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The Causes and Prevention of Cancer: The Role of Environment

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Abstract

The idea that synthetic chemicals such as DDT are major contributors to human cancer has been inspired, in part, by Rachel Carson's passionate book, *Silent Spring*. This chapter discusses evidence showing why this is not true. We also review research on the causes of cancer, and show why much cancer is preventable.

Epidemiological evidence indicates several factors likely to have a major effect on reducing rates of cancer: reduction of smoking, increased consumption of fruits and vegetables, and control of infections. Other factors are avoidance of intense sun exposure, increases in physical activity, and reduction of alcohol consumption and possibly red meat. Already, risks of many forms of cancer can be reduced and the potential for further reductions is great. If lung cancer (which is primarily due to smoking) is excluded, cancer death rates are decreasing in the United States for all other cancers combined.

Pollution appears to account for less than 1% of human cancer; yet public concern and resource allocation for chemical pollution are very high, in good part because of the use of animal cancer tests in cancer risk assessment. Animal cancer tests, which are done at the maximum tolerated dose (MTD), 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 rodents at these high doses. A plausible explanation for the high frequency of positive results is that testing at the MTD frequently can cause chronic cell killing and consequent cell replacement, a risk factor for cancer that can be limited to high doses. Ignoring this greatly exaggerates risks. Scientists must determine mechanisms of carcinogenesis for each substance and revise acceptable dose levels as understanding advances.

The vast bulk of chemicals ingested by humans is natural. For example, 99.99% of the pesticides we eat are naturally present in plants to ward off insects and other predators. Half of these natural pesticides tested at the MTD are rodent carcinogens. Reducing exposure to the 0.01% that are synthetic will not reduce cancer rates. On the contrary, although fruits and vegetables contain a wide variety of naturally-occurring chemicals that are rodent carcinogens, inadequate consumption of fruits and vegetables doubles the human cancer risk for most types of cancer. Making them more expensive by reducing synthetic pesticide use will increase cancer. Humans also ingest large numbers of natural chemicals from cooking food. Over a thousand chemicals have been reported in roasted coffee: more than half of those tested (19/28) are rodent carcinogens. There are more rodent carcinogens in a single cup of coffee than potentially carcinogenic pesticide residues in the average American diet in a year, and there are still a thousand chemicals left to test in roasted coffee. This does not mean that coffee is dangerous but rather that animal cancer tests and worst-case risk assessment, build in enormous safety factors and should not be considered true risks.

The reason humans can eat the tremendous variety of natural chemical "rodent carcinogens" is that humans, like other animals, are extremely well protected by many general defense enzymes, most of which are inducible (i.e., whenever a defense enzyme is in use, more of it is made). Since the defense enzymes are equally effective against natural and synthetic chemicals 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.

The idea that there is an epidemic of human cancer caused by synthetic industrial chemicals is false. In addition, there is a steady rise in life expectancy in the developed countries. Linear extrapolation from the maximum tolerated dose in rodents to low level exposure in humans has led to grossly exaggerated mortality forecasts.

Such extrapolations can not be verified by epidemiology. Furthermore, relying on such extrapolations for synthetic chemicals while ignoring the enormous natural background, leads to an imbalanced perception of hazard and allocation of resources. It is the progress of scientific research and technology that will continue to lengthen human life expectancy.

Zero exposure to rodent carcinogens cannot be achieved. Low levels of rodent carcinogens of natural origin are ubiquitous in the environment. It is thus impossible to obtain conditions totally free of exposure to rodent carcinogens or to background radiation. Major advances in analytical techniques enable the detection of extremely low concentrations of all substances, whether natural or synthetic, often thousands of times lower than could be detected 30 years ago.

Risks compete with risks: society must distinguish between significant and trivial risks. Regulating trivial risks or exposure to substances erroneously inferred to cause cancer at low-doses, can harm health by diverting resources from programs that could be effective in protecting the health of the public. Moreover, wealth creates health: poor people have shorter life expectancy than wealthy people. When money and resources are wasted on trivial problems, society's wealth and hence health is harmed.

Trends

Cancer caused 23% of the person-years of premature loss of life and about 530,000 deaths in the US in l993 [1]. Four major cancers (lung, colon-rectum, breast and prostate) account for 55% of the deaths. Cancer death rates in the US are decreasing, after adjusting for age and excluding lung cancer. 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 [1]. The decline ranged from 71% in the 0-4 year old group to 8% in the 74-85 year old group. 'If lung cancer were eliminated, then the overall cancer death rate would have declined over 14% between l950 and l990.' [1] The only age group that shows some increase is the over 85 group (6%). One plausible explanation for this increase is that autopsies were less common in the very old in former years. Smoking, in addition to causing the bulk of lung cancer, contributes to other malignancies such as cancers of the mouth, esophagus, 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 more than 25% for each age group under 45 and has increased for age groups over 55 years of age. 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, which is due to smoking (as is 30% of all US cancer deaths), and non-Hodgkin's lymphoma (NHL). Reasons for the increase in NHL are not clear, but smoking may possibly contribute [2, 3], and HIV is a small, but increasing, cause.

An analysis [4] by Professor Peto has come to the same conclusion. 'The common belief that there is an epidemic of death from cancer in developed countries is a myth, except for the effects of tobacco. In many countries cancer deaths from tobacco are going up, and in some they are at last coming down. But, if we take away the cancer deaths that are attributed to smoking then the cancer death rates that remain are, if anything, declining. This is reassuringly true in Western Europe, Eastern Europe and North America – and, in the "West", the death rates from other diseases are falling rapidly. For most non-smokers, the health benefits of modern society outweigh the new hazards. Apart from tobacco (and in places, HIV), the Western world is a remarkably healthy place to live.'

Although, the number of smokers is declining in the US, overall lung cancer continues to increase because of decades of delay between when a person begins smoking and the onset of the disease. The rate of lung cancer among American men appears to have peaked while the rate is still going up for American women who started smoking more recently than men.

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. Doll and Peto of Oxford University, two of the world's leading epidemiologists, in their comprehensive study on the causes of cancer point out that incidence rates should not be taken in isolation, because reported incidence rates for a disease might reflect increases in registration of cases and improvements in diagnosis [5]. The reported rise in cancer rates among men born in the 1940s com-

pared to those born in the 1890s [6] may be due to such artifacts. For example, the rapid increase in age-adjusted prostate cancer incidence without any major increases in mortality is almost certainly due largely to increased screening and incidental detection during prostatectomy for benign prostatic hypertrophy.

Major Factors that Influence Cancer Risks

Background Damage

Biochemical studies of carcinogenesis have indicated an important role of metabolic oxidative damage to DNA that is balanced by elaborate defense and repair processes. The rate of cell division, which is influenced by hormones, growth, cell killing, and inflammation is also key as this determines the probability of converting DNA lesions to mutations. These mechanisms are likely to underlie many epidemiologic observations, and together suggest practical interventions and areas for further research.

Metabolism, like other aspects of life, involves trade-offs. Oxidant by-products of normal metabolism cause extensive damage to DNA, protein, and lipid. We argue that this damage is a major contributor to aging and to degenerative diseases of aging such as cancer, heart disease, cataracts and brain dysfunction [7]. Antioxidant defenses against this damage include Vitamins C and E and carotenoids. To the extent that the major external risk factors for cancer – smoking, unbalanced diet, and chronic inflammation – are diminished, cancer will appear at a later age, and the proportion of cancer that is caused by normal metabolic processes will increase.

Oxidative damage to DNA, proteins and other macromolecules accumulates with age and has been postulated to be a major, but not the only, type of metabolic damage leading to aging [7]. By-products of normal metabolism: superoxide, hydrogen peroxide, and hydroxyl radical, are the same oxidative mutagens produced by radiation [8]. Oxidative lesions in DNA accumulate with age, so that by the time a rat is old (two years) it has about 66,000 DNA lesions per cell, which is about twice that in a young rat [7]. Mutations also accumulate with age. DNA is oxidized in normal metabolism because antioxidant defenses, though numerous, are not perfect.

Metabolic oxidants damage proteins as well as DNA [9]. In two human diseases associated with premature aging, Werner's syndrome and progeria, oxidized proteins accumulate at a much higher rate than normal [9]. Cataracts, which also represent the accumulation of oxidized protein, are a common manifestation of oxidative stresses, such as UV radiation and smoking, as well as of insufficient antioxidant protection [7, 10-12].

Diet

Though diet is thought to account for about one-third of cancer risk [5], the specific factors are only slowly being clarified. We present here a brief overview of the field.

Cancer prevention by calorie or protein restriction. In rodents a calorie-restricted diet compared to *ad libitum* feeding markedly decreases tumor incidence and increases lifespan [13-15], but decreases reproduction. Protein restriction appears to have the same effects on rodents as calorie restriction, though it is less well-studied [16]. An understanding of mechanisms for the marked effect of dietary restriction on aging and cancer is becoming clearer, and may in good part be due to reduced oxidative damage and reduced cell division rates. 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 [17, 18], for example, 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 [19].

Cancer prevention by dietary fruits and vegetables 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 [7]. 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 [20–22]. 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 protective effect appears to be about 30% [17, 20, 23]. Other work suggests a protective effect of fruit and vegetable consumption, not only on cancer, but on heart disease and other degenerative diseases of aging [7]. Eighty percent of American children and adolescents, and 68% of adults [24, 25] did not meet the intake recommended by the National Cancer Institute (NCI) and the National Research Council (NRC): five servings of fruits and vegetables per day.

Laboratory studies suggest that the antioxidants such as Vitamins C and E and carotenoids in fruits and vegetables account for a good part of their beneficial effect [7]; 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 [24, 26].

A wide array of compounds in fruits and vegetables in addition to antioxidants may contribute to the reduction of cancer. Folate deficiency, one of the most common vitamin deficiencies, causes extensive chromosome breaks in human genes [27, 28]. Approximately 10% of the US population [29] has a blood folate level lower than that at which chromosome breaks can occur [28]. In two small studies of low income (mainly African-American) elderly persons [30] and adolescents [31], nearly half had folate levels that were that low. The mechanism of damage is deficient methylation of uracil to thymine and subsequent incorporation of uracil into human DNA (4 million/cell) [28]. During repair of uracil in DNA, transient nicks are formed; two opposing nicks cause a chromosome break. High DNA uracil levels and chromosome breaks in humans are both reversed by folate administration [28]. Chromosome breaks could contribute to the increased risk of cancer and cognitive defects associated with folate deficiency in humans [28, 32-35]. Folate deficiency also damages human sperm [36], causes neural tube defects [37] in the fetus, and is responsible for about 10% of the risk for heart disease in the U.S. [38]. Plant foods also contain a wide variety of weak estrogens that may act as antiestrogens by competing with estrogenic hormones [21, 26, 39].

Other aspects of diet Although the benefits of fruits and vegetables in the prevention of cancer are most clearly supported by epidemiologic studies, strong international correlations suggest that animal (but not vegetable) fat and red meat may increase the incidence of cancers of the breast, colon, and prostate [40]. However, large prospective studies of fat intake and breast cancer have consistently shown a weak or no association with incidence of breast cancer [17]. In contrast, animal fat and red meat have been associated with colon cancer risk in numerous case-control and cohort studies; the association with meat consumption appears more consistent [41–43]. Consumption of animal fat and red meat have been associated with risk of prostate cancer in multiple studies [42, 44]. Hypothesized mechanisms for these associations include effects of dietary fats on endogenous hormone levels [45], local effects of bile acids on the colonic mucosa, effects of carcinogens produced in the cooking of meat, and excessive iron intake. Excess iron absorption (particularly heme iron from meat) is a plausible, though unproven, contributor to production of oxygen radicals [7]. 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, which is inversely related to colon cancer risk in many studies [46–48].

Alcoholic beverages cause inflammation, cirrhosis of the liver, and liver cancer [49]. Alcohol is an important cause of oral and esophageal cancer (and is also synergistic with smoking) [49] and possibly contributes to colorectal cancer [33, 50]. Breast cancer is also associated with alcohol consumption (see below).

Cooking food is plausible as a contributor to cancer [51]. 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: nitrosamines, heterocyclic amines, polycyclic hydrocarbons, and furfural and similar furans. Epidemiological studies on cooking are difficult and so far are inadequate to evaluate a carcinogenic effect in humans [52].

Tobacco

Tobacco is the most important global cause of cancer and is preventable. Smoking contributes to about one-third of US cancer, about one-quarter of US heart disease, and about 400,000 premature deaths per year in the US [53]. Tobacco is a known cause of cancer of the lung, bladder, mouth, pharynx, pancreas, kidney, stomach, larynx, esophagus [4], and possibly colon [54–56]. 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 [53]. 'Over the whole of the second half of this century (1950-2000) the total number of deaths caused by smoking in developed countries will be about 60 million' [4]. The evidence for environmental tobacco smoke as a cause of cancer is much weaker. It has been estimated to cause up to 3,000 additional cases of cancer [57, 58], though this estimate has been strongly disputed [59].

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 two to three times more ascorbate than non-smokers to achieve the same level of ascorbate in blood, but they rarely do [60–62]. Inadequate diets (and smoking) of fathers may result not only in damage to their somatic DNA but to the DNA of their sperm. When the level of dietary ascorbate is insufficient to keep seminal fluid ascorbate at an adequate level, then oxidative lesions in sperm DNA are increased 2.5 times [63]. An inadequate level of plasma ascorbate is more common among single males, the poor, and smokers [64]. Paternal smoking may increase the risk of birth defects and childhood cancer in offspring [65].

Chronic Infection, Inflammation, and Cancer

White cells and other phagocytic cells of the immune system combat bacteria, parasites, and virus-infected cells by destroying them with potent mutagenic oxidizing agents. 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 [66, 67], thereby contributing to the carcinogenic process. Antioxidants appear to inhibit some of the pathology of chronic inflammation [7].

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 [68–70]. Nearly half the world's liver cancer occurs in China [71]. 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 [72]. Biomarker measurements on populations in Africa and China confirm that these populations are chronically exposed to high levels of aflatoxin [73, 74]. In the US, liver cancer is rare. Although hepatitis B and C viruses infect less than 1% of the US population, hepatitis viruses can account for half of liver cancer cases among non-Asians [75] and even higher percentages among Asians [76].

Another major chronic infection is schistosomiasis, which is widespread in Asia and Egypt. In Asia, the eggs of *Schistosoma japonicum*, deposited in the colonic mucosa, cause inflammation and subsequent colon cancer [77]. In Egypt, the eggs of *S. haematobium*, deposited in the bladder, cause inflammation and bladder cancer [77]. *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 [77]. *Chlonorchis sinensis* infections in millions of Chinese increase the risk for biliary tract cancer [77]. *Helicobacter pylori* bacteria, which infect the stomachs of more than one-third of the world's population, are a major cause of stomach cancer, ulcers, and gastritis [77]. 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 [78].

Chronic inflammation resulting from noninfectious sources can also lead to cancer. For example, asbestos exposure leading to chronic inflammation may be in good part the reason it is a significant risk factor for cancer of the lung [79, 80].

Human papilloma virus, a major risk factor for cervical cancer, does not appear to work through an inflammatory mechanism [81]. It is spread by sexual contact, an effective way of transmitting viruses.

Hormones

Henderson, Pike and colleagues have reviewed the extensive literature indicating a large role of reproductive hormones in cancer causation possibly contributing to as much as one-third of all cancer cases [45]. Hormones are likely to act by causing cell division (see below for the role of cell division in increasing mutations). Endometrial cancer appears most exquisitely

sensitive to cumulative estrogen exposure, with risks being elevated 10- to 20-fold by long term use of exogenous estrogens [82]. Estrogens increase the division of endometrial cells, but progestogens reduce division; thus the addition of progestogens to estrogen therapy after menopause may reduce risk of endometrial cancer [45].

Ovarian cancer seems to be related to factors that increase the division of surface epithelial cells; for example, pregnancies substantially reduce the number of ovulations and the risk of this malignancy [45]. Oral contraceptives, which also block ovulation, decrease risk, by as much as 50% with five years of use [83].

Factors that increase cumulative exposure to estrogens, such as early age at menarche, late menopause, and prolonged estrogen therapy after menopause, increase risk of breast cancer [45, 84]. Breast cancer cells also proliferate in the presence of estrogens, and progestogens also appear to enhance cell division [45]. Moreover, the addition of progestogens to estrogen therapy does not reduce, and may further increase, the risk of breast cancer [85]. 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 [86], possibly due to a permanent differentiation of stem cells resulting in less proliferation [87]. Lactation modestly reduces breast cancer incidence [88, 89]. 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 [90]. Exercise may lower breast cancer risk in young women, probably through influencing hormone levels [91]. Alcohol consumption, which has been consistently associated with breast cancer risk in large prospective studies, as well as in most case-control studies [92], appears to increase endogenous estrogen levels [93]; thus, reduced consumption of alcohol may decrease breast cancer risk.

Less Important Factors that Influence Cancer Risks

Occupation

The International Agency for Research on Cancer of the World Health Organization (IARC) evaluates potential cancer risks to humans from a range of chemical exposures [94]. Half of the 60 chemicals and chemical mixtures they have 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. 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 [5] 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 [5]; however, recent estimates for asbestos-related cancer are lower [95, 96].

Exposures in the workplace can be high compared to other chemical exposures to humans, e.g., in food, air, or water. We have argued [97, 98] that increased cell division rates are important in causing mutation and cancer and, therefore, that 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, past occupational exposures have often 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, few chemicals are regulated by the US Occupational Safety and Health Administration (OSHA) as potential human carcinogens. For 75 rodent carcinogens regulated by OSHA with permissible exposure limits (PELs), we recently ranked potential carcinogenic hazards on an index (PERP: Permitted Exposure/Rodent Potency) that compares the permitted dose-rate to workers with the carcinogenic dose to rodents [99]. We found that for nine chemicals

the permitted exposures were within a factor of 10 of the rodent carcinogenic dose and for 17 they were between 10 and 100 times lower. These values are high in comparison to hypothetical risks regulated by other federal agencies. An additional 120 rodent carcinogens had no OSHA PEL, suggesting the need for further regulatory attention.

Sun Exposure

Exposure to the sun is the major cause of skin cancer; melanoma is the most serious. Exposure during the early decades of life, particularly when sufficient to cause burns, appears to be the dominant factor [100]. 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 [101]. Some formerly used drugs, such as phenacetin and diethylstilbesterol, were associated with increased cancer risk [102]. Potent immunosuppressive agents such as cyclosporin also increase the risk of a variety of cancers [103]. Estrogen replacement therapy modestly increases risk of breast cancer. Diagnostic X-rays have also contributed to malignancies [104]. 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 Environmental Protection Agency, were assumed to be true risks, the proportion of cancer that EPA could prevent by regulation would be tiny [105]. Epidemiological studies, moreover, are difficult to conduct because of inadequacies in exposure assessment and failure to account for confounding factors like smoking, diet and geographic mobility of the population. Since the focus of this paper is cancer causation, other issues in environmental protection and health are not discussed.

Air pollution

Indoor air is generally of greater concern than outside air because 90% of people's time is spent indoors, and the concentrations of pollutants tend to be higher than outdoors. The most important carcinogenic air pollutant, however, is likely to be radon, which occurs naturally as a radioactive gas that is generated as a decay product of the 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 U.S., mostly among smokers due to the synergistic effect with smoking [106–108]. Epidemiological studies of radon exposures in homes [109, 110] have failed to convincingly demonstrate an excess risk. About 50,000 to 100,000 of the homes in the U.S. (0.1%) are estimated to have annual average radon levels approximately 20 times the national average, and inhabitants receive annual radiation doses that exceed the current occupational standard for underground miners. Efforts to identify high-radon houses indicate that they occur most frequently in concentrated geographic areas [111].

Water pollution

Water pollution as a risk factor for cancer appears small. Among potential hazards that have been of concern, the most important are radon (exposure is small compared to air) and arsenate. Natural arsenate is a known human carcinogen at high doses [112, 113], and further research is needed on mechanism and dose response in humans. Chlorination of water, an important public health intervention, produces large numbers of chlorine containing chemicals as by-products, some of which are rodent carcinogens. Evidence that chlorination of water is a risk for human cancer has been judged inadequate [114].

Hereditary Factors

Inherited factors clearly contribute to some percentage of cancer, particularly childhood cancer and cancer in early adulthood. Overall, cancer increases 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 [115, 116]. 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 the genetic factors will soon 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.

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 there are some epidemiologic studies that find an association between cancer and low levels of industrial pollutants, the studies do 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 to the background of natural chemicals that are rodent carcinogens [117].

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' [118]. This statement is wrong: the vast bulk of the chemicals humans are exposed to are natural, and for every chemical some amount is dangerous.

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 [97, 119, 120]. 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 [97, 98].

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 [121]. Half of the natural pesticides tested (35/64) are rodent carcinogens [119]. 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 use of synthetic pesticides is likely to increase cancer. People with low incomes eat fewer fruits and vegetables [122] and spend a higher percentage of their income on food.

Humans also ingest large numbers of natural chemicals from cooking food. For example, more than a thousand chemicals have been identified in roasted coffee; more than half of those tested (19/26) are rodent carcinogens [117, 119] (see Table 1). There are more natural rodent carcinogens by weight in a single cup of coffee than potentially carcinogenic synthetic pesticide residues in the average US 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 that animal cancer tests and worst-case risk assessments, build in enormous safety factors and should not be considered true risks.

Because of their unusual lipophilicity and long environmental persistence, there has been particular concern for a small group of polychlorinated, synthetic chemicals such as DDT and PCBs. There is no convincing epidemiological evidence [123], nor is there much toxicological plausibility [117], that the low levels normally found in the environment are likely to be a significant contributor to cancer. TCDD, which is produced as an industrial by product as well as by burning when chloride ion is present, e.g., in incineration or in forest fires. TCDD 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 extremely well protected by many general defense enzymes, most of which are inducible (i.e., whenever a defense enzyme is in use, more of it is made) [124]. Defense enzymes are effective against both natural and synthetic chemicals, such as potentially mutagenic reactive chemicals. 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 [97, 117].

We have ranked possible carcinogenic hazards from known rodent carcinogens, using an index that relates human exposure to carcinogenic potency in

Table 1. Carcinogenicity in rodents of natural chemicals in roasted coffee

Positive: N=19	acetaldehyde, benzaldehyde, benzene, benzofuran, benzo(*a*)pyrene, caffeic acid, catechol, 1,2,5,6-dibenzanthracene, ethanol, ethylbenzene, formaldehyde, furan furfural, hydrogen peroxide, hydroquinone, limonene, styrene, toluene, xylene
Not positive: N=8	acrolein, biphenyl, choline, eugenol, nicotinamide, nicotinic acid, phenol, piperidine
Uncertain:	caffeine
Yet to test:	$\sim$ 1000 chemicals

rodents (HERP: Human Exposure Rodent Potency) [117, 119] (see Table 2). 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 [119, 120]. Our results indicate that many ordinary foods would not pass the regulatory criteria used for synthetic chemicals. However, these results do not necessarily indicate that coffee consumption, for example, is a significant risk factor for human cancer even though it is thousands of times the HERP equivalent to the one-in-a-million worst-case risk used by EPA. Adequate risk assessment from animal cancer tests requires more information about many aspects of toxicology, such as effects on cell division, induction of defense and repair systems, and species differences.

Linear extrapolation from the maximum tolerated dose 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 the allocation of resources.

If the costs were minor the issue of putting hypothetical risks into perspective would not be so important, but the costs are huge [125, 126, 127]. Costs escalate as cleanliness approaches perfection. The idea of trade-offs is not adequately dealt with in most attempts to deal with pollutants; instead it is assumed that upper bound risk assessment to one-in-a-million protects the public [127]. A Harvard Center for Risk Analysis report [128] that compared costs for risk reduction among government agencies, concluded that the money spent to save a life by EPA is often orders of magnitude higher than many other government agencies. EPA risk estimates are based on 'risk assessment' (i.e., default, worst case, linear extrapolations to one-in-a-million risk), unlike most other government agencies, so the actual discrepancy between EPA and many other agencies is even greater. Many scholars have pointed out that expensive regulations intended to save lives [129] may actually lead to increased deaths, in part by diverting resources from important health risks and in part because higher incomes are associated with lower mortality risks [130, 131]). Worst case assumptions in risk assessment is a policy decision, not a scientific one, and confuses attempts to allocate money effectively for risk abatement. Regulating trivial risks impedes effective risk management [132].

Discussion

Epidemiological evidence in humans is sufficient to identify several broad categories of cancer causation for which the evidence is strong and plausible. Since many of these are avoidable it is possible to reduce incidence rates of many types of cancer. In a monumental 1981 review of avoidable risks of cancer in the US [5], Doll and Peto attributed 30% of cancer deaths to tobacco and 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 adults has decreased, because the relative risk due to smoking has greatly increased for almost all cancers as well as cardiovascular disease [53]. This is probably due both to a declining risk of cancer death in non-smokers as well as to the fact that the lifetime impact of smoking since adolescence is being experienced only

Table 2. **Ranking Possible Carcinogenic Hazards from Average U.S. Exposures. [Chemicals that occur naturally in foods are in bold.]** *Daily human exposure:* The calculations assume an average daily dose for a lifetime. *Possible hazard:* The human exposure to a rodent carcinogen is divided by 70 kg to give a mg/kg/day of human exposure, and this dose is given as the percentage of the TD_{50} in the rodent (mg/kg/day) to calculate the *H*uman *E*xposure/*R*odent *P*otency index (HERP), i.e., 100% means that the human exposure in mg/kg/day is equal to the dose estimated to give 50% of the rodents tumors. TD_{50} values used in the HERP calculation are averages calculated by taking the harmonic mean of the TD_{50s} of the positive tests in that species from the Carcinogenic Potency Database. Average TD_{50} values, have been calculated separately for rats and mice, and the more potent value is used for alculating possible hazard. The less potent value is in parentheses.

Possible hazard: HERP (%)	Average daily US exposure	Human dose of rodent carcinogen	Potency TD_{50}(mg/kg/day)[a] Rats	Mice
140	EDB: workers (high exposure)(before 1977)	Ethylene dibromide, 150 mg	1.52	(7.45)
17	Clofibrate	Clofibrate, 2 g	169	.
14	Phenobarbital, 1 sleeping pill	Phenobarbital, 60 mg	(+)	6.09
6.8	1,3-Butadiene: rubber workers (1978-86)	1,3-Butadiene, 66.0 mg	(261)	13.9
6.1	Tetrachloroethylene: dry cleaners with dry-to-dry units (1980–90)[b]	Tetrachloroethylene, 433 mg	101	(126)
4.0	Formaldehyde: workers	Formaldehyde, 6.1 mg	2.19	(43.9)
2.1	**Beer, 257 g**	**Ethyl alcohol, 13.1 ml**	9110	(–)
1.4	Mobile home air (14 hours/day)	Formaldehyde, 2.2 mg	2.19	(43.9)
0.9	Methylene chloride: workers (1940s-80s)	Methylene chloride, 471 mg	724	(918)
0.5	**Wine, 28.0 g**	**Ethyl alcohol, 3.36 ml**	9110	(–)
0.4	Conventional home air (14 hours/day)	Formaldehyde, 598 μg	2.19	(43.9)
0.1	**Coffee, 13.3 g**	**Caffeic acid, 23.9 mg**	297	(4900)
0.04	**Lettuce, 14.9 g**	**Caffeic acid, 7.90 mg**	297	(4900)
0.03	**Safrole in spices**	**Safrole, 1.2 mg**	(441)	51.3
0.03	**Orange juice, 138 g**	***d*-Limonene, 4.28 mg**	204	(–)
0.03	**Pepper, black, 446 mg**	***d*-Limonene, 3.57 mg**	204	(–)
0.02	**Mushroom (*Agaricus bisporus 2.55 g)***	**Mixture of hydrazines, etc. (whole mushroom)**	(–)	20,300
0.02	**Apple, 32.0 g**	**Caffeic acid, 3.40 mg**	297	(4900)
0.02	**Coffee, 13.3 g**	**Catechol, 1.33 mg**	118	(244)
0.02	**Coffee, 13,3 g**	**Furfural, 2.09 mg**	(683)	197
0.009	BHA: daily US avg (1975)	BHA, 4.6 mg	745	(5530)
0.008	**Beer (before 1979), 257 g**	**Dimethylnitrosamine, 726 ng**	0.124	(0.189)
0.008	**Aflatoxin: daily US avg (1984-89)**	**Aflatoxin, 18 ng**	0.0032	(+)
0.007	**Cinnamon, 21.9 mg**	**Coumarin, 65.0 μg**	13.9	(103)
0.006	**Coffee, 13.3 g**	**Hydroquinone, 333 μg**	82.8	225
0.005	Saccharin: daily US avg (1977)	Saccharin, 7 mg	2140	(–)
0.005	**Carrot, 12.1 mg**	**Aniline, 624 μg**	194[c]	(–)
0.004	**Potato, 54.9 g**	**Caffeic acid, 867 μg**	297	(4900)
0.004	**Celery, 7.95 g**	**Caffeic acid, 858 μg**	297	(4900)
0.004	**White bread, 67.6 g**	**Furfural, 500 μg**	(683)	197
0.003	**Nutmeg, 27.4 mg**	***d*-Limonene, 466 μg**	204	(–)
0.003	Conventional home air (14 hour/day)	Benzene, 155 μg	(169)	77.5
0.002	**Carrot, 12.1 g**	**Caffeic acid, 374 mg**	297	(4900)
0.002	Ethylene thiourea: daily US avg (1990)	Ethylene thiourea, 9.51 μg	7.9	(23.5)
0.002	[DDT: daily US avg (before 1972 ban)]	[DDT, 13.8 μg]	(84.7)	12.3
0.001	**Plum, 2.00 g**	**Caffeic acid, 276 μg**	297	(4900)
0.001	BHA: daily US avg (1987)	BHA, 700 μg	745	(5530)
0.001	**Pear, 3.29 g**	**Caffeic acid, 240 μg**	297	(4900)
0.001	[UDMH: daily US avg (1988)]	[UDMH, 2.82 μg (from Alar)]	(–)	3.96

Table 2. Contd.

0.0009	**Brown mustard, 68.4 mg**	**Allyl isothiocyanate, 62.9 μg**	96	(–)
0.0008	[DDE: daily US avg (before 1972 ban)]	[DDE, 6.91 μg]	(–)	12.5
0.007	**Bacon, 11.5 g**	**Diethylnitrosamine, 11.5 ng**	0.0237	(+)
0.006	**Mushroom *(Agaricus bisporus* 2.55 g)**,	**Glutamyl-*p*-hydrazino-benzoate, 107 μg**	.	277
0.0004	**Bacon, 11.5 g**	***N*-Nitrosopyrrolidine, 196 ng**	(0.799)	0.679
0.0004	**Bacon, 11.5 g**	**Dimethylnitrosamine, 34.5 ng**	0.124	(0.189)
0.0004	[EDB: Daily US avg (before 1984 ban)]	[EDB, 420 ng]	1.52	(7.45)
0.0004	Tap water, 1 liter (1987-92)	Bromodichloromethane, 13 μg	(72.5)	47.7
0.0004	TCDD: daily US avg (1994)	TCDD, 12.0 pg	0.0000457	(0.000156)
0.0003	**Mango, 1.22 g**	***d*-Limonene, 48.8 μg**	204	(–)
0.0003	**Beer, 257 g**	**Furfural, 39.9 μg**	(683)	197
0.0003	Tap water, 1 liter (1987-92)	Chloroform, 17 μg	(262)	90.3
0.0003	Carbaryl: daily US avg (1990)	Carbaryl 2.6μg	14.1	(–)
0.0002	**Celery, 7.95 g**	**8-Methoxypsoralen, 4.86 μg**	32.4	(–)
0.0002	Toxaphene: daily US avg (1990)	Toxaphene, 595 ng	(–)	5.57
0.00009	**Mushroom (*Agaricus bisporus*, 2.55 g)**	***p*-Hydrazinobenzoate, 28 μg**	.	454[c]
0.00008	PCBs: daily US avg (1984-86)	PCBs, 98 ng	1.74	(9.58)
0.00008	DDE/DDT: daily US avg (1990)	DDE, 659 ng	(–)	12.5
0.00007	**Parsnip, 54.0 mg**	**8-Methoxypsoralen, 1.57 μg**	32.4	(–)
0.00007	**Toast, 67.6 g**	**Urethane, 811 ng**	(41.3)	16.9
0.00006	**Hamburger, pan fried, 85 g**	**PhIP, 176 ng**	4.29[c]	(28.6[c])
0.00005	**Estragole in spices**	**Estragole, 1.99 μg**	.	51.8
0.00005	**Parsley, fresh, 324 mg**	**8-Methoxypsoralen, 1.17 μg**	32.4	(–)
0.00003	**Hamburger, pan fried, 85 g**	**MeIQx, 38.1 ng**	1.99	(24.3)
0.00002	Dicofol: daily Us avg (1990)	Dicofol, 544 ng	(–)	32.9
0.00001	**Cocoa, 3.34 g**	**α-Methylbenzyl alcohol, 4.3 μg**	458	(–)
0.00001	**Beer, 257 g**	**Urethane, 115 ng**	(41,3)	16.9
0.000005	**Hamburger, pan fried, 85 g**	**IQ, 6.38 ng**	1.89[c]	(19.6)
0.000001	Lindane: daily US avg (1990)	Lindane, 32 ng	(–)	30.7
0.0000004	PCNB: daily US avg (1990)	PCNB (Quintozene), 19.2 ng	(–)	71.1
0.0000001	Chlorobenzilate: daily US avg (1989)	Chlorobenzilate, 6.4 ng	(–)	93.9
<0.00000001	Chlorothalonil: daily US avg (1990)	Chlorothalonil, <6.4 ng	828[d]	(–)
0.000000008	Folpet: daily US avg (1990)	Folpet, 12.8 ng	.	2280[d]
0.000000006	Captan: daily US avg (1990)	Captan, 11.5 ng	2690[d]	(2730[d])

[a] "." = no data in CPDB; (–) = negative in cancer test; (+) = positive cancer test(s) not suitable for calculating a TD_{50}.
[b] This is not an average, but a reasonably large sample (1027 workers).
[c] TD_{50} harmonic mean was estimated for the base chemical from the hydrochloride salt.
[d] Additional data from EPA that is not in the CPDB were used to calculate these TD_{50} harmonic means.
For exposure references see reference 119.

now. Available data on diet and cancer have increased many-fold since 1981, and generally support the earlier estimate; a slightly narrower estimated range of 20-40% seems most plausible [133]. 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 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% $\pm$ 1% to 5% $\pm$ 1%, as many new studies have supported 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 cancer incidence and mortality rates of the general population to those of Seventh-Day Adventists – who generally do not smoke, drink heavily, or eat much meat but do eat a diet rich in fruits and vegetables [134, 135]. 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 US 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 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 United States and other industrial countries life expectancy is steadily increasing and will increase even faster as smoking declines.

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