Mechanisms by Which Dietary Fat May Stimulate Mammary Carcinogenesis in Experimental Animals

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Abstract
Evidence drawn from epidemiological and experimental studies suggests that dietary fat is an important determinant of breast cancer risk and, in addition, that dietary fat acts as a modulator rather than an initiator of breast carcinogenesis. At present, however, it is not known how dietary fat exerts its tumor-promoting effects. A variety of mechanisms, some involving direct action by fat at the target organ and others involving host-mediated responses, have been proposed. The present status of one of these, namely, a mechanism based on mediation by the endocrine system, and the hormone prolactin in particular, is described. Further studies in laboratory animals are required to determine the precise cellular and molecular events which underlie the fat effect.

Introduction
Dietary Fat as a Determinant of Breast Cancer Risk. Evidence that dietary fat, as an etiological factor distinct from chemical contaminants of the diet and other environmental and genetic factors, is an important determinant of breast cancer risk is reinforced by a variety of epidemiological (1, 2, 11, 15, 16) and laboratory animal studies (3, 6, 14, 20). With few exceptions (11), the bulk of epidemiological evidence suggests that total fat intake is an accurate index of risk, particularly amongst postmenopausal women, where incidence rates are highest. Moreover, the results of laboratory animal studies conducted over the past 4 decades are highly consistent with a fat hypothesis (2, 20) and have shed light on several hereto unknown aspects of this phenomenon, namely, that (a) the effect of high-fat intake is distinct from that of obesity and is exerted primarily on the postinitiation (promotional) phase of breast carcinogenesis and (b) polyunsaturated fats apparently play a special but as yet undefined role in the tumor-enhancing effect of dietary fat. Breast cancer, therefore, is an example of a problem in which evidence from both epidemiological and experimental studies has reached sufficient proportions to warrant exploration into biological mechanisms.

Mechanisms
Postulated mechanisms by which dietary fat may influence breast cancer fall into 2 basic categories, namely, those involving direct effects of fat on tumor development and those involving indirect effects on host metabolism. Direct effects involve changes in (a) the lipid content of the cell membrane and (b) the synthesis of prostaglandins (biologically active derivatives of the essential fatty acids, arachidonate and linoleate). Indirect mechanisms involve (a) subversion of the immune system, (b) stimulation of mixed-function oxidase systems involved in carcinogen activation, (c) alterations in fecal flora and bile acid metabolism, and (d) alterations in the endocrine milieu of the host (for reviews, see Refs. 1, 15, and 16; Chart 1).

Evidence for Mediation of the Fat Effect by Prolactin
Mindful of the fact that numerous other hormones play a role in breast cancer development (i.e., insulin and progestrone, glucocorticoids), we have focused our attentions on the 2 hormones which appear, on the basis of experimental evidence, to be most essential to the growth and development of mammary tumors, namely, estrogen and prolactin (10) and have explored the possibility that the effect of dietary fat on breast cancer is mediated by way of altered endocrine function. Our studies in rats suggest that prolactin may serve as the endocrine mediator by which dietary fat exerts its tumor-enhancing effects. Evidence in support of this contention is as follows: (a) Prolactin acts as a classical promoter substance in a number of rodent mammary tumor systems (21). (b) Prolactin also serves as a liporegulatory hormone, regulating fat mobilization, deposition and transport in a variety of vertebrate species (12, 17, 19). (c) The effect of both fat and prolactin is exerted primarily on the promotional phase of breast carcinogenesis (2, 21). (d) Ingestion of high levels of dietary fat results in elevated blood prolactin concentrations in both rodents (5, 6, 8) and humans (13), regardless of sex.

Proposed Role Played by Estrogens. Taken together, these considerations suggested that prolactin, by virtue of its dual role as a liporegulatory hormone and a mammary tumor promoter, may mediate the tumor-enhancing effect of a high-fat diet on experimentally induced mammary cancer (Chart 2). The role of estrogens appears to be permissive or secondary in nature. This conclusion is based on the fact that (a) the stimulatory effect of a high-fat diet on mammary tumor development is not blocked by administration of the estrogen receptor antagonist nafoxidine-HCl (3), (b) blood estrogen concentrations are not altered in animals consuming high-fat diets (6), and (c) the tumor-enhancing effect of a high-fat diet can be demonstrated in host animals from which the ovaries have been removed (9). Since a number of experiments both in vivo (21) and in vitro (7) have demonstrated that estrogens antagonize the action of prolactin on mammary tissue at high concentrations but appear to act synergistically at low concentrations, it has been proposed that the ultimate effect of a high-fat diet is to elevate the prolactin:estrogen ratio and thereby stimulate mammary tumor development (4).

Although the role of prolactin in murine breast cancer is reasonably well established, its role in human breast cancer is poorly understood at present. Hence, it is premature to extrapolate results derived from laboratory animal studies to breast

1 Presented at the Workshop on Fat and Cancer, December 10 to 12, 1979, Bethesda, Md.
cancer in humans. Nonetheless, recent studies indicating that 40 to 60% of human breast cancers are prolactin responsive (18) suggest that the above hypothesis may serve as a useful working guide for future studies on the influence of nutrition on human breast cancer.

Future Needs

The following areas are considered to be of high priority. In terms of the influence of fat intake on mammary tumorigenesis: (a) the specific roles played by polyunsaturated and saturated fats in breast carcinogenesis; (b) interactions between dietary fat, protein, carbohydrate, and fiber in promoting mammary tumor development; and (c) the exact point(s) during the multistage progression of breast cancer at which dietary fat exerts its primary effects.

In terms of mechanism: (a) the influence of diet on the secretion of different molecular (functional) forms of prolactin; (b) the nature of the prolactin receptor and the influence of diet on its induction; (c) the precise role of estrogens and other steroid hormones in the fat effect (estrogens generated by extragonadal mechanisms, for example, could play an indirect role via a positive feedback effect on prolactin secretion); (d) the role played by prolactin in human breast cancer; and (e) the role played by nonhormonal mechanisms in the fat effect, namely, host-mediated effects such as alteration of immune responses and direct mechanisms such as prostaglandin production and membrane effects.

Summary

Taken independently, evidence from any one discipline may prove fragmentary and at times inconsistent, as Enig et al. (11) recently pointed out in an analysis of changing trends in fat consumption patterns and breast cancer incidence in the United States. However, when one considers the aggregate data, there can be little doubt that dietary fat plays an important role in the etiology of breast cancer. The central questions which remain unresolved are how much of a role does fat play and what is the underlying biological mechanism(s) by which the fat effect is exerted.

Acknowledgment

The author wishes to thank Elaine Harvey for her assistance in preparation of the manuscript.

References


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