Neutral Fats and Cancer[1]

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Abstract

High-fat diets enhance the development of mammary and intestinal tumors in animals, and dietary fat also shows a strong positive correlation with mortality from cancers of the breast and colon in human populations. In animals, dietary fat appears to act as a promoter of carcinogenesis rather than as an influence in the initiation of tumors. Polyunsaturated fats enhance mammary tumorigenesis and stimulate tumor growth more effectively than do saturated fats. However, diets containing a small amount of polyunsaturated fat and a high level of saturated fat increase mammary tumor yields as effectively as do diets containing a high level of polyunsaturated fat. Fatty acids of either the linoleate or linolenate family appear to be able to satisfy the small requirement for polyunsaturated fat. The mechanism by which dietary fat influences mammary tumorigenesis is not known but may involve hormonal effects, immune responses, or alterations in cellular membranes. Dietary fat is thought to enhance the development of intestinal tumors by stimulating production of bile acids, some of which act as promoters of tumorigenesis.

Introduction

Numerous studies over the past 40 years have consistently shown that animals on high-fat diets develop certain types of tumors more readily than do their counterparts fed low-fat diets. This effect has been observed with skin tumors and mammary tumors (2, 7) and with intestinal tumors (24, 27) but not with a number of other experimentally produced tumors (2, 7). The earlier observations failed to attract widespread attention until it was realized that epidemiological data on human populations also showed a strong positive correlation between dietary fat and mortality from cancers of the breast and colon (7). These 2 types of cancer account for a relatively high proportion of cancer deaths in Europe and North America, and the death rates have shown little or no sign of decreasing in recent years (Chart 1).

Although epidemiological observations do not by themselves establish a causative relationship between dietary fat and cancer, the supporting evidence from animal experiments makes this a likely possibility. It therefore seems worthwhile to examine this suspected relationship further by continuing to collect and analyze epidemiological data and by carrying out further experiments with animals to identify the components of dietary fat responsible for the observed effects and to determine the mechanisms involved.

Experiments with Animals

In our studies on mammary tumors induced in rats by DMBA,[3]

it was observed that unsaturated fats were more effective in promoting tumor development than were saturated fats (6, 11). However, more recent experiments (4, 13) have shown that, if saturated fats such as beef tallow or coconut oil are fed with a small amount of polyunsaturated fat, they promote mammary tumorigenesis as effectively as do the polyunsaturated fats themselves. These results indicate a dual requirement for a small amount of polyunsaturated fat together with a high level of dietary fat in order to demonstrate the effect. Once the small requirement for polyunsaturated fat is met, it does not seem to matter whether the remaining fat is saturated or unsaturated. It is of interest to know whether these 2 requirements are related, and experiments designed to shed light on this are currently under way in our laboratory.

Our studies have also indicated that the requirement for polyunsaturated fat can be satisfied by highly purified ethyl linoleate or by a fish oil containing polyunsaturated fatty acids derived mainly from linolenate (3, 5). This suggests that the effect is related to a requirement for essential fatty acids, which is not specific for fatty acids of the linoleate family. However, further studies should be carried out to confirm and extend these findings.

High-fat diets have also been found to promote the development of chemically induced intestinal tumors in rats (24, 27). The results of these experiments have given some indication that unsaturated fats are more effective than saturated fats at low levels of intake, but, at high levels of intake, saturated and unsaturated fats were found to be equally effective.

The enhancement of mammary tumorigenesis by dietary fat has been observed with spontaneous tumors as well as with tumors induced by a number of different chemical carcinogens. Furthermore, it was observed in our experiments that the effect of a high-fat diet could still be observed when the diet was instituted as late as 1 to 2 weeks after treatment with DMBA (7). These observations led to the suggestion that dietary fat acts at the promotional stage of tumorigenesis rather than affecting the process of initiation.

A hormonal mechanism was postulated by Chan and Cohen (8) who provided evidence that dietary fat increases the ratio of prolactin to estrogen in the circulation (8, 9). However, results of recent experiments in our laboratory on rats treated with DMBA failed to support this hypothesis. As illustrated in Chart 2, no correlation was found between yield of tumors and ratio of prolactin to estrogen in the circulation, as measured by radioimmunoassay. The hormonal results shown are based on determinations at the metestrus-diestrus phase of the cycle, but measurements at proestrus also failed to show any correlation with tumor yield.

There are a number of possible reasons for this lack of agreement. In the experiments of Chan et al. (8, 9), blood for hormone analysis was taken from rats anesthetized with ether, which is known to be a rapid and powerful stimulator of prolactin release (21), whereas, in our experiments, the blood was obtained from rats immediately after decapitation. It was also noted in our studies that about 40% of the rats treated with

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Breast Cancer (Female)

First (left) panel — RATE PER 100,000 POPULATION, x-axis 1954-55, 1964-65, 1974:
- IRELAND
- DENMARK
- ISRAEL
- CANADA
- BELGIUM
- USA
- GERMANY
- AUSTRIA FR
- FRANCE
- FINLAND
- CHILE
- JAPAN

Second (right) panel:
- NETHERLANDS
- ENGLAND/WALES
- SCOTLAND
- NEW ZEALAND
- SWITZ.
- N IRELAND
- SWEDEN
- AUSTRALIA
- ITALY
- NORWAY
- PORTUGAL

Cancer of the Intestine except Rectum (Male)

Left panel:
- USA
- CANADA
- AUSTRIA
- GERMANY
- BELGIUM
- DENMARK
- ITALY
- ISRAEL
- FINLAND
- JAPAN
- CHILE

Right panel:
- N. IRELAND
- AUSTRALIA
- SCOTLAND
- IRELAND
- FRANCE
- NEW ZEALAND
- ENGLAND WALES
- SWITZ.
- SWEDEN
- NETHERLANDS
- NORWAY
- PORTUGAL

Cancer of the Intestine except Rectum (Female)

Left panel:
- CANADA
- DENMARK
- USA
- BELGIUM
- GERMANY
- ISRAEL
- FRANCE
- AUSTRIA
- FINLAND
- CHILE
- JAPAN

Right panel:
- NEW ZEALAND
- N IRELAND
- IRELAND
- SCOTLAND
- AUSTRALIA
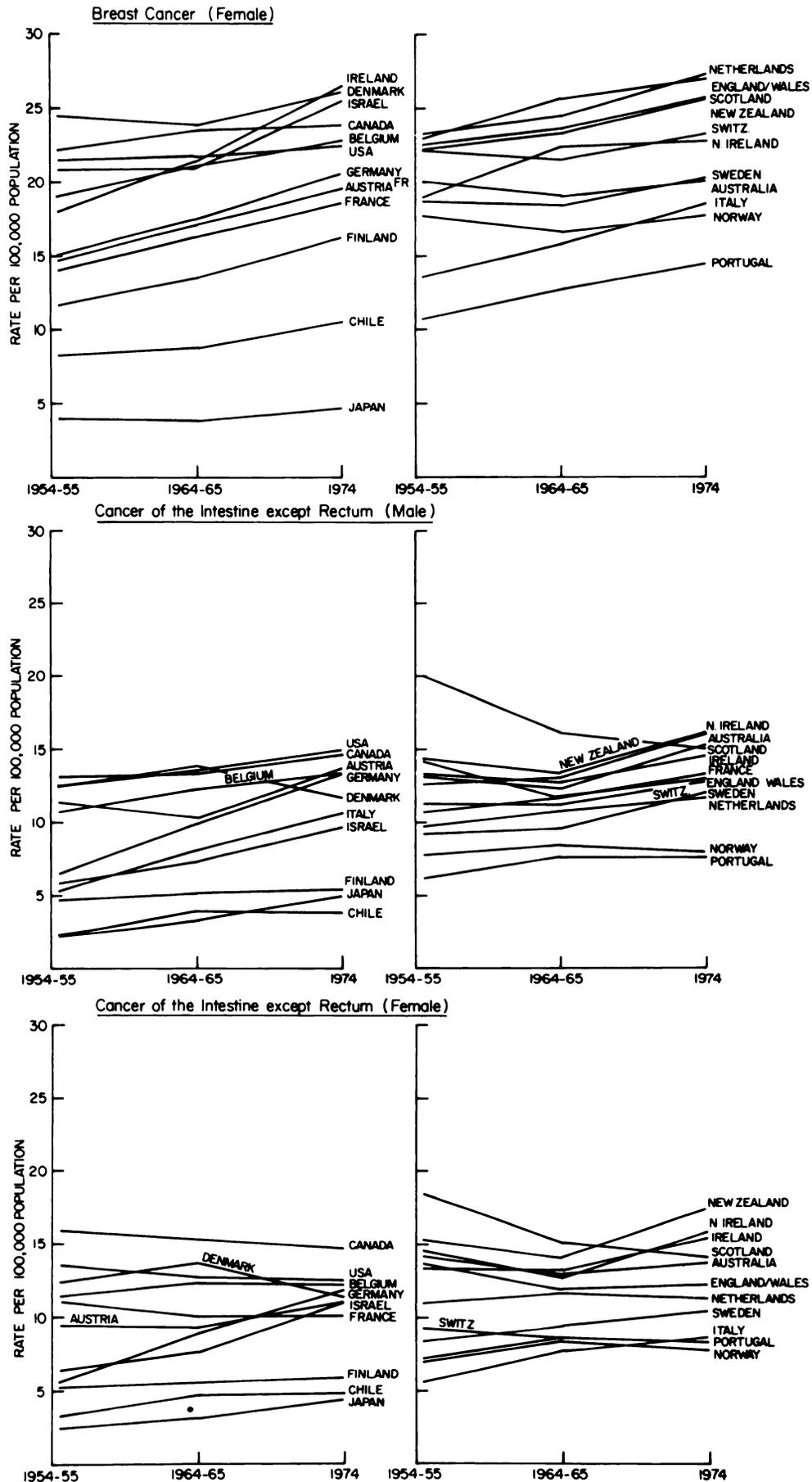- ENGLAND/WALES
- NETHERLANDS
- SWEDEN
- SWITZ
- ITALY
- PORTUGAL
- NORWAY

Chart 1. Trends in age-adjusted mortality from breast and intestinal cancers. From data collated by Segi *et al.* (25).

RATIO OF PROLACTIN (ng/ml) TO ESTRADIOL (pg/ml)
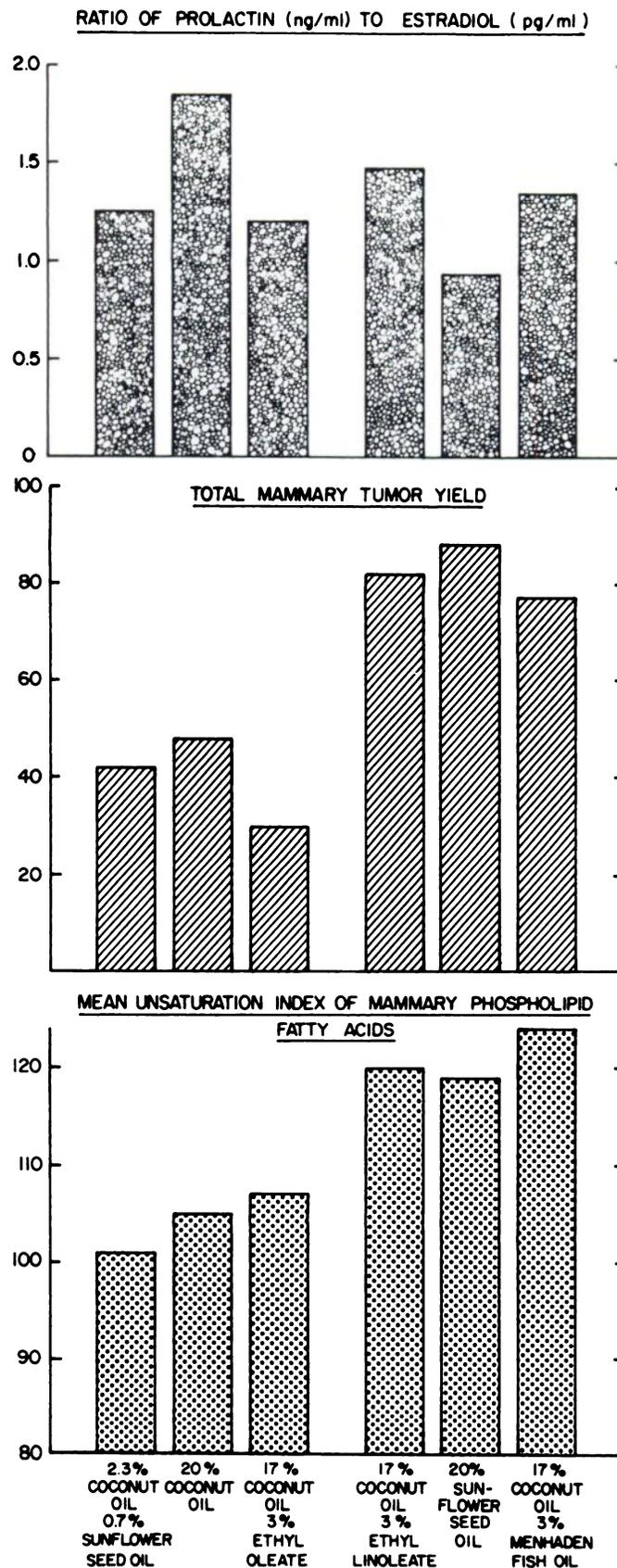
TOTAL MAMMARY TUMOR YIELD

MEAN UNSATURATION INDEX OF MAMMARY PHOSPHOLIPID FATTY ACIDS

| 2.3% COCONUT OIL 0.7% SUNFLOWER SEED OIL | 20% COCONUT OIL | 17% COCONUT OIL 3% ETHYL OLEATE | 17% COCONUT OIL 3% ETHYL LINOLEATE | 20% SUN-FLOWER SEED OIL | 17% COCONUT OIL 3% MENHADEN FISH OIL |

Chart 2. Data on plasma prolactin:estrogen ratios, tumor yields, and degree of unsaturation of mammary tissue phospholipids. From experiments of Hopkins, Kennedy, and Carroll (J. Natl. Cancer Inst., *66:* 517–522, 1981). Total tumor yields are for 20 rats in each of the dietary groups. Hormone levels were measured by radioimmunoassay on plasmas from 10 to 15 rats per group. Blood was collected after decapitation of the rats at the metestrus-diestrus phase of the cycle. The unsaturation index is defined as the sum of the products of mol % and number of double bonds per fatty acid. The results are averages based on analysis of the fatty acids of mammary phospholipids from 10 animals of each group.

DMBA did not have regular estrus cycles, and there is recent evidence that treatment with DMBA inhibits preovulatory gonadotrophin secretion and stimulates prolactin secretion (16).

The effect of dietary fat on fatty acid composition of mammary tissue phospholipids was also measured in our experiments. The results suggested that diets which increased the yields of mammary tumors also increased the degree of unsaturation of these phospholipids (Chart 2). This would presumably increase the fluidity of cellular membranes which might in turn exert an influence on development and proliferation of tumor cells.

Another possibility is that dietary fat may affect mammary tumorigenesis by altering immune responses of the host (14, 20). This topic is discussed in more detail by Vitale and Broitman (26).

Our observation of a requirement for a small amount of polyunsaturated fat as well as a high-fat diet for the promotion of mammary tumorigenesis raises the possibility that the effect is mediated by some of the biologically active products of essential fatty acids, such as prostaglandins. There is evidence that prostaglandins can act as promoters of skin tumors (19), and they may also influence immune responses (20).

The experiments of Abraham and Rao (1) and of Hopkins and West (15) have provided additional evidence that polyunsaturated fats stimulate mammary tumor growth more effectively than do saturated fats. King et al. (18) also observed that the growth rate as well as the incidence of mammary tumors induced in rats by DMBA was enhanced by feeding a diet high in polyunsaturated fat. As little as 1% corn oil in the diet stimulated the growth of transplantable mammary tumor in the experiments of Abraham and Rao (1). On the basis of studies with prostaglandin inhibitors, they suggested that this effect was not due to formation of prostaglandins, but more recent experiments of Hillyard and Abraham (12) have led to reconsideration of the possibility that prostaglandins may be involved. In a promising new approach, Kidwell et al. (17, 28) have observed that polyunsaturated fatty acids enhance the growth and survival of normal and neoplastic rat mammary epithelial cells in culture.

As indicated earlier, dietary fat also promotes the development of intestinal tumors in experimental animals but probably does so by a different mechanism. A very plausible suggestion is that dietary fat increases the production of bile acids, and some bile acids have been observed to act as promoters of tumorigenesis. This topic is considered in more detail by Reddy (22, 23).

Dietary Fat in Relation to Cancer Mortality in Humans

A major goal of experiments with animal models is to provide information which can be used for prevention or treatment of cancer in humans. It is therefore reassuring that the observed effects of dietary fat on tumorigenesis in animals are supported by the positive correlations between dietary fat and mortality from cancers of the breast and colon in humans.

In the case of breast cancer, the epidemiological data indicate that mortality correlates best with total available dietary fat, less well with animal fat, and not at all with vegetal fat (2). This may appear to conflict with the observation that unsaturated fats promote mammary tumorigenesis more effectively than do saturated fats in animals. However, our experiments with mixtures of polyunsaturated and saturated fat (4, 13) indicated that, once the small requirement for polyunsaturated fat is met, enhancement of tumorigenesis is related to the amount rather than the type of fat in the diet. If the situation is analogous in humans, the data indicate that the required amount of polyunsaturated fat would probably be supplied by the normal diet of any country. It is therefore logical to expect that total available dietary fat should show the best correlation with cancer incidence. In practical terms, this suggests that
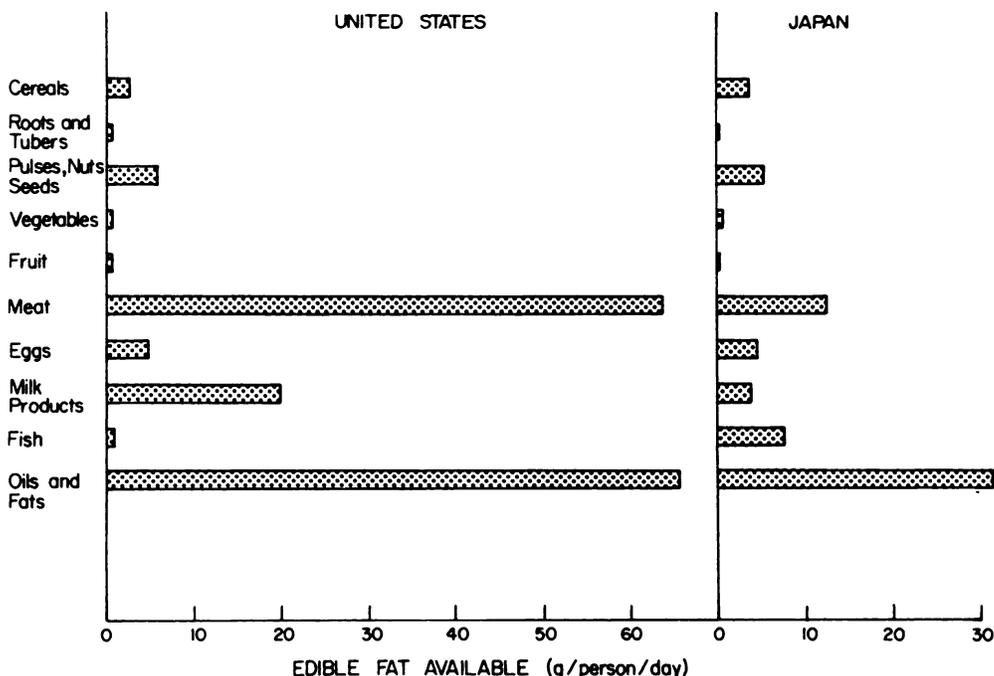

Chart 3. Sources of dietary fat in the United States and Japan. From data collected by the Food and Agriculture Organization of the United Nations (10).

reducting fat intake should decrease breast cancer incidence regardless of whether it is achieved by eliminating fats of animal or vegetal origin.

It can be seen from Chart 3 that the main sources of fat in the American diet are meats, dairy products, and visible fats and oils used as spreads, cooking fats, or salad oils. It is evident that any reduction in dietary fat must involve these dietary components. The much lower availability of fat in the Japanese diet is shown for comparison. The data in Chart 3 are based on averages for 1972 to 1974, and it is of interest to note that the amounts of available fat have increased in both the United States and Japanese diets relative to the corresponding data for 1964 to 1966 (4).

One of the major problems in cancer is the tendency of tumors to metastasize, with recurrence of the disease subsequent to removal of the primary tumor. Since experiments with animals have shown that low-fat diets provide a less favorable environment for the development and growth of tumors, it seems reasonable to think that this may also apply to metastatic growth of tumors. There is some evidence that Japanese women, besides having a lower breast cancer incidence than American women, also show a lower rate of recurrence following surgery (3). It would seem desirable to collect data on recurrence rates following surgery for breast or colon cancer in other countries with varying levels of fat intake. It may also be feasible to carry out controlled clinical trials to test the effect on recurrence of reducing fat intake following surgery. The findings to date at least offer the possibility that diet therapy may be useful in treatment as well as prevention of breast and colon cancer.

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