

Approaches for chronic disease prevention based on current understanding of underlying mechanisms¹⁻⁴

John H Weisburger

ABSTRACT Much progress has been achieved by exploring the causes of the main human cancers and of cardiovascular and cerebrovascular diseases. Even more important has been the knowledge acquired about the mechanisms underlying the development of these diseases. In many parts of the world, particularly in the West, the major cancers associated with dietary habits involve the postmenopausal breast, distal colon, prostate, pancreas, ovary, and endometrium. Current evidence suggests that the genotoxic carcinogens for all but the last 2 of these diseases stem from the traditional intake of fried and broiled foods such as meats. The surface of these foods contains a class of powerful mutagens, heterocyclic amines, which are carcinogenic to the target organs in animal models. Fish-eating populations have lower incidences of heart disease and of many types of cancers than do other populations, which may be the result of the n-3 polyunsaturated oils found in fish. Among other dietary practices that may reduce the risk of cancer and cardiovascular disease are consuming 5-9 servings of fruits and vegetables daily, which provides antioxidants such as quercetin and isothiocyanates; having a high fiber intake, including bran cereal; and drinking 1.5-2.5 L of fluids daily. Tea polyphenols found in black and green tea may have a protective effect against heart disease and some cancers. Concentrates of such desirable products have been made available in pill form to complement health-promoting personal lifestyles. Biomedical research funded by The National Institutes of Health and organizations such as the American Cancer Society has produced sound results that could lead to prevention of chronic disease. The public must heed this information to achieve long-term health. *Am J Clin Nutr* 2000;71(suppl):1710S-4S.

KEY WORDS Cancer prevention, n-6 polyunsaturated oils, tea polyphenols, genotoxic carcinogen

INTRODUCTION

Much progress has been achieved by exploring the causes of the main human cancers and of cardiovascular and cerebrovascular diseases. Even more important has been the knowledge acquired about the mechanisms underlying the development of these diseases. For example, elucidation of the relevant controlling elements in cancer has been instructive: these involve a stepwise progression from normal cells to cells with the characteristics of benign tumors, to malignant cancers, and finally to metastasis. Geographic pathology has provided leads toward

identifying causative factors, particularly nutritional patterns that influence the risk of various types of cancer. Each kind of cancer involves carcinogens that may or may not be genotoxic; those that are genotoxic yield covalent interactions with DNA and the genetic material. The effect of genotoxic carcinogens on DNA, oncogenes, and tumor suppressor genes is the basis of neoplastic transformation, or faulty translation of the genetic code, which is typical of neoplasia (1, 2). Exposure to such carcinogens can also yield hydroxy radicals or peroxides, which generate abnormal DNA and also play a role in the developmental aspects of neoplasia.

Promoters and similar substances include a set of agents involved in carcinogenesis that operate by distinct mechanisms. They do not alter the structure of oncogenes or of tumor suppressor genes, but they play a key role in neoplastic development, ie, the growth of cells transformed by genotoxic carcinogens and by having abnormal DNA. The mechanism of action implies that the effect of promoters depends heavily on dose. In part, the effect involves regulation of cell duplication rates, an important variable because the rate of cell duplication controls the rate of development of cells containing abnormal DNA. A high rate of cell duplication curtails the operation of DNA repair systems, thus locking into cells the abnormal codons that reflect neoplasia. Distinction between mechanisms operating in neoplastic transformation and those operating in neoplastic growth and development is the key to providing a rational basis for cancer prevention, especially as regards quantitative effects and reversibility. The fact that growth of neoplastic cells requires essential nutritional elements, ultimately derived from an adequate supply in the blood, provides another approach to controlling cancer development, in this case by restricting cellular nutrition (3).

Distinctions in the mechanism of action bear on risk assessment. With genotoxic carcinogens, the usual interpretation is that the effect is theoretically proportional to the dose and the dose rate without a threshold. Nonetheless, there is evidence for a

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⁴Address reprint requests to JH Weisburger, American Health Foundation, One Dana Road, Valhalla, NY 10595-1599. E-mail: john_weisburger@nyc.edu.

limited threshold (1). For example, in most of the Western world, there is some intake of foods that affect the liver, such as corn contaminated with the genotoxic liver carcinogen aflatoxin B₁, but primary liver cancer has a low incidence in the West. Thus, there is evidence for a practical level of “no effect” with aflatoxin B₁. On the other hand, in African countries such as Senegal, primary liver cancer is a major neoplasm because of an appreciable intake of aflatoxin, mainly from the use of contaminated peanuts (4). Moreover, populations in Africa often have hepatitis antigens that enhance the efficiency of carcinogenesis by increasing liver cell duplication rates; in contrast, hepatitis is relatively uncommon in the Western world.

Promoting substances usually display a threshold (1). For example, in rats, sodium saccharin requires extraordinarily high doses, 5–7.5% in the diet, to yield a relatively small number of urinary bladder cancers, mainly in males after a long latent period (5). A dose of 1% is ineffective. Human use of saccharin for almost 90 y has not been incriminated as a cause of bladder cancer.

Another example of promotion is provided by dietary fats, specifically the n–6 polyunsaturated oils, which are powerful promoters in both human and animal models of cancer of the breast, colon, prostate, and pancreas (6). This promotion is observed when the diet contains 40% of energy as fat but not with 15–20%. Among other promoters (in rats) are DDT (dichlorodiphenyltrichloroethane) and other halogenated pesticide compounds, which can induce liver cancers in rats when ingested at high doses. Lower doses that can be readily and accurately measured by chemical analytic techniques are not a cancer risk for humans (7). Unfortunately, the media often misinterpret results of bioassays of pesticides with uninformed allegations of environmental hazard.

It is important to determine whether a given product can act by a genotoxic mechanism, in which case frequent intake or exposure of humans should be controlled, especially if the effect of such a genotoxic carcinogen is also subject to promotion in specific target organs. Also, advantage can be taken of the sharp dose-response relation typical of promoting substances to minimize human risk. Agents associated with the etiology of human cancers are classified as follows: 1) genotoxic carcinogens or mixtures (chemical, viral, or associated with radiation) and 2) nongenotoxic-promoting or -enhancing stimuli (chemical or viral). It is essential to establish the amount and duration of exposure for each kind of agent and to develop methods of inhibiting the action of the agents and the risks associated with chemicals of type 1 or 2.

CAUSES OF HUMAN CANCERS

Tobacco use

Tobacco use is estimated to account for 30–40% of human cancers in most parts of the world (Table 1). Wynder in the United States and Doll in the United Kingdom, who performed the earliest analyses (around 1950) of the causes of cancer in men, reported that >90% of lung cancers were associated with smoking (8, 9). At that time, ≈70% of men were regular cigarette users. Lung cancer has increased epidemically in the United States since the 1930s, when its incidence was quite low. Incidentally, the lower rate before 1930 suggests that air pollution plays a minor role in respiratory tract cancer. Fortunately, in the United States, cigarette smoking has dropped sharply in the past 30 y and only ≈23% of men currently smoke. In men, the rate of lung cancer stabilized around 1982 and began to decline around 1988. Unfor-

TABLE 1
Types of cancer associated with tobacco smoking

| Organ | Additional factors |
|------------------------------|--|
| Oral cavity | Alcohol, chewing tobacco |
| Upper gastrointestinal tract | Inadequate quality of nutrition, alcohol, salt |
| Respiratory tract and lung | Air pollution, asbestos, mineral and radioactive dusts |
| Pancreas | High-fat diet, heterocyclic amines, others? |
| Kidneys, bladder | Diet (high protein) |
| Cervix | Human papilloma virus, poor nutritional status |

tunately, there are now more women smokers, ≈28%, and lung cancer now kills more women than breast cancer. Since the discovery of the tobacco-related nitrosamines formed during the processing of tobacco, the mechanisms underlying cancer of the oral cavity and esophagus in people who chew tobacco have been clarified (8). This habit is prevalent in India and other Southeast Asian countries, leading to a high incidence of these cancers there.

Alcohol use

The combination of cigarette smoking and drinking alcoholic beverages constitutes a high-risk situation for cancers of the oral cavity and even more so for the esophagus. Heavy drinking alone, particularly of hard liquors, also induces these cancers through mechanisms that may involve acetaldehyde (10). Both cirrhosis of the liver and liver cancer are found in chronic alcohol users (11).

Dietary habits

In many parts of the world, particular types of cancers are associated with specific dietary patterns. As noted, in some parts of Africa, primary liver cancer can result from a high dietary intake of foods containing aflatoxin B₁, especially in persons infected with the hepatitis virus.

In the United States, the incidence of cancer of the glandular stomach and mortality from that disease were high during the early part of the 20th century (Table 2). Fortunately, beginning in the 1920s, the incidence began a dramatic decline in this country as well as in other countries such as Japan, China, and Russia (12). We associated the occurrence of this disease with the traditional use of salt and saltpeter to preserve food before refrigerated storage became available (13). Vegetables and fruits are protective, but before refrigeration was introduced, they were available only seasonally. *Helicobacter pylori* also plays an enhancing role in stomach cancer.

High salt intake contributes to the occurrence of hypertension as well, and the incidence of this condition has also begun to decline, particularly in the United States. Certain subgroups have a higher incidence, however, including African Americans, whose higher rate has been attributed to extensive salt use and to genetic susceptibility (14).

In Belgium, Joossens and Kesteloot (15) reported that they convinced the public, as well as bakeries, to decrease salt use and that the incidence of hypertension and stomach cancer in that country has declined more rapidly than elsewhere in Europe. We identified a novel type of chemical, 2-chloro-4-methylthiobutanoate, to be a powerful direct-acting mutagen in salted, pickled Japanese fish, *Sanma hiraki* (16). We are testing this chemical for carcinogenicity, with emphasis on stomach cancer. Furihata et al (17) noted that this chemical induces DNA repair in gastric mucosa, similar to the effect of the classic gastric carcinogen

TABLE 2
Nutritionally linked cancers

| Site | Carcinogen from | Promoter | | Inhibitors |
|-----------------------|--|----------------------------------|-----------------------|---|
| | | From | Mechanism | |
| Esophagus | Pickled, salted foods, alcohol | Alcohol | Carcinogen activation | Yellow-green vegetables, tea ¹ |
| Stomach | Pickled, smoked foods, nitrate | Salt, <i>Helicobacter pylori</i> | Atrophic gastritis | Yellow-green vegetables, tea ¹ |
| Liver | Hepatitis antigen, mycotoxins, nitrosamines, | Hepatitis antigen | Cytotoxicity | Vaccine (possible) |
| Liver | Senecio alkaloids | Alcohol | Cytotoxicity | — |
| Colon ² | Fried foods, heterocyclic amines | Fats ³ | Bile acids | Bran fiber, calcium, vegetables, tea ¹ |
| Breast ⁴ | Fried foods, heterocyclic amines | Fats ³ | Hormonal balances | Vegetables, fruit, soyfoods, tea ¹ |
| Prostate | Fried foods, heterocyclic amines, hydroxy radicals | Fats ³ | Hormonal balances | Vegetables, fruit, cooked tomatoes, soyfoods |
| Endometrium and ovary | Hydroxy radicals | Fats ³ | Obesity, estrogen | Vegetables, fruit, weight loss |

¹Effective tea polyphenols, the active antioxidant components of black or green tea, have begun to be marketed as capsules or pills.

²Distal colon and rectum. For rectum, alcohol is an additional factor; for proximal colon, causes not clear.

³Mostly mixed fats as prevalent in Western diets, with 30–40% of energy as fats; monounsaturated oils such as olive oil as used in the Mediterranean area have little promoting action.

⁴Perimenopausal and postmenopausal breast cancer, where obesity-generated estrogen also promotes. Causes of premenopausal breast cancer are distinct, where *BRCA1* and *BRCA2* may play a role; for such early cancers, obesity does not increase risk and soy proteins may lower risk.

N-methyl-*N'*-nitro-*N*-methylnitrosoguanidine, but less strikingly so. These facts indicate that it is important to minimize salt use and to avoid salted and pickled foods in general (18).

The major cancers associated with dietary habits in many parts of the world, particularly the West, are those of the postmenopausal breast, distal colon, prostate, pancreas, ovary, and endometrium. Current evidence suggests that the genotoxic carcinogens for all but the last 2 of these diseases stem from the traditional intake of fried and broiled foods such as meats (6, 19). The surface of these foods contains a new class of powerful mutagens, heterocyclic amines, that are carcinogenic to these target organs in animal models. Several studies showed that populations that eat fried or broiled meats have a relative risk of >2 for colon and breast cancer. Nineteen such chemicals have been identified. They are present in fairly small amounts, but their action is potentiated by a promoting effect associated with n-6 polyunsaturated oils such as corn or safflower oil at 30–40% of energy in animal and human studies (6, 13). This amount of n-6 polyunsaturated oils regulates the development of neoplasms through specific dose-related mechanisms. A lower fat intake, 15–22% of energy, dramatically decreases those effects. Unfortunately, there has been a change in dietary traditions in Japan, leading to increased intake of Western-style foods. At the same time, the incidence of distal colon cancer in that country has increased (6, 13). In contrast, monounsaturated oils such as olive oil do not have such a promoting effect, and the incidence of these cancers is lower in the Mediterranean region, where such oils are mainly used. There is also a habit of eating vegetables and fruit with most meals. Epidemiologic and nutrition data plus laboratory studies in animals show that olive and canola oils do not increase the incidence of coronary heart disease and nutrition-linked cancers. Even more interesting are n-3 polyunsaturated oils (ie, fish oils). Fish-eating populations have a lower incidence of both heart disease and many types of cancers than do other populations (6, 20–22). It should be emphasized that these lower rates occur only with limited salt intake and with enough vegetables in the diet, where the main energy intake, balanced by energy use, is from complex carbohydrates such as rice, pasta, or potatoes. For persons who cannot consume fish, fish oils in gel capsules are available. Taking

3–4 capsules with the main meal each day seems to be beneficial in controlling serum cholesterol concentrations, especially in conjunction with an otherwise low-fat diet.

APPROACHES TO CHEMOPREVENTION

Vegetables and fruit

Extensive intake of vegetables and fruit is usually associated with a lower risk not only of nutritionally linked cancers but also of coronary heart disease (5, 23–26). Studies in animal models for various types of cancers have strengthened the case for high intakes of vegetables and fruits. It is recommended that 5–9 servings of such foods be part of daily nutrition (26). These foods are considered beneficial not so much because of their content of essential vitamins and minerals but because they provide antioxidants such as quercetin, isothiocyanates, and other protective chemical entities.

Bran cereal fiber

Burkitt was surprised by the frequency of intestinal diseases, including colon cancer, in British subjects living in Uganda (27). In sharp contrast, he rarely saw this condition in native Africans. Investigations showed that the Africans consumed large amounts of high-fiber foods, yielding a rapid intestinal transit time and, more important, a large stool in one or more passes per day. A parallel discovery was made in studies accounting for a lower risk of colon cancer and, in part, breast cancer in Finland, a country where people suffer from one of the highest risks of heart disease, which is associated with a high intake of saturated fats (6). It was also observed that the Finnish diet included whole-grain and rye breads, which have a high fiber content, also leading to large stools. Thus, the effectors of colon cancer and, in part, breast cancer may have been diluted by stool bulk to the point where they made no impact.

Fluid intake: tea

In the past 15 y, research has shown that we need to consider beverages as well as solid foods in health maintenance. It has

TABLE 3
Health-promoting lifestyle recommendations

- 1) Don't use tobacco in any form: smoking, chewing, or snuff dipping.
- 2) Lower total fat intake and use lipids with less risk for heart disease or cancer, such as monounsaturated oils. Consume fish several times a week.
- 3) Avoid obesity and adjust overall energy intake to energy needs; exercise (see number 12).
- 4) Increase intake of cereal bran fiber foods, including whole-grain, high-fiber bread.
- 5) Consume more vegetables, cooked tomato and soy products, and fruit, as excellent sources of vitamins, minerals, fiber, antioxidants, and other anticancer agents (5–10 daily recommended).
- 6) Avoid salted, pickled, or smoked foods; use salt sparingly (3–5 g/d).
- 7) Limit the intake of fried or broiled foods or pretreat to decrease the formation of carcinogens during cooking.
- 8) Increase intake of calcium with low-fat, or better, skim dairy products, milk, or yogurt, or certain vegetables.
- 9) Use alcoholic beverages in moderation, if at all.
- 10) Drink 1–1.5 L water or fluids per day; green and black tea, and soy milk contain health-promoting antioxidants. Another 1 L of water is eaten with foods.
- 11) Be careful about exposure to sunlight and use sunscreens, especially if you are of Celtic ancestry.
- 12) Exercise regularly, but only after health check certifying normal blood pressure and serum cholesterol concentrations to ensure cardiovascular patency.

been suggested that adults consume 1.5–2.5 L of fluids per day, including fluids that are drunk and those in solid foods. Several reports indicate that black or green tea contains antioxidant polyphenols that have a protective effect against heart disease and several lifestyle-related cancers, including cancer of the esophagus and lung as well as cancer of the colon, breast, and pancreas (28–30). Tea selectively induces cytochrome P450 enzymes and, importantly, glucuronyl transferases, which are involved in the detoxification of carcinogens. In addition, tea decreases the rates of duplication of neoplastic cells and tumor growth. Outgrowth of a health-promoting intestinal bacterial flora, lactobacilli, and of bifidobacteria is achieved by tea. Concentrates of tea polyphenols are available in capsule form. Research in this area is active and is bound to extend practical knowledge about the use of vegetables, fruit, and tea to prevent chronic disease. In fact, diets rich in antioxidants may help people avoid neoplastic and coronary heart diseases and other major chronic disabilities and are thought to be beneficial for reaching an old age in good health.

CONCLUSION


Intensive research has provided much information about the mechanisms underlying the occurrence of the main types of cancer, of heart disease, and of hypertension. This has required a multidisciplinary approach involving epidemiology, laboratory research in animal models, and in vitro studies. Personal and traditional lifestyles are considered to contribute strongly to the development of most of these diseases. Food processing or cooking can yield genotoxic carcinogens. Tobacco and alcohol have carcinogenic effects; their actions can and should be controlled or minimized. In addition, customary food habits supply specific promoting substances such as salt for stomach cancer and specific dietary fats for the Western nutritionally linked cancers, including cancer of the breast, colon, prostate, and pancreas. The

type and amount of fat are important, and lower risk can be secured by using specific kinds of fats such as olive or canola oil and by limiting total dietary fat. Bran cereal fiber can protect against cancer of the colon and possibly cancer of the breast. Daily intake of vegetables, fruit, and tea is part of a health-promoting dietary tradition. Exercise and avoidance of obesity contribute to good health. Reduction in the risk of difficult and expensive-to-treat chronic diseases can be achieved with the knowledge acquired through carefully coordinated worldwide research. Prevention is the definitive way to lower medical care costs due to degenerative diseases (**Table 3**). Sugimura (19) coined the phrase *tenju gann*, cancer at the end of a long life. We suggest it is possible to reach old age and to eventually “die old and healthy” by simply falling asleep and not waking up.

Major advances were achieved through mechanistic research on the causes of heart diseases, stroke, many types of cancer, and diabetes. In the Far East, major health problems are hypertension and stroke and cancer of the stomach, associated with excessive use of salt and salted, pickled foods and relatively low intakes of protective fruit and vegetables. We identified a possible gastric carcinogen, 2-chloro-4-methylthiobutanoate, in salted, pickled Japanese fish. In the West, heart disease and cancer of the breast, colon, rectum, prostate, pancreas, ovary, and endometrium are associated with consumption of a diet high in total fat (30–40% of energy) and too little fiber, vegetables, and fruit. Cooked meats can contain genotoxic chemicals and heterocyclic amines, elements associated with heart disease and the nutritionally linked cancers. Decreasing total fat intake; using mainly monounsaturated oils; eating more starches, such as rice, pasta, potatoes, and whole-grain bread; and maintaining a daily intake of 5–10 servings of vegetables (including cooked tomatoes and soy products) would be beneficial.

Adults should consume 2.5 L of fluids per day. Green or black tea, fruit juice, and soy milk have health-promoting properties, including antioxidants. Regular exercise contributes to good health and to the avoidance of obesity, a major problem in the United States and of increasing importance elsewhere. Avoidance of a poor lifestyle, as described herein, would likely reduce the risk of diseases important for individuals and their families and also have a major impact on lowering medical care costs.

Tobacco and cigarette use, particularly in the West, is associated with a high risk of heart attacks and cancers of the lung, pancreas, kidney, urinary bladder, and cervix, accounting for 35% of medical care expenditures. Smoking creates major health problems in other parts of the world as well. Tobacco farmers should be paid *not* to grow this crop because the clinical management of diseases caused by tobacco is expensive.

Biomedical research funded by the National Institutes of Health and organizations such as the American Cancer Society has produced sound results that could lead to prevention of chronic disease. What is still missing is a broad application by the public of this information for the long-term health of the nation and the world. Today, more health-promoting nutraceuticals are available in pill or capsule form at low cost. They could be valuable additions to state and federal nutritional support programs or to those provided by voluntary agencies such as the Red Cross and CARE. 

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