

Tumor Enhancers: Underestimated Factors in the Epidemiology of Lifestyle-Associated Cancers

by Ernst L. Wynder*

Model studies in carcinogenesis give ample evidence of synergistic, tumor-promoting and cocarcinogenic effects of environmental agents and dietary factors in regard to the induction and propagation of neoplasms. This presentation examines tumor enhancers deriving from the use of tobacco and alcohol as well as the effects of dietary fat and other food components on endocrinological and gastrointestinal factors that contribute to tumor development in the breast and colon.

It is suggested that epidemiologic surveys need to intensify investigations on the interrelationship of tumor enhancers and genotoxic agents in high risk populations and that they need to study especially the dose-response effects of such agents.

Experimental studies should focus increasingly on epidemiologic leads that suggest potential enhancers of genotoxic agents and should delineate mechanisms involved in such multistep carcinogenesis processes. This approach would be a prerequisite for chemoprevention.

Recommendations for changes of lifestyle habits and practical approaches towards reduction of tumor enhancers in consumer goods and in the environment are additional requirements for appropriate preventive strategies.

Introduction

The history of recorded environmental cancer begins in the 18th century, in an era which Shimkin calls "the age of reason" (1). In 1761, John Hill of London published his "Cautions Against the Immoderate Use of Snuff," when he associated this form of tobacco use with the occurrence of nasal polyps and cancers. In 1775, Percival Pott observed the correlation of exposure to soot with the frequent incidence of scrotal cancer in chimney sweeps. These early notations have been followed by many other clinical observations relating environmental factors to increased incidences of various forms of neoplasms and bringing into being the field of environmental cancer epidemiology and environmental carcinogenesis (1, 2). In each case, observations of the human conditions were eventually followed by attempts to uncover the specific carcinogens that might be responsible for the effects in man. However, experimental oncology had, of necessity, to be limited to testing of candidate carcinogens in laboratory animals. These model studies have given us an insight

into the mechanisms by which chemicals induce neoplasms. Berenblum and Shubik documented in the 1940s that the effects of a carcinogen could be promoted by subsequent application of a noncarcinogen (3-5) and further research with model experiments in animals has taught us the distinction between tumor promotion and cocarcinogenesis (the result of long-term coapplication of a carcinogen and a noncarcinogen) (6, 7). In addition, secondary factors, such as changes in enzyme chemistry or in the organization of cell membranes or immunological insufficiencies effect increases of tumor yield (8).

For the purpose of this review we shall group all agents other than initiators and carcinogens and all conditions that increase tumor yields under the category of "tumor enhancers," although we realize that the term "enhancement" denotes something desirable and that increased tumor yield is certainly undesirable except for the purposes of studying mechanisms in laboratory models. Tumor enhancers differ from tumor initiators or carcinogens in two important aspects: (1) their action is reversible and they function as nongenotoxic agents (8). Their effectiveness usually depends on long-term exposure and on a large total dose. This has important mechanistic as well as practical implications because the

*American Health Foundation, 320 East 43rd Street, New York, NY 10017.

dose response and the extrapolation in regard to a threshold level for these agents are different from those for genotoxins (9).

These considerations are of central importance to the cancer epidemiologist because the effects of "tumor enhancers" might only be seen at relatively high and constant dosage. Cessation of the exposure to enhancers is followed by a steep decline in tumor yield, quite in contrast to terminating the application of a carcinogen, which has little effect on the ultimate tumor yield.

In fact, the preventive oncologist needs to learn to distinguish the initiators, carcinogens and tumor enhancers in human risk assessment, if we are to look for more successful approaches towards reducing cancer risks (10, 11). The experimentalist and epidemiologist need to join forces in studying "tumor enhancers" that affect humans because as Berenblum stated "The ultimate aim of the study of experimental carcinogenesis is the prevention of cancer in man" (5). While studies on croton oil and its active constituents are of obvious academic interest, the mechanism of action of such compounds may have little or no counterpart in man. However, man is exposed to a variety of tumor enhancers or inhibitors working in unison to stimulate or prevent the development of an initiated cell.

The following are examples from cancer epidemiology that should be of equal concern to both epidemiologist and experimental oncologist.

Tobacco

It is clear from extensive experimental studies by our group and others that the complete carcinogenic effect of smoke condensate on the epidermis of mice and rabbits and the larynx of hamsters cannot

be due solely to identified or potentially present complete carcinogens (12-14). Experimental studies have, in fact, shown a tumor-promoting effect for the weakly acidic portion of the smoke and a cocarcinogenic effect for catechol, as well as for various neutral smoke constituents (12-14). The speed of decline in the rate of lung cancer of ex-smokers suggests a response to the withdrawal of tumor enhancers (Fig. 1) (15). An increased lung cancer rate was observed in the first 3 years after cessation of smoking. This is believed to be due to the fact that many who have smoked excessively, give up the habit because of severe chronic bronchitis while, in fact, the incipient cancer is already present. The decline in lung cancer risk, which eventually becomes apparent after an individual changes from nonfilter- to filter-cigarettes with a lower tar yield, might be due, in part, to a reduction in tumor enhancers which is concomitant with reduction of tar exposure (15-17). However, it might also relate to the selective reduction of weakly acidic components by smoke filtration and it might reflect the reduced exposure to tumor initiators in the smoke of low-yield cigarettes as a dose response effect. Smokers frequently counteract reduction of total particulate matter and nicotine in smoke by increasing cigarette consumption or inhaling more intensely in order to maintain a desired physiological nicotine level. Nevertheless, the reduction of total smoke particulates is likely to be of benefit in regard to reducing risks for those tobacco-related cancers that are associated with direct contact with the smoke.

Alcohol

Alcohol is a classic tumor enhancer (18, 19). It has no effect in low doses (less than two drinks per day), and it appears to have no essential effect by itself. Tobacco acts as the initiator, and alcohol abuse (all types of alcohol) acts as a tumor enhancer at least in regard to effects on the oral cavity, larynx (glottic and supraglottic) and esophagus (Fig. 2). The lung is not affected nor is the pancreas. The fact that the vocal cord is affected suggests that direct contact of the tissues with alcohol is not a necessary factor. We have been interested in the mechanisms whereby alcohol increases a smoker's risk for cancer of the upper alimentary tract, in part, because of our studies on the association of Plummer-Vinson disease and cancer of the upper alimentary tract in women (20, 21). Could the related roles of iron and riboflavin in cellular oxidation represent a common ground? Certainly, in mice riboflavin deficiency produces atrophy, hyperkeratosis, and hyperplasia of epidermal tissue, and gross abnormalities in mitochondria (20).

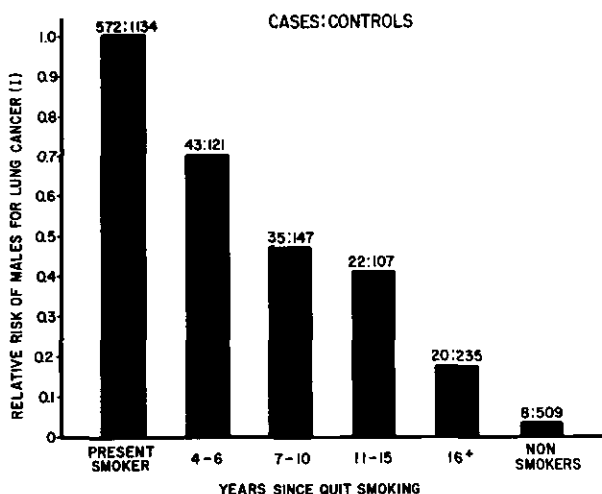


FIGURE 1. Decline of lung cancer risk in ex-smokers.

In our studies we have made the following observations (23-26). Enzyme activity is measurable for squamous cells of the hamster cheek pouch, although at a somewhat lower rate than in liver cells of the hamster. Upon consuming 35% of caloric intake in the form of ethanol, the microsomal enzyme activity in liver cells of hamsters increases. We must assume, although we have not measured this, that such increase also takes place in the squamous cells of the cheek pouch of hamsters. Increased enzyme activity in the liver cells leads to an increase in α -hydroxylation, the presumed activation mechanism of the carcinogenic nitrosopyrrolidine. It remains to be shown whether the changes in enzyme activity may render detoxification processes of polynuclear aromatic hydrocarbons less efficient, or whether there is activation in sensitive tissues. *In vivo* experiments show an increased yield in tumors of the nasal cavity and trachea in chronic ethanol-consuming hamsters treated with nitrosopyrrolidine but not in those treated with nitrosonornicotine (26).

A question remains as to whether the lower risk of beer drinkers, particularly those in countries where beer has a high vitamin B content, is due to a lower alcohol content of the beer, a dilution by high fluid intake, or a protective influence of the B vitamins, and especially of riboflavin. Should alcohol be fortified with riboflavin? Should excessive drinkers be encouraged to consume vitamin B supplements? Should we focus on more detailed studies of the nu-

tritional deficiencies which are likely to occur in individuals whose caloric intake includes an excessive amount of alcohol? This represents a challenge to the preventive oncologist, to the epidemiologist, and to the biochemist.

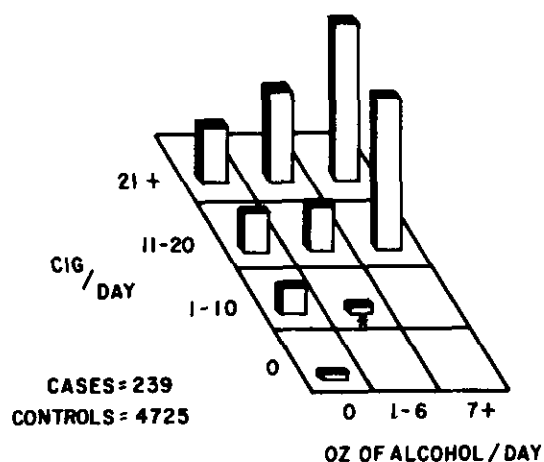
Nutrition

Dietary Fat Affecting Endocrinological Factors Related to Breast Cancer

In the rat, both estrogen and prolactin appear to be necessary factors for breast tumor growth and development, although they are not carcinogenic in themselves (27). In humans, breast cancer is significantly less common if castration has occurred before a woman reaches the late thirties (28). The risk for breast cancer is increased if menopause occurs late. In Japan, breast cancer incidence is particularly low in the postmenopausal group of patients. The rate of breast cancer increases in Japanese migrants to Hawaii but mainly in the second generation, suggesting that tumor initiation starts early in life and occurs less commonly in Japanese women than in women in the Western world (29). Breast cancer is now increasing in Japan (30). The one factor that can best account for these epidemiological observations is nutrition, particularly dietary fat content (31, 32).

Tannenbaum (33) showed more than three de-

RELATIVE RISKS OF LARYNX CANCER BY DAILY CONSUMPTION OF ALCOHOL AND CIGARETTES FOR MALES ($p < 0.05$). *not significant



RELATIVE RISKS OF ORAL CAVITY CANCER BY DAILY CONSUMPTION OF ALCOHOL AND CIGARETTES FOR MALES ($p < 0.05$). *not significant

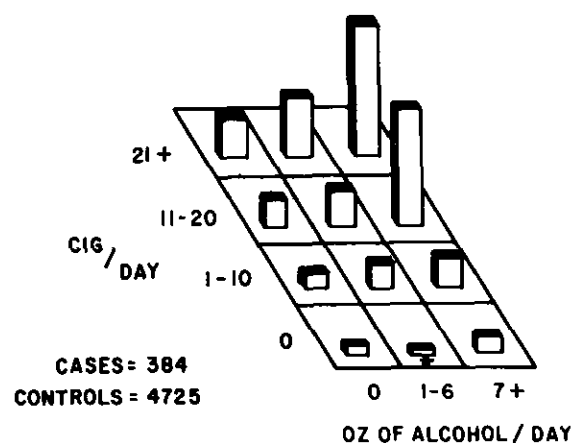


FIGURE 2. Relative risks of (left) larynx cancer and (right) oral cavity cancer by daily consumption of alcohol and cigarettes for males ($p < 0.05$). An asterisk (*) indicates values not significant.

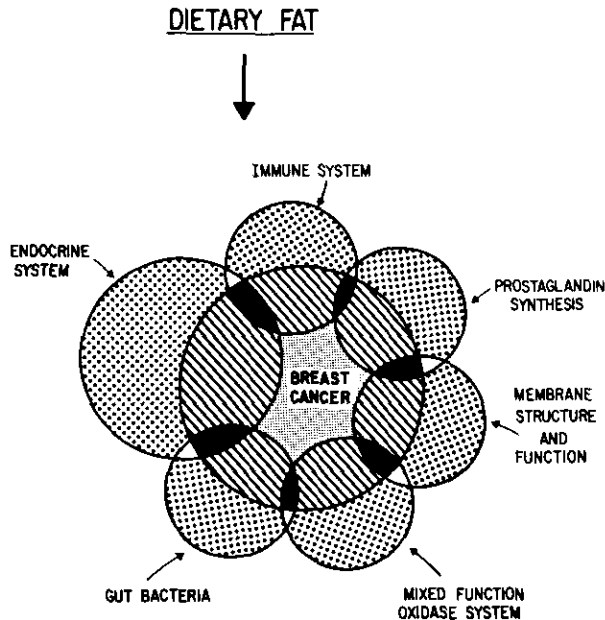


FIGURE 3. Effects of dietary fat.

ades ago that dietary fat increases the growth of spontaneous mammary tumors. These studies have been confirmed and extended by Carroll (34) and by our own group (35) using carcinogen-induced mammary tumor systems (Fig. 3). In these experiments, both saturated and unsaturated fats act as tumor enhancers. In the rat model, dietary fat has been shown to override the inhibiting effect on tumor development produced by removing the ovaries (36) and to increase the secretion of the tumor-promoting hormone prolactin, during proestrus (27). Hill (37) has shown that diet profoundly affects prolactin levels in women and that women who are on a Western diet experience reduced menstrual flow as well as a reduction of the number of days of the cycle when placed on a vegetarian diet (38). Possible pathways by which dietary fat may exert its promoting effects on mammary tumor development have been discussed and reviewed by several investigators (35, 36, 39).

The effects of dietary components may not be apparent when measuring hormones in the serum but may be distinguished by determining hormone levels in breast secretion. We have reported on the estrogen and prolactin content of breast aspirates of Finnish women who were free of breast disease (40). We noted a twofold increase in prolactin and a sixfold increase in estrogen in breast fluid as compared to serum concentrations. In ongoing studies with American and Japanese women, we observe the largest difference to occur with respect to the amount of free cholesterol in ductal aspirates, which

is more than two times higher in the Western women.

As much as 60% of nipple aspirates contain exfoliated mammary parenchymal cells many of which stain heavily for lipids. Hence it may be that at least part of the hormonal cell lipid content of ductal fluid is contributed by exfoliated cells. The quantitative and qualitative aspects of breast fluid cytology in populations of differing risk for breast cancer remains to be explored. We believe that the cellular content of breast fluids may reflect the integrity of the ductal epithelium of the breast in Western and Japanese women which, in turn, may reflect the relative differences in breast cancer risk.

We may hypothesize that the lipid nature of the breast fluid and/or the lipid content of mammary cell membranes might determine the interaction of water-soluble prolactin and fat-soluble estrogens with their respective receptors. The interaction of hormones is, of course, complicated, and it is likely that we will advance preventive strategies long before we understand the interactions of hormones such as estrogens, prolactin, or intracellular regulators such as prostaglandins in tumor enhancement. Clearly, the metabolic epidemiologist can play a role. More attention must be given to the biochemistry of breast secretion. Diet in terms of total saturated and unsaturated fat would appear to act as a modifier by affecting the hormonal milieu within the breast, a milieu that, in turn, affects carcinogenesis. It remains to be shown whether cholesterol epoxides, documented to be present in breast secretion, may play a role as tumor initiators as suggested by Petrakis et al. (41).

In terms of breast cancer epidemiology, we also need to consider that dietary fat may influence the survival of postmenopausal patients with breast cancer, a subject not part of this presentation.

Dietary Fat and Other Food Components Affecting Colon Cancer

Epidemiologic and animal studies suggest that diet is a major etiologic factor in colon cancer (27, 42). Diets high in total fat and low in fiber are associated with an increased incidence of colon cancer in man. High dietary fiber acts as a protective factor in populations consuming a high amount of total fat (43, 44).

The modifying effects of dietary factors in colon carcinogenesis are summarized in Table 1. With regard to the concept of dietary factors and colon cancer, Aries et al. (45) have suggested that the amount of dietary fat determines the levels of intestinal bile acids as well as the composition of the gut microflora, and that the gut microflora metabolizes these

Table 1. Modifying factors in colon cancer.

Dietary fat ^a	Dietary fibers ^{a,b}	Micronutrients
Increases bile acid secretion into gut	Certain fibers increase fecal bulk and dilute carcinogens and promoters	Include vitamins, minerals, antioxidants, etc.
Increases metabolic activity of gut bacteria	Modify metabolic activity of gut bacteria	Modify carcinogenesis at activation and detoxification level
Increases secondary bile acids in colon	Modify the metabolism of carcinogens and/or promoters	Act also at promotional phase of carcinogenesis
Alters immune system Stimulation of mixed function oxidase system		

^aDietary factors, particularly high total dietary fat and a relative lack of certain dietary fibers and vegetables have a role.

^bHigh dietary fiber of fibrous foods may be a protective factor even in the high dietary fat intake.

acid sterols to tumorigenic compounds active in the colon. Reddy et al. (46, 47) suggested that the dietary fat increases the excretion of bile acids into the gut, as well as modifies the activity of gut microflora which enhances the formation of secondary bile acids in the colon. These secondary bile acids act as tumor promoters in the colon (46, 47).

The mechanism of action of bile acids in colon carcinogenesis has not been elucidated. Bile acids have been shown to affect cell kinetics and proliferation in the intestinal epithelium (47). Lipkin (48) demonstrated that during neoplastic transformation of colonic cells, a similar sequence of changes leading to uncontrolled proliferative activity develops in colon cancer in humans and in rodents given a colon carcinogen. Recent studies suggest that the induction of colonic epithelial ornithine decarboxylase (ODC) activity by the bile acids may play a role in these mechanisms (49). Obviously, further studies are warranted on the mechanism of tumor-enhancing activity of various bile acids.

The possible mechanism of a protective effect of dietary fiber against colon cancer has been the subject of a recent workshop (50). The protective effect of dietary fiber may be due to adsorption, dilution or metabolism of cocarcinogens, promoters and yet-to-be-identified carcinogens by the components of the fiber (51-53). Different types of nonnutritive fibers possess specific binding properties. Dietary fiber could also affect the enterohepatic circulation of bile salts (54). Fiber not only influences bile acid metabolism, thereby reducing the formation of tumor enhancers in the colon, but also exerts a solventlike effect, in that it dilutes potential carcinogens and cocarcinogens by its bulking effect and is able to bind bile acids and certain carcinogenic compounds (53-57).

Recently, there has been considerable interest in the identification of inhibitors of carcinogenesis that may have value in the prevention of colon cancer. A

substantial number of compounds occurring naturally and synthetic substances have been shown to inhibit colon carcinogenesis (58). An example of these compounds are naturally occurring indoles, antioxidants, and micronutrients such as indole-3-carbinol, indole-3-acetonitrile, vitamins A, C, and E and selenium and synthetic antioxidants, namely butylated hydroxyanisole (BHA) and the butylated hydroxytoluene (BHT).

The suggestion that promotion may be involved in intestinal cancer has been supported by the observation that the carcinogenic response to a variety of intestinal carcinogens is enhanced by the dietary fat which in itself is not carcinogenic. Recent studies indicate that the enhanced tumorigenesis in the animals fed the high-fat diet is due to tumor promoting effects (59). Ingestion of high-fat diet increased the intestinal tumor incidence when it follows azoxymethane (AOM) (carcinogen) administration, but not when it occurs during or before AOM treatment. The carcinogenic process in the human may have similar characteristics since there is a good correlation between the findings in a variety of animal studies and those in humans. The fact that ubiquitous environmental carcinogens are present at very low concentrations suggests that tumor enhancing factors may have a preponderant influence on the eventual outcome of the neoplastic process in humans. Due to the variety of initiating agents and the possible difficulties in removing them from the environment, the promotional phase of carcinogenesis may be a more promising area for development of preventive measures.

Summary

Epidemiological studies, supported by experimental data, demonstrate that a variety of nongenotoxic factors enhance the development of cancer in man by potentiating or promoting the effect of carcino-

gens. These variables affect a preponderance of human cancers. Our recommendations are as follows.

(1) To the epidemiologist we recommend that he pinpoint further the interaction of tumor enhancers and genotoxic agents and, in particular, study the differences in dose-response effects of these agents.

Epidemiological studies of high and low risk populations and detailed investigations of outliers can contribute much to an understanding of the enhancement of carcinogenesis by environmental and lifestyle factors.

(2) To the experimentalist we suggest that he follow the epidemiologist's leads and study the mechanisms whereby certain suspected nongenotoxic agents potentiate carcinogenesis. Greater understanding of these mechanisms might permit the introduction of chemotherapeutic and chemopreventive approaches to tumor enhancers which is likely to be quite specific for a given class of tumor enhancers. The study of tumor enhancers known to affect carcinogenesis in man can be just as exciting, fruitful and, in the long run, more rewarding in reducing human cancer risk than the study of highly active promoters in model experiments which do not or only remotely relate to man's exposure.

(3) To the preventive oncologist we recommend that he counsel the individual as to lifestyle-habits and advise manufacturers and the regulatory agencies how to reduce exposure to tumor enhancers of products and environments. Since tumor enhancers are not genotoxic, since their action is reversible, and since they generally act at relatively high doses, it is likely that when the final chapter on environmental carcinogenesis is written, our greatest success may well have been the result of our ability to reduce tumor enhancers. Such reduction is most likely to occur through the appropriate interaction of all the varied disciplines now involved in environmental cancer research.

Our studies are made possible through the Core Support of our research facilities by Grant No. CA 17613 from the National Cancer Institute.

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