

Diet and Cancer Risk

Leonard A. Cohen*

Introduction

Despite the fact that over forty years ago Tannenbaum (1942) demonstrated that nutritional factors could influence the development of various types of tumors in laboratory animals, a true appreciation of the importance of nutritional factors in carcinogenesis has only recently come to light (see Natl. Acad. Sc., 1983). Three cancer sites have been shown to be diet-related with a reasonable degree of certainty, namely breast, colon and pancreas. There is some evidence that prostate cancer may also be diet-related but it is largely circumstantial. Of the three nutrition-linked cancers, evidence is strongest and most consistent for breast cancer, particularly with regard to dietary fat (Willett and McMahon, 1984). Hence, in the present report, the primary emphasis will be on breast cancer and its relation to fat intake.

Cancer lies midway along a continuum of diseases which have both nutritional (environmental) and genetic components. On one end of the continuum is a disease such as sickle-cell anemia, which is totally genetic in nature, while at the other end is scurvy, which is totally diet-dependent. However, since no more than 5% to 10% of breast cancers are found in familial aggregates (Knudson, 1977), the environmental component appears to predominate in the development of this kind of cancer.

The importance of the natural history of breast cancer to the question of prevention must be emphasized. There are at least three recognized stages in the development of cancer; initiation, promotion and progression (Sivak, 1979; Slaga et al., 1978). At present, no nutritional factor has been implicated as a causal agent in breast cancer, with the possible exception of cholesterol epoxides (Petraakis et al., 1981). Instead, nutritional factors appear to exert their primary effects as modulators of the carcinogenic process. Hence, they may influence the initiation stage, the promotional phase or possibly even the final stage, metastasis.

The initiation events are considered to be short-term, irreversible, and largely confined to the period around puberty. Promotional events, on the other hand, occur over a five to twenty-year period and are considered to be reversible in nature. Less well understood are the factors involved in the later progression stage (metastasis). Based on the above considerations, the general consensus is that the most effective strategy for breast cancer prevention is to modulate the

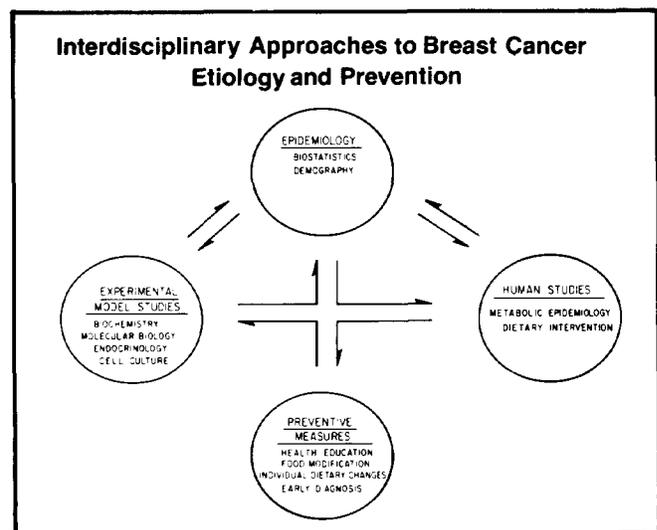
promotion stage since it is both long-term and reversible (Sivak, 1979).

Four dietary factors have been shown to enhance or inhibit the development of mammary cancer, namely, fat, anti-oxidants, the trace element selenium and vitamin A (Natl. Acad. Sc., 1983). Of the four, dietary fat has emerged as the strongest and most consistent determinant of breast cancer risk. Evidence for nutrition's role in cancer comes from four basic sources: epidemiology, laboratory animal studies, "metabolic" studies in small human populations, and large-scale clinical trials (Fig. 1). Each of these approaches has its strengths and limitations and definitive proof of a cause-effect relationship between an environmental factor and a disease entity cannot be obtained from any one approach alone. For example, epidemiological analyses are hampered by the relatively crude dietary intake data presently available. Likewise, studies in laboratory animals are hindered by species and strain-specific differences and by the perennial problem of animal-to-man extrapolation. Moreover, while a positive result from a long-term clinical trial represents the ultimate proof of a specific hypothesis, the long time span, logistic difficulties and costs of such an experiment often preclude its implementation. The interactions between these four approaches are shown schematically in Figure 1.

The Epidemiological Evidence

With regard to the epidemiological evidence, a wide variety of studies including geographic pathology (Carroll, 1975; Draser and Irving, 1973; Gray et al., 1979; Hems, 1978),

Figure 1



*L.A. Cohen, Naylor Dana Institute for Disease Prevention, American Health Foundation, Valhalla, New York 10595

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migrant studies (Buell, 1974), time-trend studies (Hirayama, 1978), retrospective case/control studies (Lubin et al., 1981; Miller et al., 1978; Phillips, 1975), and analyses of special populations such as 7th Day Adventists (Phillips, 1975), support an association between total fat intake and increased risk of breast cancer, particularly in the post-menopausal age groups. A small number of studies do not support such an association (Graham et al., 1982).

In a correlation study involving over 40 countries, Carroll (1975) found a strong positive association between total fat intake (based on FAO food balance sheets) and breast cancer mortality (Figure 2). When fat intake data was broken down into animal and vegetable categories, it was found that while animal fat intake exhibited a strong positive linear correlation with breast cancer mortality rates, vegetable fat intake exhibited no correlation whatsoever. Similar distinctions between animal and vegetable fat consumption and breast cancer rates were reported by Hirayama (1978) in a county by county comparison in Japan, and by Hems (1978) in an international correlation study, but not in a study of vegetarian nuns by Kinlen (1982).

Although most available epidemiological data suggests that excess animal fat and total fat consumption is linked to high frequencies of breast cancer world-wide, this relationship has been challenged by Enig et al. (1978). It was pointed out by Enig in a time-trend study in the U.S. that the intake of fat in the U.S. increased from 125 to 156 gms/day/per capita during the years 1909-1972. Of the 31 gm increase, only 5.8 gms consisted of saturated fats (usually associated with pork and beef consumption) whereas 25.2 gms consisted of polyunsaturated fats (PUFA), the principal component being the essential fatty acid linoleate (C18:2, n-6) (associated solely with vegetable consumption since animals cannot synthesize linoleic acid). During the same time period, there has been a steady increase in breast cancer incidence from <50/100,000 to 70/100,000 (Brian et al., 1980; Silverberg and Holleb, 1975; Conn., 1977). Based on these considerations, Enig claimed that the association between breast cancer and animal fat consumption, derived from global correlations, was of doubtful validity. It was argued that if breast cancer incidence was directly proportional to animal fat intake, per

se, then a decrease in the relative proportion of animal to vegetable fat consumption by the population as a whole should result in an overall decrease in breast cancer incidence, rather than the observed increase. Enig attributed the increasing rates of breast cancer incidence in the U.S. to the high *trans* content of vegetable oils, particularly margarine, rather than to the high linoleic acid content characteristic of vegetable oils. As will be seen later, experimental evidence in animal models supports the latter rather than the former possibility. Considerable controversy surrounds the Enig hypothesis at the present time, particularly regarding methodological issues (Applewhite, 1979; Enig et al., 1979).

As the above discussion indicates, retrospective epidemiological studies have provided valuable clues to the etiology of breast cancer. However, such studies can at best provide associations, they cannot demonstrate causation. Animal model studies, on the other hand, provide a means to test, in a prospective manner, hypotheses arrived at through epidemiological analysis. Fortunately, a wide variety of animal models are available for such studies and these have been exploited fully over the past decade.

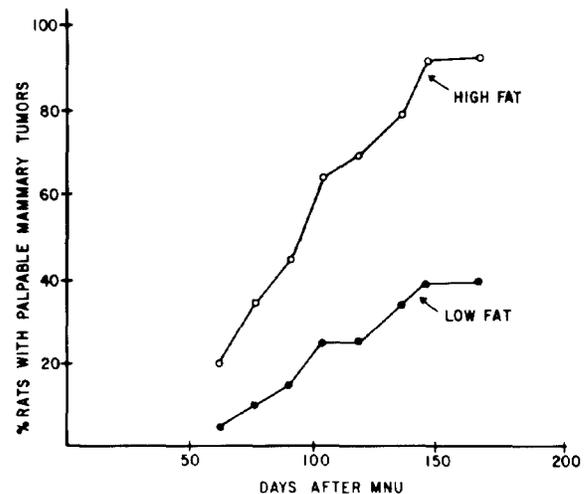
Evidence from Animal Model Studies

By far the most definitive evidence for a connection between dietary fat and breast cancer development comes from laboratory animal studies. Literally dozens of studies have been published showing that high-fat diets (40% of total calories as fat) stimulate mammary tumor development compared to low-fat diets (10% of calories as fat), and that the primary effect of fat is exerted on the promotion phase. A typical experimental result can be seen in Figure 3.

Studies of animal models have shown [1] that the fat effect is independent of obesity (Carroll and Khor, 1970; Chan et al., 1977; Waxler et al., 1979); [2] that the triglyceride content of total fat intake (as opposed to cholesterol, phospholipid and nonsaponifiables) is responsible for the fat

Figure 3

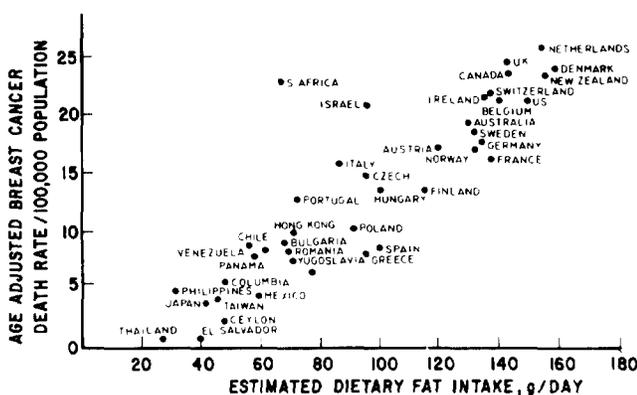
Cumulative Palpable Mammary Tumor Incidence in F344 Rats Treated with N-Nitrosomethylurea (nmu) on Day 55 and then Fed HF (20% Lard) and LF (5% Lard) Diets



(Chan, P.C. et al, JNCI 59:1279-1983, 1977)

Figure 2

Positive Correlation Between Per Capita Consumption of Dietary Fat and Adjusted Mortality From Breast Cancer



(Carroll, K.K., Cancer Res. 35:3374-83, 1975)

Table 1. Influence at Various Dietary Fat Total Mammary Tumor Incidence

Fat quantity	Fat type			
	Safflower oil	Corn oil	Olive oil	Coconut oil
23%	87% ^{a,b} (26/30)	87% (26/30)	63% (19/30)	47% (14/30)
5%	63% (19/30)	66% (20/30)	60% (18/30)	

^aTotal tumor incidence (Fibroadenoma + Adenocarcinoma)

^bStatistical comparisons:

- 1) Corn 23 vs Corn 5 p< .062 Fisher's Exact Test (1 tail)
- 2) Saff 23 vs Saff 5 p< .03 Fisher's Exact Test (1 tail)
- 3) Olive 23 vs Olive 5 p<0.5 Fisher's Exact Test (1 tail)
- 4) Saff or Corn 23 vs Coco 23 p<0.001 Fisher's Exact Test (1 tail)
- 5) Saff or Corn 23 vs Olive 23 p<0.035 Fisher's Exact Test (1 tail)
- 6) Corn 23 vs Saff 23 p<0.64 Fisher's Exact Test (1 tail)

effect (Cohen and Chan, 1982; Tannenbaum, 1942), and [3] linoleic acid plays a special role in stimulating mammary tumor development (Abraham and Hillyard, 1983; Hopkins and West, 1977; Ip et al., 1985; Kidwell et al., 1978; King et al., 1979).

Perhaps the most important contribution of these experimental studies is that they have demonstrated clearly the inadequacy of categories such as "animal" and "vegetable" fats. For example, coconut oil which is more saturated than any known animal fat has no tumor-promoting ability in any animal model yet studied (Carroll and Khor, 1970; Cohen and Thompson, 1985). It is now apparent that a more meaningful way to categorize fats is in terms of [1] the chain length (medium, long); [2] degree of saturation (monoene, diene); [3] degree of isomerisation (*cis*, *trans*), of their component acyl groups.

There is also a growing awareness of the fact that different types of fatty acids are handled differently by the body. For example, medium chain fatty acids (C8:0 and C10:0) are absorbed and transported in the body in a totally different way than long chain fatty acids. Due to their chain length, medium chain triglycerides (MCT) are absorbed via the hepatic portal systems, while long chain fats are absorbed via the lymphatic system (Bach and Babayan, 1982). Because of this, MCT are rapidly oxidized to provide energy and are rarely stored in fat depots. Moreover, diets rich in medium chain triglycerides do not promote mammary tumorigenesis (Cohen et al., 1984), most likely because they are absorbed and transported more like carbohydrate than a fat.

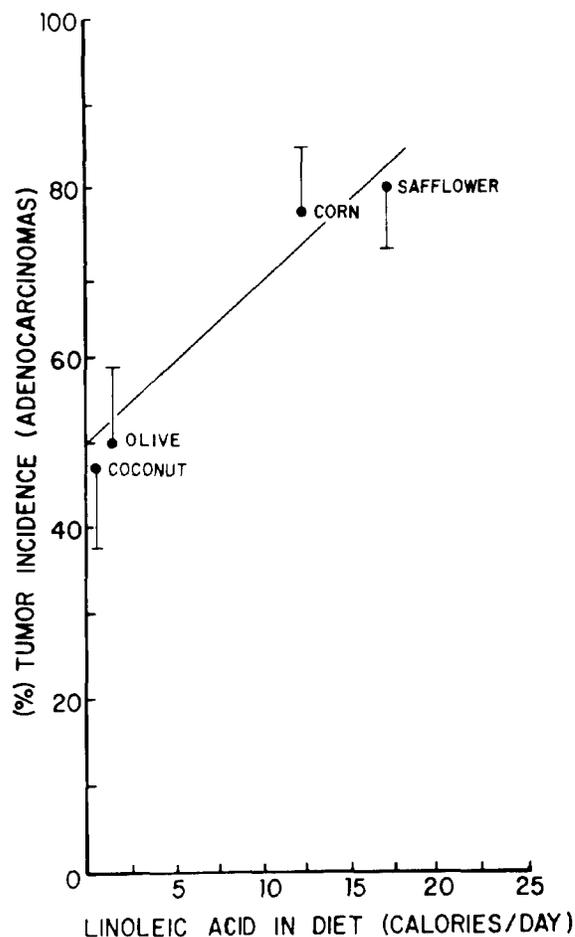
Several years ago, our laboratory launched a series of investigations into the role of dietary LA in mammary tumor promotion. Using the N-nitrosomethylurea mammary tumor model, we analyzed the influence of 4 different seed oils, safflower, corn, olive and coconut, varying widely in their LA

content (87%, 55%, 8%, 0.8%, respectively), on mammary tumor development. We also analyzed the fatty acyl group composition of the serum, and tumor lipids of each experimental group in an attempt to gain insight into mechanisms (Cohen and Thompson, 1985).

As seen in Table 1, animals fed the safflower and corn oil diets exhibited greater tumor yields and shorter latent periods than their LF counterparts, while animals fed HF or LF olive oil showed no differences in either parameter. Comparison of the 4 HF groups revealed a significant negative trend of the order safflower>corn>olive>coconut. When dietary LA was plotted as a function of tumor yield, a significant positive correlation was found among the four HF groups, but not the three LF groups (Figure 4). These results suggest that dietary LA functions as a rate-limiting factor in breast cancer under HF but not LF conditions.

The mechanism by which LA exerts its effects is uncertain, but it appears to be related to its role as a prostaglandin (PG) precursor (Horrobin, 1983; Lands et al., 1977). A hy-

Figure 4

Relationship Between Linoleic Acid Intake and Mammary Tumor Incidence in Rats Fed 4 Different Types of HF Diets

(Cohen and Thompson, Fed. Proc. 43:614 1985)

Table 2. Summary: Distribution of Linoleic Acid in Diet, Serum and Tumor Lipids, and Tumor PGs by Dietary Group

Experimental Group	LA in Diet	LA in Serum	LA in Tumor		Tumor PG	
			Neutral Lipid	Phospholipid	PGE ₂	PGF ₂
23% Safflower	82 ^a	36 ^a (±2.7)	61 (±5)	5 (±2.9)	38 ^{b,c} (±45)	76 (±30)
23% Corn	56	29 (±1.7)	43 (±6.5)	11 (±14)	23 (±31)	130 (±102)
23% Olive	7	6 (±0.5)	5.3 (±2.2)	2.6 (±1.8)	5 (±5)	64 (±6)
23% Coconut	0.8	6 (±0.4)	3.2 (±0.8)	1.4 (±0.3)	3 —	27 —

^a= Amounts expressed as mean percentages of total amount of fatty acids present (±SD)

^b= ngs PG/gm wet weight tissue (±SD)

^c= Number of samples assayed: Safflower (n=6), Corn (n=7), Olive (n=3), Coconut (n=2)

Table 3. Summary: Distribution of Arachidonic Acid in Diet, Serum and Tumor Lipids, and Tumor PGs by Dietary Group

Experimental Group	LA in Diet	AA in Serum	AA in Tumor		Tumor PG	
			Neutral Lipid	Phospholipid	PGE ₂	PGF ₂
23% Safflower	82 ^a	21 ^a (±3.1)	1.8 (±0.9)	7.3 (±4.4)	38 ^{b,c} (±45)	76 (±30)
23% Corn	56	24 (±2.2)	2.3 (±2.2)	17 (±9)	23 (±31)	130 (±102)
23% Olive	7	17 (±1.3)	0.7 (±0.3)	8.7 (±4.9)	5 (±5)	64 (±6)
23% Coconut	0.8	12 (±2.1)	4.4 (±2.5)	16 (±8.2)	3 —	27 —

^a=% of total acids (±SD)

^b= ngs PG/gm wet weight tissue (±SD)

^c= Number of samples assayed: Safflower (n=6), Corn (n=7), Olive (n=3), Coconut (n=2)

pothesis based on a PG precursor role for LA is particularly attractive in light of a number of clinical and experimental studies, suggesting that breast cancers are associated with aberrant PGE₂ production¹ (Karmali, 1980). In order to test this hypothesis, we analyzed both serum and tumor LA content as well as the content of the arachidonic acid which serves as the immediate substrate for synthesis of the 2-series PGs (PGE₂, PGF₂α). In addition, tumor PGE₂ and PGF₂α levels were assayed by RIA techniques.

It was found that total serum lipid and tumor neutral lipid fatty acid profiles closely reflected that of the diet, whereas tumor phospholipid profiles appeared resistant to diet-induced changes (Tables 2 and 3). Tumor PGE₂ levels were

elevated in animals fed diets rich in LA (safflower and corn) compared to those fed diets poor in LA (olive and coconut). While these studies suggest an association between elevated dietary LA intake, increased PGE₂ levels and increased incidence of mammary tumors, the precise sequence of events remains to be elucidated. In particular it remains to be determined which, if any, phospholipid AA pools serve as precursors for PG synthesis in mammary tumors, and whether these pools are influenced by dietary LA.

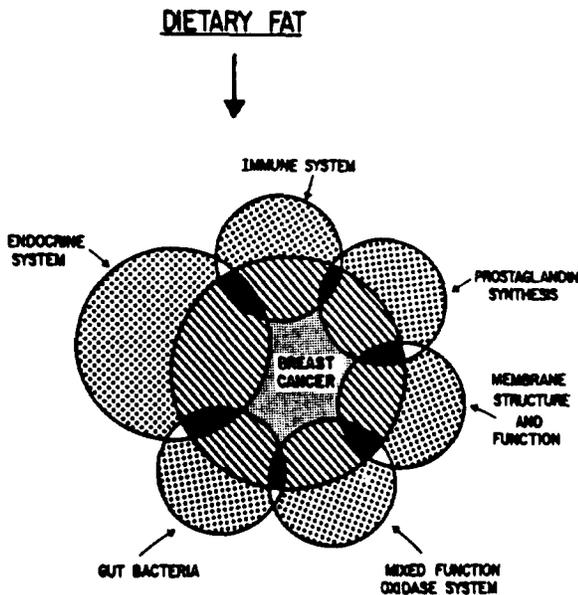
These and other studies (Carter et al., 1983; Kollmorgen et al., 1983; Rao and Abraham, 1977) have focused attention on PGs as possible mediators of the HF effect. However, other mechanisms may also be involved. As seen in Figure 5, diet-induced alterations in the endocrine system, membrane structure and function, and in gut flora metabolism could also contribute to the fat effect (Cohen, 1981).

As noted in Figure 1, one of the crucial aspects of the research effort in nutritional carcinogenesis is feedback between and across disciplines. The results of our olive oil study represent a good example of how evidence gained in

¹The mechanism of PG action in cancer is under debate. In vitro studies indicate that high PGE₂ levels may inhibit lymphocyte and macrophage reactions and thereby serve as an immunosuppressant, permitting tumors to grow in an unrestrained fashion (Cameron and O'Brien, 1982; Goodwin et al., 1980; Kunkel et al., 1981; Plescia et al., 1975).

Figure 5

Biological Mechanisms by which Dietary Fat May Exert Its Stimulatory Effects on Breast Cancer



Overlapping circles (solid colors) indicate that no single mechanism is mutually exclusive of any other mechanism. For example, an effect exerted via the immune system could also involve prostaglandin biosynthesis since immune reactions may be mediated by prostaglandins. Likewise, fat-induced changes in membrane structure could alter the activity of the membrane-bound mixed function oxidase system.

(Cohen, L.A., *Cancer Res.* 41:3803, 1981)

the laboratory can shed light on another area, in this case, epidemiology. As noted earlier, global correlations indicated an absence of any association between fat of vegetable origin and breast cancer mortality rates. In view of the experimental evidence suggesting a special role for LA (which cannot be synthesized *de novo* by animals and must be supplied in the diet from plant sources), these epidemiological data appear paradoxical. However, a partial resolution of this paradox emerges from a closer examination of Carroll's data. Two countries, namely Greece and Spain, stand off from the rest as outliers. These countries exhibit a far lower mortality rate than would be expected based on their vegetable fat consumption. For example, vegetable fat "disappearance" was approximately 60 gm/day/person in Spain, Greece, the U.S.A. and the Netherlands, yet the mortality rates were 8/100,000 in Greece and Spain and 24-26/100,000 in the U.S. and the Netherlands (see "Cancer Mortality . . .," 1981). Since olive oil represents the major source of fat in the diet in Greece and Spain (Christakis et al., 1980), these results imply that olive oil consumption confers a protective effect in these countries with regard to breast

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cancer. Since there is a trend of these countries away from dependence on olive oil, it will be important to monitor changing trends in breast cancer incidence in both countries during the next decade.

Future Studies

While it is generally accepted that an overall decrease in fat intake in the western industrialized countries would help to reduce the prevailing high incidence rates, it is not certain exactly how much fat intake should be reduced. Some suggest a reduction from the present 40% of calories to 30% of calories (see Natl. Acad. Sci., 1983). Others suggest lowering it to 20% to 25% of calories (Wynder and Cohen, 1982). Whatever the reduction, there are some lingering doubts whether the majority of individuals could adhere to such relatively ascetic eating habits. For this reason, there is a need to seek out fats which lack tumor-promoting effects. Examples of these, such as medium chain triglycerides and olive oil, are gradually appearing. The highly unsaturated long chain fatty acids of the n-3 family, namely eicosapentaenoic and docosahexaenoic acid (C20:5, n-3; C22:6, n-3) represent another promising new possibility. These fatty acids are prominent in the marine food chain and comprise an important part of the Eskimo diet (Bang et al., 1976). Eskimos are unique in that they consume one of the fattiest diets of any population (Draper, 1977) and yet have low levels of breast cancer (Nielsen and Hansen, 1980). It has been proposed that marine oils confer protection because the n-3 family competes effectively with the n-6 family for common enzymes involved in the conversion of LA to PGs (Culp et al., 1979). However, this mechanism remains to be definitively established in mammary tumor models (Jurkowski and Cave, 1985; Karmali et al., 1984).

Conclusion

Information in support of dietary fat as an important determinant of breast cancer risk is reasonably strong and consistent with regard to the epidemiological evidence. Animal model studies are highly consistent with a fat hypothesis, particularly with regard to the promotional stage of mammary carcinogenesis. Evidence drawn largely from animal models, but implicit in the epidemiological data, indicates that the type of fat, i.e., chain length, degree of saturation, and position of double bonds is an important determinant of the fat effect. Knowledge of mechanisms remains in an embryonic stage. Prostaglandins, which are biologically active derivatives of dietary linoleic acid, are one of the most promising routes for further research. Dietary recommendations for both primary and secondary prevention of breast cancer, which presently involve reduction of total fat calories from 40% to 30%-20% of calories, may have to be revised in light of new data indicating that certain fats such as marine oils, olive oil and medium chain triglycerides may lack tumor-enhancing effects.

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