of human cancers is difficult to evaluate, but believed to be small (328).

Additives

Chemicals are used to preserve food and give it color, flavor, and consistency. Food dyes were among the first chemicals investigated because of their structural similarities to accepted chemical carcinogens (24). Consumption of

chemicals by consumers who are unaware of their presence is partially responsible for the food safety laws. The laws require that newly introduced direct food additives be carefully screened in the laboratory before they may be used.

Some definitely carcinogenic chemicals, which have now been withdrawn from foods, were used for a time before their carcinogenicity in animals was discovered. These include butter yellow, thiourea, and a food preservative used in Japan. The number of cancers, if any, which these additives produced is unknown. Doll and Peto (93) estimated an attribution of less than 1 percent of total cancer mortality to food additives.

Of the many food additives presently used in the United States, three require special consideration: the artificial sweeteners cyclamates and saccharin, butylated hydroxytoluene (BHT), and nitrites and nitrates.

Cyclamates were shown to produce bladder cancer in animals (24) and were removed from commerce in 1969. OTA (282) reviewed data that show saccharin caused cancer of the bladder in rats in two circumstances: 1) in straightforward feeding studies when given over two generations, and 2) when given following the administration of a powerful carcinogen. OTA also reported positive and negative results from a number of short-term tests. Therefore, some evidence supports the conclusion that saccharin causes cancer in defined conditions. The human evidence that has been collected over the last few years fails to distinguish clearly between saccharin and cyclamates, but it is more relevant to the former as the use of saccharin began earlier (in 1902) and has continued longer. An increase in incidence or mortality from bladder cancer could not be attributed to the introduction of saccharin (16).

One epidemiologic study (175) showed that ingestion of artificial sweeteners by males increased their relative risk of bladder cancer to 1.6. (The incidence of bladder cancer among men who did not consume saccharin was taken as relative risk equal to 1.0; saccharin users had a risk 60-percent higher). The results reported in the study were consistent with those from the laboratory. In both cases cancer occurred in the bladder in males.

Subsequent epidemiologic studies have failed to confirm the relative risk of 1,6. The large case-control study of bladder cancer in the United States conducted by NCI revealed relative risks of 0.99 for males and 1.01 for females among users of artificial sweeteners in any form (174). However, Wilson (362) points out that one projection from animal studies suggests that only about 500 bladder cancer cases annually are to be expected from saccharin consumption in the United States (see also 282). The relative risk represented by 500 cases could not have been detected in the case-control study.

Doll and Peto (93) reviewed five case-control studies which examined saccharin consumption and bladder cancer. With the exception of Howe et al. (175), the relative risks in all the experiments lie very close to 1.0; some slightly higher; some lower. They conclude that the "human evidence could hardly be more null," at least for cancer of the bladder, which was the anatomic site affected by saccharin in rats (93).

BHT has been used extensively as an antioxidant for many years. It is not carcinogenic by itself, but has been reported to enhance the production of lung tumors by urethan in mice (93). Conversely, its antioxidant effect is found to inhibit the formation of active carcinogens in the laboratory (93), and similar effects might be expected to occur in vivo. It has been postulated that its use— and perhaps that of the more widely used butylated hydroxyanisole—have contributed to the decline in mortality from stomach cancer (24).

Nitrites have been used to preserve meat since the last century (also see above). According to Shubik (328), nitrites added to food Constitutes only 10 percent of the total nitrite reaching the stomach in vegetables and saliva. However, if the formation of nitrosamines and nitrosamides in the intestinal tract proves to be of practical importance, dietary nitrite may play a role in cancer formation. The National Research Council's Panel on Nitrates (cited in 93) was unable to reach any conclusions about their quantitative effect, but advised that reasonable measures be

taken to minimize human exposure to N-nitroso compounds, including the restriction of the amounts of nitrate and nitrite added to meat products.

There is great uncertainty regarding the contribution of the compounds discussed above to the formation of cancer. The possibility also exists that other additives might have detrimental effects.

Diet Summary

Dietary components discussed above, and many others, are currently the subjects of intensive research, from which some results should be known within the next few years. The outcomes may show diet to be a factor in determining cancer occurrence at many sites, particularly the stomach, large bowel, endometrium, gallbladder, and in tropical countries, the liver. Diet may also be shown to affect the incidence of cancers of the breast and pancreas, and, through the antipromoting effects of retinoids, to reduce incidence of epithelial cancers in many other tissues. If these or other hypotheses are proven, practicable means of dietary modifications may eventually be identified to reduce cancer rates.

Cairns (43) draws attention to the probable difficulty of changing cancer incidence even if a direct link is shown between a diet constituent and cancer incidence:

> Cancer of the lung is due to a pleasant and highly addictive habit, cancer of the large intestine and breast are most common in affluent countries and so are presumably associated with some desirable habit, such as a diet high in animal fats, that the rich nations can afford and the others cannot . . . . These are signs, therefore, that the campaign to prevent cancer may come into some conflict with people's immediate desires.

OCCUPATIONAL EXPOSURES

The last several years have seen a heated discussion concerning the contribution of occupational exposures to cancer in the United States. Since the formation of the Occupational Safety and Health Administration (OSHA) in 1970, 20 regulations have been promulgated and two more proposed relating to suspect carcinogenic factors in the workplace. Labor unions and public interest groups have criticized OSHA for moving slowly, while industry and their trade associations claim unnecessary irrational regulation and undue expense. In an effort to implement a comprehensive and rational policy for the regulation of carcinogens in the workplace, OSHA held **2** months of hearings in 1978 which attracted the participation of labor unions, environmental groups and spawned a major new trade association, the American Industrial Health Council (AIHC). Subsequently, OSHA promulgated "a general policy for the identification and regulation of physical and chemical substances that pose a potential occupational carcinogenic risk to humans" (278,279).

The first recognized industrial cancer was identified by Percival Pott, a British surgeon, who observed that scrotal cancer occurred more frequently in men who had been employed as chimney sweeps as boys. This led to the identification of soot as the first chemical and occupational carcinogen. In the ensuing years, many other groups of workers have been found to suffer from occupationally induced cancer. For the purpose of this assessment, occupational exposure is defined as exposure to a substance or physical agent through any route during the course of employment.

The workplace setting has proved to be the single most productive source of information in the discovery of carcinogenic substances. This is because of the defined populations involved and higher exposures which can be more easily monitored and identified. Table 17 lists carcinogens and processes found in the workplace which are associated with increased cancer risk. Occupations known to produce an elevated risk of cancer, though the specific agents responsible

Table 17.—Occupational Cancer Hazards

Agent	Cancer site or type	Type of workers exposed
Acrylonitrile	Lung, colon	Manufacturers of apparel, carpeting, blanket% draperies. synthetic furs, and wigs
4-aminobiphenyl	Bladder	Chemical workers
Arsenic and certain arsenic compounds	Lung, skin, scrotum, lymphatic system, hemangisarcoma of the liver	Workers in the metallurgical industries, sheep-dip workers, pesticide production workers, copper smelter workers, vineyard workers, insecticide makers and sprayers, tanners, miners (gold miners)
Asbestos	Lung, larynx, GI tract, pleural and peritoneal mesothelioma	Asbestos factory workers, textile workers, rubber-tire manufacturing industry workers, miners, insulation workers, shipyard workers
Auramine and the manufacture of auramine	Bladder	Dyestuffs manufacturers, rubber workers, textile dyers, paint manufacturers
Benzene	Leukemia	Rubber-tire manufacturing industry workers, painters, shoe manufacturing workers, rubber cement workers, glue and varnish workers, distillers, shoemakers, plastics workers, chemical workers
Benzidine	Bladder, pancreas	Dyeworkers, chemical workers
Beryllium and certain beryllium compounds	Lung	Beryllium workers, electronics workers, missile Parts producers
Bis(chloromethyl) ether (BCME)	Lung	Workers in plants producing anion-exchange resins (chemical workers)
Cadmium and certain cadmium compounds	Lung, prostate	Cadmium production workers, metallurgical workers, electroplating industry workers, chemical workers, jewelry workers, nuclear workers, pigment workers, battery workers
Carbon tetrachloride	Liver	Plastic workers, dry cleaners
Chloromethyl methyl ether (CM ME)	Lung	Chemical workers, workers in plants producing ion exchange resin
Chromium and certain chromium compounds	Lung, nasal sinuses	Chromate-producing industry workers, acetylene and aniline worker% bleachers, glass, pottery, pigment, and linoleum workers
Coal tar pitch volatiles	Lung, scrotum	Steel industry workers, aluminum potroom workers, foundry workers
Coke oven emissions	Lung, kidney, prostate	Steel industry workers, coke plant workers
Dimethyl sulphate	Lung	Chemical workers, drug makers, dyemakers
Epichlorohydrin	Lung, leukemia	Chemical workers
Ethylene oxide	Leukemia, stomach	Hospital workers, research lab workers, beekeepers fumigators
Hematite and underground hematite mining	Lung	Miners
Isopropyl oils and the manufacture of isopropyl oils	Paranasal sinuses	Isopropyl oil workers
Mustard gas	Respiratory tract	production workers
2-naphthylamine	Bladder, pancreas	Dyeworkers, rubber-tire manufacturing industry workers, chemical workers, manufacturers of coal gas, nickel refiners, copper smelters, electrolysis workers
Nickel (certain compounds) and nickel refining	Nasal cavity, lung, larynx	Nickel refiners
Polychlorinated biphenyls (PCBs)	Melanoma	PCBs workers
Radiation, ionizing	Skin. pancreas, brain, stomach, breast, salivary glands, thyroid, GI tract, bronchus, lymphoid tissue, leukemia, multiple myeloma	Uranium miners, radiologists, radiographer% luminous dial Painters
Radiation, ultraviolet	Skin	Farmers, sailors, arc welders
Soots, tars, mineral oils	Skin, lung, bladder, GI tract	Construction workers, roofers, chimney sweeps, machinists
Thorium dioxide	Liver, kidney, larynx, leukemia	Chemical workers, steelworkers, ceramic makers, incandescent, lamp makers, nuclear reactor workers, gas mantle makers, metal refiners, vacuum tube makers
Vinyl chloride	Liver. brain, lung, hematolymphopoietic system; breast	Plastics factory workers, vinyl chloride polymerization plant workers
Agent(s) not identified	Pancreas	Chemists
	Stomach	Coal miners
	Brain, stomach	Petrochemical industry
	Hematolymphopoietic system	Rubber industry workers
	Bladder	printing pressmen
	Eye, kidney, lung	Chemical workers
	Leukemia, brain	Farmers
	Colon, brain	Pattern and model makers
	Esophagus stomach, lung	Oil refinery workers

SOURCES: Institute of Medicine (179), International Agency for Research on Cancer (185), and the Occupational Safety and Health Administration (279a)

have not yet been identified, are also included. Many of these exposures represent substantial hazards, and it is likely that other human carcinogens exist which have not yet been detected in the workplace. This may be because the added cancer risk is small in comparison to other causes of cancer, because only a few workers have been exposed, or simply because a hazard has not been suspected and therefore not looked for. Besides the substances listed, many other industrial chemicals have been found to cause cancer in laboratory animals. It must also be borne in mind that human cancer seldom develops until one or more decades after exposure to a carcinogen, and thus it is too early to ascertain whether chemicals introduced into industry during the last few decades will affect cancer rates.

Epidemiologically demonstrating an increased risk of developing cancer from an occupational exposure generally involves results from examining large numbers of exposed people, the existence of relatively large risks, or sometimes a rare cancer, which facilitates drawing associations. Even then, years may pass before a hazard is identified. As the workplace changes, workers will be exposed to additional substances, some of which may turn out to be carcinogenic.

Estimating the proportion of today's cancers that can be attributed to occupational hazards is difficult. Determining how many future cancers may arise from past and present occupational exposures is even more speculative. As with all studies of carcinogenesis, the latent period makes it extremely problematic to associate a particular occupational exposure with an increased cancer risk. Individuals frequently change jobs which can result in exposure to numerous substances, several of which may interact with each other either to promote or to inhibit tumor formation. With rapidly changing technologies, new exposures emerge while others cease. Often, the available information is based on studies which have inadequate exposure information. Exposure data are generally poor because they are usually not collected until a hazard is recognized, or at least suspected. OSHA requires monitoring only for some of the substances which it regulates. Oftentimes employees, and even in some cases employers, are unaware of specific chemical exposures.

Certain occupational diseases are difficult to diagnose and this can lead to underreporting, as exemplified by recent letters to the New *England Journal of Medicine* concerning the inability of board-certified pathologists to identify cases of asbestosis (1,318). Studies can be designed to obtain exposure data and continuously monitor workers' health, but they are expensive. Even though no system has yet been adopted to gather these types of information, such an approach may be feasible in some industries.

Many estimates have been made of the percentage of human cancers associated with occupational exposures, most ranging from 1 to 10 percent. In most instances the bases for these estimates are not presented and the estimates themselves appear little more than informed guesses. Since epidemiologic studies do not always follow individuals for their full lifetimes, calculated risks may be underestimates. The magnitude of a detected risk is dependent upon the time elapsed between exposure and the time individuals are studied.

Higginson and Muir (165) estimated the impact of environmental factors in human cancer. They stated:

> Although occupational cancers recognized so far provide some of the most satisfactory data for identifying external agents, the absolute number of cancers due to occupational exposures would appear to be relatively small, probably 1 to **3** percent of all cancers.

Wynder and Gori (368) estimated the percent of 1976 cancer incidence in the United States attributable to occupation, From their summary figure, it appears that they estimated that the fraction of cancers attributable to occupational factors was 4 percent for men and 2 percent for women. Their explanation for these estimates is as follows:

> The data presently available are, at best, educated estimates of the relationship between specific cancers and specific occupational groups. Cole et al.[2] **(1972)** suggested that **20%**

2P. Hoover, R. Cole, and G. H. Friedell, "Occupation and Cancer of the Lower Urinary Tract, " *Cancer 29: 1250-60, 1972.*

of bladder cancers occurring in males in the Boston area are related to occupational exposure. In certain counties of New Jersey, the increased risk for this cancer appeared to be high among workers in certain chemical industries. General estimates of the percentage of all human cancers related to occupational exposure range between 1 and 10 percent.

Cole (62) estimated slightly higher figures for workplace-caused cancer:

> My estimates are less than **15** percent for men and less than 5 percent for women. These rather low figures emphasize that we are not dealing with a single major public health problem. Rather, we are dealing with a series of modest problems which are, however, of great importance in the specific industries where they occur,

Cole does not describe the data used to derive the estimate.

Higginson and Muir (166), in **a** later study estimated that 6 percent of male cancers, skin cancer included, in the Birmingham and West Midland region of England in 1968 through 1972, could be attributed to occupational exposures. Their paper describes some of the information considered.

Fox and Adelstein (126) reviewed 1970-72 British vital statistics and found that 12 percent of the differences in cancer mortality among different occupational classifications could be explained by variations associated with work and the remaining 88 percent by lifestyle factors. They describe their estimate as an "oversimplified calculation, ignoring interactions between direct and indirect influences . . . clearly very crude. "

Recently, a different approach was used to generate an estimate of workplace cancers by 10 distinguished research workers of NCI, the National Institute of Environmental Health Sciences, and the National Institute for Occupational Safety and Health (82). The report calculated the proportion of cancers "for the near term and future, " from quantitative estimates of *risk and* the numbers of workers exposed to six known carcinogens—asbestos, arsenic, benzene, chromium, nickel oxides, and petroleum fractions. This paper (82) concludes:

> Reasonable projections of the future consequences of past exposure to established carcinogens suggest that . . . occupationally related cancers may comprise as much as **20%** or more of total cancer mortality. Asbestos alone will probably contribute up to **13-18% and the data (relating** to five other carcinogens) suggest at least 10-2070 more.

The total of occupationally related cancers from those six exposures is then 23 to 38 percent of the overall cancer total, to which must presumably be added the effects of other occupational carcinogens not included in the calculation. This report has been widely misquoted as an assessment of the contribution of occupational exposures to present cancer rates and is frequently discussed and criticized because of the magnitude of the estimates and their divergence from previous estimates.

While this report has not been submitted for publication, it has been widely circulated and reviewed (c f., 9,93,332,345). The two reviews that have been published are discussed below.

Toxic Substances Strategy Committee (TSSC) Review

TSSC (345) identified several methodological aspects which might have caused the HEW (82) paper to overestimate or to underestimate the contribution of occupational factors to the overall cancer rate.

Overestimating

1. The number of cases of lung cancer associated with asbestos may have been overestimated by attributing all cases of lung cancer among asbestos workers to asbestos exposure.
2. Exposures to the examined carcinogens were probably higher in the past than they have been recently.
3. Estimates of the number of workers exposed may have been too high since: a) workers who were employed in more than one of the six industries, a likely possibility in the chromium and nickel industries, might have been counted twice, and b) estimates of the

number of exposed persons still alive and thus at risk may be exaggerated. This is particularly so with regard to the asbestos industry.

Underestimating

1. The six industries examined are not the only ones believed to have carcinogens in the workplace.
2. Epidemiologic data on which the estimates are based do not reflect total lifetime risk.
3. Identifying unexposed groups to use for comparison is difficult and the comparison group used may be at a higher risk then the least exposed members of the population.

The TSSC report concludes (345):

> Because it is difficult to quantify the impact of all these factors, one cannot tell whether the factors which lead to overestimation and those which lead to underestimation balance each other out.

Doll and Peto Review

Doll and Peto (93) examined the calculations in the OSHA paper and in their view, the estimates:

> . . . could not be regarded as having any validity, primarily because the implicit assumption was made that the industrial conditions that had been recognized as giving rise to gross hazards of occupational cancer were typical of the condition to which 11.9 million workers in the United States were currently exposed.

Doll and Peto (93) used a different approach to estimate the proportion of cancers associated with occupational exposures. Rather than focusing on individual occupational hazards, they based their assessment on the contribution of occupational factors to individual cancer sites and arrived at an estimate of approximately 4 percent with an acceptable range from 2 to 10 percent.

Lung cancers caused by asbestos contribute the largest proportion to the estimates made both by Doll and Peto (93) and by HEW (82). Hogan and Heel (171) have completed a careful analysis of asbestos and cancer and conclude that it may be associated with as much as 3 (range: 1.4 to 4.4) percent of all cancers now or likely in the near future. This inference is considerably less than the 13 to 18 percent estimated by HEW (82).

Occupational Exposure Summary

Despite all of the arguments that have surrounded the estimates of workplace associated cancers, almost every estimate fits comfortably in the range of 10 ± 5 percent. Uncertainties about unknown carcinogens confound the estimates. Regardless of the exact number of cancers associated with the workplace, the identification of causes is most important. Preventive measures can reduce exposures only to identified risks. Recently, an unusual number of melanomas in a nuclear research installation (89) and of brain tumors among oil industry workers (55) have triggered further studies. These examples emphasize the value of workplace monitoring.

AIR AND WATER POLLUTION

Determining the health effects of pollution is difficult, particularly from low-level chronic exposures. The absolute risk from each pollutant is likely to be low and the resulting disease may not appear for many decades, as is the case with cancer. Direct measurement of the incremental risk from these pollutants using epidemiologic methods, against the background of more potent carcinogens, for instance tobacco, presents extreme methodological problems. There is often little variation between individuals in the type and extent of exposure to pervasive pollutants, and where measurable differences do exist, confounding variables often hinder adequately demonstrating an effect or the lack of one. It is therefore often necessary to rely on indirect sources of evidence that a pollutant is carcinogenic: short-term laboratory experiments that

demonstrate mutagenicity or other toxic effects, animal bioassays, and epidemiologic data derived from groups exposed to high levels of pollutant chemicals. The latter are often obtained in special situations, usually occupational, where people are exposed to much larger amounts than the general public.

Air Pollution

Air pollution is primarily a problem of major cities but it can move in and out of different areas and affect everyone. The Census Bureau (35) estimates that over 70 percent of the U.S. population lives in urban centers and that this number is increasing with each passing year. The amount and type of air pollution in a given region changes not only with the time of day, but from day to day and year to year, making meaningful measurement difficult. Air pollution can be generally classified as a secondary environmental stressor, aggravating existing disease conditions or increasing the risk of disease in those predisposed to ill health **(326).**

A variety of carcinogenic substances has been identified in air—e. g., asbestos, arsenic, PAH—and EPA has promulgated several regulations under section 112 of the Clean Air Act to limit exposure to these substances. Table 17 (see Occupational *Exposures)* lists several recognized occupational carcinogens which may escape into the atmosphere in the course of industrial activity and constitute a potential cancer hazard.

Morbidity and mortality due to chronic obstructive lung disease—asthma, bronchitis, and emphysema —are probably the most important long-term health effects of air pollution. Urban areas generally have a higher death rate from chronic obstructive lung disease and lung cancer than more rural environments **(54,205).** This has been used as the basis for suggesting that atmospheric pollution is an etiologic factor in the development of cancer. However, like many apparently simple observations, this one is plagued by conflicting and confounding factors. Individuals residing in urban centers generally have smoking, drinking, and eating habits different from their rural counterparts, and their risk of infection and exposures to industrial environments also varies. In addition, urban areas tend to have more accurate death certification and disease diagnosis which might bias collected statistics. Epidemiologic studies that examine the health effects of air pollution must deal with these factors.

Many airborne carcinogens are believed to interact synergistically with tobacco and occupational exposures. Since cigarette smoking is the predominant cause of lung cancer, it is a primary suspect for explaining the observed urban/rural gradient. There have been numerous attempts to disentangle the health effects of smoking from environmental pollution. Unfortunately, many studies have compared broad categories of smoking habits, such as “smokers” versus “nonsmokers” or “never smoked” versus “ever smoked” which reduces the probability of discerning any effects. More specific categories—e.g., taking into account number of years smoked, age at which smoking began, number of cigarettes smoked per day—are necessary to evaluate any urban/rural variation. In addition, other important differences may exist in smoking habits between urban and rural dwellers, for instance, in the tar and nicotine content, inhalation habits, and other factors contributing to differences in effective dose of carcinogen received (see Tobacco). Most studies concentrating on nonsmokers have failed to demonstrate, or found only a slight difference, in lung cancer rates between nonsmokers in urban and rural environs, suggesting that airborne carcinogens by themselves can be responsible for only a small portion of the disease. Several have suggested that the effects of smoking a given amount may be greater in urban than rural areas (for review, see 91).

One of the most extensive investigations into the effects of air pollution is a cohort study conducted by ACS. Data concerning men without known carcinogenic occupational exposure produced “little or no support to the hypothesis that urban air pollution has an important effect on lung cancer death rates” (154). When lung cancer rates for men with occupational exposure were compared to those for men without occu-

pational exposures, the authors found a relative difference of 26 percent in large metropolitan areas, 18 percent in smaller metropolitan areas, and 7 percent in nonmetropolitan areas. These differences, as Hammond and Garfinkel suggest, may be due to different types of occupational exposures in the different areas. However, an alternative explanation is that the higher ratio of lung cancer maybe due to an attribute of the place of residence, air pollution being one possible factor. In a reevaluation of these data, it was estimated that approximately 10 percent of lung cancer in the ACS population could be attributed to an "urban effect" after accounting for smoking and occupation (61). Studies which concentrate on nonsmokers or the nonoccupationally exposed do not permit investigating any interactive effects.

Another method for estimating the influence of pollution on the cancer rate is to extrapolate from instances of high exposure. Occupational studies that include measurements of the concentration of carcinogens in the respired air are especially useful for this purpose. Measurements of the concentration of B(a)P are frequently used because it appears to be a good indicator of the concentration of PAH. However, it should be noted that B(a)P is not a perfect indicator of PAH in air, nor does it accurately reflect the carcinogenic potential of total air pollution. For instance, some non-PAH fractions of air pollution are as active as PAH in causing changes in cell cultures, which is **a** measure related to carcinogenicity (294).

Pike and his colleagues **(294)** concluded that 1 ng B(a)P per m^3 in city air causes 0.4/100,000 extra cases of lung cancer per year. In 1977, an international symposium at the Karolinska Institute in Stockholm, reached a similar conclusion **(54):**

> . . . combustion products of fossil fuels in ambient air, probably acting together with cigarette smoke, have been responsible for cases of lung cancer in large urban areas, the numbers produced being of the order of 5 to 10 **cases** per 100,000 males per year . . . The actual rate will vary from place to place . . . depending upon local conditions.

These estimates must be used with caution since they are directly dependent on the concentration of the different air pollutants, many of which have been changing over time. In 1959, BaP concentrations ranged from 1 ng/m^3 to approximately 60 ng/m^3; most nonurban areas had levels below 1 ng/m^3. Recent monitoring by EPA found that the average concentration of B(a)P in **26** urban areas decreased from approximately 4 ng/m^3 in the late 1960's to 0.5 ng/m^3 in 1977 (70). Doll and Peto (93) estimated that the current contribution of atmospheric B(a)P and associated combustion products to the production of lung cancer is unlikely to account for more than 1 percent of future cases of lung cancer.

Similar calculations have been made for other carcinogenic substances including airborne arsenic and asbestos (93). These suggest that contributions to the overall cancer rate from these agents should be small. Higher levels of pollutants and therefore greater risk may exist around particular sources of pollution as exhibited by the significantly increased mortality from lung cancer found in residents of counties with copper, lead, or zinc smelters or refineries (28). The amount of asbestos commonly present in urban air is 1,000 to 10,000 times less than the most stringent occupational regulations, although the general public is exposed continuously to this low level. At present, there is no evidence to indicate that the risk to the general public from these sources is measurable.

Also included under the heading of atmospheric pollution is the effect on the general population of mining and milling of uranium and other radioactive ores and of radioactive fallout due to testing of nuclear weapons. The HEW Interagency Task Force on the Health Effects of Ionizing Radiation (182) estimated that for 1978 the U.S. population collective dose was 1 million to 1.6 million person-rem. Based on the risk estimates derived from the linear model of the NAS Committee on the Biological Effects of Ionizing Radiation (BEIR) III (158 to 403 excess cancer deaths per million persons from continuous lifetime exposure to 1 rad/yr) one can estimate that atmospheric radiation accounts for

an upper limit of 645 fatal cancers per year. The lower limit of risk can be considered to approach zero.

The other class of atmospheric agents given considerable attention because of a potential effect on cancer rates are the chlorofluorocarbons. Chlorofluorocarbons, used extensively as refrigerants and aerosol propellants, persist in the atmosphere and, it is argued, eventually reach the stratosphere where they react with ozone, reduce its concentration, and hence permit more ultraviolet light to reach the surface of the Earth. This occurrence would result in an increase in the incidence of skin cancer, including melanoma. The issues involved, which are complex and based on a number of unproved assumptions about physical and chemical processes, have been reviewed by the National Academy of Sciences (NAS) (70,264). They found that if global release of chlorofluorocarbons were to continue at 1977 rates, the ozone concentration would eventually decline by 16.5 percent, with a reduction of about 8 percent by the year 2030 (70). A 16-percent ozone depletion is predicted to eventually cause several thousand more cases of melanoma each year in the United States and several hundred thousand more cases of other less serious skin cancers (70). This is approximately the same order of magnitude predicted by Urbach (354). The present contribution of chlorofluorocarbons to overall cancer incidence is likely to be much less.

Until recently, air pollution was a problem believed to be limited to outside air or dirty workplaces. Several studies have found that indoor air pollution may be a more serious health hazard than outdoor air pollution (140). It has been shown that a single smoker can pollute indoor air with around 1-1.5 ng/m^3 B(a)P (260). NAS was asked by EPA to examine the variables which are contributing to indoor air pollution, their sources, and possible health hazards. To date, this issue has not been looked at in a systematic way though many people spend a large percentage of their time in the indoor environment. The General Accounting Office **(140)** suggested that the Clean Air Act be amended to provide EPA the responsibility and necessary authority to address indoor air pollution in the nonworkplace.

In sum, determining the proportion of the total cancer rate attributable to air pollution is not possible with the available data. In most studies, air pollution and smoking are seen as interactive in cancer production. Whatever the correct percentage of cancer associated with air pollution, most researchers in this area believe that it is small. Doll and Peto (93) estimated that 2 percent of cancer mortality, representing approximately 8,000 cancer deaths, can be attributed to industrial pollution of air, water, and food, principally accounted for by the uncertain effects of combustion products of fossil fuels in urban air. This relatively small percentage does not mean that efforts to control air pollutants should be minimized. Air pollution is responsible for many serious detrimental health effects other than cancer and uncontrolled pollution might someday be found to impact more dramatically on cancer rates. Greater attention should be directed at discerning whether atmospheric pollutants act as initiating and/or promoting agents. If air pollution is acting as a secondary stressor, then its role as a promoter may prove to be most important.

Drinking Water Pollution

The extent to which water pollution is a causative agent for cancer is even less certain and more debated than is the role of air pollution. The passage of the Safe Drinking Water Act, Public Law 93-523, December 1974, was prompted by the recognition that organic and inorganic chemicals, including substances identified as known or suspect carcinogens and mutagens were present in drinking waters. The sources for these contaminants are numerous: industrial pollution, agricultural runoff, leachate from waste disposal sites, and of particular recent interest, byproducts of the disinfection of drinking water.

In the mid 1970's, EPA set up various programs, such as the National Organics Reconnaissance Survey, to evaluate the nature and extent of organics in drinking water. Primary em-

phasis was on detecting a class of organics, the trihalomethanes, formed during water treatment with chlorine and believed to be the most ubiquitous group of organics found in drinking water. Levels have been found to range from below 1 ug/liter to above 300 ug/liter. The Federal Government has recently sought to reduce exposure to trihalomethanes by promulgating a regulation establishing a "maximum contaminant level" of 100 ug/liter total trihalomethanes for all community water systems serving 10,000 persons or more that add a disinfectant in the treatment of their water (107).

Much attention has been centered on the relatively high concentrations of synthetic organics found in untreated drinking water from ground water sources in certain areas of the United States. The extent to which these waterborne pollutants contribute to human carcinogenesis has been evaluated by the examination of both laboratory and epidemiologic data. Many of these studies were reviewed by the NAS Safe Drinking Water Committee (266,270) as mandated by the Congress. (These reports stand as references for many issues concerning the health effects of drinking water contaminants.)

The numerous epidemiologic studies that have examined the association between drinking water and cancer have been of varying reliability and have taken many forms. These studies suggest an association between constituents in drinking water and cancer mortality (169). However, the degree and extent of the association is disputed. NAS discussed and evaluated 10 of the studies which focused on the relationship of trihalomethanes and cancer mortality. All but one of the studies were found to demonstrate a statistical association between exposure and excess cancer rate, but excess cancer at no single anatomical site was associated with exposure. The epidemiologic analyses do not have the extrapolation difficulties of animal experiments, but they are plagued by confounding variables such as exposures to other sources of carcinogenic stimuli, including smoking, which were generally not accounted for. Many of the studies utilized the cancer deaths rates of a region and related them to the water quality of that region. The difficulty with this approach is twofold: 1) an individual's place of death may differ considerably from where that person resided during most of his water-drinking life, and 2) the data on water quality are extremely limited, often reflecting the water quality of only one water source in a region.

Prior to 1970, about 100 different organic compounds has been identified in water (169). In the past, organic pollutants were measured by crude, nonspecific methods such as biochemical oxygen demand and total organic content. Today, analytical techniques permit detection of chemicals in minute quantities, and many are found in concentrations of parts per trillion. NAS (270) found that over 700 volatile organic compounds contaminate U.S. drinking water. Volatile substances make up only 10 percent of the total organic content of water and approximately 90 percent of this component has been identified and quantified. On the other hand, only 5 to 10 percent of the nonvolatile constituents of drinking water have been characterized **(266).** As technology improves and detection methods become more sensitive, an ever-increasing number of compounds may be detected in drinking water.

In a report for the Council on Environmental Quality, Crump and Guess (74) reviewed five of the recent case-control studies on cancer risk associated with drinking water quality in this country. While inadequacies were identified in each of the studies (74):

> . . . increased risks . . . are large enough to be of concern yet small enough to be very difficult to separate from confounding risks associated with other environmental factors.

Rectal cancer risk ratios for chlorinated v. unchlorinated water were found to range from 1.13 to 1.93. In three of the studies the risk ratios were statistically significant. Statistically significant risk ratios were also found in three of the studies for colon cancer and in two studies for bladder cancer. Although the studies did not indicate a consistently increasing cancer risk with increasing exposure to organic contaminants, one study did show such a relationship

for rectal cancer and another was suggestive for colon cancer.

Crump and Guess made crude estimates of the possible range of carcinogenic risks from consuming ground water (from wells) containing various levels of synthetic organic chemicals. They computed an upper risk limit of **7.5** x 10^{-4} or about one case per 1,300 persons from consuming water from a hypothetical well containing the highest detected concentrations of commonly found contaminants. Levels to which most Americans are exposed are typically much lower. The estimate is based on summing the individual upper limits on human risk derived by a procedure which tends to produce exaggerated estimates of human risk. On the other hand, only risks from chemicals known to be present in the wells and for which positive carcinogenicity data exist, were considered in the estimate (74). Crump and Guess also computed an upper limit on the lifetime total cancer risk associated with an average concentration of chloroform to be 1.8 x 10^{-4} or about one case per **5,000** persons. The actual risk is probably much lower.

The NAS Safe Drinking Water Committee lists 19 carcinogens and 3 suspected carcinogens identified in or thought to be in drinking water **(266).** NAS estimated the 95-percent upper confidence limit of cancer risks to humans from lifetime exposure to water containing 1 ug/1 of each of these compounds. These estimates are displayed in table 18 and are compared with risk estimates computed by EPA's Carcinogen Assessment Group. It is interesting to note that in many cases a tenfold to hundredfold difference exists between the two estimates. These differences are due to the use of different extrapolation models and the use of point rather than interval estimates.

The problem of evaluating the effects of multiple exposures is acutely relevant to waterborne pollutants because of the multitude of compounds found in drinking water. Bioassays have rarely attempted evaluation of synergistic or antagonistic effects. Therefore, these estimates may not accurately reflect the human carcinogenic risk from these compounds.

Table 18.—Concentration of Drinking Water Contaminants and Calculated Excess Cancer Risk

	NAS[a]	CAG[b]
	10^{-5}	10^{-5}
	Ug/l[c]	Ug/l[c]
Acrylonitrile	0.77	0.034
Arsenic	—	0.004
Benzene	—	3.0
Benzo (a) pyrene	—	—
Beryllium	—	0.02
Bis (2-chloroethyl) ether	0.83	—
Carbon tetrachloride	9.09	0.086
Chlordane	0.056	0.012
Chloroform	0.59	0.48
DDT	0.083	—
1,2-Dichloroethane	1.4	1.46
1,1-Dichloroethylene	—	.28
Dieldrin	0.004	—
Ethylenedibromide	0.11	0.0022
ETU	0.46	—
Heptachlor	0.024	2.4
Hexachlorobutadiene	—	1.4
Hexachlorobenzene	0.034	—
N-nitrosodimethylamine	—	0.0052
Kepone	0.023	—
Lindane	0.108	—
PCB	0.32	—
PCNB	7.14	—
TCDD	—	5.0 x 10-'
Tetrachloroethylene	0.71	0.82
Trichloroethylene	9.09	5.8
Vinyl chloride	2.13	106.0

[a] Standardized to 10^{-5} risks from National Academy of Sciences, *Drinking Water and Health* (266) for consumption of 1 l/water/day
[b] Recalculated to exclude aquatic food intake from Cancer Assessment Group, *Ambient Water Quality Criteria* (104) Standardized to 1 l/water/day intake
[c] Average adult water consumption is 2 l/day.

SOURCE Office of Technology Assessment

As more chemicals are tested, additional substances found in drinking water will be shown to be carcinogenic. Two substances identified in drinking water, toxaphene and 1,2 dichloroethane, not considered carcinogenic by NAS in 1977, have since been shown by NCI to be carcinogenic in animals. Two additional compounds, bromodichloromethane and chlorodibromomethane, found in most drinking water systems surveyed by EPA, have not been appropriately tested for carcinogenic properties but have been shown to be mutagenic in the Ames test (169). In 1978, NCI (203) published a list of 23 recognized or suspected carcinogens, 30 mutagens and 11 tumor promoters which have been found in American drinking water.

Turning from the organics to inorganic, several studies have attempted to correlate levels of

carcinogenic trace metals in water supplies, with cancer rates. Associations of high levels of arsenic in drinking water with cancer of the skin and other sites were found in Taiwan and Argentina (203,370). Berg and Burbank (25) compared concentrations of eight carcinogenic metals in water supplies with State cancer mortality rates. They found strong correlations with cadmium concentrations and cancer mortality; no significant correlations with iron, cobalt, and chromium; a low but not biologically interpretable level of significance with nickel and arsenic; and some correlations with lead and beryllium which correspond to known biological activities.

Asbestos, an established human carcinogen, is also of some concern since it has been found to contaminate water supply systems. No relationship between asbestos in drinking water and cancer has been found but available data are very limited.

Experimental and epidemiologic data provide some evidence that a carcinogenic hazard exists from drinking water contaminants, but does not permit adequate quantification. Most attention on quantifying risk estimates from waterborne carcinogens has focused on chloroform, since it alone has consistently generated dose-response data sufficient for extrapolating human risk. An ad hoc study group of the EPA's Hazardous Material's Advisory Committee (158) estimated the risk as follows:

> The level of risk, estimated from consideration of the worst case [Miami, 311 ppb] and for the expected cancer site for chloroform (the liver), might be extrapolated to account for up to 40% of the observed liver cancer incidence.

The results of a large NCI case-control study which is examining possible relationships between water quality and bladder cancer are expected in 1981. Information was obtained in that study on a wide range of demographic and exposure factors and a data bank on water quality was created for more than 1,000 utilities serving many of the people in the study. That information will hopefully permit linking an individual's risk factors with disease state. In addition, a case-control interview study to investigate relationships between drinking water and colorectal cancer is being conducted (74).

CONSUMER PRODUCTS

Consumer products are a class of agents that are so numerous that it is only possible to echo the uncertainty with which pollutants were discussed in the previous section. Detergents and other surfactants, hair dyes and other cosmetics, solid or foam plastics, paints, dyes, polishes, solvents, fabrics, and even the processed paper and the printer's ink in this report are but a few. It is likely that some of these products are already causing, unnoticed, a number of today's cancers, and it is quite possible that after prolonged exposure substantial risks might be detected in the future.

The difficulty in assessing cancers associated with exposure to consumer products is that the dose is usually low, and the exposed population tends to be very large. An adequate assessment of the carcinogenic effect of a consumer product might require a study of a million people, whereas a study of only 1,000 workers might be adequate in an occupational setting. Further, while occupational exposure to a carcinogen is frequently limited to a group of relatively healthy workers, consumer exposure includes subpopulation groups usually considered to be "at high risk," such as infants, small children, the elderly, and the infirm,

For most consumer products, available laboratory and human evidence is insufficient to determine whether they pose a cancer risk. The magnitude of the potential health hazard becomes apparent when one begins to examine population exposure to different consumer products. In 1973, U.S. production of aerosol products was estimated at 2.9 billion units. A recent Consumer Product Safety Commission (CPSC) study indicated that manufacturers removed trichloroethylene (TCE), a widely used

solvent in aerosol formulations, from consumer aerosol product formulas after TCE was shown to be carcinogenic in tests at NCI (117). The extent to which aerosol products containing TCE has impacted on today's cancer rates or how many future cancers will result from past exposures is difficult to evaluate.

Attempts at quantifying potential adverse effects associated with consumer exposure to carcinogens are relatively new. In 1977, CPSC estimated that exposure of children to TRIS-treated clothing could result in an excess risk of cancer of up to 180 cases per million exposures. Other examples of estimated consumer risk include up to **2,000** lifetime excess respiratory cancer deaths per million persons exposed to asbestos-containing patching compounds; paint stripper containing **52** percent benzene may present an excess risk of death from leukemia of up to 50 per million people exposed; and people living in a residence insulated with urea-formaldehyde foam may beat an excess cancer risk of up to **290** per million people exposed (117).

At this time it is impossible to assess the contribution of consumer products to the overall cancer rate. Many industrial products have been introduced so recently that even if they do prove hazardous their effects would not yet be apparent. Doll and Peto (93) attribute "less than 1 percent" of all cancer deaths to such products, but stress that there is too much ignorance for complacency to be justified.

MEDICAL DRUGS AND RADIATION

Medical practices have resulted in some devastating health crises, from the fatal puerperal fevers of the 19th century maternity wards to the millions who were exposed in utero to diethylstilbestrol (DES) and are now experiencing a variety of adverse health effects, including at least one type of cancer. Only drugs which have been associated with cancer in humans will be discussed in detail, but limited or inconclusive evidence exists for many others, and still others have not been investigated (see table 19).

The production of cancer, although always an undesirable side effect, is not necessarily a bar to the use of a drug if the risk of cancer development is materially less than the medical gains brought about by the treatment—e.g., by the use of alkylating agents, immunosuppressive drugs and radiotherapy in the treatment of cancer. The risks in some cases are known, as with some cancer chemotherapy agents, but more often are not suspected. Detection of disproportionate adverse effects through case reports and epidemiologic studies have caused the abandonment of certain agents and treatments for particular uses, for instance, inorganic trivalent arsenic, chlornaphazine, DES during pregnancy, and the radioactive agents thorium and thorotrast.

The causal link between in utero exposure to DES, a synthetic estrogen, and subsequent development of a rare type of vaginal cancer in females (and possibly testicular cancer in males) about 20 years later is a well-publicized example of unsuspected risk. Between 4 million and 6 million Americans (mothers, daughters, sons) were exposed to DES since about 1945 (258) in efforts to prevent spontaneous abortions. As later became evident, DES was an ineffective therapy (90).

In this case, in spite of the long latency between in utero exposure and cancer development two or three decades later, the connection was made between exposure and disease. The facilitating factor in this case was the near nonexistence of the cancer type in the general population at the ages in which the disease was seen. However, had the effect been a small excess of a common cancer, it is doubtful that the association would have been uncovered. Since the original association was uncovered, other possible adverse effects have been suspected in DES mothers, daughters and sons.

In cases of agents for which some risk is known or suspected, the use of the agent is continued under controlled conditions, in the belief

Table 19.—Drugs Associated with Cancer in Humans

***Drugs established as human* carcinogens**

Drug	Malignancy
Radioactive drugs: **Phosphorus (P^{32})** **Radium** **Mesothorium** Thorotrast	**Organs where concentrated:** **Acute leukemia, osteosarcoma, nasal sinus carcinoma, angiosarcoma** of the liver
Chlornaphazine	Bladder cancer
Arsenic	Skin cancer
Methoxypsoralen	Skin cancer
Alkylating agents: Melphalan, chlorambucil, dihydroxybusulfan, busulphan, and others	Acute nonlymphocytic leukemia other sites?
Cyclophosphamide	Bladder cancer
Immunosuppressive agents—Azothioprine	Lymphoma, skin cancer, soft-tissue sarcoma melanoma? liver and gallbladder? lung adenocarcinoma?
Androgenic-anabolic steroids	Hepatocellular carcinoma
Steroid contraceptives	Endometrial carcinoma, liver tumors (benign) breast cancer? cervical cancer? ovarian cancer? choriocarcinoma? melanoma?
Estrogens: DES (prenatal) Conjugated estrogens	Vaginal adenocarcinoma Endometrial carcinoma breast cancer? ovarian cancer?
Phenacetin-containing drugs	Renal pelvis carcinoma bladder cancer?

Suspect drugs for which human evidence of carcinogenicity is either inconclusive or conflicting

Drug	Malignancy
Chloramphenicol	Leukemia
Iron Dextran	Soft tissue sarcoma (site of injection)
Dilantin	Lymphoma
Phenobarbital	Brain tumors, liver cancer
Amphetamines	Lymphoma
Reserpine	Breast cancer
Progesterone (Depo-Provera)	Cervical cancer
Phenylbutazone	Leukemia
Crude tar ointment	Skin cancer
Clofibrate	Gastrointestinal and respiratory malignancies

Suspect drugs for which human studies have as yet not yielded evidence of carcinogenicity

Isoniazid

Metronidazole

Antimetabolites (Methotrexate, 5-Fluorouracil)

***Suspect* drugs as yet unevaluated in humans**

Dapsone

Griseofulvin

Phenothiazines

Oxytetracycline

Chloroquin

SOURCE Hoover and Fraumeni ("73)

that the benefit will prove to outweigh the harm. Many of the known hazardous drugs are used in the treatment of relatively uncommon serious conditions and the sum of the cancers caused by them can amount to no more than a few score throughout the entire country each year. However, some drugs, including oral contraceptives, and estrogens are or have been used extensively. These and the medical use of ionizing radiation, also known to be carcinogenic, are discussed below.

Oral Contraceptives

Oral contraceptives are taken by over 80 million healthy women the world over **(366),** spurring international concern about possible health effects, Not surprisingly, the possibility of increased cancer risk after long-term use and a long latent period has been the focus of major epidemiologic efforts.

The evidence to date has clearly implicated one type of sequential oral contraceptive (an estrogen and a progestin taken separately during the first and second halves of the monthly cycle), the use of which has been abandoned, with some cases of endometrial cancer in young women. Conversely, there is some evidence that users of combination type oral contraceptives **(an estrogen** and a progestin taken together in the same pill) may be at slightly lower risk for endometrial cancer (360).

In animal tests, both breast and liver cancers have been induced by components of oral contraceptives. A small number of benign liver tumors in humans have been associated with certain types of oral contraceptives, and though not cancers in the usual sense, they can cause fatal internal hemorrhage. No controlled study has yet evaluated the possible risk of malignant liver tumors (173).

Studies of breast cancer in oral contraceptive users have thus far yielded no clear-cut evidence for either increased or decreased risk, except perhaps some increase for **women** already at high risk (see p. 99, *Sexual Development, Reproductive Patterns, and Sexual Practices* for a full discussion of risk factors). Cervical cancer also has been studied extensively with no consistent findings.

There is some evidence to suggest that oral contraceptives may reduce the risk of ovarian cancer. The reduction may be related to lowered levels of ovulatory activity, since high levels have been associated with an increased risk of ovarian cancer.

Because oral contraceptives have been part of the American lifestyle for a relatively short period, large numbers of users have not reached old age, the period of greatest cancer risk. Until such time, perhaps within the decade, the full effects cannot be known. Even then, because there are many types of oral contraceptives, some of which already have been shown to have different effects, and because formulations and dosage levels have changed significantly over time, risks identified for that first cohort may not apply to today's users. Overall, evaluating the evidence available at this time, oral contraceptives do not appear to be a major cause of cancer, but do require continued epidemiologic attention.

Menopausal Estrogens

The use of "replacement estrogens" to relieve menopausal symptoms became widespread in the 1960's. A sharp rise in the incidence of endometrial cancer followed through the mid-1970's in what has been termed "one of the largest epidemics of iatrogenic disease , . . in this country" (194). A cause-and-effect relationship was established through epidemiologic studies, precipitating a decline in the use of these agents. Shortly after the levels of use dropped, incidence began to fall toward previous levels, and the "epidemic" appears to be largely over. Fortunately, these endometrial cancers have a relatively good prognosis, and while morbidity increased sharply, mortality attributable to estrogen therapy has not paralleled the incidence trend. Estrogen therapy is still prescribed for some women, generally for shorter periods of time than previously. Used in this way, the risk of endometrial cancer appears much lower, though some cases may still occur, but the ben-

efits of therapy are thought to outweigh the residual risk.

Evidence has been accumulating that breast cancer risk may be increased by menopausal estrogen therapy (173), particularly among women who develop benign breast disease while taking estrogens (93). Unlike the case of endometrial cancer and estrogen therapy, where increased and decreased risk follow closely the temporal pattern of usage, change in breast cancer risk appears to require many years to manifest itself.

Other associations between menopausal estrogens and cancer have been suggested. The Boston Collaborative Drug Surveillance Program (30) reported increased gallbladder disease, which is a strong risk factor for cancer of the gallbladder, among women who had estrogen therapy. Some studies have suggested an increased risk of ovarian cancer; others a decreased risk of some reproductive-site cancers (173). Because of these uncertainties and the long latent periods associated with many cancers, continued long-term followup is required to determine if associations exist, and if so, the magnitude of the risks.

Other Drugs of Known Carcinogenicity

Certain alkylating agents, a class of drugs used primarily in the treatment of cancer, have been convincingly associated with acute nonlymphocytic leukemia, known to have a relatively short latent period, and one agent in particular, cyclophosphamide, with bladder cancer. As survival improves for some treated cancers, increases may be seen in some other solid tumors, which generally have longer latent periods than leukemia.

Immunosuppressive agents, used widely in transplant patients, greatly increase the risk of lymphoma, and result in moderate increases in tumors at several other sites. The sites which show an increase are similar to those encountered with genetically determined immune deficiency syndromes and other conditions associated with immunodeficiency.

The initial report of a program designed to screen large numbers of commonly used drugs for carcinogenicity has recently appeared (133). The followup period has been only 4 years, and 53 possible associations have been identified, some with increased risk and some with decreased risk of cancer. Until a longer followup period has elapsed, no conclusions of causality can be reached. The importance of this type of surveillance mechanism lies in its long-term utility, in identifying carcinogens and generating hypotheses.

The Interagency Task Force on the Health Effects of Ionizing Radiation (182) estimated that the collective dose of radiation received by the U.S. population for medical purposes, mainly diagnostic, amounts to about 18 million person-rem per year. Using the linear model from BEIR III (268), which produces a conservatively high estimate, the risk of all types of cancer ranges from **158** to **403** fatal cancers per million person-rem. Applying these values to the total population yields an estimate of between **2,844** and **7,254** fatal cancers per year. Using the least conservative model, the lower risk estimate approached zero. However, some of the medically associated radiation would have been received by people with an expectation of life that was too short for any significant chance of developing radiation-induced cancer (because of illness or age) and the total effect may be somewhat less.

Although well over half of the total population receives some medical radiation, the most susceptible members of the population—unborn fetuses—are of particular concern. Stewart, et al. (333) in England and MacMahon (216) in the United States first identified a risk to children who had been exposed in utero, which has been corroborated by numerous studies since. There is also evidence that the risk of childhood cancer is increased by X-rays of the mother even before pregnancy **(327),** suggesting that both germ cell (in this case, ovum) mutations as well as somatic (in the cells of the developing child) may be important.

Pelvimetry, a radiographic examination used to determine the pelvic dimensions of the mother and the fetal headsize, is the major source of ionizing radiation to fetuses. It has

been estimated that in recent years, 6 percent (about 200,000/yr) of all births have received routine pelvimetry, and rates are much higher in some places (46,198). The Food and Drug Administration (FDA) panel on X-ray pelvimetry, in a statement adopted by the American College of Radiology concluded that, "Pelvimetry is not usually necessary or helpful in making the decision to perform a cesarean section." A similar statement approved by the American College of Obstetricians and Gynecologists states that: "X-ray pelvimetry provides little additional information to physicians involved in the management of labor and delivery." Both groups recommend that pelvimetry be limited to individual cases meeting specific criteria for usefulness, and should not be used as a routine examination (39). Although the actual numbers of childhood cancers caused by medical radiation may be modest, the number could easily be reduced by reductions in irradiation at least during and probably prior to pregnancy.

Unnecessary and unproductive radiation is not limited to pelvimetry. The Bureau of Radiological Health (FDA) has addressed this issue by beginning to prepare a series of documents addressing patient selection, conduct of examinations, and interpretation of results in radiographic procedures (38).

Doll and Peto (93) have estimated that about 1 percent of 1977 cancer deaths probably are attributable to medical practice. They go on to say that the number of ways in which drugs might in principle increase or decrease cancer incidence rates is almost limitless.

Higginson and Muir (163) attributed about 1 percent of all cancers in the Birmingham and West Midland region of England (1968-72) to iatrogenic causes. They note that the widespread use of estrogen therapy in the United States might indicate a higher proportion for U.S. women. Wynder and Gori (368) estimated that about 4 percent of 1976 U.S. cancer uncidence was associated with exogenous hormones.

SEXUAL DEVELOPMENT, REPRODUCTIVE PATTERNS, AND SEXUAL PRACTICES

Sexual development and reproductive patterns affect the development of a number of cancers, affecting females to a greater degree than males. The course of sexual development itself may be heavily influenced by such factors as diet and body composition (fat-to-lean ratio), and reproductive patterns are often influenced by economic and social conditions. Reproductive and dietary factors might well interact multiplicatively in the production of these cancers and there will be overlap between what is preventable through diet and through reproductive factors. Doll and Peto (93) have estimated that about 7 percent (6 percent from breast, ovarian, and endometrial cancers and 1 percent from cervical cancer) of all cancers might be prevented by measures affecting the mechanisms of reproduction and sexual factors.

Some evidence is consistent with cervical cancer in women being associated with infectious agents and less certain evidence associating other genitourinary cancers with infection. If this is true, some cancer-causing agents may be transmitted as venereal diseases.

Cancers of the Breast, Ovary, and Endometrium

The probability that environmental factors contribute heavily to cancer of the breast, endometrium, and ovary is supported by international comparisons and studies of migrants. The highest rates are found in white women in the United States and Western Europe and the lowest among Asian women (see table 20) (184). Lifestyle differences, particularly in diet and reproductive patterns, are probably important contributors to the rate differences. Migrant studies in the United States have shown that the

Table 20.–Selected International Age-Standardized incidence per 100,000 for Cancers of the Breast, Corpus Uteri, Cervix Uteri, Ovary, Prostate, Testis and Penis

	Females			
	Breast	Corpus uteri	Cervix uteri	Ovary
Oxford, United Kingdom	54.5	9.4	11.4	11.7
Alameda County, Calif., blacks	56.6	13.6	28.0	10.3
Alameda County, Calif., whites	76.1	33.3	12.3	13.5
Osaka, tJapan	12.1	0.9	16.2	2.8
Ibadan, Nigeria	15.3	1.6	21.6	7.0

	Males		
	Prostate	Testis	Penis
Oxford, United Kingdom	19.2	2.6	0.7
Alameda County, Calif., blacks	75.0	0.5	
Alameda County, Calif., whites	40.4	4.4	0.6
Osaka, Japan	2.7	0.7	0.5
Ibadan, Nigeria	10.0	0.1	0.2

SOURCE Data from International Agency for Research on Cancer (184)

initially lower rates for Mexican-Americans (234) move toward the higher rates for whites in the United States after a generation or two, owing to shifts in lifestyle toward those of the American population,

ACS (6) estimates that 110,000 women in the United States will develop breast cancer in 1981, and that 37,000 women will die from the disease. Breast, the leading site of cancer death in women today, will account for approximately 19 percent of all female cancer deaths in 1981. A host of studies has established a set of factors that characterize women at high risk for breast cancer (219). Age, geographic area of residence, age at first childbirth, age at menarche (beginning of menstrual function), age at menopause (cessation of menstrual function), history of benign breast disease, and familial history of breast cancer are the major predictors.

International comparisons of breast cancer risk by age has provided the basis for hypotheses which have been examined in further epidemiologic studies. In areas where incidence is high (e.g., North America and Western Europe) the rate increases throughout life, often with a break, where incidence decreases or at least ceases to rise, at about 50 to 55 years of age, after which it increases steeply once again. In areas of low incidence (e.g., most areas of Asia and Africa), rates increase through middle age, decreasing after about age 50. Intermediate patterns occur in areas of intermediate incidence (e.g., Southern Europe and South America) (219).

One basic hypothesis following from the study of age-specific rates is that breast cancer is best described as two diseases: one occurring premenopausally and the other postmenopausally, each with different causes. De Waard (79) presents some additional arguments from epidemiologic research favoring this hypothesis. Paffenbarger, Kampert, and Chang (289) have recently added weight to the arguments against the hypothesis, based on a large case-control study of breast cancer, concluding that overall the evidence supports a "common cause subject to modifying influences" for all breast cancer. The weight of evidence does not yet allow concluding whether breast cancer should be described as one disease or two.

Age at first childbirth is a strong predictor. Giving birth to the first child after age 30, or having no children at all place one at a greater risk than giving birth to the first child before age 20 (238). A pregnancy must go to full term for any protective effect. It is widely believed that the first stimulus to lactation, whether or not breast feeding is carried out, may be the factor of consequence. Miller and Bulbrook (238), reporting on a meeting of the Multi-Disciplinary

Project on Breast Cancer of the International Union against Cancer, speculate:

> A population that achieved a 5-year reduction in age at first delivery might achieve a 30-percent reduction in incidence of breast cancer.

An analysis of population-based cancer mortality rates (27) supports the correlation between nulliparity and higher rates. The data suggest that, if the current pattern continues, the decreasing fertility trends of the 1960's and 1970's may foretell increased breast cancer rates for women in this decade.

Age at menarche has also been shown to have some degree of predictive value in nearly all breast cancer studies, with a lower age indicating a higher risk. Tulinius et al., (346) in their study of Icelandic women, found a "slight influence" remaining after adjustment for parity and age at first pregnancy. Henderson et al. (162) found that women with menarche before age 13 had 1-1/2 times the breast cancer risk of a woman with later menarche.

Age at menarche, itself, maybe influenced by environmental factors, notably nutrition. Population-based data reveal a steady decline in the age at menarche for American women, thought to be attributable to improved nutritional status (238). The effect of this on future breast cancer rates is uncertain. Early studies in rats correlated body size, more than age, with onset of menarche (121). Similarly, observations in humans, including a recent look at menarche and disturbances in the menstrual cycle of ballet dancers (134), provide evidence that lean body mass is related to later menarche. Later age at menopause brings increased risk. Women with natural menopause after age 55 have about twice the risk of developing breast cancer as do women with natural menopause before age 45 (219).

Breast cancer risk has a strong familial component that has not been entirely explained by lifestyle similarities among relatives. First-degree (sisters, mothers and daughters) and second-degree (nieces and aunts) relatives of women with breast cancer have two to three times the risk of the general population. Relatives of women with bilateral breast cancer are at higher risk, and are more likely to be diagnosed at an earlier age and to develop bilateral disease than are relatives of women with unilateral disease (15).

Gray, Henderson, and Pike (144) looked at the higher rate of breast cancer in U.S. white women compared with U.S. black women. They found that the relationship between black and white rates is not constant. Below age 40, black women have higher rates than whites, while after age 45, black rates were 20 to 30 percent lower than those for whites. This can be only partially explained by differences in age at menarche, but a full explanation has not been demonstrated.

Cancers of the endometrium and ovary share at least two important risk factors with breast cancer. They are all associated with high-fat diets and women who have not borne children are at an increased risk for all three types compared to women who have borne children. Occurrence of either breast or ovarian cancer increases the risk of a cancer developing at the other site. Breast cancer also increases the risk of future endometrial cancer (324). Ovarian hormonal activity may be the influencing factor in alI of these sites.

Cancer of the Cervix

There is a striking association between cancer of the uterine cervix and the number of sexual partners a woman has had. The death rate for this cancer among nuns is much lower than it is for the general population (129), suggesting the involvement of a venereally transmitted agent. A possible candidate is a virus (Herpes simplex type II) which has been found in association with both cervical cancer and other cervical cell abnormalities **(244).** Some study results support this hypothesis, but the data are considered only suggestive at this point, and no conclusion of causality can be drawn.

The number of deaths from cervical cancer (ACS projects 7,200 in 1981) has decreased and continues to decline, partially due to the more widespread use of cervical screening **(6).** Based on the assumption that the majority of cervical

cancers are caused by infective processes, Doll and Peto (93) estimate that prevention or treatment of infection might reduce total cancer mortality by 1 percent.

Cancers of Male Reproductive Organs

International comparison and a study of Ugandan men has shown a correlation of higher rates of penile cancer in areas where circumcision is not generally practiced and where penile hygiene is poor (163),

Age-standardized incidence rates for prostate cancer vary between about 3/100,000 in Japan and 40/100,000 in U.S. whites, to a high of about 75/100,000 for some U.S. blacks (184), suggesting an environmental etiology. Feminella and Lattimer (119) found an increase in cervical carcinomas among wives of cases. A common, perhaps viral, etiology is suggested; however it is not substantiated by some population-based rates, for instance, a lower rate of prostatic cancer and a higher rate of cervical cancer occurs among Mexican-Americans as compared to U.S. blacks (163).

Testicular cancer is highly associated with abnormalities of sexual development, particularly cryptorchidism (failure of the testes to descend into the scrotum) (208). Cancer occurs in 11 to 15 percent of undescended testes (s). The association may be direct or a third factor, perhaps endocrinological, may predispose individuals to both conditions.

NATURAL RADIATION

One would like to think that at least Mother Nature would not place a carcinogenic burden on the people of this planet. This unfortunately is not the case. Several types of natural radiation cause concern regarding carcinogenicity, the most important of which, ultraviolet radiation and ionizing radiation, were among the first factors recognized as human carcinogens.

Ultraviolet Radiation

Ultraviolet radiation (or ultraviolet light) is associated with some lip cancers, with a large proportion of squamous-cell carcinomas and is the principal cause of basal-cell carcinoma of the face and neck in light-skinned people. The evidence for the association includes prevalence on sun-exposed **areas, increased incidence** in lightly pigmented people, and increased incidence with greater insolation and greater time outdoors. Basal-cell carcinomas account for over 75 percent of all skin cancers, but appropriate treatment cures about 95 percent (159). The squamous- and basal-cell carcinomas are referred to as nonmelanoma skin cancer. Approximately 400,000 cases occur annually– as many cancers as occur at all other sites combined (66). Fortunately, most are not fatal.

NCI conducted a nonmelanoma skin cancer survey in eight locations in the United States during the period 1977-78, as mandated by the Clean Air Act Amendments of 1977. Men were found to be at greater risk of cancer than were women. The average age-adjusted incidence rate for white males was 310/100,000 and for white females 172/100,000 (250). An increase of **15** to **20** percent was reported in incidence as compared to the rate estimated from the Third National Cancer Survey (TNCS). This increase may be due, in large part, to changes in clothing styles and greater exposure to sunlight than was customary years ago.

Ultraviolet radiation has also been associated with the far more serious skin cancer, malignant melanoma. However, the data are less convincing since the distribution of cancers on the body does not directly correspond to the degree of exposure. In 1978, there were approximately 6,000 deaths from malignant melanoma in the United States. ACS **(6)** estimates that there will be 14,300 new cases and 6,700 deaths from melanoma in 1981. Melanoma is the leading cause of death from all diseases of the skin and is unquestionably increasing in frequency.

Incidence and mortality rates from skin cancer in different countries correlate fairly closely

with the intensity of ultraviolet radiation. The disease is most prevalent in people receiving large amounts of sunlight, and it is a recognized occupational hazard for individuals working outdoors. The maps prepared by Mason, et al. **(223), which** depict average age-adjusted cancer mortality rates on a county-by-county basis, convincingly demonstrate higher risk of skin cancer in the Southeast United States. TNCS found the annual incidence rate for nonmelanoma skin cancer to be 539/100,000 in the Dallas-Fort Worth, Tex., area as compared to 174/100,000 in Iowa.

An individual's risk of developing skin cancer is strongly influenced by genetic makeup. A higher risk exists for those with phenotypic characteristics such as fair complexion, light eye and hair color, and poor ability to tan. By contrast, skin cancer is very rare in deeply pigmented populations. In addition, several different types of chemicals can augment the carcinogenic properties of ultraviolet radiation, including some used as medications and in cosmetics.

As discussed in the *Air Pollution* section, the use of chlorofluorocarbons has been restricted in the United States because of the belief that they may react in the stratosphere to reduce the thickness of the ozone layer and cause an increase in ultraviolet radiation reaching the surface of the Earth. NAS (70) estimated that global release of chlorofluorocarbons at 1977 rates could result in several hundred thousand additional cases of nonmelanoma skin cancer and several thousand melanomas in the next century. (For additional information on the possible carcinogenic impact from release of chlorofluorocarbons, see *Air Pollution.)*

Higginson and Muir (166) estimated that 10 percent of male and female cancers in the Birmingham and West Midland region of England could be attributed to sunlight. Doll and Peto (93) attribute 90 percent of lip cancers (in conjunction with smoking), 50 percent or more of melanomas, as well as 80 percent of other skin cancers to ultraviolet radiation. This accounts for between 1 and 2 percent of all cancer deaths if these proportions are applied to 1978 U.S. cancer deaths.

Ionizing Radiation

About half of the average U.S. exposure to ionizing radiation comes from natural sources. Of the remainder, most comes from diagnostic medical exposures, and smaller amounts come from medical therapy, occupational exposures, and from radioactive pollutants. (Those exposures are discussed in *Medical Drugs and Radiation, Occupation,* and *Air Pollution,* respectively.) Cosmic rays and the minute amounts of radioactive isotopes that occur in our bodies and in all natural materials are the major sources of natural background radiation.

The quantitative dose-response relationship between cancer and low-level ionizing radiation has been the cause of much debate. Until 30 years ago, it was commonly assumed that ionizing radiation did not cause cancer unless the exposures were high enough to cause clinically detectable damage to the irradiated tissue. This assumption is now known to be false, although the dose-response relationship at low levels is still not known with certainty.

Organs and tissues differ in their susceptibility to carcinogenic effects induced by radiation. Leukemia was the first form of cancer associated with exposure to ionizing radiation, but we now know that cancer may be induced by radiation in many tissues of the human body and that the risk of inducing solid tumors exceeds that of leukemia (268). The major cancer sites affected are the breast in women and the thyroid, lung, and digestive organs in both sexes. Solid tumors have a longer latency period (10 to more than 30 years) than the few years before the excess risk for leukemia manifests itself. The total cancer risk from radiation is greater for women than men, principally because of the contribution of breast cancer.

More information is available on the dose-response relationship between radiation and cancer than any other, but there is still much controversy over the appropriate extrapolation model to use for estimating the cancer risk from ionizing radiation. In July 1980, NAS officially released BEIR III (268). The estimates for the risks from ionizing radiation used by BEIR 111 were derived principally from human experi-

ences with much higher doses than most people receive. The most important of these are data from populations exposed to atomic blasts in Hiroshima and Nagasaki, patients exposed to therapeutic radiation, and various occupational groups such as uranium miners and radium watch dial painters. Disagreement persists in the field of radiation carcinogenesis over the appropriateness of these high-exposure populations for estimating low-level risks.

The development and release of the BEIR 111 report illustrates the diverging and changing opinions concerning the appropriate methodology for extrapolating from the measured effects of high doses of ionizing radiation to the most probable effects of low doses. A draft of the BEIR 111 report was released for public comment in May 1979 but was retracted when it was learned that a majority of the committee supported a model different from the one presented.

Some members of the committee felt that for low doses, a linear model overestimated the risk and a pure quadratic model, which estimates a lower risk, could be used as a lower bound. However, others felt that the linear model was more accurate. Because of this disagreement, a consensus panel was assembled and it adopted the linear-quadratic model: the pure quadratic model produces the lowest estimate, the linear the highest, and the linear-quadratic estimates an intermediate risk. Depending on which model is used, estimates of mortality from all forms of cancer will differ by about one order of magnitude.

The committee also could not agree on whether the cancer risk from radiation would have an additive or multiplicative effect on the general cancer rate. Throughout the report, excess risk is given as both an *absolute* (additive) and as a *relative* risk. The relative approach assumes that the excess risk increases gradually and continuously, proportional to the spontaneous risk, which increases with **age** for nearly all cancers. The absolute approach assumes a constant number of additional cancers throughout life.

The BEIR III report (268) makes various attempts at estimating cancer risk from different types of exposure but does not quantify the risk from low-dose radiation:

> . . . the degree of risk is so low that it cannot be observed directly and there is great uncertainty as to the dose-response function most appropriate for extrapolating in the low-dose region.

It further states:

> It is by no means clear whether dose rates of gamma or x radiation of about 100 mrads/yr are in any way detrimental to exposed people . . .

For the purpose of this assessment, the risks derived for continuous lifetime exposure to 1 rad/yr of low-dose (gamma or X-ray) radiation is the most relevant, though it is an order of magnitude higher than average natural background radiation. Table 21 displays both absolute and relative risk estimates generated by BEIR III.

The BEIR III report estimated that the average whole body dose of natural background radiation in the United States is approximately 100 mrem/yr. The dose of radiation received varies with altitude and geographical location. Using a figure of 220 million Americans, one can estimate that the population as a whole would be exposed to 22 million person-rem of background radiation.[3] Although BEIR III did not attempt to estimate the risk of cancer induced by low-dose radiation, it would not be incorrect to compute an upper limit of risk from the linear model since this is the only model which assumes that dose and effect are proportional. Using the range of risk estimates, 158-403 excess cancer deaths per million persons per rad, yields estimates of 3,476 and 8,866 cancer deaths per year attributable to background radiation. These figures represent between 0.9 and 2.2 percent of all cancer deaths, and are comparable with 3-percent estimates by Doll

[3] In 1972, EPA estimated that the average dose of natural background radiation for a person living in the United States is 130 mrem. Based on this estimate, the Interagency Task Force on the Health Effects of Ionizing Radiation estimated that the U.S. population is exposed to 20 million person-rem, but this is in error because dividing 20 million person-rem by 130 mrem produces a quotient of 154 million people. The population is nearer 220 million.

and Peto (93) and Jablon and Bailar (191). The lower estimate can be considered to approach zero, in keeping with risks derived from other models, including the quadratic model.

Table 21.—Estimates of Excess Cancer Mortality From Continuous Exposure to 1 Rad/Year of Low-Level (background-type) Radiation by Three Dose-Response Models and Two Risk Projection Models

Estimates of excess annual cancer mortality from continuous exposure to 1 rad/year of low-level (background-type) radiation (excess deaths/million exposed and percentage of normal expectation of cancer deaths)

		Risk projection model	
Dose-response model		Absolute	Relative
	Normal expectation of cancer deaths	167,300	167,300
Linear quadratic	Excess deaths: number	4,751	12,920
	Percent of normal	2.8	7.7
Linear	Excess deaths: number	11,250	30,520
	Percent of normal	6.7	18.2
Quadratic	Excess deaths	[a]	[a]

[a]Not calculated because estimates very close to zero

Estimates of excess lifetime cancer mortality from continuous exposure to 1 rad/year of low-level (background-type) radiation (excess deaths/million exposed)

	Risk projection model	
Dose-response model	Absolute	Relative
Linear quadratic	67	182
Linear	158	403
Quadratic	—	—

SOURCE: Tables adapted from (270)

INFECTION

Infection, particularly viral infection, has long been thought to be a cause of cancer. This idea is partially based on the observation that neoplasms appear in many animal species following viral infections, and specific animal tumor viruses have been convincingly identified. However, epidemiologic evidence indicates that cancer is not a contagious disease. People who come into close contact with cancer patients, such as nurses, doctors, and spouses of patients, are at no higher risk of developing the disease than others. Reports are occasionally published of the occurrence of an unusually large number of cases of rare cancers, but such clusters can be expected to occur periodically by chance. It is more plausible that certain viruses exist which are important in the development of some types of cancer, but that they are widespread in the community. It is probably not the virus itself, but a variety of other factors which determine whether the virus will lead to the development of the disease. These may include genetic and hormonal factors, chemical carcinogens, and defective immune mechanisms, which appear to exert an effect in only a small proportion of those exposed.

The strongest evidence implicating a viral infection in human cancer causation concerns Epstein-Barr virus (EBV) and hepatitis B virus, believed responsible for several cancer types which are relatively rare in the United States. Epstein-Barr is a herpesvirus which is strongly associated with Burkitt's lymphoma and naso-

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pharyngeal carcinoma (93,304). EBV occurs ubiquitously and is known to be the specific cause of infectious mononucleosis. It is postulated that the viral DNA integrates into the genetic material of a human stem cell and that cell becomes the parent of a malignant clone. Epidemiologic data and the detection of Epstein-Barr viral DNA in lymphoma cells supports the association between the virus and these two cancers. The association with nasopharyngeal carcinoma, found in the Far East, is not so strong as with Burkitt's Iymphoma, which occurs mainly in children in central Africa and New Guinea. Nasopharyngeal carcinoma is believed to involve a stronger genetic component, since Chinese migrating to the United States have a much higher incidence of the disease than U.S. whites and blacks, but the rate is lower than among Chinese remaining in the Far East (128). The unusual geographical distribution suggests that the virus may act as a cocarcinogen and that additional factors, such as immunosuppression as a result of malaria, may be involved.

Hepatitis B virus is associated with chronic liver infection which often advances to hepatocarcinoma. A greater prevalence of active hepatitis B infection has been demonstrated in patients with primary hepatocellular carcinoma as compared with matched controls and the general population (304). The virus is believed to be the initiating agent, but promoting agents such as aflatoxin may be important cofactors **(304).** Two other herpesviruses are suspected of being associated with cancer: herpes simplex virus type 2 with cervical cancer, and less closely, cytomegalovirus with prostatic and cervical cancers.

The vast majority of human cancers are not characterized by the presence of viral DNA in the genetic material of cells. This may, of course, be because the methods currently used to detect the presence of a virus are not sufficiently sensitive, or it may be that viruses are not often associated with cancer.

Doll and Peto (93) suggest that viral infection may eventually be shown to be an essential factor in the production of some cancers:

- cancer of the uterine cervix—women with multiple partners are at high risk (see *Sexual Development, Reproductive Patterns, and Sexual Practices);*
- cancer of the penis—wives of penis cancer patients are at high risk for cancer of the uterine cervix;
- acute lymphatic leukemia in children—disease may recur in donor cells after a marrow transplant; and
- reticulosarcoma —occasional appearance shortly after receiving doses of immunosuppressive drugs.

If all of the above cancers depended on viral infection, the proportion of cancers attributable to infection would be about 4 percent (93). The proportion may be considerably larger if, like diet, infectious agents act by indirect means to contribute to the production of cancers. Viruses may promote the development of cancer by causing tissue death, thereby stimulating the division of stem cells and sensitizing them to the action of chemical carcinogens. It is possible for instance, that this is the mechanism whereby hepatitis B virus is associated with the development of liver cancer.

Infection with bacteria or parasites may also contribute to the production of cancer. The *Diet* section discusses the possible role of intestinal bacteria in producing or destroying carcinogenic metabolizes in the large bowel and of salivary duct bacteria in converting nitrates into nitrites and hence facilitating the formation of N-nitroso compounds in vivo. Bacterial infection associated with the development of chronic bronchitis has been thought to increase the risk of lung cancer in cigarette smokers (93), possibly by impairing the efficiency of the mechanism for clearing the bronchi and hence permitting more prolonged contact between inspired carcinogens and the bronchial stem cells. A similar role for infection may also explain the association between ulcerative colitis and colorectal cancer, and that between schistosomiasis, a parasitic infection of the bladder common in parts of Africa, and the development of bladder cancer.

The examples cited are unlikely to be the only ways in which infection affects the risk of developing cancer; but even if they were, the range of estimates for its contribution to the overall cancer rate would be large. Rapp **(304)** speculated that if herpesviruses are eventually shown to be involved in all cancers of the male and female genitourinary systems, then those with active venereal disease would have a 1 per 70-100 risk of developing the disease:

> This estimate is based on the number of new genitourinary cancer cases per year in the United States **(100,000** for females and **70,000** for males) in a population containing about 14 million active cases . . . of venereal disease due to herpesviruses.

If one applies this reasoning to 1978 U.S. cancer deaths, approximately 15 percent of all cancer mortality would be associated with infection. This estimate is extremely tentative—there is much more certainty around the association with cervical *cancer* than other genital sites. Doll and Peto (93) suggested a figure about 10 percent as **a** very uncertain best estimate, within a very wide range of acceptable estimates, of the proportion of cancer deaths attributable to infection, distributed as follows:

> . . . 5% perhaps attributable to the action of viruses and a token figure of 5% to allow for the possible role of other infective agents in determining the conditions under which cancer is produced in vivo. The likely role of infectious agents in the etiology of cancer of the uterine cervix provides a lower limit of at least 1%, but we can at present make no useful guess at the upper limit.

OTHER OR UNKNOWN ASSOCIATIONS

Two basic classes of "other" associations will be considered:

1. Associations with cancers which as yet remain unidentified, but which, when elucidated, will most likely fall into categories that have been discussed in this chapter.
2. Associations of agents or exposures with cancers of the future. These may have been introduced recently, but have not yet produced cancers, or may be introduced in the future.

Causes of Cancers Occurring Today

The agents associated with and/or responsible for many of today's cancers have not been identified. For example, although **cancers of the breast,** colon, rectum, and stomach are associated in some way with dietary factors, a causal relationship has not been found for cancers at those sites. Additionally the incidence of some cancers, myelomatosis and non-Hodgkins lymphoma, for example, appear to be increasing but no evidence associates those cancers with even a broad category of factors.

The search for environmental factors associated with cancer will undoubtedly continue. Observed differences in rates between populations, within countries, and through international comparisons will result in advancing new hypotheses and promoting further studies.

Some suggested associations that were not discussed above are likely to be further investigated, but currently few data exist about them. Biological factors, like immunologic control, may normally limit the onset of disease, and a breakdown of this mechanism which may be brought on by an environmental agent, could increase the propensity for cancer development. Similarly, psychological factors such as stress may create an internal milieu suitable for tumor growth. There is some animal evidence to support this hypothesis but it is limited. Studies of patients in mental hospitals are not supportive of an increased risk (93). Psychological stress does have a recognized role in causing people to smoke, drink, overeat, and take part in other harmful activities which may directly or indirectly increase their risk of cancer.

New Cancer Associations

Hazards exist today which may not have caused any cancers, but which may do so in the future. A timely example is hazardous wastes that have been improperly disposed of in areas commonly termed "dumps." EPA has estimated that there are more than 50,000 improperly operated dump sites containing hazardous waste that are not being properly operated. Of these, they estimate that 30,000 pose a significant health risk. The carcinogenic potential of the myriad chemicals in these dumps is unknown at present. (An OTA assessment about nonnuclear industrial wastes, which will look at health risks, among other things, is to be completed in late 1982.)

Hundreds of new chemicals are introduced into commerce each year. Some of these may present cancer risks. Exposures may be through many routes—pollution, occupation, consumer products, foods, or others.

Table 22.—Estimates of the Percentage of Total Cancer Associated with Various Factors

Factor	Estimate	Time period to which estimate applies	Author
Tobacco			
	30% U.S. mortality, males and females combined	1977	Doll and Peto (93)
	25-35°/0 U.S. male mortality population	1960-72	Hammond and Seidman (155)
	5-100/o U.S. female mortality	1960-72	Hammond and Seidman (155)
	24-38% various populations	—	Enstrom (100)
	430/0 US. male incidence	1980	U.S. Surgeon General (287)
	18°/0 U.S. female incidence	1980	U.S. Surgeon General (287)
	51% . U.S. male mortality	1980	U.S. Surgeon General (287)
	260/o U.S. female mortality	1980	U.S. Surgeon General (287)
	300/o male cancers, England[a]	1968-72	Higginson and Muir (166)
	7% female cancers, England[a]	1968-72	Higginson and Muir (166)
	28% U.S. male incidence[b]	1976	Wynder and Gori (368)
	80/0 U.S. female incidence	1976	Wynder and Gori (368)
Alcohol			
	4-50/. of mortality, males and females combined	1978	OTA based on Schottenfeld (323)
	140/0 U.S. male mortality	1974	Rothman (313)
	12% U.S. female mortalitv	1974	Rothman (313)
	3% U.S. mortality, males and females combined (approximately 4.6% for males and 1°/0 for females)	1977	Doll and Peto (193)
	4% U.S. male incidence[b]	1976	Wynder and Gori (368)
	1% U.S. female incidence[b]	1976	Wynder and Gori (368)
	50/0 male cancers, England[a] (tobacco/alcohol)	1968-72	Higginson and Muir (166)
	3% female cancers England[a] (tobacco/alcohol)	1968-72	Higginson and Muir (166)
Diet			
	4094. U.S. male incidence	1976	Wynder and Gori (368)
	600/o U.S. female incidence	1976	Wynder and Gori (368)
	350/o U.S. mortality, males and females combined	1977	Doll and Peto (93)
Occupation			
	4% U.S. male incidence	1976	Wynder and Gori (368)
	2% U.S. female incidence	1976	Wynder and Gori (368)
	6% male cancers, England[a]	1968-72	Higginson and Muir (166)
	2% female cancers, England[a]	1968-72	Higginson and Muir (166)
	<15% U.S. male cancers	Not specified	Cole (62)
	< 5% U.S. female cancers	Not specified	Cole (62)
	23-38°/0 U.S. incidence, males and females combined	Near term and future	HEW (82)
	6.8% U.S. male mortality	1977	Doll and Peto (93)
	1.20/0 U.S. female mortality	1977	Doll and Peto (93)

Table 22.–Estimates of the Percentage of Total Cancer Associated with Various Factors (Continued)

Factor	Estimate	Time period to which estimate applies	Author
Asbestos			
	13-18°/0 U.S. cancers	Near term and future	HEW (82)
	30/0 (1 .4-4.4°/0) U.S. cancers	Now or likely in near future	Hogan and Heel (171)
Air pollution			
	20/0 U.S. mortality	Future	Doll and Peto (93)
Consumer products			
	<1% U.S. mortality, males and females combined	1977	Doll and Peto (93)
Infection			
	5%?-10%?? U.S. cancers	Present and future	Doll and Peto (93)
	150/0 U.S. mortality	1978	Rapp (304)
Lifestyle			
	30% male cancers, England[a]	1968-72	Higginson and Muir (166)
	630/o female cancers, England[a]	1968-72	Higginson and Muir (166)
Radiation, natural and medical:			
Ultraviolet			
	10°/0 male cancers, England[a]	1968-72	Higginson and Muir (166)
	10°/0 female cancers, England[a]	1968-72	Higginson and Muir (166)
Unspecified radiation			
	1% male cancers, England[a]	1968-72	Higginson and Muir (166)
	1% female cancers, England[a]	1968-72	Higginson and Muir (166)
Ultraviolet and X-ray			
	8°/0 U.S. male incidence	1976	Wynder and Gori (368)
	8°/0 U.S. female incidence	1976	Wynder and Gori (368)
Natural ionizing			
	O-(0.9-2.2°/0) U.S. mortality	1978	OTA based on BEIR lll (268)
	30/0 U.S. mortality	1978	Doll and Peto (93)
	30/0 U.S. mortality	1978	Jablon and Bailar (191)
Medical drugs and radiation			
	10/0 U.S. mortality, males and females combined	1977	Doll and Peto (93)
	10/0 male and female cancers combined, England[a]	1968-72	Higginson and Muir (166)
	4°/0 U.S. incidence, males and females combined (refers only to exogenous hormones)	1976	Wynder and Gori (368)
Sexual development, reproductive patterns and sexual practices			
	7°/0 U.S. mortality, males and females combined	1977	Doll and Peto (93)
Other or unknown			
	?%	Present and future	Doll and Peto (93)
	15°/0 male cancers, England[a]	1968-72	Higginson and Muir (166)
	11% female cancers, England[a]	1968-72	Higginson and Muir (166)

[a]Birmingham and West Midland Region.
[b]Estimated from graphic presentation.

SOURCE: Office of Technology Assessment.