Differential Effects of Dietary Linoleic Acid on Mouse Skin-Tumor Promotion and Mammary Carcinogenesis

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Abstract

On the basis of reports of rat mammary- and pancreas-tumor models, we hypothesized that an increase in consumption of linoleic acid (LA) would also cause an enhancement in mouse skin-tumor promotion. SENCAR mice were placed on diets containing 0.8%, 2.2%, 3.5%, 4.5%, 5.6%, 7.0%, or 8.4% LA, 1 week after initiation with 7,12-dimethylbenz(a)anthracene and 3 weeks before starting promotion with 12-O-tetradecanoxyphorbol-13-acetate. An inverse correlation \( r = -0.92 \) was observed between papilloma number and level of LA; however, there was little difference in tumor incidence. A relationship between diet and carcinoma incidence was also found. The fatty acid composition of epidermal phospholipids reflected the dietary LA levels. 12-O-Tetradecanoxyphorbol-13-acetate induced epidermal prostaglandin \( \text{E}_2 \) levels generally decreased with increasing dietary LA. To determine whether this inverse correlation between dietary LA and tumor yield was due to species differences or organ-model differences, a mammary carcinogenesis experiment was performed. SENCAR mice were fed the 0.8%, 4.5%, and 8.4% LA diets. All mice received 6 mg 7,12-dimethylbenz(a)anthracene, administered intragastrically at 1 mg/wk. Tumor appearance was delayed in the 0.8% LA diet group, and a positive dose-response relationship between dietary LA and mammary-tumor incidence was observed. These studies suggest that the effect of dietary LA on tumor development is target tissue specific rather than species specific.

Introduction

When the level of fat has been held constant and the effect of type of fat has been evaluated, a relationship between the degree of saturation and tumor incidence has been noted in a number of studies. In particular, Carroll and Khor (1) reported that mammary tumor incidence was greater with diets containing PUFAs, compared with diets containing saturated fatty acids. Further work by Carroll and Hopkins (2) suggested that a particular level of PUFAs was needed to support mammary tumorigenesis and that a higher level of PUFAs had little effect. To more clearly define the essential fatty acid requirement for mammary tumorigenesis in rats treated with DMBA, Ip et al. (3) used 20% fat diets containing 0.5% to 11.5% LA, the major fatty acid in these diets. Tumor incidence increased with increasing dietary LA up to 4.4%; essentially no additional increase was seen with 8.5% or 11.5% LA (3). This led to the development of the concept of a saturating level of LA for permitting optimal mammary tumor development (4). This concept, however, appears to be specific to the mammary gland, in that, when these same diets were used in azaserine-induced pancreatic carcinogenesis in rats, the greatest number of tumors occurred with >4% LA (5).

A functional role for LA in supporting mammary tumor development appears to be related to the production of \( \text{PGE}_2 \). The availability of the precursor of \( \text{PGE}_2 \), AA, can be modulated by the level of LA, because desaturation and elongation reactions convert LA to AA. A positive association was reported among dietary LA, tumor \( \text{PGE}_2 \) levels, and incidence of chemically induced mammary tumors (6). Additionally, the prostaglandin synthetase inhibitor indomethacin reduced mammary tumor incidence (7, 8). Several other studies also suggested that enhancement of mammary-tumor incidence by high-PUFA diets is through synthesis of prostaglandins (reviewed in Ref. 9).

These studies raised the question of whether other organ models, in which prostaglandins are also critically involved in tumor development, would respond in a manner similar to that of the rat mammary model. Our laboratory has begun to address the question of whether initiation-promotion in mouse skin would be affected comparably. The importance of AA metabolism in tumor promotion in mouse skin is well established (reviewed in Ref. 10). Several studies indicate that (a) arachidonate metabolites elicit inflammation, an event also induced by tumor promoters (11), (b) exogenous application of prostaglandins with a phorbol ester tumor promoter modifies tumor development (10), and (c) inhibitors of various parts of the arachidonate cascade cause an inhibition of tumor incidence (10).

On the basis of biological activity of arachidonate and the requirement of its metabolites in skin-tumor promotion and the report (12) that high-corn oil, high-fat diets enhance promotion, compared with low-corn oil, low-fat diets, we postulated that alterations in the consumption of LA (18:2, \( n = 6 \)), the precursor to AA (20:4, \( n = 6 \)), would result in changes in tumor development. Specifically, it was predicted that, in a constant-fat diet, higher dietary levels of LA would be associated with a higher tumor number and that there might not be a saturating level of LA such as was observed in rat mammary-tumor studies (3, 4). This paper describes the approaches testing these hypotheses and the results of reported (13, 14) and ongoing studies. The first approach was to determine the effects of constant-fat diets with different ratios of saturated fatty acids to corn oil on the incidence and number of papillomas and carcinomas in mouse skin. In addition, the metabolic fate of dietary LA was investigated with regard to changes in LA and AA content in epidermal phospholipids and whether changes in dietary LA would alter the extent of several phorbol ester-induced events. The second approach was to determine whether the previously reported effects of these diets in rat mammary carcinogenesis (3) occurred in the SENCAR mouse mammary gland.
Materials and Methods

Diets. Diets were obtained from Teklad (Madison, WI). The corn oil used in the diets was research-grade Mazola, supplied to Teklad by Best Foods, Inc., (Union, NJ). All diets were based on the AIN-76 formulation (15), with modification for fat quantity. The fat was supplied as corn and/or coconut oil, in proportions providing specific levels of LA (Table 1). Diets were stored at 4°C, and fresh diet was supplied three times weekly, in glass jars with stainless steel lids. Food consumption was estimated as the difference in weight of the supplied food and the amount remaining 48 h later.

Skin-Model Tumor Study. Groups of 30 female SENCAR mice, 4 weeks of age, purchased from the NCI-Frederick Cancer Research Facility (Frederick, MD), were assigned at random, housed 10/cage, and maintained in climate-controlled, pathogen-free quarters with a 12-h light-dark cycle. Body weights were determined weekly for 23 weeks. Animals were maintained on the 5%-fat diet (Table 1) for 3 weeks before initiation with a single application of 2.5 μg DMBA to the dorsal surface. Animals were maintained on the 5%-fat diet for 1 week after initiation, when they were switched to one of the seven experimental diets (Table 1) that contained 15% fat. After 3 weeks on the experimental diets, twice-weekly treatment with topical application of 1 μg TPA was begun and continued for 15 weeks, as described (14). Tumor number was determined weekly.

Epidermal Phospholipid Fatty Acid Content. Groups of seven SENCAR mice were placed on the experimental diets for 4 weeks before being killed. Lipid was extracted from the epidermis, and separation of the four major phospholipids, PC, phosphatidylethanolamine, phosphatidylserine, and phosphatidylcholine, was achieved by thin-layer chromatography, as previously described (14). The phospholipids were extracted (phosphatidylserine and phosphatidylcholine) were combined because of low abundance and poor chromatographic separation), and the fatty acids were methylated before analysis by gas-liquid chromatography (14). The LA and AA contents of each phospholipid class were expressed as a percentage of the total fatty acids of that phospholipid.

Analysis of Skin PGE2. Groups of 16 SENCAR mice fed each of the experimental diets were topically treated with either acetone (eight mice/diet group) or 4 μg TPA in acetone (eight mice/diet group). Six h later (previously determined to represent a peak of PGE2 production; data not shown), they were killed and the skin of the dorsal surface was quickly frozen in liquid nitrogen. For assay, a 1.5-cm2 area of epidermis was chipped into methanol. After homogenization, a sample was removed for determination of DNA content (16) and the remainder was extracted, as previously described (14), for determination of PGE2 levels by radioimmunoassay. The level of epidermal PGE2 is expressed as pg PGE2 per mg DNA.

Mammary-Tumor Study. Groups of approximately 40 female SENCAR mice, 4 weeks of age, were subjected to the diet regimen described above, except that only the lowest (0.8%), middle (4.5%), and highest (8.4%) LA diet groups were used in the tumor experiment. All mice received a total dose of 6 mg DMBA, administered intra-gastrically at 1 mg/week, starting at 8 weeks of age (17). When palpable tumors reached approximately 1 cm in size, the mice were killed and all tumors were removed for histological analysis.

Statistics. Analysis of variance was performed on all sets of data. The Fisher protected least significance difference was used to determine statistically significant differences between groups. For the average number of papillomas per mouse, analysis of variance of the regression equations by diet groups was performed using BMDP-1R, Multiple Linear Regression (BMDP Statistical Software, Inc., Los Angeles, CA). Statistical evaluation of the cumulative probability of an animal having a mammary adenocarcinoma used the computer program BMDP1L life-table and survival functions (Biomedical Computer Programs, University of California, Los Angeles, CA). The Breslow and Mantel-Cox tests were used to derive P values.

Results

Skin-Tumor Experiment. To address the question of whether the association between increasing dietary LA and increasing tumor incidence was generally applicable to other models, a mouse skin-tumor study was conducted with diets with constant total-fat but differing LA contents. The effects of diet on both tumor incidence and number were assessed. As described (14), little difference in tumor latency was observed among diet groups, although for those animals fed the highest levels of LA, tumors appeared 1 week later than those in animals fed lower levels of LA (Fig. 1, upper). Although early in the experiment tumor incidence was higher in the four groups fed the lowest levels of LA, the final papilloma incidence at 13 to 15 weeks was 90–100% for all groups, with no apparent relationship to dietary LA level.

Significant differences in papilloma number between diet groups occurred, showing a strong inverse correlation (r = −0.92) between tumor number and the dietary level of LA (Fig. 1, lower). At 15 weeks the groups fed 0.8% LA, the lowest level, averaged 11.7 tumors/mouse, whereas the groups fed 8.4% LA averaged 5.4 tumors/mouse. The dose-response relationship was not linear. The tumor number data appeared to fall into two groups, with the four lowest-LA diets clustered at the high end of the spectrum and the three highest-LA diets clustering near the low end of the spectrum (P < 0.002). When these two groupings were compared, the overall tumor yield was approximately 50% lower for the high-LA diet grouping.

The cumulative carcinoma incidence was determined at monthly intervals (Table 2). The calculation of incidence was confounded by the high mortality rate (due to ulcerative dermatitis) between 20 and 28 weeks for the lowest (0.8% and 2.2%-LA) diet groups. In general, the association between level of dietary LA and survival showed that the mortality rate was highest for the lowest-LA diet groups. The principal cause of death after 25 weeks was carcinoma.

Epidermal Fatty Acid Composition. Because the tumor data derived from the mouse skin model did not agree with reports on the effects of these diets on other organs (3, 5), studies were conducted to determine whether modulation of dietary LA would alter the fatty acid profile of epidermal lipids. As previously shown (14), alterations in the fatty acid composition of epidermal membranes did occur. The effect of dietary LA on the LA and AA composition of phospholipids isolated from epidermal membranes is shown in Table 3. Of principal interest was the PC fraction, which is the phospholipid that undergoes the highest turnover in response to TPA (18). For the 0.8% and 2.2% LA groups, the percentage of LA in PC was similar, but it was significantly higher (P < 0.05) with higher LA diets and reached a maximum in the 8.4% LA diet group. Regression
analysis showed a significant positive correlation (P < 0.01) between dietary LA levels and accumulation of LA in epidermal PC. In contrast, there was an overall reduction of AA in the PC fraction with increasing dietary LA; regression analysis showed a negative correlation (P < 0.22) between dietary LA and AA in epidermal PC.

Similar changes were seen for LA and AA in the other phospholipids; however, few changes were noted in other fatty acids (14). The major saturated fatty acids, i.e., palmitic (16:0) and stearic (18:0), and the monounsaturated oleic acid (18:1) did not follow any discernable pattern or trend. The overall ratio of polyunsaturated to saturated fatty acids remained relatively constant across all diet groups.

PGE2 Production. The effect of these diets on tumor promoter-induced epidermal PGE2 was assessed, to elucidate the reason for the apparent suppression of tumor promotion by dietary LA. Epidermal PGE2 levels were measured 6 h after topical treatment with either acetone or TPA, a time previously determined to correspond to one of the several peaks of PGE2 production that occur after TPA treatment (19, 20). As previously described (14) and as shown in Fig. 2, TPA treatment caused a large increase in PGE2 in all diet groups, although the extent was, in general, negatively correlated with dietary LA (P < 0.05). The 0.8% and 2.2% LA diet groups differed significantly (P < 0.05) from all other diet groups, which did not differ among themselves.

Mammary Tumor Study. To ensure that the findings in the mouse skin model were the result of organ-specific differences and not species-specific differences, we recently carried out a mammary carcinogenesis study in SENCAR mice fed the same diets as in the skin study. In this study, palpable mammary tumors arose sooner than reported with the use of similar protocols (17), enlarged rapidly, and caused morbidity within several weeks of appearance. To obtain non-necrotic tumors, mice were killed when a tumor reached approximately 1 cm in diameter. This procedure precluded determination of tumor multiplicity. Mammary tumor data were thus calculated only as a percentage of mice bearing a histologically verified carcinoma.

Tumor appearance (Fig. 3) was delayed in the lowest-LA diet group (0.8% LA). During the first 15 weeks of the study, the incidence was always greatest in the highest (8.4%)-LA diet group, followed by the 4.5% and the 0.8% LA groups. When the 0.8% LA diet group was compared with the 8.4% LA group, the incidence was significantly different (P = 0.025). When the effects of dietary LA were compared in the two different organ models, increasing dietary LA had opposite effects in the two models (Fig. 4).

The mammary carcinogenesis study was terminated at 18 weeks after the last DMBA treatment, when only 10–20% of the animals were still alive. Deaths from causes other than carcinoma did not differ among diet groups (data not shown). In order of frequency, these causes were lymphomas, unknown pathologies resulting in enlarged spleens and emaciation, and sarcomas, which occurred late in the experiment. Histological analysis of all mammary tumors revealed that the majority (60–75%) were adenosquamous carcinomas; the remainder were of several types, including adenocarcinoma (type A) and undifferentiated carcinomas. All adenosquamous carcinomas had variable histology across the tumor, denoted by both well differen-

- 2051s

Table 2 Cumulative carcinoma incidence

<table>
<thead>
<tr>
<th>Diet (%) LA</th>
<th>23*</th>
<th>29</th>
<th>33</th>
<th>37</th>
<th>41</th>
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</thead>
<tbody>
<tr>
<td>0.8</td>
<td>15</td>
<td>40</td>
<td>47</td>
<td>56</td>
<td>69</td>
</tr>
<tr>
<td>2.2</td>
<td>18</td>
<td>47</td>
<td>87</td>
<td>88</td>
<td>94</td>
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<tr>
<td>3.5</td>
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<td>45</td>
<td>61</td>
<td>68</td>
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<td>4.5</td>
<td>37</td>
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<td>90</td>
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<td>100</td>
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<td>35</td>
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<td>67</td>
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<td>36</td>
<td>71</td>
<td>86</td>
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<td>8.4</td>
<td>7</td>
<td>15</td>
<td>50</td>
<td>59</td>
<td>68</td>
</tr>
</tbody>
</table>

* Weeks.
Table 3 Percentage of AA and LA in the phospholipid fractions of mouse epidermis

<table>
<thead>
<tr>
<th>Phosphatidylcholine</th>
<th>0.8°</th>
<th>2.2</th>
<th>3.6</th>
<th>4.5</th>
<th>5.6</th>
<th>7.0</th>
<th>8.4</th>
</tr>
</thead>
<tbody>
<tr>
<td>18:2</td>
<td>16.5 ± 4.3</td>
<td>17.6 ± 1.9</td>
<td>20.9 ± 3.6</td>
<td>23.8 ± 3.9</td>
<td>22.3 ± 2.8</td>
<td>22.7 ± 3.7</td>
<td>24.2 ± 3.1</td>
</tr>
<tr>
<td>20:4</td>
<td>4.9 ± 0.8</td>
<td>5.5 ± 2.4</td>
<td>3.7 ± 1.1</td>
<td>2.9 ± 0.3</td>
<td>3.0 ± 0.6</td>
<td>2.8 ± 1.0</td>
<td>4.4 ± 1.2</td>
</tr>
<tr>
<td>Phosphatidylethanolamine</td>
<td>13.2 ± 3.7</td>
<td>15.0 ± 1.7</td>
<td>18.5 ± 3.3</td>
<td>15.4 ± 5.4</td>
<td>18.2 ± 2.9</td>
<td>18.4 ± 4.6</td>
<td>18.5 ± 2.6</td>
</tr>
<tr>
<td>18:2</td>
<td>9.9 ± 1.7</td>
<td>14.4 ± 5.8</td>
<td>13.7 ± 3.8</td>
<td>14.8 ± 5.0</td>
<td>8.9 ± 1.2</td>
<td>11.2 ± 2.1</td>
<td>12.9 ± 1.0</td>
</tr>
<tr>
<td>20:4</td>
<td>6.6 ± 4.7</td>
<td>14.4 ± 4.5</td>
<td>ND°</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>15.4 ± 3.3</td>
</tr>
<tr>
<td>Phosphatidylserine/inositol</td>
<td>8.1 ± 2.6</td>
<td>1.6 ± 4.0</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>6.7 ± 0.5</td>
</tr>
<tr>
<td>18:2</td>
<td>4.9 ± 0.8</td>
<td>5.5 ± 2.4</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>9.2 ± 1.7</td>
</tr>
<tr>
<td>20:4</td>
<td>16.5 ± 4.3</td>
<td>17.6 ± 1.9</td>
<td>20.9 ± 3.6</td>
<td>23.8 ± 3.9</td>
<td>22.3 ± 2.8</td>
<td>22.7 ± 3.7</td>
<td>24.2 ± 3.1</td>
</tr>
</tbody>
</table>

° Diets (% LA)
° ND, not determined.

tiated and poorly differentiated regions. In many of the tumors, the more central regions had areas of extensive keratinization. The histological appearance of these tumors agrees with the descriptions by Medina (21) of mammary tumors found in different strains of mice treated with carcinogens.

Discussion

Type of fat, in a 15% fat diet, can have profound effects on the development of tumors in the mouse-skin multistage carcinogenesis model. Specifically, diets with a high proportion of corn oil, the active component of which is believed to be LA, appear to suppress the formation of both benign (papilloma) and subsequently malignant (carcinoma) tumors. Similar effects of dietary LA on tumor promotion were also observed in DBA2 mice (14) and in SENCAR mice using 10% fat diets (13).

To understand the mechanisms by which dietary LA influences skin-tumor promotion, consideration must be given to the several metabolic fates and functions of LA in the skin. First, there has been much interest in the role of eicosanoids in skin-tumor promotion. Numerous studies showed that TPA induces the release of free AA from membrane phospholipids (10), which greatly increases the synthesis of prostaglandins and lipooxygenase products (10, 19-20, 22). Inhibitors of AA metabolism inhibit both skin tumor promotion in mice (10) and chemically induced mammary tumorigenesis in rats (23,
24), indicating an involvement of eicosanoids in tumor development in both organs. Cohen et al. (25) showed that increasing dietary LA correlated with enhanced mammary tumor PGE2 production. In skin, however, we observed an inverse correlation between dietary LA and TPA-induced epidermal PGE2 levels. Such a reduction in PGE2 levels could result from either reduced substrate availability, competition with other fatty acids, or altered regulation of the metabolic enzymes. The substrate for PGE2 synthesis, AA, is not provided directly by the diet but instead is synthesized from LA by a series of elongation and desaturation reactions. Liver is the primary site for this conversion (26); the epidermis of several species, including rat, guinea pig, and mouse, have little if any desaturase activity (Ref. 27 and data not shown). An inverse correlation was found between dietary LA and AA levels in membrane PC in skin (14). This reduction in AA is consistent with a lack of desaturase and elongase activity in skin and may at least partially explain the reduced PGE2 production after TPA treatment. It was also reported that the metabolism of AA to PGE2 can be inhibited by several fatty acids, including LA, linoleic acid, and oleic acid (28, 29). Multiple mechanisms may thus account for the imperfect correlation observed between AA and PGE2 levels. Reducit in PGE2 is associated with reduction in tumor number (14), a relationship also observed with anti-inflammatory agents (10). However, the relationship is not ideal (14), indicating that reduction of eicosanoids is probably not the only mechanism of inhibition of tumor promotion by high dietary LA.

In addition to its effects on eicosanoid production, LA can have profound effects on the regulation of cellular proliferation and differentiation and on the integrity of the permeability barrier. There is substantial evidence (30, 31) that LA can be metabolized by 15-lipoxygenase (normally responsible for the metabolism of AA to 15-hydroxy-eicosatetraenoic acid) to HODEs. Biological activity of HODEs has only recently been demonstrated and includes 13-HODE inhibition of tumor-cell adhesion (32, 33). A recent report (34) suggests that, although lipoxygenase-mediated oxidation of LA is not a major process in normal epidermis, it may be significant in pathological conditions such as psoriasis (35, 36) and, therefore, possibly tumor promotion. LA also contributes to the barrier function of the skin, which is principally due to LA-rich ceramides (37). Because the composition and concentration of lipids making up the barrier affect the penetration of topically applied agents (37, 38), it is possible that increasing dietary LA decreases the ability of TPA to penetrate. Further investigation is clearly warranted, to determine whether the mechanisms described above are involved in the suppression of tumor promotion by dietary LA.

The possible effect of saturated fatty acids on skin-tumor promotion also needs consideration. In the experimental diets used in this study, the level of saturated fatty acids decreased with increasing LA. There are several reports that maintenance of animals on diets high in saturated fatty acids prolongs the latent period for tumor appearance and inhibits tumor incidence (4, 39, 40). Although alterations in membrane fluidity have been implicated (39), how this alters critical cellular processes remains to be determined.

The relationship between dietary LA level and tumor development in mouse skin (14) is quite different from, and in fact appears to be opposite, that reported for rat mammary gland (3, 4) and rat pancreas (5). Because there are many examples of organ specificity with regard to types or effects of promoting agents or their modifiers, and because it is also possible that there could be species differences in the disposition of essential fatty acids between rat and mouse, a mammary carcinogenesis experiment was carried out in SENCAR mice fed the same diets as used in the skin study. The positive association between level of dietary LA and mammary-tumor incidence clearly establishes that organ-site differences, rather than species differences, exist. The outcome of this mouse mammary study did differ from those of studies using rats (3, 4), in that a significant increase in incidence was observed with LA levels higher than 4.5%. In this respect, the mouse mammary model is similar to the rat pancreas (5), in that a maximum level of LA, with respect to tumor yield, has not been observed.

Another aspect that must be taken into account is that the mechanisms involved in the promotion stage of skin carcinogenesis are different from the mechanisms involved in chemical carcinogenesis of mammary tissue. The two model systems differ in several important aspects. Foremost, the mammary model does not use exogenous or xenobiotic tumor promoters. Prolactin and estrogen may act as endogenous promoting agents in the mammary model, but they do not produce an inflammatory state in the mammary gland. In mouse skin, topical application of tumor promoters causes inflammation, a condition involving production of high levels of eicosanoids. There is some evidence that TPA-induced inflammation causes the overlying epidermis to become hyperplastic (41), an event essential for promotion (42). In the mammary gland, increased proliferation is also required but is the result of gland development in the young female. In this carcinogenesis model, it has been suggested that prostaglandins may be critical growth-stimulatory factors. In this respect, both the mammary and skin carcinogenesis models have in common the elements of increased proliferation and elevated eicosanoids. The extent to which these or other factors are major determinants or modulators of tumorigenesis in either organ remains uncertain.

The conclusions that emerge from this study are 2-fold. First, they emphasize the need to better understand the basic mechanisms of tumorigenesis in the different organ models. It is difficult to explain the current disparity in the effects of dietary fats on tumorigenesis at different organ sites without such understanding. Second, more studies are needed before recommendations are made to alter the human diet for cancer prevention, particularly in light of the increasing incidence of skin cancer.

References

8. Carter, C. A., Ip, M. M., and Ip, C. A comparison of the prostaglandin synthetase inhibitors indomethacin and carprofen on 7,12-dimethyl-


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