Dietary Fat, Immunological Response, and Cancer in Rats

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Abstract

Immunocompetence can be modified by dietary means. Quality and quantity of fat have been associated with differences in tumor induction and immunological response in animals, and epidemiological observations have indicated that certain dietary lipids are associated in some obscure way with changes in tumor incidence in human populations. Data presented at this Workshop indicate that dietary fats are associated with an enhancement of cancer of the breast, prostate, and colon in human populations and with cancer of the breast and possibly the liver in animal models. Polyunsaturated fats are more enhancing, but cholesterol, other dietary sterols, and their degradation products appear to influence cancer induction either directly or indirectly. Fats appear to be involved in promotion rather than initiation of the carcinogenesis process. That this is not established, however, indicates that an immunological mechanism may be involved in these phenomena.

Quality and quantity of dietary fat influence lipid metabolism and sterol synthesis. Obesity depresses immune functions, and further, is involved in some obscure manner with endometrial cancer in women. Lipemia is associated with aberrations of immune function in people; polyunsaturated fats (a) decreased rejection crisis in renal transplant patients and (b) suppressed delayed hypersensitivity to skin tests in cancer patients and control subjects with evidence for a regulatory role by unsaturated fats on lymphocyte reactivity, possibly through effects on prostaglandins and hormone synthesis. The oxidation products of cholesterol exhibit profound effects over some aspects of immune response, and plasma lipoproteins and their subjects are involved in some manner with immunoregulatory aspects of lymphocytes, inhibiting in vivo and in vitro functions. Clearly, dietary and endogenous lipids influence immunocompetence and, in this manner, probably susceptibility to cancer.

Introduction

An animal’s nutritional state may appreciably influence its response to various stresses and the way it metabolizes exogenous or endogenous chemicals in the liver (20, 22). In addition, the immunocompetence can be modified by dietary means (19). In a number of studies, we have observed a marked dietary effect on tumor induction by various chemical carcinogens. Quality and quantity of fat have been associated with differences in tumor induction and immunological response (1). Epidemiological observations and experimental animal studies have indicated that certain dietary factors are associated in some obscure way with changes in tumor incidence in human populations and in experimental animals. The major focus of this Workshop is on fat’s influence on cancer in human populations and in experimentally induced tumors. This brief presentation addresses certain aspects of fat and cancer, in particular, the quality and quantity of fat and how it may relate to tumors of selected organ sites and how a high-fat diet affects immunocompetence. A more extensive review of fat and cancer is included in other sections of these proceedings. Reference to a few epidemiological studies and some specific animal experiments are described here.

Materials and Methods

Male Sprague-Dawley rats (Charles River Breeding Laboratories, Inc., Wilmington, Mass.), about 4 weeks old, 45 to 50 g body weight, were fed diets ad libitum from weaning for various periods of time. Thirty to 50 animals were used in each trial. Rats were housed individually in screen-bottomed stainless-steel cages in climate-controlled animal facilities and were weighed when placed on the experimental diets and weekly thereafter. For further experimental details, consult the various references cited. The data given here relate primarily to effects of fats on tumor induction and, where appropriate, effects on the immunological response.

Results

Rats fed a diet high in beef fat (28%), with enough corn oil (2%) to prevent essential fatty acid deficiency, were significantly more susceptible to induction of colon tumors by dimethylhydrazine than those fed a lower concentration of fat (Ref. 22; Table 1). Not only did the incidence of colon tumors increase with high dietary fat, but the number of tumors per tumor-bearing rat increased at both carcinogen dose levels.

Additional studies (9), using the same dietary regimen and the same carcinogen dosages, revealed an increased total number of colon tumors and an increased percentage of the colon occupied by lymphoid follicles in the high-fat, high-carcinogen group (Table 2).

In further studies (20) designed to compare effects of saturated and unsaturated fats on aflatoxin B1-induced liver tumors, tumor incidence increased and lymphocyte response to mitogen stimulation decreased in rats fed corn oil (Table 3); lymphocyte response was diminished regardless of whether or not the carcinogen was administered. These 3 examples clearly illustrate that fat has a profound effect on chemically induced...
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Table 2
Dietary fat and lymphoid tissue associated with rat colon tumors

<table>
<thead>
<tr>
<th>Diet</th>
<th>Dimethylhydrazine dose (mg/kg)</th>
<th>% of colon occupied by folliclesa</th>
<th>No. of colon tumors</th>
<th>Mucinous adenocarcinomas</th>
<th>Adenocarcinomas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>300</td>
<td>8.4</td>
<td>43</td>
<td>23</td>
<td>77</td>
</tr>
<tr>
<td>High-fat</td>
<td>300</td>
<td>9.4</td>
<td>83</td>
<td>6</td>
<td>94</td>
</tr>
<tr>
<td>Control</td>
<td>150</td>
<td>9.6</td>
<td>12</td>
<td>8</td>
<td>92</td>
</tr>
<tr>
<td>High-fat</td>
<td>150</td>
<td>7.6</td>
<td>33</td>
<td>6</td>
<td>94</td>
</tr>
</tbody>
</table>

a Taken from Ref. 9, with permission. Tumors were induced by dimethylhydrazine.

Discussion

It has been shown conclusively that quality and quantity of dietary fat influences tumor incidence in animals, particularly in the mammary glands, colon, and prostate, and to a lesser extent in the liver. Colon, mammary, and prostate cancer in human populations have also been associated positively with dietary fat content (1). Also, in mice and rats, dietary fat enhances mammary and liver tumors and other selected tumors of various target organs (11, 23-26).

Although numerous attempts have been made to associate saturated fats with breast and colon cancer in human populations, none have been definitive. An increased incidence of cancer in arteriosclerotic patients treated with polyunsaturated fatty acid-enriched diets over an 8-year period revealed difficulties in attempting to assess human data (21).

Many investigators have raised the question of how dietary lipids may influence the immune system in relation to both infectious disease and cancer. Some studies have shown that saturated fats increase resistance to tuberculosis, indicating that fat affects the immune system (10).

Genetically obese mice have impaired immunity as demonstrated by diminished ability to react to a contact sensitizing agent, reduced capacity to reject skin grafts, and diminished ability to generate cells that are active in cytotoxic systems (15). In other studies, hyperlipidemic rabbits exhibited decreased resistance to infection as did obese dogs (27). These observations are associated in some way with the immune system (8, 19).

More recent studies have demonstrated that polyunsaturated fatty acids regulate lymphocyte reactivity (6, 14, 16-18). When animals were fed polyunsaturated fatty acids (compared to saturated fatty acids), skin grafts survived for a longer period of time, response to mitogens was decreased, and renal transplants survived for longer time periods; there were also other indications that polyunsaturated fatty acids depressed the immune system.

Prostaglandins and hormonal mediation have been implicated in some studies with polyunsaturated fatty acid effects and the response of the immunological system (12). Hypercholesterolemia also decreases resistance to infection and transplantable tumors, diminishes lymphocyte response to sheep and RBC and other antigens, and "turns off" the incorporation of labeled acetate into cholesterol (2, 12, 13). Cholesterol synthesis is an important event leading to cell proliferation and response to antigen; impairment of this activity is associated with elevated dietary cholesterol, which profoundly affects immune functions.

Finally, as opposed to the direct dietary effects of various fats on the immune responses, plasma lipoproteins exert important influences on immunocompetence and are tools for studying the effects of endogenous processes on tumor immunobiology (3-5, 7). Effects of lipoprotein subsets on immunoregulatory properties, specific receptors, and other aspects of fats and cancer mediated through the immune system clearly help us to understand the modulation of carcinogenic processes by fats.

References

10. Hedgcock, L. W. Effect of dietary fatty acids and protein intake on experi-
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