

## REVIEW ARTICLE

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# Dietary Fat and Breast Cancer: A Brief Update on Current Knowledge

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**ABSTRACT.** Descriptive epidemiologic data suggest a relationship between consumption of high fat diets and breast cancer; although these data can be potentially confounded by other causative exposures. Results of published case-control and cohort studies are inconclusive. Nevertheless, dietary fat significantly affects mammary tumorigenesis in mice and rats in

laboratory experiments. We will review current epidemiologic and animal studies, explain the possible mechanisms of how dietary fat may affect breast cancer, and provide preliminary dietary recommendations. *Key words: Breast cancer, Dietary fat, Epidemiology*

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Since the 1960's, ecologic studies have been showing a relationship between per capita intake of fat and breast cancer incidence and mortality rates (1). These studies have indicated that breast cancer incidence rates are five to eight times higher in countries with high fat intake, compared to countries with lower fat intake (1-4). Among epidemiologic studies, ecologic studies have been the most consistent in showing a relationship between dietary fat and breast cancer (5). Four types of ecologic analyses have been used: international, national, migrant and time-trend studies.

International studies have correlated fat disappearance data with breast cancer incidence and mortality rates among countries. In 1987 a meta-analysis was performed using data from ten international studies relating fat and breast cancer risk (5). This analysis found an association between per capita intake of fat and breast cancer mortality or incidence in all ten studies. Statistical significance was found in the seven studies that formally tested the strength of the association (5). More recent international studies

have also found significant associations (6,7). A regression analysis of the data from 21 countries found highly statistically significant positive associations between fat intake and breast cancer mortality. The association was stronger for postmenopausal women. Positive associations were found for saturated and polyunsaturated fat ( $P=0.0004$  and  $P=0.03$ , respectively), whereas no association was found for monounsaturated fat ( $P=0.97$ ) (6). A study using data from 25 countries found similar results (7). Saturated fat intake resulted in a highly significant positive association with breast cancer mortality in a multiple regression analysis, and dietary polyunsaturated fat, whenever significant, correlated positively with mortality (7). In this study postmenopausal women also showed higher correlations with mortality rates than the premenopausal group (7). Correlation analyses have also been made using regional data. An analysis of six national correlational studies found a positive association for total fat in four of them (5).

Findings from migrant studies support the role of lifestyles in breast cancer development. It has been found that Japanese living in Hawaii have breast cancer rates 3.5 times higher than Japanese living in Japan. This increase in risk correlates with an increase in fat consumption, among other lifestyle changes (8).

Several time-trend studies (6,7,9,10) have also found statistically significant results for total fat, being stronger for postmenopausal women (6). One study found that changes over time in saturated fat intake had a significant positive association with breast cancer mortality (7).

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Nevertheless, we should be aware of the limitations that have been attributed to these ecologic studies. Among them are: 1) the information is population-based and is not specifically representative of individual breast cancer patients, 2) dietary information does not always take into account home production of food, 3) the intercorrelation of dietary components make it difficult to identify the one with etiological importance, 4) inconsistency in the reports regarding food production, 5) errors in the estimates of breast cancer mortality and incidence rates, and 6) the presence of confounding factors correlated with diet (11). Although results from ecologic studies are consistent, all the limitations mentioned above have not allowed a definitive interpretation.

### Dietary Fat and Breast Cancer Studies

**Case-control studies.** Case-control studies, in general, have not provided consistent results in the association between dietary fat and the development of breast cancer (5). However, statistically significant positive results from several case-control studies support an association between dietary fat and postmenopausal breast cancer (12,13). In 1990 a meta-analysis of the original data from 12 case-control studies was published (12). In this analysis an estimated odds ratio of 1.48 ( $P < 0.0001$ ) was found for total fat intake and breast cancer among postmenopausal women, while no association was shown among premenopausal women ( $OR=1.13$ ,  $P=0.21$ ). When the effect of fat saturation on postmenopausal breast cancer was analyzed to distinguish any differential contribution, saturated fat ( $OR=1.46$ ; 95% CI: 1.23-1.72;  $P < 0.0001$ ) and monounsaturated fat ( $OR=1.41$ ; 95% CI: 1.19-1.67;  $P < 0.0001$ ) showed stronger effects than polyunsaturated fat ( $OR=1.25$ ; 95% CI: 0.91-1.71;  $P=0.16$ ). In contrast, an analysis of 8 case-control studies found only two studies (13,14) that showed statistically significant positive results (5). In one of them, the association was exclusive to postmenopausal women (13). Recent studies have indicated positive associations for total fat for premenopausal and postmenopausal women (15,16), and total (17) and saturated fat (18,19) for postmenopausal women.

The inconsistent results of case-control studies have also been attributed to methodological problems (20). Being a retrospective analysis, case-control studies are affected by random and systematic errors (20). A random error can be estimated from statistical theory and should not be considered to have a strong effect on the results (20). On the other hand, a systematic error, or bias, can result in an incorrect estimate of the association between the exposure and risk of disease (21). In addition to the

systematic errors that can occur in retrospective studies (20,21), many factors have been identified to introduce systematic errors in case-control studies that analyze the effects of past diet. The most common factors identified have been the data collection methods, the respondent's demographic characteristics, the time interval between the dietary assessment and the recalled diet, and dietary factors such as changes in diet and frequency of consumption (20).

**Cohort studies.** Cohort studies assessing the relationship between dietary fat and the risk of breast cancer began to appear in the late 80's as a mechanism to provide an answer to the inconsistent results of case-control studies (11). The data from cohort studies is considered to be free from two of the most common sources of bias of case-control studies, namely, selection bias and information bias (21). Results from several cohort studies conducted to date have not been supportive of an association between total dietary fat and breast cancer when comparing the highest category of fat intake with the lowest. Some studies (22,23) have shown a significant positive association ( $RR=2.01$ ; 95% CI: 1.19-3.41;  $P=0.01$ ) and a nonsignificant positive association ( $RR=1.38$ ; 95% CI: 0.86-2.21;  $P=0.18$ ) between total fat intake and postmenopausal breast cancer using multivariate analysis.

Few cohort studies regarding the relation of fat and postmenopausal breast cancer have included data on specific types of fat. One study (23) showed a marginally significant positive association ( $RR=1.49$ ; 95% CI: 1.01-2.20;  $P=0.052$ ) for polyunsaturated fatty acids. Howe et al. showed a marginally significant positive association ( $RR=1.39$ ; 95% CI: 0.94-2.06;  $P=0.05$ ) for saturated fat (24), and the Nurses' Health Study showed a significant protective effect ( $RR=0.67$ ; 95% CI: 0.48-0.92;  $P=0.003$ ) for monounsaturated fat (25).

The failure of cohort studies to show a consistent and strong relationship between dietary fat and breast cancer has been attributed to the difficulty in collecting accurate dietary information and to the possible influence of diet during childhood (11,22).

**Animal studies.** A number of studies have shown that the amount and type of dietary fat are determinants in the development of mammary tumors in rodents (21,28). Growing evidence indicates that increased amounts of dietary fat increase the development of mammary tumors in different rodent models such as spontaneous (29,31), carcinogen-induced (32), metastatic (33,34) and transplantable (33,35). In general, rodents fed high fat diets develop greater size and number of mammary tumors and/or have a reduced latency period of tumor appearance when compared to rodents fed low fat diets (31). This

effect of dietary fat has been found to be consistent in the promotion stage of the tumorigenic process (31,33). There is also evidence that supports some effect in the initiation stage, but a consistent relationship has not been demonstrated (36). Results from several studies suggest that there is a threshold level for dietary fat because once a diet reaches a critical level of fat, further increases in fat do not seem to result in a parallel increase development of the tumors. Studies where the fat content of the diet was doubled from 10% to 20% of body weight failed to show significant increases in tumor development (25,37,38). In addition, a study found evidence that suggests a threshold level of dietary fat in the 5% to 20% range using a spontaneous model where a constant level (3.3% by weight) of linoleic acid was maintained. In this study an increase in mammary tumor development was seen when dietary fat was increased from 5% to 11%, but when dietary fat was increased from 11% to 20%, no further development was observed (39). The type of fat is also a determinant of mammary tumor growth. Saturated, monounsaturated and polyunsaturated fats have shown to have different effects on mammary tumor development (27,32,39). Again, evidence points out that the type of fat affects mammary gland tumorigenesis mainly during the promotion stage (27,28,38,48).

Different rodent models have found an inhibitory effect for saturated fat, when compared to polyunsaturated fat (27,40,41). In a drug-induced tumor model using 7,12 dimethyl-benzanthracene (DMBA) or N-fluorenylacetamide, a diet high in beef fat (30%) suppressed tumor growth compared to a diet containing 15% vegetable oil (27). This suppressive effect of saturated fat has been found to be smaller if saturated fat is replaced with small amounts of polyunsaturated fat. Diets containing 3% sunflower seed oil and 17% of either beef tallow or coconut oil yielded double amounts of mammary tumor compared to a diet 20% saturated fat (32). The polyunsaturated fatty acid which seems to be most significant for mammary tumor growth is linoleic acid (18:2) (41). These results suggest that certain amount of polyunsaturated fat, specifically the essential fatty acid (EFA) linoleic acid, is required for mammary tumor growth. It has been demonstrated that malignant human mammary cells have a higher requirement for growth of linoleic acid than normal cells (42) and that the EFA requirement for DMBA-induced mammary tumors in a diet with 20% total fat is around 4% (40). Results regarding the effect of monounsaturated fat on mammary tumor development have been inconsistent. High levels of dietary olive oil in spontaneous mammary (41,43) and carcinogen-induced (26,44) tumor models have had either an inhibitory or no significant effect. Also no effect of

monounsaturated fat has been found in transplantable tumor models (39).

Proposed mechanisms of action of dietary fat in the development or inhibition of rodent mammary tumors are the following:

*Depressed immune system activity.* There is evidence that suggests that diets high in fat can depress the action of the immune system through changes in the qualitative expression of the cytotoxic T-lymphocytes. A model using a transplantable mouse mammary tumor found that a diet high in saturated or unsaturated fat reduced the responsiveness of individual cytotoxic T-lymphocytes (45). Furthermore, DMBA-induced mammary tumorigenesis has been most pronounced in rats following a high fat diet and having the least responsive lymphocytes compared to rats fed low fat diets (46). Thus the level of fat in the diet may have a relation with the susceptibility to mammary tumor cell growth. However, other mechanisms of how dietary fat affects mammary tumor growth appear to be involved because the addition of unsaturated fatty acids to cultured media has enhanced the growth of normal and carcinomatous cells in vitro, where the action of the immune system is not a plausible explanation (47,48).

*Prostaglandin synthesis.* Prostaglandins of series 1 (PGE1) and 2 (PGE2) have been found to be critical stimulatory factors in the enhancement of mammary tumorigenesis in diets high in unsaturated fat (49). PGE1 and PGE2 are synthesized from linoleic acid through the intermediate dihomo- $\gamma$ -linolenic acid and from arachidonic acid, respectively. Prostaglandins from both series have shown an inhibitory effect of lymphocyte response, possibly through the stimulation of cyclic 3', 5'-adenosine monophosphate synthesis, which regulates the expression of immediate and delayed-hypersensitivity. As PGE1 and PGE2 suppress cell-mediated immune responses, it is possible that tumor cells acquire some protection against immunological destruction (for review see reference 50). This hypothesis is supported by evidence showing that an increased ingestion of fish oil (eicosapentaenoic acid, EPA, 20:5) and docosahexaenoic acid (DHA, 22:6) inhibited the growth of mammary carcinoma in the R3230 rat (51). It is important to mention, as has been previously reported, that the inhibitory effects of EPA and DHA are not exclusive of prostaglandin synthesis because, although when prostaglandin inhibitors were added to neoplastic cells along with fish oil, the inhibitory effect was not depressed (52).

*Lipid peroxidation.* Lipid peroxidation products are believed to have a greater role in the promotion stage of carcinogenesis than in the initiation stage because it is at

that moment that diets high in fat have been found to have a consistent enhancing effect of mammary tumors (53,54). Although there are few studies addressing the mammary tumor enhancement effect of lipid peroxidation products, some studies using diets supplemented with antioxidants have found evidence that support the promotion effect of lipid peroxidation products. When diets high in unsaturated fatty acids were supplemented with antioxidant substances (butylated hydroxytoluene, BHT) (55), propyl gallate (56), vitamin E plus selenium (57), vitamin A (58), the enhancing effect of fat upon DMBA-induced mammary tumor was reduced. Analyses of these and other studies (58) led to suggest that one autoxidation product of linoleic acid, 13-hydroxylinoleic acid (13-HODE), may be responsible for the mammary tumor enhancement effect of fat via an enhancement of the activity of critical mitogenic peptide growth factors (53,54). However, it has been suggested that the inhibitory effect of BHT and propyl gallate (55,56) on mammary tumor growth resulted as an action of antioxidants on DMBA metabolism (57).

On the other hand, the mammary tumor inhibitory effect reported for fish oil may be due in part to secondary products of lipid peroxidation (53,54). Recent studies have shown a relationship between the inhibitory effect of fish oil, carcinoma growth suppression and the level of accumulation of secondary products of lipid peroxidation. In these studies (60,61), the addition of large amounts of antioxidants to fish oil diets was found to reduce the amount of thiobarbituric acid reactive substances (TBARS) in the tumor tissue and reduced the inhibitory effect of fish oil (62,63). The inhibitory action of secondary products of fish oil peroxidation may be via the inhibition of cell proliferation by damaging cell membranes, changing cellular composition and/or cytoskeleton assembly (53,58). Moreover, an increase in mammary tumor cell death has been reported in athymic nude mice bearing human breast carcinoma cell lines (64). Secondary products of lipid peroxidation may induce cell death by inactivating polymerase reactions, forming inter and/or intramolecular linkages between amino acid sulfhydryl groups and biomolecules DNA, RNA and proteins, and by inhibiting polyamine synthesis (53).

*Membrane fluidity.* Increased membrane fluidity has been associated to an increased cell division (65). Cell membrane fluidity can be altered by a variety of factors such as changes in phospholipid proportions, activation of membrane receptors, temperature, and by some pharmacological agents. In addition, dietary fat has also been found to alter the fluidity of cell membranes. Unsaturated fatty acids appear to be the most related to

tumorigenesis by increasing membrane fluidity and altering a number of cellular processes. Among the processes that can be affected are hormone binding or responsiveness, membrane associated enzymes, tumor associated antigens, prostaglandin biosynthesis (51), and expression of nuclear function (62). However, contradictory results have been obtained from rodent models where long polyunsaturated fatty acids have shown tumor inhibitory effects even when they would be expected to increase membrane fluidity and promote tumorigenesis (for a review see reference 51).

*Gene expression.* There is evidence indicating that dietary fat can affect gene expression (63,64). In a high fat diet (23.5% wt/wt), corn oil was found to accelerate the expression of the mouse mammary tumor virus (MMTV) proviral DNA sequence present at the Mtv-1 locus in C3HF mice. This report suggests that high levels of dietary fat can influence the initiation stage of mammary tumorigenesis at the molecular level via effects on gene transcription (63). These results are consistent with an earlier study reporting the effect of dietary fat on the expression of the H-ras gene in mammary tumor development in carcinogen-induced tumors in rats (64). To date, no report has been published that totally confirms a direct effect of dietary fat on gene expression in humans.

*Caloric consumption.* The action of dietary fat on mammary tumorigenesis has been attributed to its caloric contribution instead of a metabolic action of fat per se. Many studies have shown that caloric restriction has a consistent inhibitory effect on the development of mammary tumors. Results from a study comparing the effect of lowering caloric consumption vs. lowering fat intake suggest that very large reductions in fat intake are required to produce an equivalent mammary tumor inhibition to that of a small reduction in caloric consumption. Even though there are many reports that demonstrate a role of fat (instead of energy from fat) in mammary tumor development using different rodent models, a recent review concluded that the enhancing effect of high fat diets is a phenomenon dependent upon an ad libitum type of feeding protocol. This conclusion was based on results from studies where caloric restriction, in addition of suppressing the development of mammary tumors, appears to block the differences in tumorigenesis between rats fed low and high fat diets (for a review see reference 53).

*Intercellular communication.* Metabolic cooperation, a type of intercellular communication, has been suggested to play a role in tumor growth. Evidence shows that many tumor-promoting fatty acids have been found to affect metabolic cooperation in different ways. Various fatty acids such as linoleic acid (18:2), linolenic acid (18:3),

oleic acid (18:1), palmitoleic acid (16:1) and myristoleic acid (14:1) have been shown to inhibit metabolic cooperation, while stearic acid (18:0), palmitic acid (16:0) and myristic acid (14:0) do not disturb this communication. It has been suggested that the differential effects may be associated with the carbon chain length. However, considering that proliferating cells communicate less than non-proliferating cells, the metabolic cooperation effect of unsaturated fatty acids (18:2, 18:3, 18:1, 16:1, 14:1) could be due to an enhancement of cellular proliferation or metabolic intermediaries such as certain prostaglandins (for a review see reference 57).

*Endocrine system.* There are studies that suggest that rodent mammary tumorigenesis is enhanced by a chronic hypersecretion of the pituitary-ovarian axis hormones, and that this hypersecretion is due to high intakes of dietary fat. However, future studies could confirm a fat induced hypersecretion only for the thyroid gland. Another observation that does not support the high fat intake-hypersecretion hypothesis is that tumor models that are not responsive to hormones from the pituitary-ovarian axis have shown increased tumor development with increased fat intake. In contrast, a mechanism in which a high fat diet stimulates cell proliferation by increasing hormone responsiveness through activation of protein kinase C has been more accepted. Protein kinase system is calcium, phospholipid, and diacylglycerol (DAG) dependent. DAGs containing unsaturated fatty acids have been considered more effective than DAGs containing saturated fatty acids. Hyperalimentation of unsaturated fatty acids would change the composition of membrane lipids, and DAGs can increase the activity of protein kinase C system by combining with it. There is evidence of a direct relationship between protein kinase C activity and cellular proliferation. Although recent studies reported that unsaturated fatty acids are not necessary for the activation of protein kinase C, it is still believed that this mechanism is in part responsible for the mammary tumor effect of high fat diets (for a review see reference 57).

### Dietary Recommendations

The Food and Nutrition Board's Committee on Diet and Health has recommended that dietary fat should not exceed 30% of caloric intake, and that saturated fatty acids should provide 10% of calories or less (64). For polyunsaturated fatty acids, the recommended dietary intake is between 7% and 10% of calories (64) and, at least 3% of calories must come from linoleic acid (65). Although these recommendations attempt to help the

general population to lower their risk of cardiovascular diseases and certain types of cancer, animal studies indicate there is a fat threshold between 10% to 40% of calories from fat (5% to 25% by weight) (39,53). Thus, lowering fat intake to around 30% of calories may not be enough to obtain a significant decrease in the risk of breast cancer. It is our personal opinion that total dietary fat should be around the 20% mark, half of it (10%) should be polyunsaturated (a balance of omega 6 and omega 3 fatty acids), and the other half should be mostly monounsaturated with a minimum hydrogenation. Also, it has been shown in animal studies that a specific amount of linoleic acid is necessary for mammary tumor growth (for a review see reference 53). Although the evidence is not conclusive, and acknowledging that linoleic acid is an essential fatty acid, recommendations to lower linoleic acid intake and increase omega-3 fatty acids seem logical to reduce breast cancer risk. To date, there are no specific recommendations for monounsaturated fat.

Findings are in agreement with results from ecologic studies but not with results from cohort studies. There has been disagreement by one expert with this recommendation of restricting intake of fats (66), nevertheless given the laboratory results available we wholeheartedly support it.

### Resumen

Estudios epidemiológicos descriptivos sugieren una relación entre el consumo de una alimentación alta en grasas con cáncer de mama pero estos resultados pueden estar afectados debido a otras posibles asociaciones causales. Los resultados de estudios de casos y controles y estudios de cohortes son inconclusos. Sin embargo, la grasa alimentaria afecta significativamente la tumorigénesis mamaria en ratones y ratas experimentales. Este artículo revisará los estudios epidemiológicos y estudios en animales, explicará los posibles mecanismos de como la grasa alimentaria puede afectar el cáncer de la mama y se expondrá unas recomendaciones dietarias preliminares.

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