Similarity between trans Fat and Saturated Fat in the Modification of Rat Mammary Carcinogenesis

Sandra L. Selenskas, Margot M. Ip, and Clement Ip

Department of Breast Surgery [S. L. S., C. I.] and Grace Cancer Drug Center [M. M. I.], Roswell Park Memorial Institute, Buffalo, New York 14263

ABSTRACT

Commercial hydrogenation of vegetable oils results in the introduction of trans fatty acids. In the present study, we have investigated the effect of feeding a diet which contained approximately 38% trans isomers (designated trans fat) on the induction of mammary tumors by dimethylbenz(a)anthracene in rats. The corresponding control fat (designated cis fat), which had a similar fatty acid composition, consisted of only cis isomers. Since both the trans and cis fats were rather saturated, a comparison was also made between these 2 types of fat and corn oil, which contains about 60% linoleic acid (C_{18:2}). Each fat was present in the diet at 2 levels, 5 and 20% by weight. Although rats fed the 20% trans fat or cis fat diets had a slightly higher tumor incidence and yield than those on the corresponding 5% fat control diets, the difference was not statistically significant. In contrast, rats fed the 20% corn oil diet developed a much greater number of tumors than did rats fed a diet containing only 5% corn oil. Further analysis of the data showed that diets containing either trans fat or cis fat were much less effective than were the corn oil diets in promoting the development of mammary neoplasia at either the 5 or 20% level. Our results thus suggest that trans fat behaves very much like a saturated fat in the modification of mammary tumorigenesis. A determination of the fatty acid content of the mammary fat pad indicated that its composition generally reflected the dietary fatty acid intake, with the incorporation of trans isomers into the mammary tissue found to be dependent on the quantity of trans fat in the diet.

INTRODUCTION

Since the turn of this century, the daily per capita consumption of fat has gradually increased in the United States from 125 g in 1909 to 168 g in 1979 (29). Virtually all of the increase can be accounted for by vegetable fats, most of which are subjected to a series of processing steps to convert them from triglycéride form of similar fatty acid composition and in the cis configuration should be used as a control. The use of the parent fat source (from which the hydrogenated fat is derived) as control would be misleading, since the 2 lipids would have different fatty acid profiles. In the present study, we have investigated the effect of feeding a diet which contained approximately 38% trans fatty acids (designated trans fat) on the induction of mammary tumors by DMBA in rats. The corresponding control fat (designated cis fat), which had a similar fatty acid composition, consisted only of cis isomers. Since both the cis and trans fats were rather saturated in nature, a comparison was made between these 2 types of fats and corn oil, which contains about 60% linoleic acid (9-cis-C_{18:1}). Fatty acid analysis was also performed in the mammary fat pads obtained from these animals.

MATERIALS AND METHODS

Animals and Diets. Female Sprague-Dawley [Crl: CD(SD)BR] rats were purchased from Charles River Breeding Laboratories (Wilmington, MA) at 40 days of age. All animals were fed Purina laboratory chow pellets up to the time of carcinogen administration, at which point they were randomly divided into 6 groups of 25 rats each according to the synthetic diet given. The different diets were started 3 days after DMBA intubation. The diets contained either trans fat, cis fat, or corn oil; each was present in the diet at 2 levels, 5% by weight (control level) or 20% by weight (high fat). The composition of the diets is given in Table 1; the type of fat used in this study is discussed below. These diets were formulated according to the method of Newberne et al. (25) in such a way that all nutrients except fat and dextrose were equivalent on a caloric basis. Rats were housed in a temperature- and light-controlled environment with food and water available ad libitum.

Edible Oils indicate that most liquid or solid cooking fats contain 5 to 25% trans isomers, while most stick margarines contain 20 to 35% trans isomers. There is currently no reliable information on the consumption of trans fat in the United States. Although ruminant fats (primarily from dairy products and beef) contribute a small amount of trans fatty acids to our diet, it is estimated that the majority of trans fat intake is from partially hydrogenated vegetable oils.

There is growing evidence in the literature that diets rich in fat enhance mammary tumorigenesis in laboratory animals (33). However, very little is known about the relationship between trans fat and cancer. A recent report by Awad (4) suggested that ingestion of elaidic acid (9-trans-C_{18:1}) reduced the survival time of mice bearing the Ehrlich ascites tumor. Results from this experiment are difficult to interpret, however, since the control animals in this study were fed olive oil, which is high in esterified oleic acid (9-cis-C_{18:1}). Hence, a comparison was made between a free fatty acid and a triglyceride.

Food products contain trans fatty acids as triglycerides. In order to properly evaluate the effect of trans fat intake, a lipid in triglyceride form of similar fatty acid composition and in the cis configuration should be used as a control. The use of the parent fat source (from which the hydrogenated fat is derived) as control would be misleading, since the 2 lipids would have different fatty acid profiles. In the present study, we have investigated the effect of feeding a fat which contained approximately 38% trans fatty acids (designated trans fat) on the induction of mammary tumors by DMBA in rats. The corresponding control fat (designated cis fat), which had a similar fatty acid composition, consisted only of cis isomers. Since both the cis and trans fats were rather saturated in nature, a comparison was made between these 2 types of fats and corn oil, which contains about 60% linoleic acid (9-cis,12-cis-C_{18:2}). Fatty acid analysis was also performed in the mammary fat pads obtained from these animals.
The fatty acid composition of the 3 different types of fat, as determined by gas chromatography, is shown in Table 2. The trans fat stock was a partially hydrogenated mixture of 50% soybean oil and 50% cottonseed oil. It was high in monoenes and low in dienes and other polyenes. About 38% of the fatty acids were in the trans configuration, primarily as trans-monoenes (Table 2, Footnote a). The cis fat was blended to attain a fatty acid composition similar to that of the trans fat and consisted of 58% olive oil, 40% cocoa butter, and 2% coconut oil. There was no detectable trans fatty acid in the cis fat. Compared to both trans fat and cis fat, corn oil contained a much higher percentage of polyunsaturated fatty acids in the form of linoleic acid (9-cis,12-cis-C,). All fats were provided by member companies of the Institute of Shortenings and Edible Oils.

The cis,cis-lipoxygenase assay reported in Table 2 measures cis,cis-methylene-interrupted double bonds, as in linoleic acid. It should be noted that this value corresponded very closely to the level of C fatty acid found in cis fat and corn oil, suggesting that the isomer is linoleic acid. In contrast, the cis,cis-lipoxygenase value was below detectable levels for trans fat. Thus, the C fatty acids in the trans fat could be present as the following isomers: trans-cis-C, cis-trans-C, cis-cis-C, or trans, cis-trans-C,. Both cis,trans and trans,trans isomers of C, are devoid of essential fatty acid activity. Considering the virtual absence of linoleic acid in the trans fat, 1% of corn oil was added to the trans fat diets to prevent essential fatty acid deficiency. The same amount of corn oil was also added to the cis fat diets to minimize differences in fatty acid composition between the cis fat and trans fats. Therefore, the control fat diets contained 4% trans or cis fat plus 1% corn oil, and the high-fat diets contained 19% trans or cis fat plus 1% corn oil. As a matter of convenience, the control fat and high-fat trans or cis diets will be referred to as 5 and 20% trans or cis fat diets, respectively, in the text. The concentrations of linoleic acid and trans acids in each diet are shown in Table 3.

Tumor Induction. Mammary tumors were induced by intragastric administration of 5 mg of DMBA (Sigma Chemical Co., St. Louis, MO) at 50 days of age. The method of DMBA administration has been described in detail previously (18). Rats were palpated weekly to determine the appearance and location of the tumors. All animals were sacrificed 24 weeks after DMBA treatment and, at autopsy, were examined for nonpalpable tumors. All tumors were excised, fixed in Bouin’s reagent, and sectioned for histology. Mammary tumor pathology was confirmed according to the criteria of Young and Hallowes (37). Only adenocarcinomas are reported in "Results."

Differences in the palpable tumor incidence curves were analyzed using the computer program BMDPL1 (7). This program is set up to perform a 2 x 2 contingency table of the tumor incidence for each week of the experiment. The Mantel-Cox statistic generated at the end is a generalized Savage test, which compares observed events with expected events. Tumor incidence at the final time point (consisting of palpable plus nonpalpable tumors) was analyzed by x2 analysis.

Fatty Acid Analysis of Mammary Tissue. Groups of 8 rats were fed their respective diets for 2 months starting at 50 days of age. The animals were sacrificed, and the mammary fat pads were removed and immediately frozen in liquid nitrogen for subsequent fatty acid analysis. Total lipids were extracted with chloroform:methanol (2:1, v/v) by the method of Olivecrona (27), and fatty acid methyl esters were prepared by refluxing the total lipid extracts with 2% H2SO4 in methanol in a nitrogen atmosphere. The fatty acid methyl esters were analyzed by gas chromatography according to the following specifications: instrument, Hewlett-Packard 5880A; column, phosphoric acid-stabilized diethylene glycol succinate (10% w/v) on Supelcoport, 80/100 mesh, stainless steel, 6 feet x 0.125 inch; detector, flame ionization (300°); injection port, 300°; temperature program, 180–210°, 2°/min; hold time, 10 min. Fatty acid standards were obtained from NuChek Prep (Elysian, MN). The mammary tissue fatty acid methyl ester preparations were analyzed for total trans fatty acids by the method of Madison et al. (22).

RESULTS

Chart 1 shows the percentage of incidence of palpable mammary tumors from the 6 dietary groups as a function of time after DMBA administration. In rats fed either the trans fat or cis fat in their diets, animals that were maintained at the 20% fat level had a higher tumor incidence compared to those maintained at the 5% fat level. The difference, however, was not statistically significant when the data were analyzed over the entire duration of the experiment. This was in contrast to animals fed the corn oil diets; the tumor incidence in the 20% corn oil group was significantly higher than that observed in the 5% corn oil group (p < 0.01). Further analysis of the data showed that tumor incidence in rats fed the 20% corn oil diet was significantly higher than that in rats maintained on either the 20% cis fat or the 20% trans fat (p < 0.01). At the 5% fat level, the tumor incidence in the corn oil group was significantly higher than that in the trans fat group (p < 0.02) but was only marginally higher than that in the cis fat group (p = 0.06). This experiment thus suggests that the promoting effect of a high-fat diet on tumorigenesis is more pronounced when a polyunsaturated fat is used. Both the trans fat and cis fat, being rather saturated in nature, are much less effective in the enhancement of mammary tumorogenesis.

Chart 2 shows the time course of palpable mammary tumor development on a cumulative basis. Results, in general, appeared to parallel the incidence curves. Even though rats fed the 20% trans or cis fat diets developed more tumors than did those...
on the 5% fat diets, the difference was not nearly so great as that between rats fed the corn oil diets. A summary of the final tumor yield, including nonpalpable tumors discovered at autopsy, is presented in Table 4. It can be seen that rats given the 20% corn oil diet developed a total of 72 tumors, whereas those fed the 5% corn oil diet only had a total of 28 tumors. At either the 5 or 20% fat level, both trans fat and cis fat groups had a much smaller number of tumors than did the corresponding corn oil groups. Since the cis fat was the appropriate control for the trans fat in this experiment, it can be concluded that trans versus cis isomerization of fatty acids has no detectable effect in the modification of mammary carcinogenesis. Interestingly, as shown in Table 4, there was no difference in the number of tumors per tumor-bearing rat among the 6 dietary groups. However, the trend still persisted that multiple tumors were more prevalent in rats fed the 20% corn oil diet.

The growth curves of rats ingesting the different diets are shown in Chart 3. Regardless of the type or level of fat in their diets, the rate of growth was quite comparable among the 6 groups, suggesting that the differences in tumorigenesis could not be accounted for by differences in caloric intake. It can also be implied from the weight gain chart that rats fed the trans fat diets were not suffering from essential fatty acid deficiency, which would otherwise be manifested by a slower growth rate.

The fatty acid analysis of the mammary fat pads, including the determination of trans isomers, is shown in Table 5. In general, the fatty acid composition of the mammary tissue seemed to reflect the dietary fat composition. Mammary fat pads from rats fed the corn oil diet had a higher linoleic acid (C18:2) and a lower oleic acid (C18:1) content than did those from rats fed either the trans or cis fat. Moreover, the tissue levels of linoleic acid and arachidonic acid (C20:4) increased with increasing linoleic acid intake (compare Table 5 with Table 3). Rats fed trans fat had the lowest levels of these 2 fatty acids, whereas rats fed corn oil had the highest level. With respect to the incorporation of trans isomers, about 9.7% of the fatty acids in the mammary fat pads were found to be in the trans configuration in rats ingesting 4% trans fat (plus 1% corn oil), and 26% of the fatty acids were trans isomers in rats fed 19% trans fat (plus 1% corn oil). No trans isomers were detected in animals fed either cis fat or corn oil.

**DISCUSSION**

The present study shows that tumor incidence and total tumor yield were not significantly different in rats fed either the trans fat or the cis fat. Thus, it can be concluded that trans versus cis isomerization of fatty acids has no detectable effect in modifying mammary tumorigenesis. Both fats were less effective than was corn oil, a polyunsaturated fat, in promoting the development of mammary neoplasia when added at a 20% level in the diet. Since the trans and cis fats used in this study contained approximately 55% oleic acid and 35% saturated fatty acids, with very little polyunsaturated fat, it might be concluded that polyunsaturated fat is more effective than is monounsaturated or saturated fat in promoting mammary carcinogenesis. That the issue is much more complex than this, however, is suggested by several
studies from other laboratories. Carroll (9), for example, demonstrated that olive oil, which contains approximately 72% oleic acid, 14% saturated fatty acids, and 8% linoleic acid (31), was just as effective as was corn oil in promoting mammary carcinogenesis. This is in contrast to our present study, which demonstrates a differential effect when corn oil and cis fat are compared. The reason for this discrepancy is not apparent at the present time; however, similar discrepancies are noted when 2 other relatively saturated fats, lard and beef tallow, are examined. These 2 fats, which contain 41 and 36% oleic acid, respectively (comparable to our cis fat), have different effects on mammary tumorigenesis. In an experiment designed to study the promotional effects of various types of fat on DMBA-induced mammary tumorigenesis, Hopkins and Carroll (15) demonstrated that lard was more effective in stimulating tumorigenesis than was beef tallow and, in their particular experiment, lard was shown to be just as effective as was the highly polyunsaturated sunflower seed oil in increasing tumor yield, which, in turn, was exactly twice as effective as was beef tallow. In a similar experiment, except that the high-fat diets were fed both before and after carcinogen administration, Chan et al. (10) reported that mammary tumorigenesis was stimulated to the greatest extent by corn oil and to the least extent by beef tallow. The effect of lard was midway between that of the 2 other fats.

The effectiveness of lard in contrast to that of beef tallow in the above experiments may be explained by the observations of Hopkins and Carroll (15) that there appears to be an essential fatty acid requirement for tumor growth. These workers found that diets containing 3% sunflower seed oil (polyunsaturated fat) and 17% beef tallow or coconut oil (saturated fats) enhanced tumorigenesis as much as did a diet containing 20% sunflower seed oil. Rats on these diets developed at least twice as many tumors as those fed diets containing either 3% sunflower seed oil or 20% of the saturated fats alone. Their findings indicate that there is a requirement for polyunsaturated fat in mammary tumorigenesis which is not satisfied by fats such as coconut oil or beef tallow but can be provided by adding 3% sunflower seed oil to the diets containing these fats. Lard, which contains approximately 10% linoleic acid (31), would appear to meet this essential fatty acid requirement when fed at a 20% level in the diet. The picture that is emerging from all of these studies is that the relationship between fat and mammary tumorigenesis is much more complex than was envisioned previously. Based on the evidence in the literature, considerations should be given not only to the level of fat and the geometric configuration of the fatty acids but also to the levels of individual fatty acids such as linoleic and oleic acids. In addition, although must studies appear to suggest that the effect of dietary fat is exerted mainly at the promotional stage of carcinogenesis, Rogers and coworkers

**Table 4**

<table>
<thead>
<tr>
<th>Type of fat</th>
<th>Level of fat (%)</th>
<th>Tumor incidence</th>
<th>Total no. of tumors</th>
<th>Tumors/tumor-bearing rat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trans fat</td>
<td>5</td>
<td>4/25 (16)</td>
<td>9</td>
<td>2.3 ± 0.5</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>8/25 (32)</td>
<td>18</td>
<td>2.3 ± 0.4</td>
</tr>
<tr>
<td>Cis fat</td>
<td>5</td>
<td>6/25 (24)</td>
<td>16</td>
<td>2.7 ± 0.9</td>
</tr>
<tr>
<td>Corn oil</td>
<td>5</td>
<td>11/25 (44)</td>
<td>28</td>
<td>2.5 ± 0.3</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>20/25 (80)</td>
<td>72</td>
<td>3.6 ± 0.5</td>
</tr>
</tbody>
</table>

* Includes rats with nonpalpable tumors discovered at autopsy.
* Numbers in parentheses, percentage.
* Mean ± S.E.
* Tumor incidence in the 5% corn oil group was significantly different from that in the 5% trans fat group (p < 0.02).
* Tumor incidence in the 20% corn oil group was significantly different from that in the 5% corn oil group, the 20% trans fat group, and the 20% cis fat group (p < 0.01).

**Table 5**

<table>
<thead>
<tr>
<th>% of total fatty acids</th>
<th>14:0</th>
<th>16:0</th>
<th>18:0</th>
<th>18:1</th>
<th>18:2</th>
<th>18:3</th>
<th>20:0</th>
<th>20:3</th>
<th>20:4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trans fat</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5%</td>
<td>1.6 ± 0.09</td>
<td>22.9 ± 1.5</td>
<td>4.2 ± 0.45</td>
<td>51.2 ± 1.6</td>
<td>8.9 ± 0.54</td>
<td>1.6 ± 0.11</td>
<td>0.17 ± 0.01</td>
<td>0.38 ± 0.08</td>
<td>9.7 ± 0.86</td>
</tr>
<tr>
<td>20%</td>
<td>1.1 ± 0.05</td>
<td>15.6 ± 0.9</td>
<td>7.1 ± 0.94</td>
<td>58.6 ± 1.3</td>
<td>9.5 ± 0.32</td>
<td>1.7 ± 0.26</td>
<td>0.19 ± 0.01</td>
<td>0.30 ± 0.06</td>
<td>26.0 ± 1.1</td>
</tr>
<tr>
<td>Cis fat</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5%</td>
<td>1.4 ± 0.12</td>
<td>22.5 ± 1.0</td>
<td>4.3 ± 0.64</td>
<td>54.2 ± 1.4</td>
<td>9.0 ± 0.73</td>
<td>0.16 ± 0.02</td>
<td>0.55 ± 0.09</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20%</td>
<td>0.79 ± 0.05</td>
<td>15.8 ± 1.3</td>
<td>5.9 ± 0.84</td>
<td>61.5 ± 1.5</td>
<td>11.0 ± 0.8</td>
<td>0.19 ± 0.02</td>
<td>0.51 ± 0.14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corn oil</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5%</td>
<td>1.3 ± 0.06</td>
<td>22.0 ± 1.1</td>
<td>3.2 ± 0.43</td>
<td>35.9 ± 2.0</td>
<td>28.4 ± 1.9</td>
<td>0.81 ± 0.15</td>
<td>0.26 ± 0.04</td>
<td>0.14 ± 0.02</td>
<td>0.87 ± 0.12</td>
</tr>
<tr>
<td>20%</td>
<td>0.58 ± 0.07</td>
<td>13.3 ± 0.8</td>
<td>2.8 ± 0.23</td>
<td>27.4 ± 0.4</td>
<td>50.2 ± 1.0</td>
<td>0.97 ± 0.07</td>
<td>0.34 ± 0.04</td>
<td>0.29 ± 0.08</td>
<td>1.4 ± 0.26</td>
</tr>
</tbody>
</table>

* Mean ± S.D. (8 rats/group).
have reported recently that, in contrast to the study of Hopkins and Carroll (15), lard had no effect when fed after DMBA administration (34), but it stimulated tumorigenesis when fed before or before and after carcinogen exposure (30). Hence, the timing of feeding of the high-fat diet may also be critical in terms of subsequent effects on tumorigenesis.

In order to provide some perspective into our experimental design in relation to human consumption of trans fat, the trans fat stock we used in this study contained about 38% trans isomers, a figure that is in the upper range of that present in most table spreads and cooking oils available in the consumer market. As shown in Table 3, rats fed a ration of 19% trans fat (plus 1% corn oil) would ingest 7.2 g of trans fatty acids/100 g of diet. Based on 1972 data, Enig et al. (14) calculated that the trans fat consumption in the United States was about 8% of total fat. Assuming that a typical American diet consists of about 20% fat by weight, the quantity of trans fatty acid intake would be equivalent to 1.6 g/100 g of food. Aside from this quantitative difference, our trans fat stock was high in trans-monoene, which is also the predominant trans isomer in commercially hydrogenated fat products. Thus, animals in the present experiment were fed trans acids that are qualitatively similar to those in the American diet, except in proportionately larger amounts.

Although there is some debate as to the accuracy of the figure quoted by Enig et al. (14), a reliable estimate of trans fat intake has not been published either by the United States Department of Agriculture or by the food industry. Autopsy samples from American subjects indicated that trans fatty acid concentrations ranging from 2 to 6% were found in the adipose tissue (26). In animals fed hydrogenated fat for 1 to 6 months, accumulation of certain geometric isomers in tissues at levels above those present in the diet has been reported (16, 20, 28, 36). The disposition may be selective, with the adipose tissue generally containing the highest concentration. In the present study, we found that, in rats fed a diet containing 1.5 or 7.2 g of trans acids/100 g of food, the levels of trans isomers in the mammary fat pad were approximately 9.7 and 26% of total lipid, respectively. Thus, it seems reasonable to assume that the level of trans acid incorporation into tissues is dependent on the quantity of trans fat in the diet (12).

It has been well established that trans fatty acids are readily absorbed and are incorporated mainly into the neutral triglyceride fraction (6). Several workers have reported that trans fatty acids are oxidized at rates equivalent to those of the corresponding cis isomers (2, 11, 21, 32). On the other hand, in vitro studies have shown that mitochondria from rats fed trans fatty acid were more susceptible to swelling and have a lower rate of oxidation (17), although it should be pointed out that these rats were apparently deficient in essential fatty acid. Kinsella et al. (19) have reported recently that high levels of dietary trans-trans-C_{18:2} impair Δ6-desaturase activity and decrease prostaglandin synthesis. Although there is legitimate concern as to the biochemical consequence of this metabolic perturbation, suffice it to note that trans-trans-diienes are present in only trace amounts in hydrogenated fats (23). In general, several carefully controlled long-term animal studies have shown that feeding high levels of trans-monoenes, in the presence of adequate linoleic acid, did not result in any overall deleterious efforts (1, 24).

Awad (3) has also reported that elaidic acid is incorporated into tumor phospholipid, which is a major component of cell membranes. The orientation of a trans double bond is associated with straightening of the hydrocarbon chain, thus enabling the trans isomer to resemble more closely a saturated molecule. Such structural alteration could conceivably influence the fluidity and topography of the cell membrane, which, in turn, may affect the social behavior of cells and, consequently, the metastatic ability of cancer cells. Wicha et al. (35) have shown that saturated fatty acids are less effective than are unsaturated fatty acids in enhancing the growth rate of normal and neoplastic mammary epithelial cells in culture. In an in vitro metabolic cooperation study involving mutant and wild-type cells, it has been shown that unsaturated fatty acids are more potent than are saturated fatty acids in inhibiting intercellular communication (5).

In addition to the study by Awad (4) on the effect of elaidic acid on tumor development and host survival, cited earlier, a preliminary report by Brown (8) has also appeared recently comparing the effects of different types of dietary fat, including trans fat, in relation to their degree of saturation on the induction of spontaneous and dimethylhydrazine-induced tumors in mice. In general, he found that there was no significant difference between fats high in cis-monoene, cis-diene, or trans-monoene. Thus, few studies have actually investigated the effect of trans fat on cancer, and none that we are aware of has used cis fat with similar fatty acid composition as the appropriate control. In conclusion, our study has demonstrated that a fat with a high content of trans fatty acids does not promote mammary tumor formation to any greater extent than does a comparable fat with a high content of cis fatty acids.

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