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Publication Date

1998

DOI

10.1111/j.1753-4887.1998.tb01651.x

Peer reviewed

Dietary Fat, Breast Cancer, and Nonspecific Immunity

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Introduction

Numerous experimental and epidemiologic studies provide compelling evidence linking dietary fat with increased risk of cancer at select sites, notably breast, colon, and prostate. There is an extensive amount of experimental evidence showing that the degree of saturation and concentration of dietary fat can influence breast tumorigenesis. In general, studies in rodents showed that high levels of dietary fat led to an increased incidence of breast tumors compared with animals fed a moderate or low level of dietary fat. Moreover, linoleic acid may be the most effective fatty acid in the promotion of mammary tumorigenesis. In contrast, some epidemiologic studies have reported a positive correlation between breast cancer and dietary fat intake, while a few have reported that no correlation existed. Unfortunately, data on humans do not permit clear distinction between the effects of different types of fat, and the mechanisms by which dietary fat can promote tumorigenesis at select sites remain to be determined.

Although it has been reported for over 20 years that lipids can affect immune response, limited attention has been focused on this area. Rather, the interactions of lipids, particularly those from dietary sources, and the relationship of lipids to coronary heart disease have received much of the scientific attention. While numerous studies have used *in vitro* models for assessment of lipid effects on immunity, few have used *in vivo* models. Because macrophages can play a pivotal role in both specific and nonspecific immunity as well as potentially kill tumor cells, we have investigated how dietary fats may alter tumoricidal activity and some of the possible mechanisms by which that occurs. Thus, the purpose of this paper will be to review some of the experimental and epidemiologic studies that have focused on dietary fat and breast cancer. We will address how dietary fats could alter macrophage tumoricidal functions and the possible mechanisms by which that alteration occurs, notably alterations in signal transduction. We hope to demonstrate that dietary fat can be associated with alterations of macrophage functions.

Dietary Fat Influences on Human Breast Cancer

Evidence for a relationship between dietary fat and human breast cancer comes from epidemiologic studies, which often show conflicting results. Although suggestive of a relationship, epidemiologic studies are potentially confounded by many suspected breast cancer risk factors. Ecologic or international correlations are strong for a positive relationship between increased dietary fat intake and increased risk (Carroll and Khor 1975, Armstrong and Doll 1975). Likewise, studies of populations migrating from a low-incidence to a high-incidence country acquire breast cancer at rates similar to the population in their new home country within a few generations (Ziegler et al. 1993). Other types of human studies include case-control and cohort studies in which the focus for data analysis has been on total dietary fat intake (Willett 1995). Case-control studies generally have shown little effect of dietary fat on breast cancer. Fish consumption may be weakly associated with risk, but generally levels of n-3 fatty acid consumption are so low that comparisons are difficult to make. Although no significant association between total fat intake and risk of breast cancer has been generally reported for case-control studies, meta-analysis has indicated a positive association for total fat intake and breast cancer in postmenopausal women (Howe et al. 1990). In contrast, cohort studies indicate few associations between dietary fat and breast cancer risk. For example, in a pooled analysis of all large prospective studies, there was no specific relationship between total fat intake and breast cancer risk (Hunter et al. 1996). There are several drawbacks that limit this interpretation of these studies, which include the generally narrow range of energy derived from dietary fat (Hunter et al. 1996, Hunter and Willett 1993). More importantly, most studies focus on correlations between dietary fat intake and breast cancer incidence in women *over* 40 years of age. Because dietary fat may influence the development of breast tissue, determining dietary fat consumption patterns in adolescence, when the breast is developing, and the eventual

incidence of cancer may be the most relevant and informative study.

Epidemiologic studies have attempted to determine whether correlations exist between specific fats and breast cancer. Although *trans* fatty acid intake has been suggested to have a possible relationship to breast cancer in the few studies in which it was evaluated, no significant association was seen (London et al. 1993). In contrast, several recent studies have demonstrated that the consumption of olive oil, a mainly monounsaturated fat, was inversely related to breast cancer risk (London et al. 1993, Martin-Moreno et al. 1994, Trichopoulou et al. 1995). With respect to polyunsaturated fat and breast cancer risk, investigators reported no specific relationship between polyunsaturated fat consumption and breast cancer risk in postmenopausal women from a pooled analysis of 12 case-control studies (Howe et al. 1990). However, those studies, like many others, failed to control for the intake of other types of fat when assessing the influence of polyunsaturated fat. Although fish oil has not been directly examined, fish consumption has been used as a surrogate for n-3 fatty acids. It seems to have a weak association with risk (Kaizer et al. 1989, Hursting et al. 1990, Guo et al. 1994). However, in some countries, the consumption of n-3 fatty acids from fish is relatively small compared with total polyunsaturated fat intake. Studies of fish oil supplementation may yield different results and potentially important findings. Nevertheless, large-scale trials with an appropriate population may help to resolve whether specific relationships exist between dietary fat and the development of breast cancer.

Influence of Dietary Fat on Experimental Breast Tumorigenesis

Fatty acids added to mammary tumor cells in culture may have an influence on their proliferation. For example, addition of linoleic acid (18:2n-6) to cultures of a rat mammary carcinoma stimulated proliferation. Oleic acid (18:1n-9) had even a greater stimulatory effect, whereas stearic (18:0) produced an inhibition (Wicha et al. 1979). Similar effects were produced with an estrogen-independent breast cancer cell line (Rose and Connolly 1989). Interestingly, three human and three mouse estrogen-independent cell lines had their growth stimulated by 18:2n-6, whereas estrogen-dependent cell lines were not affected by 18:2n-6 in vitro (Rose and Connolly 1990, Buckman et al. 1991, Rose et al. 1994a, Grammatikos et al. 1994).

For over 50 years, numerous investigators have demonstrated that high-fat diets can enhance the development of mammary tumors in rodents (Tannenbaum 1942). It has been well established that dietary fat influences the incidence, growth, and spread of mammary tumors in laboratory animals (Cohen 1986, Rogers and Lee 1986, Erickson and Hubbard 1990, Cave 1996). When a 20% fat diet was provided as corn or sunflower oil, which are rich in 18:2n-

6, there was enhanced development of mammary tumors after treatment with DMBA. In contrast, an equivalent amount of predominantly saturated fat, such as butter, coconut oil, or tallow, resulted in no increased tumorigenesis. Because the polyunsaturated vegetable oils used in those studies of dietary fat and mammary tumorigenesis contained high levels of the essential fatty acid, 18:2n-6, several studies have focused specifically on the effect of 18:2n-6 (Hopkins and Carroll 1979, Ip et al. 1985). Carcinogen-induced mammary tumorigenesis in rats increased proportionately when the level of 18:2n-6 in the diets increased from 0.5% (wt/wt) to 4%. These results suggest that a threshold level exists for dietary fat and 18:2n-6; further increases in the levels of these nutrients do not result in a parallel increase in mammary tumor development.

The relationship of specific dietary fatty acids and experimental mammary tumorigenesis have been studied by a number of investigators. One such group is the *trans* fatty acids, which may be formed during partial hydrogenation of vegetable oils. During hydrogenation, the double bonds not only rearrange, creating a geometric isomer, but the position of the double bonds can also be shifted. In studies in which the proper controls have been used, it has been shown that *trans* fatty acids behave similar to *cis* fatty acids with respect to tumor development. Studies that have used hydrogenated oils only without appropriate controls matched for positional and geometric isomers have reported a potential effect of the fatty acid (Selenskas et al. 1984, Erickson et al. 1984). The influence of oleic acid (18:1n-9) on breast tumorigenesis has been studied by feeding either olive oil or high 18:1n-9 safflower oil. Generally, those studies have provided inconsistent results (Welsch 1992). One of the problems with those studies is that olive oil can vary greatly in its content of 18:2n-6, which could explain the varied results observed. However, available evidence does not support the hypothesis that 18:1n-9 may inhibit tumorigenesis.

Polyunsaturated fats from fish oil, such as eicosapentaenoic (20:5n-3) and docosahexaenoic (22:6n-3), have been shown to suppress mammary tumor growth. The influence of another n-3 fatty acid, linolenic (18:3n-3), on tumorigenesis has also been studied. Generally, the protective effect observed for fish oils has been demonstrated with carcinogen-induced, transplantable, and spontaneous tumors (Cave 1991, Welsch 1995). Although differential results have been observed, those may be attributed to several factors: differences in dietary design; the use of different fish oils (some which tend to be more palatable than others); antioxidants in the diet; the concentration of 18:2n-6 in the diet; and potential interaction with other fatty acid components, notably the n-3 fatty acids. Because of potential peroxidation, the amount and types of antioxidants in the diet may be particularly important. Work by some investigators (Rose et al. 1994b) also

demonstrates that the growth and metastasis of various tumors are effected by the ratio of n-3 to n-6 polyunsaturated fatty acids. In addition, those dietary changes can influence the tumor fatty acid composition as well as the amount and type of eicosanoid metabolites produced. High dietary concentrations of n-3 fatty acids inhibit the production of PGE₂. Analysis of data from many animal experiments also indicates that total caloric intake is an important determinant of tumorigenesis (Albanes 1987). However, body weight may be a more sensitive indicator for this effect than calorie intake alone. Although the mechanisms by which body weight influences mammary tumorigenesis are not known, it is important to control for caloric intake in studies that focus on dietary fat.

Mechanisms by Which Dietary Fat May Alter Tumorigenesis

Although the exact mechanisms by which diet may alter mammary tumorigenesis are not agreed upon, there is experimental evidence to support several possibilities. Some of those include: alteration in specific and nonspecific immune response; alteration of eicosanoid production; alteration in energy metabolism; modulation in hormones secreted; as well as several others (Table 1). Normal endocrine function may depend upon fatty acid levels; however, the nature of the interaction still remains controversial. Although some studies have demonstrated that low levels of dietary fat were associated with reduced hormone levels, other studies using unanesthetized rats have shown no change in plasma estradiol, progesterone, or prolactin after feeding high-fat diets (Wetsel et al. 1984). Even without altered hormone secretion or metabolism, enhanced activity may result from changes in receptor binding or altered molecular signaling. Like other polypeptide hormones, mammotrophic hormones bind to receptor sites located in the cell membrane, which could be influenced by the membrane fatty acid composition. For example, a decrease in prolactin binding as well as reduced mammary tumor cell growth were observed after a large reduction in polyunsaturated fatty acid intake (Cave and Erickson-Lucas 1982, Cave and Jurkowski 1984). In contrast, addition of only 3% corn oil reversed that effect.

We have focused on alteration of nonspecific immune function because it has been demonstrated that dietary

fat can alter select components of an immune response (Erickson 1986, Erickson et al. 1992). Macrophages may play a very important role in maintaining homeostasis. For example, macrophages have phagocytic capability that allows them to remove debris and serum proteins. In the process, they can defend against microbial invasion, kill tumor cells, and respond to injury and inflammation. Many of those functions are not constitutively expressed, but are induced in response to a number of exogenous or endogenous signals. That process of macrophage activation may be in response to exposure to various signals. An understanding of regulation of macrophages and their many functions may depend upon an understanding of substrate utilization and autoregulatory products. Dietary fatty acids are an example of an important substrate whose metabolism results in the production of important regulatory compounds. Because macrophages can play a pivotal role in both specific and nonspecific immunity and can potentially kill tumor cells, we will focus on how dietary fats alter tumoricidal activity and then two possible mechanisms by which that can occur.

Dietary Fat Alteration of Macrophage Tumoricidal Activation

Dietary fatty acids, particularly those n-3 fatty acids associated with marine fish oils, may be very effective in selectively altering macrophage functions. To assess how oils rich in n-3 fatty acids compared to oils rich in n-6 fatty acids could differentially alter macrophage tumoricidal capacity, C57BL/6 mice were fed isocaloric diets from menhaden fish oil (MFO) or safflower oil (SAF). Those dietary fatty acids were incorporated into macrophages and selectively altered the fatty acyl composition of the lipids. After activation with 100 ng/mL lipopolysaccharide (LPS) for 24 hours, macrophages from mice fed SAF killed fewer tumor cells than macrophages from animals fed MFO (Somers et al. 1989). Because the anti-inflammatory effects of dietary MFO may be due to alteration of eicosanoid metabolites, macrophage tumoricidal activity was assessed after addition of the prostaglandin (PG) inhibitor indomethacin. Addition of the inhibitor resulted in enhanced levels of tumor cell kill by macrophages from mice fed SAF and no alteration in cytolytic capacity of macrophages from mice fed MFO (Figure 1). Changing the diet may also alter the eicosanoid metabolites produced. Macrophages from mice fed SAF produced three times more PGE₂ than macrophages from mice fed MFO. These results indicate that dietary fat may alter the capacity of macrophages to kill tumor cells, possibly by a mechanism that involves prostaglandins (Somers et al. 1989).

Macrophages may kill tumor cells using a number of various mediators, including tumor necrosis factor- α (TNF- α), reactive oxygen intermediates, reactive nitrogen intermediates, neutral proteases, as well as several others. Although several of these mediators may be influenced

Table 1. Possible Means By Which Dietary Fat Could Alter Mammary Tumor Growth

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- Alteration in specific or nonspecific immune response.
 - Change in the type and amount of eicosanoid metabolite produced.
 - Alteration in lipid-based inflammatory mediators.
 - Production of peroxides.
 - Alteration in mammogenic hormones.
 - Modulation of gene expression.
 - Alteration in energy metabolism.
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Figure 1. Dietary fat alteration of macrophage tumoricidal activity. Macrophages from mice fed safflower oil (SAF) or menhaden fish oil (MFO) were incubated with 100 ng/mL LPS with or without 10^{-6} M indomethacin (INDO) for 24 hours. Cytolysis was measured 16 hours later.

by dietary fat, we will focus on TNF- α , an important inflammatory mediator. Induction of TNF- α synthesis can have wide-ranging effects on host physiology and many specific cell types. Although regulation of TNF- α can occur at multiple levels, production may be inhibited by PGE₂. However, the mechanisms by which fish oil-containing diets alter TNF- α production remains unknown. To determine how dietary fatty acids may differentially regulate TNF- α synthesis, mice were fed either MFO or SAF. Macrophages from both groups produced relatively large quantities of TNF- α after 8 hours of LPS stimulation while mice fed MFO produced more TNF- α after 24 hours than macrophages from mice fed SAF (Somers and Erickson 1994). The differential levels of TNF- α secreted by macrophages from mice fed MFO were not due to continuous production of bioactive TNF- α , and production was completed by 8 hours after LPS treatment (Figure 2). Lack of TNF- α secretion after 8 hours and very limited TNF- α transcription after 24 hours indicate that suppression was more complex than termination of transcription.

Macrophages have receptors on their surface that can bind TNF- α . Macrophages from mice fed SAF were able to remove secreted TNF- α , whereas macrophages from mice fed MFO were unable to do the same. To examine whether PGE₂ may be associated with the removal of the secreted TNF- α , macrophages from mice fed either SAF or MFO were treated with LPS, indomethacin (to block endogenous PGE₂ production), and exogenous PGE₂ (to suppress TNF- α production). The amount of PGE₂ required to inhibit 50% of the TNF- α secretion at 8 hours was the

Figure 2. Dietary fat modulation of TNF- α production. TNF- α bioactivity produced after incubation with LPS for 8 or 24 hours or from 8–24 hours was determined.

same. However, after 24 hours, macrophages from mice fed SAF required one log less PGE₂ than macrophages from those fed MFO to suppress 50% of the TNF- α . Commensurate with the alteration in TNF- α production was an alteration in the number of high affinity PGE₂ receptors. A concentration of PGE₂ that did not alter synthesis of TNF- α appeared to influence the clearance of secreted, soluble TNF- α .

Changes In Lipid-based Inflammatory Mediators

Platelet-activating factor (PAF) is an inflammatory mediator that may be synthesized by a variety of cells including macrophages. PAF has the ability to prolong inflammation by stimulating the production of cytokines such as TNF- α . Moreover, PAF has the ability to stimulate the production of eicosanoids. Unlike TNF- α , physiologic concentrations of PAF have not been shown to be cytotoxic to tumor cells. Thus, a possible role of PAF may be to initiate or stimulate tumoricidal activity. PAF alone was not very effective at stimulating macrophage cytolysis of tumor cells, which are not sensitive to TNF- α . However, when interferon- γ (IFN- γ) was added in conjunction with PAF, macrophage cytolytic activity was significantly increased (Howard and Erickson 1995).

Because several mediators associated with inflammation such as LPS, PGE₂, and TNF- α have been shown to regulate MHC class II expression, Ia in mice, we sought to determine whether PAF would have a similar effect. Ia expression was optimal following a 3-hour exposure to PAF. When added during incubation with PAF, PGE₂ inhibited macrophage Ia expression at concentrations as low as 10^{-9} M. Since PAF could induce Ia expression in macrophages and since PAF can alter PGE₂ production, the in-

Figure 3. Effect of dietary fat on PAF-induced macrophage Ia expression.

fluence of dietary n-3 fatty acids on PAF-induced Ia expression was assessed. PAF induced Ia expression in macrophages of mice fed MFO more than in macrophages of mice fed SAF (Figure 3).

An increase of cytosolic Ca^{2+} [Ca^{2+}]_i and protein kinase C activation are early intracellular events in macrophages, associated with the PAF-signaling pathway (Chao and Olson 1993). To assess whether the signal transduction pathway was altered by dietary fat, we measured PAF-stimulated increase of [Ca^{2+}]_i in macrophages from mice fed either SAF or MFO containing diets. Macrophages from MFO-fed mice had a much greater response after treatment with PAF, than macrophages from SAF-fed mice (Figure 4). Similar to the hyperresponsiveness to PAF of macrophages from MFO-fed mice, macrophages treated in vitro with eicosapentaenoic acid (20:5n-3) or docosahexaenoic acid (22:6n-3) showed a greater increase in [Ca^{2+}]_i than 18:2n-6-treated macrophages. Collectively, these results show that the in vitro treatment of macrophages with n-3 fatty acids, which are most commonly found in MFO, enhanced PAF signaling similarly to macrophages from mice fed MFO-rich diets (Chakrabarti et al. 1997).

There may be several possible mechanisms for the hyperresponsiveness of macrophages from MFO-fed mice to PAF. First, the effect of MFO may be related to suppression of PGE_2 production. Endogenous PAF and possibly other eicosanoids may have a negative effect on the PAF-signaling pathway, and the reduced PG biosynthesis by macrophages from mice fed MFO may have resulted in hyperresponsiveness to PAF. However, that was probably not a mechanism because maximum [Ca^{2+}]_i rise occurred within 10–20 seconds after PAF stimulation, and

Figure 4. PAF-stimulated [Ca^{2+}]_i increase in macrophages from mice fed the experimental diets. Macrophages were loaded with FURA-2, PAF added (arrow) and changes in [Ca^{2+}]_i measured.

minutes to hours are required after PAF stimulation for sufficient PGE_2 to accumulate to suppress macrophage function. In addition, blocking cyclooxygenase metabolism by indomethacin did not alter [Ca^{2+}]_i in macrophages of SAF or MFO-fed mice. A second possibility is that dietary n-3 fatty acids have altered PAF receptor number, affinity, or both, resulting in the hyperresponsiveness of macrophages from MFO mice to PAF. Macrophages from all diet groups showed a similar pattern of specific saturable binding of [^3H]-PAF. Thus, the PAF receptor number and affinities were not altered by dietary n-3 fatty acids. A third possibility is that dietary n-3 fatty acids increased the signal transducing activity through the PAF receptor without altering receptor affinity or number. Binding of PAF to its specific receptor is associated with signaling

across the membrane through the G protein to the effector, phospholipase C (PLC) (Chao and Olson 1993). Several studies have shown that alteration of the chemical properties of the membrane environment of the substrate phosphatidylinositol 4,5-bisphosphate can modulate the catalytic properties of PLC. Mastoparan can activate G-protein linked PLC, without the involvement of the G-protein linked receptor. If PLC in macrophage from mice fed MFO have a higher potential, then mastoparan should cause a higher Ca^{2+} mobilization in MFO macrophages than in SAF macrophages. Stimulation of macrophages with a mastoparan analogue resulted in higher Ca^{2+} responses in MFO than SAF macrophages. In addition, the activity of PLC in macrophages of mice fed MFO was greater than that of macrophages of mice fed SAF (Figure 5) (Chakrabarti et al. 1997).

These results have shown that PAF can play a modulatory role in the activation for $\text{TNF-}\alpha$ as well as non $\text{TNF-}\alpha$ -mediated tumoricidal activity of macrophages (Howard and Erickson 1995, Howard and Erickson 1996). PAF, along with its role as a potent proinflammatory mediator, was also capable of inducing a macrophage function associated with specific immunity, Ia expression, which was altered by diets rich in n-3 fatty acids such as fish oil. Dietary n-3 fatty acids enhanced the PAF-signaling pathway by increasing the signal transduction through the PAF receptor in macrophages. The mechanism by which n-3 fatty acids increase the signal transduction capacity of the PAF receptor is likely to involve an increase in the potential of PLC due to changes in the phospholipid composition of the plasmalemma.

Conclusion

As we have shown, experimental evidence shows that the saturation and concentration of dietary fat can influence breast tumor growth and metastasis. In contrast, epidemiologic studies have reported either no or a positive correlation between breast cancer and dietary fat intake. Although the exact mechanisms by which dietary fat promotes mammary tumorigenesis are not known, we have focused on alteration in immunity. Specifically, we have investigated how dietary fats alter tumoricidal activity and possible mechanisms by which that can occur. Dietary fish oil significantly decreased the ability of activated macrophages to kill tumor targets compared with macrophages from mice fed safflower oil. Mice fed the two experimental diets also produced different amounts of $\text{TNF-}\alpha$, which was associated with altered production and response to PGE_2 . Dietary fat also differentially influenced specific immunity, such as the expression of MHC class II antigens. Associated with changes in dietary fat and altered macrophage function were changes in signal transduction. Macrophages from mice fed fish oil had a greater increase in intracellular calcium after treatment with PAF than macrophages from mice fed safflower oil. Those dif-

Figure 5. Effects of dietary fat on PAF-stimulated PLC activity.

ferences were related to an alteration in the PAF signaling pathway by increased phospholipase C activity without altered PAF receptor number and affinity. Thus, dietary fat may alter the capacity of macrophages to kill tumor cells through modulation of PGE_2 production and action as well as specific components of signal transduction.

Acknowledgments. The author's work was supported by grant 1RB-0404 from the University of California, Breast Cancer Research Program.

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