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Review

The causes and prevention of cancer

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ABSTRACT **Epidemiological evidence indicates that avoidance of smoking, increased consumption of fruits and vegetables, and control of infections will have a major effect on reducing rates of cancer. Other factors include avoidance of intense sun exposure, increases in physical activity, and reduction of alcohol consumption and possibly red meat. A substantial reduction in breast cancer is likely to require modification of sex hormone levels, and development of practical methods for doing so is a high research priority. Resolution of the potential protective roles of specific antioxidants and other constituents of fruits and vegetables deserves major attention. Mechanistic studies of carcinogenesis indicate an important role of endogenous oxidative damage to DNA that is balanced by elaborate defense and repair processes. Also key is the rate of cell division, which is influenced by hormones, growth, cytotoxicity, and inflammation, as this determines the probability of converting DNA lesions to mutations. These mechanisms may underlie many epidemiologic observations.**

We discuss the causes of cancer with an emphasis on mechanisms. As causes and mechanisms become clear, prevention becomes possible. Henderson *et al.* (1) reviewed the causes of cancer in 1991, following by a decade the comprehensive review of Doll and Peto (2).

Trends

Cancer was estimated to cause 23% of the person-years of premature loss of life and about 530,000 deaths in the United States in 1993 (3). Four major cancers (lung, colon–rectum, breast and prostate) account for 55% of the deaths. According to the 1993 SEER update from the National Cancer Institute, the age-adjusted mortality rate for all cancers combined (excluding lung and bronchus) has declined from 1950 to 1990 for all individual age groups except 85 and above (3). The decline ranged from 71% in the 0- to 4-year-old group to 8% in the 74- to 85-year-old group. "If lung cancer were eliminated, then the overall cancer death rate would have declined over 14% between 1950 and 1990." Smoking, in addition to causing about 90% of lung cancer, contributes to other cancers, such as mouth, esophagus, stomach, kidney, pancreas, bladder, leukemia, and possibly colon; if these were taken into account the decline would be greater.

If lung cancer is included, overall cancer mortality has decreased for each age group under 45 and has increased for age groups over 55. The decreases in cancer deaths during this period have been primarily from stomach, cervical, uterine, and rectal cancer. The increases have been primarily from lung cancer, due to smoking (which causes 30% of all U.S. cancer deaths), and non-Hodgkin lymphoma (NHL). Reasons for the increase in NHL are not clear, but smoking may possibly contribute (4, 5), and human immunodeficiency virus is a small, but increasing cause.

To interpret changes in mortality rates, one must consider both changes in incidence rates (the number of people newly diagnosed with the cancer) and effects of treatment. Incidence rates have been increasing for some types of cancer in part due to early detection. Doll and Peto (2) pointed out that incidence rates should not be taken in isolation, because they may reflect increases in registration of cases and improvements in diagnosis. The reported rise in cancer rates among men born in the 1940s compared with the 1890s (6) may be due to such artifacts. For example, the rapid increase in age-adjusted prostate cancer incidences without major increases in mortality is almost certainly due largely to increased screening and incidental detection during prostatectomy for benign prostatic hypertrophy.

Mechanisms of Carcinogenesis

Mutations. Mutations in several critical genes can lead to tumors (7). Mutations in the tumor-suppressor gene p53 are found in about half of human tumors. The p53 protein guards a cell cycle checkpoint, and inactivation of p53 allows uncontrolled cell division.

DNA Lesions. DNA lesions (damaged bases or chromosome breaks) have a certain probability of giving rise to mutations when the cell divides. Endogenous DNA damage is high (8). An exogenous mutagen produces an increment in lesions over the background rate of endogenous lesions. The mutagenic effectiveness of a particular lesion depends on its rate of excision by DNA repair enzymes and on the probability that it gives rise to a mutation when the cell divides.

Cell Division. This is a critical factor in mutagenesis, because when the cell divides a DNA lesion can give rise to a point mutation, deletion, or translocation (9–11). Thus, an important factor in the mutagenic effect of an agent is the increment it causes over the background cell division rate in those cells that matter. Those cells that appear to matter most for cancer are the stem cells, which are not discarded, whereas their daughter cells are. Increasing the cell division rate of stem cells increases mutation and therefore cancer. As expected, there is little cancer in nondividing cells. Increased cell division, and therefore an increased risk for cancer, can be caused by such diverse agents as increased levels of particular hormones (12), excess calories, chronic inflammation, or chemicals at doses causing cell division (13–16). If both the rate of DNA lesions and cell division are increased, then there will be a multiplicative increase in mutagenesis, for example, by high doses of a mutagen which also increases cell division through cell killing and consequent cell replacement. Chronic dosing at high levels of chemicals that do not damage DNA can also cause cell killing and consequent cell division and thus increase cancer. Studies of cell division in stem cells, and the signaling systems responsible for stem-cell proliferation, are active and important areas of research.

Cell Cycle Checkpoints. These checkpoints prevent division of cells with too many DNA lesions, thus inhibiting the formation of mutations. This defense, like

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DNA repair, is not perfect. The sensing of lesions in transcribed genes is done by the transcription apparatus that makes mRNA (17, 18). The presence of lesions appears to induce DNA repair and also to halt cell division at a cell cycle checkpoint. The mechanism may be that the p53 protein, which controls the G_1-to-S checkpoint, is associated with the replication and repair protein RPA (19, 20). When DNA damage occurs, RPA appears to bind to single-strand DNA and release p53 (19, 20), which in turn causes a block of cell division at the checkpoint, thus preventing conversion of lesions to mutations (M. Botchan, personal communication). In addition, p53 is involved in triggering cell death (apoptosis) (21), so that a higher level of DNA lesions may lead to an apoptotic signal (22).

Defense Systems. Defense systems such as the glutathione transferases protect DNA against mutagens. These defenses are almost all inducible and, thus, buffer cells from increments in reactive electrophilic chemicals that can cause DNA lesions (23). DNA repair enzymes, almost all of which are inducible, buffer the cell against increments in DNA lesions. Therefore, the effect of a particular chemical insult is dependent on the level of each defense, which in turn is dependent on the past history of exposure. Defenses can be partially disabled by lack of particular micronutrients in the diet (e.g., antioxidants) (8).

Major Risk Factors

Endogenous Damage. To the extent that the major exogenous risk factors for cancer—smoking, chronic inflammation, and unbalanced diet—are diminished, cancer will appear at a later age, and the proportion of cancer that is caused by endogenous processes will increase.

Oxidant by-products of normal metabolism cause extensive damage to DNA, protein, and lipid. We argue that this damage (the same as that produced by radiation) is a major contributor to aging and to degenerative diseases of aging such as cancer, heart disease, cataracts, and brain dysfunction (8). Antioxidant defenses against this damage include ascorbate, tocopherols, and carotenoids. Degeneration of somatic cells during aging appears, in good part, to contribute to degenerative diseases.

DNA is oxidized because antioxidant defenses are not perfect. The number of oxidative hits to DNA per cell per day is estimated to be about 100,000 in the rat and roughly 10 times fewer in the human (8). DNA repair enzymes efficiently remove most, but not all, of the lesions formed. Oxidative lesions in DNA accumulate with age, so that by the time a rat is old (2 years) it has about a million DNA lesions per cell, which is about twice that in a young rat (8). Mutations also accumulate with age (24).

The proximity of mitochondrial DNA (mtDNA) to oxidants generated during oxidative phosphorylation results in 10 times the oxidative damage of nuclear DNA (25). The cell defends itself against this high rate of damage by a constant turnover of mitochondria, thus presumably removing altered mitochondria that are producing more oxidants. Nevertheless, oxidative lesions accumulate with age in mtDNA at a higher rate than in nuclear DNA (8). Oxidative damage could account for the mutations in mtDNA that accumulate with age (26, 27). Mitochondria produce more oxidants with age and may be a weak link in aging (27).

Oxidants damage proteins as well as DNA (28). The protective proteolytic enzymes that hydrolyze oxidized proteins are not sufficient to prevent an age-associated accumulation of oxidized proteins. In two human diseases associated with premature aging, Werner syndrome and progeria, oxidized proteins accumulate at a much higher rate than normal (28). Fluorescent age pigments, which are thought to be due in part to crosslinks between protein and lipid peroxidation products, also accumulate with age (29).

Further understanding of the role and mechanism of endogenous damage could lead to new prevention strategies for cancer and other degenerative diseases.

Diet. Diet is thought to account for about one-third of cancer in the United States (2), but the specific factors are only slowly being clarified. A brief overview of the field is presented, emphasizing mechanism.

Calorie or protein restriction and cancer prevention. In rodents a calorie-restricted diet compared to *ad libitum* feeding markedly decreases tumor incidence and increases lifespan but decreases reproduction (30, 31). Protein restriction, though less well studied, appears to have similar effects (32). Darwinian fitness in animals appears to be increased by hormonal changes which delay reproductive function during periods of low food availability because the saved resources are invested in maintenance of the body until food resources are available for successful reproduction (33, 34). Lower mitotic rates are observed in a variety of tissues in calorie-restricted compared with *ad libitum* fed rodents (35, 36) and are likely to contribute to the decrease in tumor incidence (37). Though epidemiological evidence on restriction in humans is sparse, the possible importance of growth restriction in human cancer is supported by epidemiologic studies indicating higher rates of breast and other cancers among taller persons (38)—e.g., Japanese women are now taller, menstruate earlier, and have increased breast cancer rates. Also, many of the variations in breast cancer rates among countries, and trends over time within countries, are compatible with changes in growth rates and attained adult height (39).

Dietary fruits and vegetables and cancer prevention. Consumption of adequate fruits and vegetables is associated with a lowered risk of degenerative diseases such as cancer, cardiovascular disease, cataracts, and brain and immune dysfunction (8). Nearly 200 studies in the epidemiological literature have been reviewed and relate, with great consistency, the lack of adequate consumption of fruits and vegetables to cancer incidence (40–42). The quarter of the population with the lowest dietary intake of fruits and vegetables compared to the quarter with the highest intake has roughly twice the cancer rate for most types of cancer (lung, larynx, oral cavity, esophagus, stomach, colon and rectum, bladder, pancreas, cervix, and ovary). The protective effect for hormonally related cancers is weaker and less consistent: for breast cancer the protection appears to be about 30% (38, 40, 43). Only 9% of Americans met the intake recommended by the National Cancer Institute and the National Research Council (38, 44, 45): two servings of fruits plus three of vegetables per day.

Antioxidants in fruits and vegetables may account for a good part of their beneficial effect as suggested by mechanistic studies. However, the effects of dietary intakes of the antioxidants ascorbate, tocopherol, and carotenoids are difficult to disentangle by epidemiological studies from other important vitamins and ingredients in fruits and vegetables (40, 41, 44, 46). Also, it is unlikely that all compounds sharing antioxidant properties would have similar effects against all types of cancer, since each antioxidant has a unique function and distribution within the body. Further, even though a specific antioxidant may play a critical role in limiting cancer incidence, the levels already present in a particular population may be sufficient, so that greater consumption would not be of benefit.

Only a few randomized trials in humans have evaluated antioxidants as possible protective agents. In a trial conducted in rural China, a combination of antioxidant supplements appeared to reduce the incidence of gastric cancer (47), a disease which has been repeatedly associated with low intake of fruits and vegetables. However, supplements of β-carotene did not reduce recurrences of skin cancer, and vitamins C and E and β-carotene did not reduce recurrences of colon polyps (48, 49). In a recent large study of 30-year, heavy smokers in Finland (50), β-carotene supplements appeared to sightly increase the risk of lung cancer, coronary heart disease, and total mortality, in contrast to the findings of protection by intakes of fruits and vegetables in many observa-

tional studies. A modest dose of vitamin E was unrelated to risk of lung cancer in this study, perhaps because vitamin C, which was not given, is necessary to regenerate vitamin E. The duration of the Finnish study (six years) may have been insufficient to observe a protective influence that might operate in the early stages of carcinogenesis. Present epidemiological evidence regarding the role of greater antioxidant consumption in human cancer prevention is thus inconsistent. Nevertheless, biochemical data indicating massive oxidative damage to DNA, proteins, and lipids, as well as indirect evidence, such as heightened oxidative damage to human sperm DNA with insufficient dietary ascorbate (51), indicate the need for further investigation of the wide variety of potentially effective antioxidants, both natural and synthetic.

Folic acid and other compounds in fruits and vegetables may contribute to the reduction of cancer. Low folic acid intake causes chromosome breaks in rodents (52) and humans (53, 54) and increases tumor incidence in some rodent models (55). Folic acid is required for the synthesis of DNA nucleotides, and folate deficiency causes breaks in DNA through misincorporation of uracil (53). Low folate intake has been associated with several neoplasms, including adenomas and cancers of the colon (56–58). Deficient intake of folic acid appears to be common in U.S. diets as evidenced by elevated blood homocysteine levels (59, 60) and by the clear relationship with neural-tube birth defects (61). About 15% of the U.S. population (62), and about half of low-income Black children (63) or Black elderly (64), are at a level (<4 ng/ml of serum) where chromosome breaks have been seen (53). Dietary fiber, obtained only from foods of plant origin, may lower the risk of colon cancer (65). Vitamin A, which is derived from some carotenoids as well as from animal sources in the diet, regulates cell differentiation and reduces tumor incidence in many animal models and possibly humans (66). Fruits and vegetables may also reduce cancer risk because they contain antioxidants such as flavonoids, inducers of detoxifying enzymes such as indoles, and weak estrogens that act as antiestrogens (see *Hormones*) (41, 46, 67).

Other aspects of diet. Strong international correlations have suggested that animal (but not vegetable) fat and red meat may increase the incidence of cancers of the breast, colon, and prostate (68, 69). However, large prospective studies of fat intake and breast cancer have consistently shown a weak or no association (38). In contrast, animal fat and red meat have been associated with colon cancer risk in numerous case-control and cohort studies, but the association with meat consumption appears more consistent (70, 71). Consumption of animal fat and red meat has been associated with prostate cancer in multiple studies (72, 73). Hypothesized mechanisms for these associations include effects of dietary fats on endogenous hormone levels (1), proliferative effects of bile acids on the colonic mucosa, effects of rodent carcinogens produced in the cooking of meat, and excessive iron intake. Excess iron absorption (absorption of heme iron from meat is unregulated) is a plausible, though unproven, contributor to production of oxygen radials (8). Some experimental evidence suggests that increased calcium antagonizes high-fat-induced proliferation, thus reducing the risk of colon cancer (74, 75); however, case-control and cohort studies have yielded divergent results (76). Physical activity is inversely related to colon cancer risk in many studies and some of the large geographical differences in colon cancer rates that have been attributed to dietary factors are probably due to differences in physical activity (77, 78, 153). Further research on the mechanism of the beneficial effects of exercise is warranted.

Chinese-style salted fish, particularly when consumed in childhood, is associated with nasopharyngeal cancer (81).

Cooking of food is plausible as a contributor to cancer. A wide variety of chemicals are formed during cooking. Four groups of chemicals that cause tumors in rodents have attracted attention because of mutagenicity, potency, and concentration (79–81). (*i*) Nitrosamines are formed from nitrogen oxides present in gas flames or from other burning. Surprisingly little work has been done on the levels of nitrosamines in fish or meat cooked in gas ovens or barbecued, considering their mutagenic and carcinogenic potency. (*ii*) Heterocyclic amines are formed from heating amino acids or proteins. (*iii*) Polycyclic hydrocarbons are formed from charring meat. (*iv*) Furfural and similar furans are formed from heating sugars. Heating fat generates mutagenic epoxides, hydroperoxides, and unsaturated aldehydes and may also be of importance. Epidemiological studies on cooking are difficult and so far are inadequate to resolve a carcinogenic effect in humans (81).

Alcoholic beverages cause inflammation and cirrhosis of the liver and liver cancer (82). Alcohol is an important cause of oral and esophageal cancer (and is also synergistic with smoking) (82) and possibly contributes to colorectal cancer (83). Breast cancer is also associated with alcohol consumption (see below).

Tobacco. Tobacco is the most important global cause of cancer and is preventable. Smoking contributes to about one-third of cancer, and one-quarter of heart disease, and about 400,000 premature deaths per year in the U.S. (84). Tobacco is a known cause of cancer of the lung, bladder, mouth, pharynx, pancreas, kidney, stomach, larynx, esophagus (85), and possibly colon (86–88). It causes even more deaths by diseases other than cancer. Tobacco is causing about three million deaths per year worldwide in the 1990s and will, if present rates of smoking continue, cause about 10 million deaths per year a few decades from now (84). The evidence for environmental tobacco smoke as a cause of cancer is much weaker: it has been estimated to cause up to 3000 additional cases of cancer in the United States (89, 90), though this estimate has been strongly disputed (91).

The carcinogenic mechanisms of tobacco smoking are not well understood. Smoking is a severe oxidative stress, and smoke contains a wide variety of mutagens and rodent carcinogens. The oxidants in cigarette smoke (mainly nitrogen oxides) deplete the body's antioxidants. Thus, smokers must ingest 2–3 times more ascorbate than nonsmokers to achieve the same level of ascorbate in blood, but they rarely do (92–94).

Chronic Infection, Inflammation, and Cancer. Leukocytes and other phagocytic cells combat bacteria, parasites, and virus-infected cells by destroying them with nitrogen oxide and superoxide, which react to form peroxynitrite, a powerful mutagenic oxidizing and nitrating agent; hypochlorite, a mutagenic chlorinating and oxidizing agent; and hydrogen peroxide, a mutagenic oxidizing agent. These oxidants protect humans from immediate death from infection but also cause oxidative damage to DNA, mutation, and chronic cell killing with compensatory cell division (95, 96), thereby contributing to the carcinogenic process. Antioxidants appear to inhibit some of the pathology of chronic inflammation (8).

Chronic infections contribute to about one-third of the world's cancer. Hepatitis B and C viruses are a major cause of chronic inflammation leading to liver cancer, which is one of the most common cancers in Asia and Africa (97–99). Hepatitis B and C viruses infect about 500 million people worldwide. Vaccinating babies at birth is potentially an effective method to reduce liver cancer and is routinely done for hepatitis B in Taiwan.

The mutagenic mold toxin aflatoxin, which is found in moldy peanut and corn products, appears to interact with chronic hepatitis infection in liver cancer development (100). In the United States, liver cancer is rare. Although hepatitis B and C viruses infect <1% of the U.S. population, hepatitis viruses can account for half of liver cancer cases among non-Asians (101) and even more among Asians (102).

Schistosomiasis infection is widespread in Asia and Egypt. In Asia, the eggs of *Schistosoma japonicum*, deposited in the colonic mucosa, cause inflammation and colon cancer (103). In Egypt, the eggs of

Schistosoma haematobium, deposited in the bladder, cause inflammation and bladder cancer (103). *Opisthorchis viverrini*, a liver fluke, infects millions of people in Thailand and Malaysia. The flukes lodge in bile ducts and increase the risk of cholangiocarcinoma (103). *Chlonorchis sinensis* infections in millions of Chinese increase the risk of biliary tract cancer (104). *Helicobacter pylori* bacteria infect the stomachs of more than one-third of the world's population and cause stomach cancer, ulcers, and gastritis (103). In wealthy countries the infection is often asymptomatic, which suggests that inflammation may be at least partially suppressed, possibly by adequate levels of dietary antioxidants (105).

Human papilloma virus, a major risk factor for cervical cancer, does not appear to work through an inflammatory mechanism (106). It is spread by sexual contact, an effective way of transmitting viruses.

Asbestos exposure leading to chronic inflammation may be in good part the reason it is a significant risk factor for cancer of the lung (107, 108) (see below).

Nonsteroidal antiinflammatory drugs, particularly aspirin, may be useful in prevention of colon cancer (154).

Hormones. Henderson *et al.* (1) have reviewed the extensive literature indicating a role of sex hormones in cancer causation, likely through causing cell division, and possibly contributing to as much as one-third of all cancer cases. Endometrial cancer appears most exquisitely sensitive to cumulative estrogen exposure, with risks elevated 10- to 20-fold by long-term use of exogenous estrogens (109). Estrogens increase the division of endometrial cells, but progestogens reduce division; thus the addition of progestogens to estrogen therapy after menopause may reduce the risk of endometrial cancer (1).

Ovarian cancer seems to be related to factors that increase the division of surface epithelial cells; e.g., pregnancies substantially reduce the number of ovulations and therefore cell division and risk (1). Oral contraceptives, which also block ovulation, decrease risk, by as much as 50% with five years of use (110).

Factors that increase cumulative exposure to estrogens, such as early age at menarche, late menopause, and prolonged estrogen therapy after menopause, increase the risk of breast cancer (1, 111). Breast cancer cells proliferate in the presence of estrogens, and progestogens also appear to enhance cell division (1). Moreover, the addition of progestogens to estrogen therapy does not reduce, and may possibly further increase, the risk of breast cancer (112). Pregnancy has a complex relation with breast cancer, as risk is initially increased for a period of one to two decades (probably due to hormonal stimulation), but lifetime incidence is ultimately reduced (113, 114), possibly due to a permanent differentiation of stem cells resulting in less proliferation (115). Lactation modestly reduces breast cancer incidence (116). The evidence that hormones influence the incidence of breast cancer suggests ways of reducing incidence. One proposal is to develop a hormonal contraceptive that mimics the effect of an early menopause; this might reduce breast cancer risk by half (117). Exercise may lower breast cancer risk in young women, probably through influencing hormone levels (118). Alcohol consumption, which has been consistently associated with breast cancer risk in large prospective studies, as well as in most case-control studies (119), appears to increase endogenous estrogen levels (120); thus, reduced consumption of alcohol may decrease breast cancer risk. Foods, such as soybeans, that contain weakly estrogenic substances that compete with more potent endogenous estrogen might also reduce the risk of breast cancer (41, 46, 67).

Less Important Risk Factors

Occupation. Half of the 60 chemicals and chemical mixtures the International Agency for Research on Cancer has evaluated as having sufficient evidence of carcinogenicity in humans are occupational exposures, which tend to be concentrated among small groups of people who have been chronically exposed at high levels (121). These include workplace exposures such as "rubber industry" or "coke production" as well as exposure to specific aromatic amines, petrochemicals, metals, etc. The issue of how much cancer can be attributed to occupational exposure has been controversial, but a few percent seems a reasonable estimate. Doll and Peto (2) have discussed difficulties in making such estimates, including the lack of accurate data on history of exposure and current exposures, as well as confounding factors such as socioeconomic status and smoking. Lung cancer was by far the largest contributor to Doll and Peto's estimate of the proportion of cancers due to occupation. The preeminence of smoking as a cause of lung cancer confounds the interpretation of rates in terms of particular workplace exposures—e.g., asbestos. Asbestos appears to multiply rather than just add to the effect of smoking. In contrast, asbestos alone is a known risk factor for mesothelioma. Asbestos was estimated to cause a high proportion of occupational cancers (2); however, recent estimates for asbestos-related cancer are lower (122, 123).

Exposures in the workplace can be high compared with other chemical exposures to humans—e.g., in air or water. We have argued (10, 11) that increased cell division rates are important in causing mutation and cancer and, therefore, the extrapolation from the results of high-dose animal cancer tests to low-dose human exposures cannot be done without considering the mechanism of carcinogenesis for the chemical. However, some past occupational exposures have been high, and comparatively little quantitative extrapolation may be required from high-dose rodent tests to high-dose occupational exposures. Since occupational cancer is concentrated among small groups exposed at high levels, there is an opportunity to control or eliminate risks once identified. However, in contrast to other federal agencies such as the Environmental Protection Agency (EPA), few chemicals are regulated by the U.S. Occupational Safety and Health Administration (OSHA) as potential human carcinogens. For 75 rodent carcinogens regulated by OSHA with permissible exposure limits (PELs), Gold *et al.* (124) recently ranked potential carcinogenic hazards on an index (PERP) that compares the permitted dose-rate to workers with the carcinogenic dose to rodents. It was found that for 9 chemicals the permitted exposures were within a factor of 10 of the rodent carcinogenic dose and for 17 they were 10–100 times lower than the rodent dose. These values are high in comparison to hypothetical risks regulated by other federal agencies.

Sun Exposure. Exposure to the sun is the major cause of skin cancer, with melanoma being of the utmost importance. Exposure during the early decades of life, particularly when sufficient to cause burns, appears to be the dominant factor (125). Prevention of skin cancer is feasible if fair-skinned people become aware of this information and take protective measures.

Medical Interventions. Some cancer chemotherapeutic drugs, particularly alkylating agents, cause second malignancies, most commonly leukemias, lymphomas, and sarcomas (126, 127). Some formerly used drugs, such as phenacetin and diethylstilbesterol, were associated with increased cancer risk (128). Potent immunosuppressive agents such as cyclosporin also increase the risk of a variety of cancers (129), and estrogen replacement therapy increases risk of endometrial and breast cancer. Diagnostic x-rays have contributed to malignancies (130). Although these side effects should weigh in therapeutic decisions, the overall contribution of medications and diagnostic procedures to cancer incidence is small.

Pollution. Synthetic pollutants are feared by much of the public as major causes of cancer, but this is a misconception. Even if the worst-case risk estimates for synthetic pollutants that have been made by the EPA were assumed to be true risks, the proportion of cancer that EPA could prevent by regulation would be tiny (131). Epidemiological studies, moreover, are difficult to conduct because of inadequacies in exposure assessment and failure to account for

confounding factors such as smoking, diet, and geographic mobility of the population.

Air Pollution. Indoor air is generally of greater concern than outside air because 90% of people's time is spent indoors, and concentrations of pollutants tend to be higher than outdoors. The most important carcinogenic air pollutant is likely to be radon, which occurs naturally as a radioactive gas that is generated as a decay product of radium present in trace quantities in the earth's crust. Radon enters houses primarily in air that is drawn from the underlying soil. Based on epidemiological studies of high exposures to underground miners, radon has been estimated to cause as many as 15,000 lung cancers per year in the United States, mostly among smokers, due to the synergistic effect with smoking (132–134). Epidemiological studies of radon exposures in homes have failed to convincingly demonstrate an excess risk (135, 136). About 50,000–100,000 of the homes in the United States (0.1%) are estimated to have annual average radon levels ≈20 times the national average, and inhabitants receive annual radiation doses that exceed the current occupational standard of underground miners. Efforts to identify high-radon houses indicate that they occur most frequently in concentrated geographic areas (137). In high-radon areas, homes can be tested and high levels can be reduced inexpensively with available technology (133).

A recent large study has reported an association between lung cancer and outdoor air pollution when sulfates are used as an index, but not when fine particles are used; diet was not controlled for (155).

Water pollution. Water pollution as a risk factor for cancer appears small. Among potential hazards, the most important are radon (exposure is small compared with air) and natural arsenate, which is a known human carcinogen (138, 139). Research is needed on mechanism and dose–response of arsenate in humans.

Chlorination of water, an important public health intervention, produces large numbers of chlorinated by-products, some of which are rodent carcinogens. The evidence has been judged inadequate for an association between human cancer and chlorinated water (140). An earlier association with bladder cancer and colon cancer has not been confirmed in a recent case-control, interview study, but an association with rectal cancer was observed (K. Cantor, personal communication).

Hereditary Factors

Inherited factors clearly contribute to cancer, particularly childhood cancer and cancer in early adulthood. Overall cancer rates increase exponentially with age except for a blip on the curve for childhood cancer, which is thought to be mainly due to inheriting a mutant cancer gene (141, 142). Heredity is likely to affect susceptibility to all cancers, but to what extent is not clear, though it is obvious that skin color plays a large role in sun-associated cancers such as melanoma. With the rapid progress of molecular biology, hereditary factors will become understood. Factors other than heredity play the dominant causative role for most major cancers, as indicated by the large differences in cancer rates among countries, the observation that migrants adopt cancer rates close to those of their host populations, and the large temporal changes in the rates of many cancers. While there is little evidence that hereditary factors affect lung cancer (143), the attributable risk for breast cancer appears to be in the range of 10% (144). Identification of those at high genetic risk can be particularly important if modifiable factors can be identified that interact with genetic susceptibility and if sensitive methods of screening exist, such as colonoscopy.

Distractions

The idea that there is an epidemic of human cancer caused by synthetic industrial chemicals is not supported by either toxicology or epidemiology. Though some epidemiologic studies have found an association between cancer and low levels of industrial pollutants, the studies did not correct for diet, which is a potentially large confounding factor; moreover, the levels of pollutants are low and rarely seem plausible as a causal factor when compared with the background of natural chemicals that are rodent carcinogens (79).

Animal Cancer Tests and the Rachel Carson Fallacy. Carson's fundamental misconception was "For the first time in the history of the world, every human being is now subjected to contact with dangerous chemicals, from the moment of conception until death" (145). This is wrong: the vast bulk of chemicals humans are exposed to are natural, and for every chemical some amount is toxic.

Animal cancer tests are usually done on synthetic chemicals at the maximum tolerated dose (MTD) of the chemical. These results are being misinterpreted to mean that low doses of synthetic chemicals and industrial pollutants are relevant to human cancer. About *half* of the chemicals tested, whether synthetic or natural, are carcinogenic to rats or mice at these high doses (11, 146, 147). A plausible explanation for the high proportion of positive results is that testing at the MTD frequently can cause chronic cell killing and consequent cell replacement, which is a risk factor for cancer that can be limited to high doses (10, 11, 15, 16).

The great bulk of chemicals ingested by humans is natural, by both weight and number. For example, 99.99% of the pesticides in the diet are naturally present in plants to ward off insects and other predators (148). Half of the natural pesticides tested (29 of 57) are rodent carcinogens (79). Reducing exposure to the 0.01% that are synthetic, either to individual chemicals or to mixtures, will not appreciably reduce cancer rates. On the contrary, fruits and vegetables are important for reducing cancer; making them more expensive by reducing the use of synthetic pesticides is likely to increase cancer. People with low incomes eat fewer fruits and vegetables (149) and spend a higher percentage of their income on food.

Humans also ingest large numbers of natural chemicals from cooked food. For example, more than a thousand chemicals have been identified in roasted coffee; more than half of those tested (19 of 26) are rodent carcinogens (79). There are more natural carcinogens by weight in a single cup of coffee than potentially carcinogenic synthetic pesticide residues in the average U.S. diet in a year, and there are still a thousand known chemicals in roasted coffee that have not been tested. This does not necessarily mean that coffee is dangerous but does indicate that animal cancer tests and worst-case risk assessments build in enormous safety factors and should not be considered to reflect true risks.

Because of their unusual lipophilicity and long environmental persistence, there has been particular concern for a small group of valuable polychlorinated synthetic chemicals such as 1,1-bis(4-chlorophenyl)-2,2,2-trichloroethane ("dichlorodiphenyltrichloroethane", DDT) and polychlorinated biphenyls (PCBs). There is no convincing epidemiological evidence (150), nor is there much toxicological plausibility, that the levels usually found in the environment are likely to be a significant contributor to cancer. 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD), which is produced naturally by burning when chloride ion is present and is an industrial by-product, is an unusually potent rodent carcinogen but seems unlikely to be a significant human carcinogen at the levels to which the general population is exposed.

The reason humans can eat the tremendous variety of natural "rodent carcinogens" in our food is that, like other animals, humans are well protected by general defense enzymes, most of which are inducible (i.e., when a defense enzyme is in use, more of it is made) (23). Defense enzymes are effective against both natural and synthetic chemicals, such as potentially reactive mutagens. One does not expect, nor does one find, a general difference between synthetic and natural chemicals in ability to cause cancer in high-dose rodent tests (11, 79).

We have ranked possible carcinogenic hazards from known rodent carcinogens, using an index that relates human exposure to carcinogenic potency in rodents (HERP) (79). Our ranking does not estimate risks, which current science does not have the ability to do. Rather, possible hazards of synthetic chemicals are put into perspective against the background of naturally occurring rodent carcinogens in typical portions of common foods. The residues of synthetic pesticides or environmental pollutants rank low in comparison to the background, despite the fact that such a comparison gives a minimal view of hypothetical background hazards because so few chemicals in the natural world have been tested for carcinogenicity in rodents. Linear extrapolation from the MTD in rodents to low-level exposure in humans for synthetic chemicals, while ignoring the enormous natural background, has led to exaggerated cancer-risk estimates and an imbalance in the perception of hazard and allocation of resources.

The tremendous variety of chemicals that occur naturally in food, some in high concentrations relative to their toxicity, may play some role in causing human cancer, and research is needed to identify potentially important human carcinogens.

Discussion

Since many of the known causes of cancer are avoidable, it is possible to reduce the incidence rates of many types of cancer. In their 1981 review of avoidable risks of cancer in the United States, Doll and Peto (2) attributed 30% of cancer deaths to tobacco and roughly 35% to dietary factors, although the plausible contribution of diet ranged from 10% to 70%. Other factors were judged to contribute far less. Since that time the contribution of smoking appears to have increased somewhat (35% seems more likely), even though the prevalence of smoking in U.S. adults has decreased, because the relative risk due to smoking has greatly increased for almost all cancers as well as cardiovascular disease (84). This is probably because of the declining risk of cancer death in nonsmokers and because the lifetime impact of smoking since adolescence is being experienced only now. Available data on diet and cancer have increased manyfold since 1981 and generally support the earlier estimate; a slightly narrower estimated range of 20–40% seems more plausible (151). In general, new data have most strongly emphasized the inadequate consumption of protective factors rather than excessive intake of harmful factors. The estimate for diet is revised slightly downward largely because the large international contrasts in colon cancer rates are probably due to differences in physical activity as well as diet. The Doll and Peto (2) estimate for the dietary contribution to breast cancer of 50% is still plausible, even though this may not be avoidable in a practical sense if rapid growth rates are the most important underlying nutritional factor. The estimate for alcoholic beverages can be increased slightly from 3% to 5%, as many new studies support associations with breast and colon cancer. Data subsequent to 1981 have not provided a basis to alter the earlier estimates for other causes appreciably.

One approach to estimating the population impact of adopting major lifestyle factors associated with low cancer risk is to compare the general population with Seventh-Day Adventists, who generally do not smoke, drink heavily, or eat much meat but do eat a diet rich in fruits and vegetables (152). Substantially lower mortality rates of lung, bladder, and colon cancers are experienced in this group; overall cancer mortality is about half that of the general U.S. population. While this comparison has limitations—better use of medical services may contribute to reduced mortality, and imperfect compliance with recommendations may underestimate the impact of lifestyle—the results strongly suggest that a large portion of cancer deaths can be avoided by using knowledge at hand. Incidence rates rather than mortality rates provide a similar picture, although the differences are somewhat less. For breast cancer the healthy behavior of Seventh-Day Adventists was not sufficient to have a major impact on risk.

Decreases in physical activity and increases in smoking, obesity, and recreational sun exposure have contributed importantly to increases in some cancers in the modern industrial world, whereas improvements in hygiene have reduced other cancers related to infection. There is no good reason to believe that synthetic chemicals underlie the major changes in incidence of some cancers. In the industrial countries life expectancy is steadily increasing and will increase even faster as smoking declines. Further research on the ways in which diet influences cancer risk is important because it is likely to have the greatest impact on future prevention strategies.

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