Ann. Rev. Nutr. 1988. 8:167–83

DIETARY FAT AND CANCER RISK: Evidence and Research Needs

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INTRODUCTION

The process of carcinogenesis is exceedingly complex and influenced by external factors in many ways. There are numerous examples in which the same substance may initiate, enhance, or inhibit the process, depending on experimental conditions. One important but by no means singular example is the synthetic antioxidant butylated hydroxyanisole (BHA), which is used as a food additive to prevent rancidity. BHA has been shown repeatedly to inhibit carcinogenesis in a variety of systems (64). However, at much higher feeding levels BHA is carcinogenic for the rat forestomach (32). Such observations provide important challenges to our understanding and knowledge of the origins of cancer as well as to our capacity to meaningfully regulate human exposure to carcinogenic hazards.

0199-9885/88/0715-0167$02.00

Dietary fat has been found in some epidemiologic studies to correlate with increased risk for cancers at some sites (notably breast and colon cancer) and with decreased risk for cancers at other sites (notably esophageal and gastric cancer). There is evidence from animal experiments supporting both of these seemingly contradictory results. However, the results of experimental studies indicate that mechanistic considerations are far more complicated than previously recognized. It would seem reasonable to conclude that a thorough understanding of mechanism is necessary before we can confidently apply the experimental data to the prevention of cancer in humans.

Two-Stage Model for Carcinogenesis

Current understanding of the process of carcinogenesis is embodied in the two-stage model, *initiation* followed by *tumor promotion* (6). During initiation, a normal cell is altered so as to become a latent cancer cell. This is presumably accomplished when a carcinogen interacts with and subsequently alters the genetic apparatus of the cell. During the stage of tumor promotion, the altered genes are expressed, a process leading ultimately to autonomous cellular growth that is no longer responsive to normal physiologic growth regulatory signals.

The two-stage model provides a tool for developing hypotheses with regard to possible effects of exogenous agents (like dietary fat) on carcinogenesis. For example, a substance may affect initiation by altering carcinogen metabolism or by directly reacting with the activated form of a chemical carcinogen. It could also act by simply diluting or adsorbing carcinogens, thereby preventing their entry into cells, as has been proposed for dietary fiber (35, 38, 44). Alternatively, it could enhance carcinogen uptake, as has been proposed to explain the increased cancer risk associated with ethanol consumption (56a).

A substance may also affect tumor promotion. Since tumor promotion is more poorly understood than initiation it is more difficult to cite specific mechanisms, but dietary factors have also been shown to enhance or inhibit this stage of carcinogenesis. High levels of vitamin C (22) or butylated hydroxytoluene (52) are examples of enhancers and vitamin A is an example of an inhibitor (6) of tumor promotion. The environmental contaminant TCDD (2,3,7,8-tetrachlorodibenzo-*p*-dioxin) can either promote or inhibit promotion, depending on dose (52a).

DIETARY FAT AND INITIATION OF CARCINOGENESIS

Positive Effects

There is little evidence that dietary fat might initiate carcinogenesis in mammals. The cyclopropenoid fatty acids, sterculic and malvalic acids, have been

reported to produce hepatocarcinomas when fed to trout and may therefore be weak initiators of carcinogenesis in that species, but the effect has not been duplicated in mammals (27). It has been postulated that for man and other mammals DNA damage leading to the initiation of carcinogenesis may be induced by oxidized fats and/or the products of lipid oxidation (1a). However, rodent feeding studies with oxidized fat have not supported these hypotheses. Moreover, there is little reason to suppose that feeding high-fat diets will necessarily result in the accumulation of fat oxidation products within body cells. Indeed, the mammary tissue of mice fed diets high in corn oil had less malonaldehyde than that from mice fed a diet low in corn oil under conditions where the mice on the high-fat diet developed more 7,12-dimethylbenz[a]-anthracene (DMBA) induced mammary tumors (40).

There is limited evidence that certain fats, notably fat from animal sources, may enhance initiation. Sylvester et al (60) reported that female Sprague-Dawley rats fed 20% beef tallow or 20% lard prior to DMBA administration developed more mammary tumors than animals fed 20% palm oil, 20% corn oil, or 5% corn oil. The authors could not identify a hormonal basis for this observation and suggested that it might have been due to contaminants or additives in the tallow and lard rather than to the fats per se. Additional work should be done to clarify this intriguing report. Using another tumor system, Nauss et al (44, 45) found no difference in tumor incidence or multiplicity between Sprague-Dawley rats fed diets containing 24% beef tallow or corn oil during both the initiation and promotion stages of 1,2-dimethylhydrazine-induced colon carcinogenesis.

Inhibitory Effects

There is considerable epidemiologic evidence linking dietary fat to decreased risk of cancer of the stomach (24, 29) and cancer of the esophagus (a link that remains even after correction for cigarette smoking and alcohol consumption, both of which are established risk factors for this disease) (62, 70). It has been proposed that dietary fat might reduce stomach cancer risk by protecting the gastric mucosa (29). Thus, dietary fat might reduce exposure of the gastric epithelial cells to initiating and/or and promoting factors.

There are also very important and pertinent data (30), from a major ongoing prospective epidemiologic study in Japan, relating to possible interactions between meat and vegetables in the diet and colon cancer risk (Table 1). Among Japanese consuming green and yellow vegetables on a daily basis, reduced risk for colon cancer is strongly correlated with the daily consumption of meat. Specifically, the standardized mortality rate per 100,000 was 3.87 for persons consuming meat on a daily basis, and 13.67 for those who did not consume meat on a daily basis. By contrast, for persons who did not consume green and yellow vegetables daily, meat consumption had little

apparent relation (18.43 versus 14.9 deaths per 100,000 respectively, among those who did or did not consume meat daily). Previously Graham (25) and Stemmermann et al (59) had also reported inverse correlations between fat consumption and colon cancer risk (i.e. the more fat in the diet, the lower the risk for colon cancer).

Hirayama's provocative findings (30; Table 1) will undoubtedly spur new investigations into nutrient interactions as well as possible synergistic relationships among anticarcinogenic factors in foods of both plant and animal origin. The results of such studies may prove pivotal in unraveling the diet/cancer enigma.

We have found that certain derivatives of the essential fatty acid linoleic acid can inhibit the initiation of mouse epidermal carcinogenesis by DMBA (26). The mechanism appears to include (but may not be limited to) inhibition of cytochrome P-450 activity, an enzyme complex involved in carcinogen metabolism.

A proposed mechanism for heat-induced formation of the anticarcinogenic linoleic acid derivatives is shown in Figure 1. The active material, designated by the acronym CLA, consists of four isomeric derivatives of linoleic acid, each containing a conjugated double-bond system. The data in Figure 2 show that CLA inhibits the initiation of mouse epidermal carcinogenesis by DMBA.

CLA has been isolated from human serum, bile, and duodenal juice (14). The origin of CLA in these materials remains unknown but heat-processed meats and other fatty foods should be investigated as possible contributing sources. We are finding both free CLA and triglycerides containing CLA in various cooked meat and dairy products, in some cases the concentration reaches more than a thousand parts per million, which has led us to estimate that in the US CLA consumption may be several hundred milligrams per person per day (26).

It may be productive to compare dietary levels of CLA with the amounts of CLA in the body fluids of persons who are at low or high risk for the cancers believed to be diet related. Our working hypothesis is that CLA consumption

Table 1 Relationship between daily meat or vegetable consumption and colon cancer risk (from a prospective epidemiologic study) (30)

Dietary pattern	Colon cancer risk (rate per 100,000)
Neither meat nor vegetables on a daily basis	14.9
Meat but not vegetables on a daily basis	18.43
Vegetables but not meat on a daily basis	13.67
Meat and vegetables on a daily basis	3.87

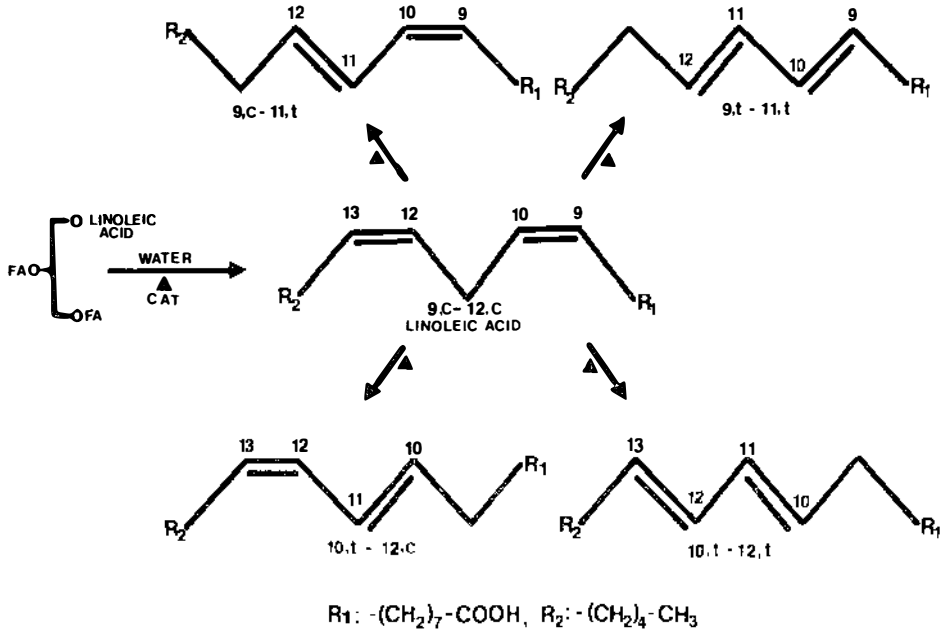

Figure 1 Model for the formation of CLA (isomeric derivatives of linoleic acid containing a conjugated double-bond system) in ground beef during frying. From (26).

and its consequent presence in body fluids might represent a contributing protective factor against these cancers, particularly when other putative protective factors are also present [e.g. beta-carotene and vitamins A and E, which alone do not correlate well with cancer reduction in humans (45a, 67)].

DIETARY FAT AND TUMOR PROMOTION

Positive Effects: Enhancement of Tumor Promotion

DEFINITION OF TERMS High-fat diets have been referred to as being "promoting" (10, 18). Oleic acid is a weak tumor promoter when applied directly to mouse epidermis (57), but there is little evidence that dietary oleate or other fatty acids exert such an effect and several investigators have questioned the use of the term tumor promoter in reference to dietary fat (28, 40). In the DMBA rat mammary cancer model, tumor yield was found to be directly proportional to the length of time that a high-fat diet was fed irrespective of whether it was fed before or after the initiating event (exposure to the DMBA) (19, but see also 60). Moreover, dietary fat will not enhance tumor appearance if the dose of the initiating carcinogen is too low, that is, "sub-

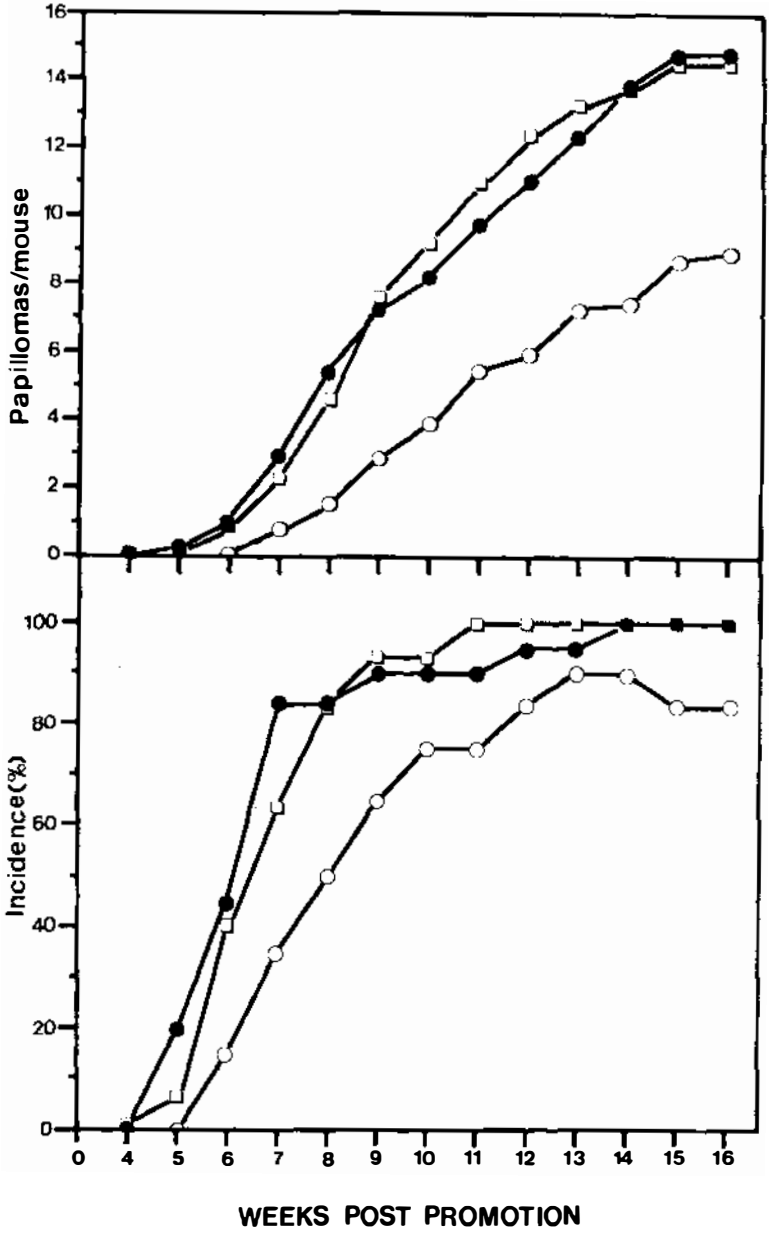

Figure 2 Inhibition of DMBA-initiated epidermal tumors by CLA. Data points indicate the cumulative number of tumors or tumor incidence for mice treated with synthetic CLA *(open circles)*, linoleic acid *(closed circles)*, or acetone *(open squares)* as a function of weeks of tumor promotion. Tumor promotion was effected by twice-weekly application of TPA beginning one week after initiation. See (26) for experimental details.

carcinogenic" (19, 40). In both of these cases dietary fat does not fit the definition of a tumor promoter (3).

The classic tumor promoter 12-*o*-tetradecanoylphorbol-13-acetate (TPA) enhances tumor appearance only when given after the initiating carcinogen and is effective following treatment with a "sub-carcinogenic" dose of the carcinogen. Furthermore, TPA promotes tumor growth by directly triggering key biochemical events. By contrast, the mechanism of enhancement of carcinogenesis by high-fat diets is much less well understood but appears to be largely indirect, complicated by factors such as ad libitum feeding (see below), and likely involving changes in hormone balance that in turn affect the promotion stage of certain cancers (6, 50). Hence, it would seem more precise to refer to dietary fat as a modulator of carcinogenesis, capable of enhancing or inhibiting the process depending on experimental design.

THE LINOLEIC ACID CONNECTION There is also considerable confusion over the question of "type of fat." "Dietary fat" is of course not a single entity but rather a class of related substances that contain differing amounts of various fatty acids. Of the various fatty acids commonly found in foods, only one, linoleic acid, has been shown clearly and unequivocally to enhance carcinogenesis when fed to rodents, a fact that must be appreciated if one is to properly interpret experiments on the effects of different dietary fats on the promotion of carcinogenesis. Furthermore, the amount of dietary linoleic acid required for optimal tumor development exceeds considerably the amount required by young rats for optimal growth (33, 34).

Carroll & Khor (13), using the DMBA rat mammary carcinogenesis model, reported that feeding diets high in polyunsaturated fatty acids produced more tumors than feeding diets high in saturated fatty acids. It was then shown that supplementing diets high in saturated fatty acids with a small amount of a fat high in polyunsaturated fatty acids abolished the difference (12, 31). Other investigators made similar observations, and most recently Ip and coworkers (33, 34) demonstrated that the dietary linoleic acid requirement for optimal tumor development was 5% by weight (in contrast, 1% linoleic acid is sufficient to satisfy the nutritional needs of young growing rats). Once this requirement is met, additional dietary fat from presumably any source will be equally "enhancing" (hydrogenated coconut oil was tested).

In addition to mammary carcinogenesis, a requirement for linoleic acid has been demonstrated for carcinogen-induced rat pancreatic carcinogenesis (56). Furthermore, the data of Sakaguchi et al (58) support the conclusion that linoleic acid is also required for optimal development of carcinogen-induced colon tumors in rats, although this interpretation was not considered by the investigators.

The mechanism of enhancement of tumor development by linoleic acid is not yet known. Prostaglandin synthesis or changes in mammary cell mem-

branes have been discussed (10, 66), but there is as yet no clear mechanistic model that can be experimentally tested. However, the observation that dietary linoleic acid can reduce fatty acid synthesis (16) may be important, particularly with regard to membrane fatty acid composition when high levels of linoleate are fed. Given the significance of this topic, there is a critical need for research to delineate clearly the mechanism whereby linoleic acid enhances tumor development.

Cohen et al (18) suggested that oleic acid may oppose linoleic acid in the enhancement of mammary tumor development in rats. This proposal was developed to explain the relatively low rate of mammary cancer among women in Greece and Spain, who consume diets high in olive oil. While this hypothesis is interesting, the data presented in its support by Cohen et al (18) are not strongly convincing because the linoleate content of the test diets was not constant. To test this hypothesis rigorously it will be necessary to test the effect of feeding mixtures of linoleic and oleic acids in various predetermined ratios. Chan et al (15) reported similar levels of mammary tumor incidence and multiplicity in DMBA-initiated female F344 rats fed diets containing approximately the same amount of linoleate (1.6 or 1.2 kcal from linoleate, respectively) but widely differing amounts of oleate (11.7 or 2.9 kcal from oleate, respectively). Further, Carroll & Khor (13) found that DMBA-initiated female Sprague-Dawley rats fed diets containing 20% olive, corn, cottonseed, soybean, or sunflower seed oils developed similar numbers of mammary tumors. Neither of these observations (13, 15) are consistent with the proposal of Cohen et al (18).

It is also not clear why it is necessary to explain the low rate of mammary cancer among Greek and Spanish women with such a hypothesis. For example, one might just as well ask why Mormons in the US exhibit low rates of mammary (and colon) cancer. Mormons are not vegetarians and in fact consume at least as much dietary fat as non-Mormon Americans (20). Moreover, Doll & Peto (20) concluded that for colon cancer in Great Britain "No good correlation is observed with . . . fat, or beef." Perhaps these low cancer rates are due to factors other than fat consumption per se. A large, well-conducted prospective epidemiologic study (68) failed to confirm a relationship between dietary fat consumption and breast cancer risk (see also 26a, 35a). Moreover, the relatively low death rate from breast cancer among US Seventh-Day Adventist women has been attributed in part to the result of earlier diagnosis and treatment rather than to dietary practice (71).

Much of the confusion and controversy concerning effects of the type of fat on carcinogenesis, and the lack of replication of experimental data by different laboratories (51), may be attributed to the failure to appreciate fully the importance of the linoleic acid content of diets for experimental carcinogene-

sis investigations. It is to be hoped that this regrettable situation will not persist.

FREE FATTY ACIDS, BILE ACIDS, AND CALCIUM One of the most prominent hypotheses on the relationship between colon cancer risk and dietary fat intake centers on the effects of free fatty acids and bile acids on the colonic epithelium (42). The ionized forms of these substances have been shown to be both irritating and toxic to colonic epithelial cells. Diets high in fat could lead to excessive levels of ionized bile and fatty acids in the colonic lumen, and the resulting irritation, if continued for a long time, could increase cancer risk by affecting the promotion (and possibly also the initiation) of colon carcinogenesis.

According to this model, a major factor in mitigating the proposed deleterious effects of ionized free fatty acids and bile acids is calcium, which might decrease risk by binding the ions to produce insoluble calcium salts that would be inactive. Additionally, dietary fiber could produce opposing effects by, on the one hand, binding calcium and preventing its interaction with bile and free fatty acids, while on the other providing a substrate for gut microorganisms and thereby lowering the pH of the colonic lumen, which would in turn reduce the concentration of the ionic forms of the bile and fatty acids. This could possibly explain some of the discrepancies in the epidemiologic evidence concering colon cancer and dietary fiber (35, 38, 44).

An attractive aspect of this interesting model is the finding that dietary calcium supplements reduced the rapid rate of proliferation of colonic epithelial cells in human subjects at high risk for familial colonic cancer, which suggests that cancer risk may also have been reduced (42). While it was not proved that the ingested calcium acted by binding to bile and/or fatty acids (8) these observations nonetheless fit with epidemiologic reports of an association between reduced colon cancer risk and the consumption of dairy products (23).

As interesting as this model is, however, it does not appear to account for other epidemiologic reports of reduced colon cancer among the residents of Utah, where beef and fat consumption are substantial (20), nor does it explain the findings of Hirayama (30; Table 1) that daily meat consumption correlated with decreased colon cancer risk among Japanese who ate green and yellow vegetables daily. Moreover, high-fat diets are not always found to enhance colon cancer development in animal experiments (44, 45), and even when they are, calcium supplementation may not mitigate the effect (8a). These observations raise the possibility of multiple interacting factors (for example, dietary linoleic acid, the concentrations of calcium, types of fiber, bile and free fatty acids in the colon, cancer inhibitors, alcohol consumption, and caloric intake and expenditure) all of which may influence risk while none by itself

is rate limiting in an absolute sense for the disease. Complicating this scenario are individual differences in physiologic response and genetic composition.

OXIDATION PRODUCTS It has been proposed that fatty acid oxidation products may be involved in tumor promotion (1a, 10, 66). For example, Bull et al (9) reported that hydroperoxy and hydroxyl derivatives of linoleic and arachidonic acids stimulated DNA synthesis and induced ornithine decarboxylase (ODC) activity in rat colon in vivo. Both the stimulation of DNA synthesis and the induction of ODC activity are considered to be markers of tumor promotion. There are also reports that antioxidants were effective in reducing tumor enhancement by diets high in linoleic acid. Unfortunately, in some of these studies it is not possible to separate possible effects on tumor promotion from effects on carcinogen metabolism (66).

On the other hand, there is little evidence that feeding diets containing oxidized, rancid fats will either initiate or promote carcinogenesis (1a), which suggests that other dietary factors (e.g. calcium) might mitigate the potentially deleterious effects of the oxidized products of unsaturated fatty acids. The apparent specificity of linoleic acid (but not other more unsaturated fatty acids such as linolenic acid) in enhancing tumor development argues against the hypothesis that oxidation per se is important in tumor enhancement by dietary fat, as does the report of Lane et al (40) that mammary tissue from mice fed diets high in corn oil had less malonaldehyde than mammary tissue from mice fed diets low in corn oil. Carroll (10) has proposed that specific fat oxidation products produced by cellular enzymes (lipoxygenases, cyclooxygenase) may provide the link between the fat oxidation and prostaglandin hypotheses. While interesting, the extent to which the consumption of fat would be rate limiting for such an effect is not clear, a consideration that might be expected to be further complicated by the genetic heterogeneity of human populations.

AD LIBITUM FEEDING AND THE CALORIE EFFECT Over 50 years ago it was discovered that caloric restriction reduced cancer risk, retarded the onset of senility, and increased the lifespan for rodents (47–51, 65). This phenomenon, subsequently named "the calorie effect," remains one of the most impressive and effective inhibitors of carcinogenesis that we know of. It was actively investigated prior to 1950 but relatively little work has been conducted on it since that time. However, a revival of interest in the calorie effect is now developing (1, 51).

The fact that the calorie effect has not had much impact on modern cancer research is apparently more than anything else perceptual. For example, Doll & Peto (20) concluded that "more interest might have been aroused . . . if the freely fed mice had been described as obese instead of the mice on the restricted diet being described as small!"

It is a matter of record that the ad libitum feeding regimen has become the

standard for diet/cancer studies even though it can hardly be called normal. Moreover, ad libitum feeding is subject to considerable variation depending on factors such as housing conditions, diet, and strain (54). Rodents in the wild do not have free access to food and they have not evolved to expect or require it. Rather, when food is freely available rats and mice will eat to excess and become pathologically obese, depending on strain and diet. Roe (55) has lamented this fact, calling it an unfortunate accident of history that we have come to regard ad libitum feeding as normal. We still do not know the optimal caloric intake for laboratory rodents, and this issue may be complicated by strain differences. Determining the precise relationship between caloric intake and the enhancement of tumor development for the various commonly used strains of laboratory rodents is a critically important research need.

The importance of these considerations is further indicated by the observation that the calorie source can affect the amount of physiologically available energy (4, 21). Specifically, calories from dietary fat may provide more physiologically usable energy than calories from carbohydrate or protein, particularly for sedentary animals that are not in the rapid growth phase. The biochemical basis for this observation is not fully understood, but it is in part the result of the need to synthesize body fat from dietary carbohydrate and/or protein when low-fat diets are fed, a process that is inefficient. By contrast, body fat is efficiently synthesized from the additional fat available in higher fat diets. This observation is not limited to rats fed under ad libitum conditions. For example, we have found that F344 rats fed a diet containing 30% corn oil ad libitum or under conditions of modest (about 15%) calorie restriction (relative to controls) exhibited equivalent ratios of body fat to lean body mass (5).

Differences in efficiency of calorie use dependent on source should be kept in mind when interpreting data from experiments where high-fat versus low-fat diets were fed. The familiar Atwater values of 4 kcal/g of carbohydrate or protein and 9 kcal/g of fat refer to metabolizable energy and are appropriate for designing isocaloric diets, but they must be used with caution in interpreting experiments. For example, in the study cited above we also found that the group of F344 rats fed the diet containing 30% corn oil under the condition of about 15% calorie restriction exhibited a higher ratio of body fat to lean body mass than a group fed an isocaloric diet containing only 5% corn oil under ad libitum conditions (5). Hence, calorie intake per se does not necessarily correlate with amount of body fat relative to lean body mass. The extent to which this may relate to the calorie effect and the promotion of carcinogenesis has yet to be rigorously determined.

Among the important questions that have not yet been satisfactorily answered is the extent to which calorie restriction may decrease cancer risk in the absolute sense (48). Much evidence suggests that calorie restriction not

only extends the lifespan of rodents but also reduces the proportion of animals that die of cancer, but in some studies this was not so: the percentage of animals ultimately developing cancer was not affected (although the length of life prior to cancer development was extended) (reviewed in 48).

It is also worth asking how much calorie restriction is required, and how soon in life must it commence, for the tumor development period to be significantly increased irrespective of whether the fraction of animals ultimately developing cancer is affected. These questions have not yet been adequately answered, although there are some interesting leads. For example, in ongoing studies to be published elsewhere we are finding that a 15–20% level of calorie restriction produces a greater anticarcinogenic effect in Fischer F344 than in Sprague-Dawley rats. Weindruch & Walford (65) reported that dietary restriction beginning at one year of age extended the lifespan of mice by 10–20%, and decreased death by spontaneous lymphoma.

In addition to specific effects of calorie restriction on tumor promotion, there is need for additional study of the effects of calorie restriction on immune system function. This has been reviewed in depth elsewhere (4).

The biochemical mechanism whereby the calorie effect, particularly modest calorie restriction of 15–20%, inhibits carcinogenesis is not yet adequately understood. Female rodents subjected to severe (40%) calorie restriction display smaller ovaries and uteri, become anestrous, exhibit large cyclic variations in liver glycogen, and maintain relatively high levels of liver glycogen during fasting as a result of gluconeogenesis (7). This is a consequence of the increased production of ACTH and the decreased production of gonadotropins that are induced by severe calorie restriction. Under more modest conditions of calorie restriction (15–20%) the estrous cycle is not affected, but at 12 months of age such animals display serum prolactin levels that are about one half of those of rats fed ad libitum (2). Glucocorticoid levels were not simultaneously studied but based on other investigations (63) it may be concluded that, during the time when food was not available to the restricted animals, glucocorticoid levels were elevated, because of the need for gluconeogenesis. It is also expected that the extent to which these biochemical changes occur under a given level of calorie restriction will vary among strains.

ENERGY EXPENDITURE Closely related to calorie intake is the question of energy expenditure. There is a considerable and growing body of epidemiologic evidence indicating that energy expenditure may be an important factor in determining human cancer risk. In a number of studies increased physical activity has been linked to decreased risk for mammary or colon cancer; thus energy expenditure may be an important (but until recently often overlooked) factor in determining human cancer risk (51).

There are also animal data to support this hypothesis and provide mechanistic information. Cohen (17) initiated mammary carcinogenesis in female F344 rats by injecting *N*-nitrosomethylurea and found that subsequent voluntary exercise reduced tumor incidence from 67% (ad-libitum-fed controls) to 40% (animals given access to exercise wheels). Interestingly the exercised rats consumed approximately 20% more food and exhibited a 12% higher body weight compared to the ad-libitum-fed controls, which indicates that energy expenditure may exert an anticarcinogenic effect that is independent of the calorie effect per se. We have reported very similar results using Sprague-Dawley rats (49).

An important key to tumor reduction seems to be *voluntary* exercise. Others (61, 69) reported that forced exercise increased carcinogen-induced mammary tumor risk in rats, and there may be an interesting interaction between forced exercise and dietary fat consumption (69). There is a crucial need for experiments aimed at reconciling the apparently contradictory effects of voluntary versus forced exercise on mammay tumor promotion. It will also be important to determine if expending calories through thermogenesis is as effective as voluntary physical activity in reducing tumor risk.

Inhibitory Effects

Karmali (37) and Carroll (11) have proposed that two omega-3 fatty acids found in fish oil, eicosapentaenoic and docosahexaenoic acids, inhibit mammary tumor promotion in rats by inhibiting arachidonic acid metabolism and the production of prostaglandins, thromboxanes, and leukotrienes. They further extended this hypothesis to explain differences in cancer rates among residents of Greenland and Iceland. However, as attractive as this hypothesis may be, the inhibiting effects have not yet been demonstrated under conditions where a control diet and a diet containing fish oil and the same level of linoleic acid were consumed at isocaloric levels by animal subjects. Such a demonstration is essential in order to separate possible protective effects of fish oil consumption from the calorie and linoleate effects. If this can be accomplished it will then be possible to proceed with mechanistic studies.

Little work has been done on the possibility that other fatty acids might inhibit tumor promotion in animal models. The recent report (58a) that palmitic acid inhibits TPA-induced tumor promotion in mouse epidermis is of considerable interest and should be pursued.

CONCLUSIONS

The issue of dietary recommendations for the prevention of cancer is controversial because our knowledge of nutrition/cancer relationships is incomplete (26a, 35a, 39, 46). Mechanistic studies are urgently needed. It will

be possible to extrapolate from animal data to humans only as we gain understanding of the biochemical mechanisms for specific effects and the likelihood of their occurrence in humans. In this regard rigorous biochemical investigation of the effects of energy intake and expenditure on carcinogenesis is particularly important.

There are also exciting new leads on possible nutrient interactions, particularly in the data reported by Hirayama (30) and in the possibility that some nutrients may mitigate the possible deleterious effects of others (e.g. calcium versus fatty and bile acids). Moreover, the possibility of synergistic interactions among cancer inhibitors in foods of both animal and plant origin should be investigated. It is very important that those involved in nutrition/cancer research remain open-minded and receptive to the possible impact on their research of new findings in related areas. Interdisciplinary approaches should be encouraged. The solution to the diet/cancer puzzle is clearly more complicated than we might wish, but in this complexity lie many opportunities.

ACKNOWLEDGMENTS

Research data from the author's laboratory was supported in part by the College of Agricultural and Life Sciences, University of Wisconsin–Madison; Public Health Service Training grant 5-T32CA-09451 from the Division of Extramural Activities, National Cancer Institute; and by other grants and unrestricted gift funds administered through the Food Research Institute, University of Wisconsin–Madison.

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