# Role of Lipids in Tumorigenesis

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## ABSTRACT

High fat diets are associated with increased mortality from cancer at various sites, including breast, colon, rectum, prostate, ovary and pancreas. Additional evidence for this association has been obtained for some sites (e.g. mammary gland and colon) by studies on experimental animals. Dietary polyunsaturated fats increase the yield of mammary tumors in rats more effectively than saturated fats, apparently because of their higher content of essential fatty acids. Saturated and polyunsaturated fats are about equally effective in enhancing the yields of colon tumors in rats. Dietary fat appears to act as a promoter rather than an initiator of tumorigenesis, although the exact mechanisms of action are not known. Mammary tumorigenesis in rats can be inhibited by reducing the level of dietary fat after a period of promoting with a high fat diet. Decreasing the present high levels of fat in American diets might help to reduce cancer incidence and mortality.

## INTRODUCTION

Evidence has been accumulating in recent years that diet, particularly dietary lipids, plays an important role in tumorigenesis. This evidence has been reviewed in a number of publications, most of which consist of proceedings of symposia or workshops (1-6). A comprehensive review of diet, nutrition and cancer also has been prepared recently by a Committee of the Assembly of Life Sciences, National Research Council (7). This report has stimulated considerable controversy, some of which has been published by the Council for Agricultural Science and Technology (8).

On the basis of their review of the literature, the Committee on Diet, Nutrition, and Cancer concluded "that of all the dietary components it studied, the combined epidemiological and experimental evidence is most suggestive for a causal relationship between fat intake and the occurrence of cancer." The purpose of the present article will be to review briefly some of the evidence on which this conclusion was based. Further details may be found in the original report (7) and in other publications referred to above (1-6).

## EPIDEMIOLOGICAL DATA

Intercountry comparisons have shown positive correlations between the amount of fat available for consumption and mortality from cancer at various sites in the body, including breast, colon, rectum, prostate, ovary and pancreas (9). Data for breast and colon are illustrated in Figure 1 (10). Cancer at other sites, such as liver and stomach, is not positively correlated with dietary fat, but cancers that do show this positive correlation are responsible for a large proportion of cancer deaths in the United States and Canada (11).

The data on which such correlations are based are subject to many inaccuracies, but it seems clear that mortality from cancers of the breast and colon is much lower in a country like Japan than in the United States, since good records are maintained in both countries. Furthermore, differences such as these appear to be related to environment rather than heredity, since mortality from breast cancer and colon cancer in Japanese immigrants in the United States increases with time until it approaches that of the American population as a whole. Similar shifts in mortality patterns have been observed in other immigrant populations (12).

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## STUDIES ON EXPERIMENTAL ANIMALS

The existence of a positive correlation between cancer mortality and dietary fat does not necessarily mean that they are causally related. However, supporting evidence has come from studies on experimental animals. Mammary cancer develops more readily in animals fed high fat diets compared to those fed low fat diets (9,10), and similar observations have been made for intestinal tumors (13). Recent studies also have indicated that dietary fat can influence the development of pancreatic tumors in rats (14).

In our studies on mammary tumorigenesis, diets high in polyunsaturated fats produced a marked increase in tumor yield, compared to low fat diets or diets high in saturated fats (9). It appears that there is a requirement for essential fatty acids as well as for a high fat diet, and that the more saturated fats are ineffective because they contain insufficient amounts of essential fatty acids (15). The two requirements may be related, since at lower levels of dietary fat a higher degree of polyunsaturation was required to produce an increase in tumor yield (16). Dietary polyunsaturated fat also was observed to enhance the yield of pancreatic tumors more effectively than saturated fat (14), but the type of fat appears to be less imporant in the case of intestinal tumors (13).

In human populations, breast cancer mortality correlates best with total dietary fat intake (10,17), and it seems probable that the dietary fat in most countries would be sufficiently unsaturated to provide the necessary amounts of essential fatty acids. Thus, one might expect that the amount of fat in the diet would have a greater influence on breast cancer than the type of fat, as observed in the epidemiological data.

## MECHANISM OF ACTION

Cancer is a multi-step process, and the evidence indicates that dietary fat affects the promotional stage rather than initiation of tumorigenesis (9,16). High fat diets increase the yield of spontaneous mammary tumors as well as those induced by various carcinogens, and there is no indication that the fat itself is acting as a carcinogen. The enhancement in tumor yield can still be observed when animals are fed a high fat diet only after treatment with a carcinogen capable of inducing mammary tumors (9).

The exact mechanism by which dietary fat affects tumorigenesis is not known, but a number of possibilities have been suggested (13,15,16,18). In the case of mammary tumors, this might involve an alteration in hormonal balance, whereas dietary fat may affect intestinal tumors by stimulating production of bile acids, some of which have been shown to act as tumor promoters (13). Other possibilities include effects on the composition and properties of cellular membranes, effects on the immune system, and increased production of peroxidized products or biologically active compounds, such as prostaglandins, derived from polyunsaturated fatty acids (15).

Whatever the mechanism, evidence that dietary fat acts as a promoter of carcinogenesis suggests that the process can be influenced at later stages by the fat content of the diet. Experiments with rats have, in fact, shown that mammary tumorigenesis can be inhibited by reducing the level of dietary fat after a period of promoting with a high fat

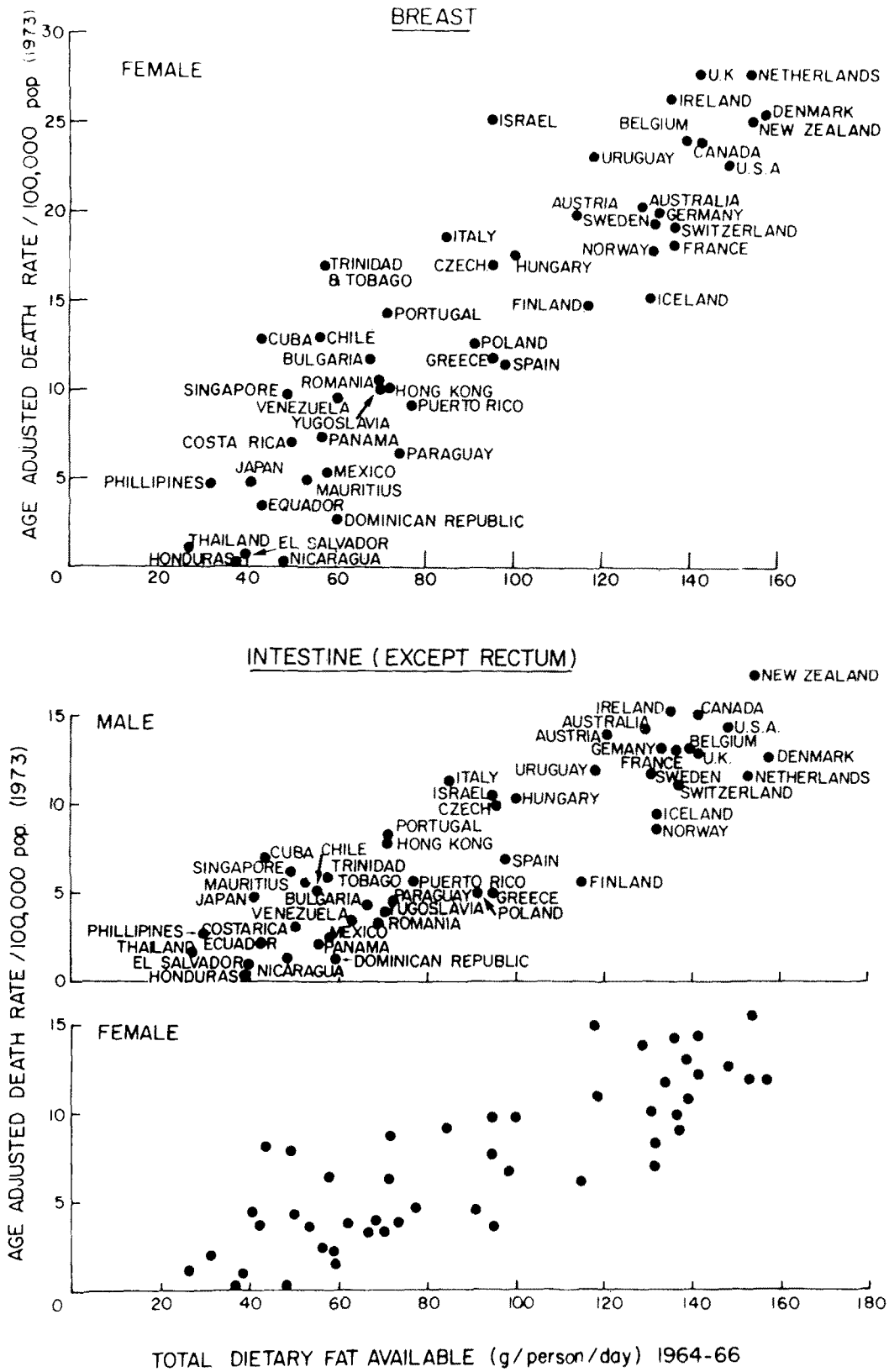


**FIG. 1. Correlations between total dietary fat available and age-adjusted death rates from breast cancer and intestinal cancer. Reproduced from Carroll (10).**

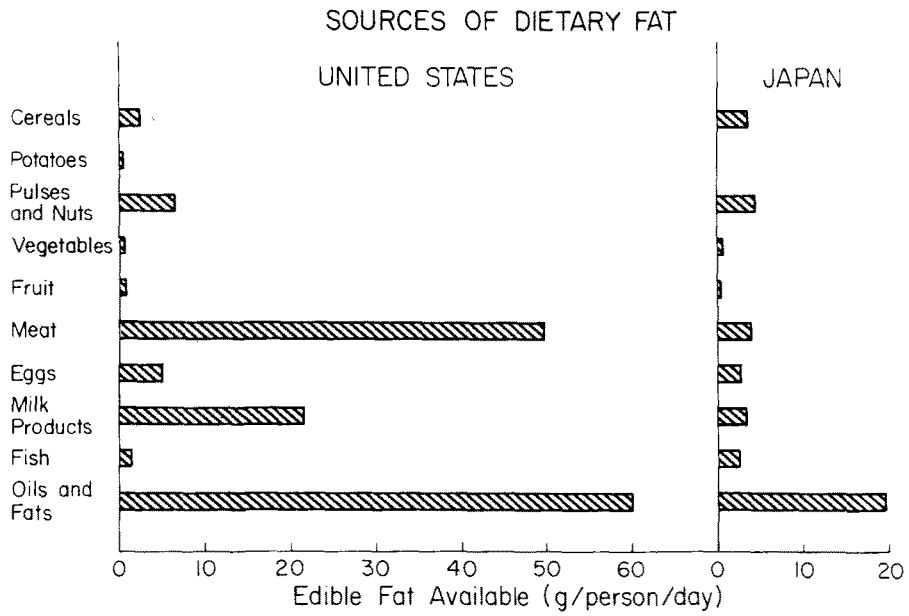


**FIG. 2. Sources of available dietary fat in the United States and Japan. Reproduced from Carroll and Hopkins (21).**

diet (16). A more recent study in our laboratory showed that decreasing the dietary fat from 20% to 10% by weight (i.e. from about 40% to 20% of calories) reduced the yield of tumors to about the same extent as complete removal of fat from the diet (19). If breast cancer in humans is similarly influenced by dietary fat, it might be possible to improve the prognosis of breast cancer patients by reducing their fat intake, with the aim of inhibiting development and proliferation of metasteses which constitute one of the major problems in breast cancer. In this connection, it is of interest that Japanese women not only have a lower incidence of breast cancer than American women, but also experience a lower recurrence rate when cancer develops (20).

## SOURCES OF DIETARY FAT

In order to devise diets of lower fat content, information on the sources of dietary fat is required. As illustrated in Figure 2, visible fats and oils used as spreads, cooking fats and salad oils, are the largest source of fat in the American diet. The next major source is meat, but the amount indicated in the diagram may overestimate its contribution, since fat often is trimmed from meat and also can be lost during cooking. Dairy products are the only other major source of dietary fat in the United States diet. Foods such as eggs and nuts are relatively high in fat, but are not consumed in sufficient quantities to make a large contribution to the total intake (Fig. 2).

## PROS AND CONS OF DECREASING FAT INTAKE

Aside from its possible effects on carcinogenesis, a reduction in dietary fat intake has been advocated for some time as a means of reducing the incidence of cardiovascular disese (22). There also have been suggestions that other chronic diseases of Western civilization may be largely due to consumption of a diet that is high in fat and relatively low in complex carbohydrate and fiber (23).

It is important to consider, however, whether there may be disadvantages in reducing dietary faty intake. The main function of dietary fat is as a source of calories, but it also provides essential fatty acids and fat-soluble vitamins, and facilitates absorption of fat-soluble vitamins from the gut.

There are some segments of the population, such as infants under one year of age, for whom a high fat diet is desirable. The rapid growth occurring at this stage of life requires a high caloric intake relative to body weight, and milk is relatively high in fat. It therefore would appear unwise to reduce the fat intake of infants.

Fat enhances the flavor and texture of food and by stimulating the appetite may help to maintain weight in elderly people or people with debilitating diseases, where weight loss is a problem. High fat diets also may be appropriate for people engaged in heavy manual labor or working in a cold environment, who thus require a relatively high caloric intake. For sedentary, middle-aged individuals, however, some reduction in the level of dietary faty probably is desirable and may decrease the likelihood of developing some of the chronic diseases, including cancer, that are common in our society.

Attempts to reduce dietary fat intake inevitably will involve eating less of some of the high fat foods referred to above. This could be achieved by using less fat as spreads and salad oils, reducing the amount of fat used in cooking, and eating less high fat meat and dairy products. It is important, however, to maintain a balanced diet in order to avoid deficiencies of required nutrients.

Normal humans eating a varied diet are unlikely to become deficient in essential fatty acids, but this possibilty still must be considered (24). Deficiencies of fat-soluble vitamins also are possible, but could be avoided by use of dietary supplements. Foods such as meat and dairy products contain many essential non-fatty nutrients and thus contribute to a well-balanced diet. As pointed out earlier, some high fat foods such as eggs, which also contain valuable essential nutrients, do not contribute unduly to the total fatty intake because they are consumed in relatively small amounts.

In closing, it should be emphasized that there are as yet insufficeient data to conclude that a reduction in dietary fat will lead to a decrease in cancer incidence and mortality, although the evidence points in that direction. More work is needed to assess the relative advantages and disadvantages of reducing the level of fat in the American diet. At pre-

sent, it appears that many individuals would benefit from a lower dietary fat intake, but care should be taken to achieve this by adjusting the relative proportions of low and high fat foods so as to maintain a well-balanced diet.

ACKNOWLEDGMENT

The National Cancer Institute of Canada supported this work.

REFERENCES

1. Workshop on Fat and Cancer, edited by D.J. Fink and D. Kritchevsky, Cancer Res. 41:3677 (1981).
2. IUNS Workshop on Nutrition and Cancer, Nutr. Cancer 2:197 (1981).
3. Nutrition and Cancer: Etiology and Treatment, edited by G.R. Newell and N.M. Ellison, Raven Press, New York, 1981.
4. Molecular Interrelations of Nutrition and Cancer, edited by M.S. Arnott, J. van Eys and Y.–M. Wang, Raven Press, New York, 1982.
5. Dietary Fats and Health, AOCS Monograph 10, edited by E.G. Perkins and W.J. Visek, American Oil Chemists' Socity, Champaign, IL, 1983.
6. Workshop Conference on Nutrition in Cancer Causation and Prevention, Cancer Res. Suppl. 43:2385s (1983).
7. Diet, Nutrition, and Cancer, Report of a Committee on Diet, Nutrition and Cancer, Assembly of Life Sciences, National Research Council, National Academy Press, Washington, DC, (1982).
8. Diet, Nutrition, and Cancer: A Critique, Special Publication No. 13, Council for Agricultural Science and Technology, Ames, IA, 1982.
9. Carroll, K.K., and H.T. Khor, Progr. Biochem. Pharmacol. 10:308 (1975).
10. Carroll, K.K., J. Environ. Pathol. Toxicol. 3(4):253 (1980).
11. World Health Statistics Annual, Vital Statistics and Causes of Death, World Health Organization, Geneva, 1980.
12. Gori, G.B. Diet and Nutrition in Cancer Causation. Nutr. Cancer 1:5 (1978).
13. Reddy, B.S., L.A. Cohen, G.D. McCoy, P. Hill, J.H. Weisburger and E.L. Wynder, Adv. Cancer Res. 32:237 (1980).
14. Roebuck, B.D., J.D. Yager Jr. and D.S. Longnecker, Cancer Res. 41:888 (1981).
15. Carroll, K.K. G.J. Hopkins, T.G. Kennedy and M.B. Davidson, Progr. Lipid Res. 20:685 (1981).
16. Carroll, K.K., The role of dietary fat in carcinogenesis, in Dietary Fats and Health, AOCS Monograph 10, edited by E.G. Perkins and W.J. Visek, American Oil Chemists' Society, Champaign, IL, 1983, p. 710.
17. Carroll, K.K., Cancer Res. 35:3374 (1975).
18. Hopkins, G.J., and C.E. West, Life Sci. 19:1103 (1976).
19. Carroll, K.K., and R. Kalamegham, Lipid components and cancer, in Environmental Aspects of Cancer: The Role of Macro and Micro Components of Foods, edited by E.L. Wynder, G.A. Leveille, J.H. Weisburger, and G.E. Livingston. Food Nutrition Press, Inc., Westport, CT, 1983, p. 101.
20. Wynder, E.L., and L.A. Cohen, Nutr. Cancer 3:195 (1982).
21. Carroll, K.K., and G.J. Hopkins, Lipids 14:155 (1979).
22. Rationale of the Diet-Heart Statement of the American Heart Association. Report of the AHA Nutrition Committee, Arteriosclerosis 2:177 (1982).
23. Burkitt, D.P., S. Afr. Med. J. 61:1013 (1982).
24. Holman, R.T., JAOCS 55:774A (1978).

[Received June 20, 1984]

# The Biochemistry of Selenoproteins

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## ABSTRACT

There currently are 7 known bacterial selenoenzymes. All but thiolase contain selenocysteine (Se-Cys), presumably at the active site, and all but thiolase catalyze oxidation-reduction reactions. Selenide appears to be a central intermediate in selenium (Se) metabolism in animals, and it may be the precursor used for formation of the Se-Cys moiety in glutathione peroxidase (GSH-Px). The incorporation of Se into GSH-Px appears to occur via a post-translational mechanism, but the nature and extent of Se-Cys formation in higher animals has not been established. GSH-Px deficiency remains a logical explanation for a number of Se-deficiency signs, but other known selenoproteins and other functions may match up with defects apparently not prevented by GSH-Px.

## INTRODUCTION

Many of the topics and the compounds discussed in this symposium in association with carcinogenesis reappear when considering the biochemistry of selenium. The discovery in the early 1970's that Se was an integral part of the enzyme GSH-Px (1) provided new support for the antioxidant theory of vitamin E function and, along with the discovery of superoxide dismutase (2), suggested that oxidative and/or free radical attack on cellular components may be responsible for the toxicity of a number of drugs. Some of these prooxidant or procancerous species are even more toxic when administered to Se-deficient animals, indicating that the biochemical functions of Se may be related to the processes involved in carcinogenesis.

Some of the anti-cancer activity of Se undoubtedly is related to the cytotoxicity of inorganic Se. The pharmacological effects of Se excess will not be the subject of this article. Instead, this article will review the biochemistry of Se and the effects of Se deficiency in animals as it relates to the biochemical functions of Se. The main sections of this review will discuss (1) bacterial selenoenzymes, (2) Se-Cys and GSH-Px, (3) Se metabolism, (4) GSH-Px function, (5) some of the selenoproteins and (6) functions of Se in animals apparently not related to GSH-Px. Recent reviews in related areas of Se biochemistry are available (3-6).

The story concerning Se essentiality in the US began in the late 1940's, when Klaus Schwarz came to the US from Germany. In Germany he had been studying dietary liver necrosis, a disease that could be prevented by either dietary vitamin E or the sulfur amino acids (7). After arriving in the US, he found that rats fed diets based on American brewer's yeast did not develop this disease. Rats fed torula yeast-based diets, however, developed liver necrosis in 3 to 4 weeks. Schwarz then isolated the organic factor present in American brewer's yeast that would protect against dietary liver necrosis, calling it factor-3 (8). In 1957 he identified Se as the crucial component in factor-3 (9). Factor-3 never has been fully characterized, but Schwarz and coworkers (10) have reported that several dialkyl diselenides have activities equivalent to factor-3 and were more active than