

Cows' Milk Fat Components as Potential Anticarcinogenic Agents¹

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ABSTRACT The optimum approach to conquering cancer is prevention. Although the human diet contains components which promote cancer, it also contains components with the potential to prevent it. Recent research shows that milk fat contains a number of potential anticarcinogenic components including conjugated linoleic acid, sphingomyelin, butyric acid and ether lipids. Conjugated linoleic acid inhibited proliferation of human malignant melanoma, colorectal, breast and lung cancer cell lines. In animals, it reduced the incidence of chemically induced mouse epidermal tumors, mouse forestomach neoplasia and aberrant crypt foci in the rat colon. In a number of studies, conjugated linoleic acid, at near-physiological concentrations, inhibited mammary tumorigenesis independently of the amount and type of fat in the diet. In vitro studies showed that the milk phospholipid, sphingomyelin, through its biologically active metabolites ceramide and sphingosine, participates in three major antiproliferative pathways influencing oncogenesis, namely, inhibition of cell growth, and induction of differentiation and apoptosis. Mice fed sphingomyelin had fewer colon tumors and aberrant crypt foci than control animals. About one third of all milk triacylglycerols contain one molecule of butyric acid, a potent inhibitor of proliferation and inducer of differentiation and apoptosis in a wide range of neoplastic cell lines. Although butyrate produced by colonic fermentation is considered important for colon cancer protection, an animal study suggests dietary butyrate may inhibit mammary tumorigenesis. The dairy cow also has the ability to extract other potential anticarcinogenic agents such as β -carotene, β -ionone and gossypol from its feed and transfer them to milk. Animal studies comparing the tumorigenic potential of milk fat or butter with linoleic acid-rich vegetable oils or margarines are reviewed. They clearly show less tumor development with dairy products. *J. Nutr.* 127: 1055–1060, 1997.

KEY WORDS: • *milk fat* • *anticarcinogens* • *conjugated linoleic acid* • *sphingomyelin* • *butyric acid*

The considerable emphasis placed on cancer research during the past 25 y has resulted in remarkable insight into the molecular biology of the cell and improved treatment of cancer by surgery, radiation and chemotherapy. There have been pronounced declines in death from some cancers, notably Hodgkin's disease, Burkitt's lymphoma, lymphocytic leukemia, testicular cancer and a range of childhood carcinomas. However, there is little change in survival rates for patients with the most common types of invasive and metastatic carcinoma of the epithelia of the breast, lung, oropharynx, pancreas, colon, bladder and prostate (Sporn 1996). This argues for a change in emphasis from treatment to prevention.

Most cancers have a multifactorial etiology with both genetic and environmental factors contributing to risk. A review of epidemiologic studies suggests that about 35% of cancer deaths are attributable to diet with a range of 20 to 60% for the various sites (Doll 1992). The food we eat contains components that may either help cause or help prevent cancer (Ames et al. 1995, Doll 1996). The evaluation of natural components with cancer prevention properties in food is now an important element of overall cancer prevention strategy. Most investigations involve components of vegetable origin;

however, this review outlines recent research which indicates that milk fat contains a number of components with anticarcinogenic potential.

CONJUGATED LINOLEIC ACID

Conjugated linoleic acid (CLA)² is a collective term to describe one or more positional and geometric isomers of linoleic acid (*cis*-9, *cis*-12 octadecadienoic acid). Conjugated double bonds are usually at positions 9 and 11 or 10 and 12; each double bond can be in either the *cis* or *trans* configuration. In animal experiments, CLA inhibited 7,12-dimethylbenz[a]anthracene (DMBA)-induced mouse epidermal tumors (Ha et al. 1987) and benzo[a]pyrene-induced mouse forestomach neoplasia (Ha et al. 1990). In mice, DNA-adducts, formed in a number of organs after administration of the grilled-beef heterocyclic amine 2-amino-3-methylimidazo[4,5-f]quinoline (IQ), were inhibited by CLA (Zu and Schut 1992). Feeding CLA also protected against IQ-adduct formation in the rat colon, and, importantly, the number of aberrant crypt foci per colon (a microscopically determined early preneoplastic marker of malignant potential in the process of colon carcinogenesis) was markedly inhibited (Liew et al. 1995).

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² Abbreviations used: CLA, conjugated linoleic acid; DMBA, 7,12-dimethylbenz[a]anthracene; DMH, 1,2-dimethylhydrazine; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A; IQ, 2-amino-3-methylimidazo[4,5-f]quinoline.

In rat mammary tumor models, CLA has proved a potent anticarcinogen. Feeding CLA 2 wk before DMBA administration and continuing until the conclusion of the experiment resulted in a significant reduction in tumor incidence (Ip et al. 1991). Another experiment using a lower dose of carcinogen showed that as little as 0.1 g CLA/100 g diet caused a reduction in the number of mammary tumors (Ip et al. 1994). These two experiments demonstrated that CLA acted in a dose-dependent manner at up to 1 g/100 g of diet after which there was no further benefit. Short-term feeding of CLA from weaning (21 d of age) to time of carcinogen administration (50 d) only, also resulted in suppressed tumor production when either DMBA or methylnitrosourea were used as carcinogens (Ip et al. 1994). This period of 21–50 d corresponds to the maturation of the rat mammary gland to adult stage morphology. Inhibition of mammary tumors by CLA was not influenced by the amount or type of fat in the diet (Ip et al. 1996). All isomers of CLA were incorporated into tissue triacylglycerols but only the *cis*-9, *trans*-11 isomer was incorporated into membrane phospholipids and is assumed to be the biologically active isomer (Ha et al. 1990, Ip et al. 1991).

It is important to learn from these experiments that feeding CLA only during the postweaning and peripubertal period and before carcinogen administration affords protection against subsequent mammary tumor development. On the other hand, when rats with mature mammary glands do not receive CLA supplementation until the time of tumor induction, then feeding for life is required to gain protection. This is an important clue to understanding the process of mammary carcinogenesis, and studies on the interaction of CLA, other fatty acids, developing mammary tissue and carcinogens should follow.

In cell culture studies, physiologic concentrations of CLA inhibited the proliferation of human malignant melanoma, colorectal and breast cancer cells (Shultz et al. 1992) and three lung adenocarcinoma cell lines, but not a glioblastoma cell line (Schonberg and Krokan 1995). Mechanisms by which CLA influences carcinogenesis, although well studied, are largely unresolved, and may vary for different sites, age, duration of exposure and stage of carcinogenesis. Various studies suggest that CLA may act by antioxidant mechanisms (Ha et al. 1990, Ip et al. 1991), prooxidant cytotoxicity (Schonberg and Krokan 1995), inhibition of nucleotide synthesis (Shultz et al. 1992), reduction of proliferative activity (Ip et al. 1994) and inhibition of both DNA-adduct formation (Zu and Schut 1992) and carcinogen activation (Liew et al. 1995).

CLA in milk fat. Milk fat is the richest natural dietary source of CLA, which is almost entirely the *cis*-9, *trans*-11 isomer (Parodi 1977). This is produced in ruminant animals as a first intermediate in the biohydrogenation of dietary linoleic acid by a linoleic acid isomerase from the rumen bacteria *Butyrivibrio fibrisolvens*. A review of country and seasonal variations in CLA concentration of milk fat by Riel (1963) showed a range of 8.6–100 $\mu\text{mol/g}$. Seasonal variation was very marked, with values during the summer period often up to three to four times higher than winter values. CLA content of other dairy products, depot fat from ruminant and nonruminant animals, vegetable oils and a wide variety of other foods, is reported by Chin et al. (1992), Fogerty et al. (1988) and Lin et al. (1995). For Australian milk fat and ruminant meat (Fogerty et al. 1988, Parodi 1977), CLA values were up to two to three times higher than comparable American products (Chin et al. 1992). This may reflect the usual year-round availability of fresh pasture in the major Australian milk-producing regions. Nevertheless, factors responsible for variation in product CLA content require further investigation.

Dietary modification of CLA levels in tissues. Human depot fat, bile, duodenal juice and blood serum contain CLA (Parodi 1994). Britton et al. (1992) and Huang et al. (1994) were able to increase blood CLA levels in human subjects by feeding CLA-rich diets.

This is significant because Ip et al. (1994) calculated that mammary tumor reduction in rats fed a diet containing as little as 0.1 g/100 g diet extrapolated to an amount only slightly higher than estimated human consumption in the United States. They were tempted to speculate that the presence of CLA in the Western diet may play a role in moderating the effect of high fat consumption on breast cancer risk. Indeed, CLA was suggested as a possible factor responsible for the inverse association between milk consumption and breast cancer risk in a recently reported Finnish prospective study (Knekt et al. 1996). Interestingly, Fogerty et al. (1988) found breast milk from women of the Hare Krishna religious sect contained twice as much CLA as milk from conventional Australian mothers (40.0 vs. 20.7 $\mu\text{mol/g}$). This was attributed to the butter and ghee (milk fat) diets consumed habitually by the Hare Krishna women. In India, where ghee is often used, various religious communities have age-adjusted breast cancer rates which vary up to threefold (Jussawalla et al. 1985). This suggests an interesting case-control study on the association between consumption of cow and buffalo ghee, other CLA-rich products and incidence of breast cancer in Indian women.

SPHINGOMYELIN AND METABOLITES AS TUMOR SUPPRESSOR LIPIDS

Sphingomyelin (*N*-acylsphingosine-1-phosphocholine or ceramide phosphocholine) is a phospholipid preferentially located in the outer leaflet of the plasma membrane of most mammalian cells. In bovine milk, phospholipids account for 0.2–1.0 g/100 g of total lipids, where they are associated with the milk fat globule membrane. When milk is processed, this membrane is disrupted and the phospholipids may relocate to the aqueous phase. The degree of transfer depends upon the type and severity of treatment. Sphingomyelin represents about one third of total milk phospholipids; variation in content is influenced by season and the cows' stage of lactation (Parodi 1996).

In addition to its structural function in membranes, it is now recognized that sphingomyelin, through its biologically active metabolites ceramide and sphingosine, plays an important role in transmembrane signal transduction and cell regulation (Hannun 1994, Merrill 1991, Zhang and Kolesnick 1995). A sphingomyelin pathway of signal transduction has recently been identified. Extracellular agonists, such as certain cytokines, hormones or growth factors, stimulate their cell-surface receptors to activate a sphingomyelinase (a specific form of phospholipase C), which cleaves sphingomyelin to generate cellular ceramide and phosphocholine. Ceramide in turn acts as a second messenger for the action of the extracellular agonist, transmitting the signal towards the nucleus through multiple downstream targets. Important among these are protein kinase C (zeta isoform), ceramide-activated protein phosphatase and ceramide-activated protein kinase. These targets have a role in activation of a number of factors such as the transcription factor NF κ B, which participates in the control of cell proliferation; dephosphorylation of the retinoblastoma gene product (pRb), a tumor suppressor gene that plays an important role in cell-growth suppression and regulation of cell-cycle progression; and downregulation of expression of the proto-oncogene *c-myc*, which plays an important role in both cell proliferation and apoptosis. These ceramide-mediated pathways are related to three important cell-regulating func-

tions that exert antiproliferative effects in cells, i.e., differentiation, cell-cycle arrest and programmed cell death or apoptosis (Hannun 1994, Hannun and Linardic 1993, Jarvis et al. 1996, Merrill et al. 1993).

Ceramide may be hydrolyzed intracellularly by ceramidase to produce sphingosine. Sphingosine is also associated with a number of cell-regulating pathways. It is a potent inhibitor of protein kinase C, which is closely associated with tumor progression and metastatic potential and can modulate the activity of some other protein kinases and enzymes involved in cell regulation (Hannun and Linardic 1993, Merrill 1991, Merrill et al. 1993). Sphingosine can downregulate c-myc gene expression and can induce pRb dephosphorylation, cell differentiation and apoptosis (Hannun and Linardic 1993, Merrill 1991, Merrill et al. 1993, Ohta et al. 1995). Ceramide and sphingosine participate in three major antiproliferative pathways of cell regulation, i.e., inhibition of cell growth, induction of cell differentiation and induction of apoptosis. Because these pathways may contribute to the suppression of oncogenesis, the bioactive metabolites of sphingomyelin are referred to as tumor suppressor lipids (Hannun 1994).

Animal dietary studies with sphingomyelin. Can dietary sphingomyelin influence the reviewed antiproliferative pathways? The digestion of sphingomyelin and the absorption of its metabolites are poorly understood. An early study by Nilsson (1968) and a recent one by Schmelz et al. (1994) suggest that sphingomyelin is digested throughout the whole length of the small intestine and colon. The major metabolites, ceramide and sphingosine, pass from the lumen to intestinal cells where they are utilized to resynthesize sphingomyelin and other sphingolipids, which then largely pass to the circulation. In rats, Imaizumi et al. (1992) found that sphingomyelin-rich sphingolipid diets increased serum phospholipid sphingomyelin in a dose-dependent manner. These studies suggest that dietary sphingomyelin may be beneficial to the small and large intestine and perhaps to tissues supplied by circulating sphingomyelin.

To date, the anticarcinogenic effect of dietary sphingomyelin has been examined in only one study. Dillehay et al. (1994) fed female CF1 mice diets supplemented with milk sphingomyelin after initiation with the carcinogen 1,2-dimethylhydrazine (DMH). Mice fed sphingomyelin had a 20% incidence of colon tumors compared with 47% in controls ($P = 0.08$). Note, however, that the supply of sphingomyelin was exhausted after 28 wk. At this time, tumors had not developed in a group of sample animals; thus the remaining animals were fed the control diet for an additional 24 wk. Further, no additional benefit was observed when supplementation was increased above the lowest concentration tested (0.025 g sphingomyelin/100 g diet). In another experiment, the number of colonic aberrant crypt foci was significantly lower in sphingomyelin-treated mice. These results, obtained with a limited supply of sphingomyelin, short feeding time and limited numbers of mice, offer exciting prospects for further research.

BUTYRIC ACID

A unique feature of milk fat from ruminant animals is the presence of butyric acid. Butyrate is a potent inhibitor of proliferation and an inducer of differentiation and apoptosis in a number of cancer cell lines (Hague and Paraskeva 1995, Lupton 1995, Mandal and Kumar 1996). At the molecular level, butyrate causes histone hyperacetylation and DNA hypermethylation. Both of these events are associated with downregulation or inactivation of oncogene expression. Butyrate may also play a role in the prevention of tumor invasiveness

and metastasis by inhibiting urokinase, a facilitator of malignant cell penetration to the substratum (Young and Gibson 1994).

The colon is the organ mostly associated with butyrate, which results from fermentation of nonabsorbed carbohydrate by colonic microflora. Butyrate is utilized by colonocytes as an important energy source or passes from the basolateral membrane to the portal circulation where most is rapidly cleared by the liver with little reaching other tissues (Young and Gibson 1994). Although butyrate inhibits proliferation in colon cancer cell lines, paradoxically, it stimulates proliferation in normal colonocytes. This is not considered preneoplastic, however, because it is the cells of the colonic crypt base that are dividing and not those at the crypt surface, which remain differentiated (Velazquez et al. 1996). Colonic generation of butyrate is considered one factor associated with the protective effect of dietary fiber for colon cancer. In a rat model, there were significantly fewer DMH-induced colon tumors associated with high butyrate concentrations in the distal colon in animals fed fiber than in those fed soluble fiber, which did not raise colonic butyrate levels (McIntyre et al. 1993). Not all data, however, support a protective role for butyrate and fiber in colon cancer. The discordant evidence is reviewed by Lupton (1995).

Parenteral administration of sodium butyrate to treat patients with leukemia met with little success because butyrate had a short plasma half-life and was rapidly metabolized (Miller et al. 1987). To prolong plasma half-life, more stable butyrate derivatives are being developed. However, even esterification as part of a triacylglycerol may improve the half-life of orally administered butyrate in plasma (Newmark and Young 1995). In addition, synergy with other dietary micronutrients may reduce the plasma concentrations of butyrate required to exert a physiological effect. Accordingly, 1, 25-dihydroxycholecalciferol, the active metabolite of cholecalciferol, enhanced butyrate-induced differentiation in a human colon cancer cell line (Tanaka et al. 1989). Similarly, Chen and Breitman (1994) found that retinoic acid, at concentrations found in normal blood plasma, reduced about 10-fold the concentration of butyrate required to induce differentiation in a human myeloid leukemia cell line. Milk fat is a major dietary source of vitamin A and β -carotene and contains cholecalciferol (fortification with cholecalciferol occurs in some countries). The use of these fat-soluble vitamins in cancer prevention is frequently reviewed and will not be covered here.

Bovine milk fat contains from 7.5 to 13.0 mol/100 mol butyric acid. Because dibutyrylacylglycerols are present in trace amounts only, this means that about one third of milk fat triacylglycerols contain one molecule of butyrate. On ingestion, lipase-mediated hydrolysis of butyrate commences in the stomach and will be complete on reaching the proximal small intestine. Liberated butyrate is absorbed from the intestinal lumen to the enterocytes; it then passes directly to the portal circulation for transport to the liver where most is metabolized (Parodi 1996). Can butyrate from this source or together with colonic generated butyrate, as a result of a high fiber diet, modulate carcinogenesis at sites other than the colon? The evidence is meager; however, Yanagi et al. (1993) found that the addition of 6 g/100 g sodium butyrate to a basal diet containing 20% safflower oil-based margarine significantly reduced the incidence of DMBA-induced rat mammary carcinomas and adenocarcinomas. Clearly, this aspect of butyrate cancer protection merits further study.

ETHER LIPIDS

Alkylglycerols, alkylglycerophospholipids and their derivatives, referred to as ether lipids, are potent antineoplastic

agents which inhibit growth, show antimetastatic activity and induce differentiation and apoptosis in cancer cells (Berdal 1991, Diomedede et al. 1993). Bovine milk fat neutral lipids contain ~0.01% of 1-*O*-alkylacylglycerols, whereas the phospholipids have ~0.16% of 1-*O*-alkylacylglycerophospholipids. Trace amounts of 1-*O*-(2-methoxyalkyl) acylglycerols are present in both neutral lipids and phospholipids (Hallgren et al. 1974). Studies in rodents and humans showed that 1-*O*-alkyl-*sn*-glycerols liberated from dietary ether lipids in the intestinal lumen were readily absorbed without cleavage of the ether bond, transported to the liver and other organs where they were directly utilized to synthesize membrane alkylglycerolipids and plasmalogens (Das et al. 1992). A role for dietary ether lipids in cancer prevention has not been reported.

MILK FAT VS. OTHER DIETARY FATS IN CARCINOGENESIS

Although milk fat contains a number of potential anticarcinogenic compounds, is there any evidence to suggest that it has a restricting effect on cancer development? Epidemiologic studies have not addressed this issue because milk fat is rarely consumed as a single dietary entity. A number of studies have shown that dairy product consumption may decrease risk at some sites; however, because milk proteins (McIntosh et al. 1995), calcium (Newmark and Lipkin 1992) and lactic acid bacteria (Goldin et al. 1996) also have anticarcinogenic properties, it is not possible to isolate the effect of milk fat exposure in these studies.

There are a few studies in which milk fat or butter was compared isocalorically with vegetable oils or margarines in animal models of carcinogenesis. In an early study, Carroll and Khor (1971) found that all fats fed at 20% of diet resulted in high tumor incidence (% of animals with tumors); however, vegetable oils enhanced DMBA-induced rat mammary adenocarcinomas more than butter and some other saturated fats. Female Sprague-Dawley rats were given DMH or DMBA to induce either colon or mammary tumors. They were fed basal diets containing 15 g/100 g butter oil (B) or 15 g/100 g corn oil (C) with skimmed milk powder (M) or casein and sucrose (S) to provide four treatments, MB, MC, SB and SC. Subsequent colon tumor incidence was 46, 83, 46 and 78%, respectively (Klurfeld et al. 1983a). When Klurfeld et al. (1983b) fed rats these diets from weaning, DMBA-induced mammary tumor incidence was MB (20%), MC (58%), SB (26%) and SC (56%). However, when the diets were not introduced until after initiation, tumor incidence was higher at 56, 70, 70 and 100%, respectively.

Yanagi et al. (1989) fed female mice after weaning either a basal diet or that diet enriched with 20% butter, margarine (64 g linoleic acid/100 g fatty acids) or safflower oil. The incidence of spontaneous mammary tumor development, mainly adenocarcinomas, was significantly less in the butter-fed group (21%) than in the margarine- (43%) and safflower oil- (44%) fed groups. Similar diets were then fed to female rats from 1 wk before tumor induction with DMBA. The percentage of mammary tumor incidence was as follows: basal diet (which contained only 4.9% fat) 44%, butter 36%, margarine 63% and safflower oil 46%. To determine if the inhibitory effect of butter on mammary tumor development was due to milk lipids, Yanagi et al. (1992) fed rats under similar conditions either a basal diet (4.6% fat) or the basal diet supplemented with dried whole milk (8.9% fat), skim milk (3.9% fat) or milk cream (20.8% fat). In this case, rats fed the high milk fat cream diet did not have enhanced tumor development (42.3%) compared with rats fed the basal diet (42.3%), dried

whole milk diet (60%) or the skim milk diet (52%). Next, Yanagi et al. (1994) fed rats a basal diet supplemented with margarine (60 g linoleic acid/100 g fatty acids) at the 5, 10 and 20% levels. This resulted in a mammary tumor incidence of 40, 70 and 80%, respectively. When 20% butter replaced 20% margarine in the diet, rats had a nonsignificantly lower tumor incidence of 70%. However, total tumor numbers (99 vs. 48), average tumor numbers (6.19 vs. 3.42) and average tumor diameter (11.6 vs. 9.6 mm) were significantly lower in the butter group. Cope and Reeve (1994) recently demonstrated that, compared with butter and milk fat, polyunsaturated margarine and sunflower oil enhanced both ultraviolet (UV) light and UV light/DMBA-induced photocarcinogenesis in a hairless mouse model.

These animal models, in which high total fat intake itself is a risk factor for colon cancer (Reddy 1992) and mammary cancer (Welsch 1992), clearly demonstrate that milk fat-based diets produce fewer tumors than polyunsaturated vegetable oil-based diets. The studies, however, were of insufficient design to determine adequately if the differences were due to the anticarcinogenic components of milk fat or to the known potential for linoleic acid to promote carcinogenesis in animal models of colon cancer (Reddy 1992), mammary cancer (Ip et al. 1985, Welsch 1992) and skin cancer (Reeve et al. 1988). Further studies of appropriate design in which linoleic acid and energy intake are balanced should be conducted to resolve this point. For obvious ethical reasons, animal models must be used; although such models have greatly enhanced our understanding of carcinogenesis, caution should be exercised in extrapolating data to a clinical situation.

FUTURE PROSPECTS

The dairy cow has a special ability to act as an efficient biological extractor and converter of pharmacological compounds from pasture and other feedstuff, ordinarily not suitable for human consumption, and transfer them to milk. A well-known example is the intake of β -carotene from pasture. During absorption and transport, a portion of β -carotene is converted to vitamin A in the intestine and liver, and both are subsequently transferred to milk. Cottonseed meal is often used as a protein supplement for dairy cows. The meal contains the polyphenolic pigment gossypol. Gossypol exhibits antineoplastic and antiproliferative action on a variety of human epithelial cancer cell lines (Hu et al. 1994). Milk from cows, treated with the U.S. federal government limit of 450 ppm gossypol, significantly inhibited proliferation in both hormone-dependent drug-sensitive and multidrug-resistant human breast cancer cell lines as well as a rat esophageal cancer cell line in a dose-dependent manner (Hu et al. 1994).

The pasture species alfalfa (lucerne) contains the isoprenoid β -ionone, an end ring analog of β -carotene, which is transferred to milk (Yu et al. 1994). β -Ionone is a potent anticarcinogenic and tumor-suppressing agent, whose action is linked to the suppression of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase activity, resulting in arrest of cell division at the G₁/S interface of the cell cycle (Elson 1995). DMBA-induced rat mammary tumor incidence was reduced from 90% in control rats to 30% in rats whose diets were supplemented with β -ionone (Elson and Yu 1994). Similarly, administration of pravastatin and simvastatin, serum cholesterol-lowering drugs that act by inhibiting HMG-CoA reductase activity, significantly reduced the incidence of DMH-induced colon tumors in mice (Narisawa et al. 1994). Studies on the effect of dietary cholesterol on cancer at various sites have shown conflicting results. However, two recent studies,

using animals whose serum cholesterol was sensitive to dietary cholesterol, found that dietary cholesterol significantly inhibited methylnitrosourea-induced rat mammary tumorigenesis (El-Sohehy et al. 1996a) and azoxymethane-induced aberrant crypt foci in the colon of mice (El-Sohehy et al. 1996b). In both of these studies, dietary cholesterol produced an elevation in serum LDL cholesterol levels. The authors believe that LDL cholesterol entering cells via the LDL-receptor acts as a negative feedback inhibitor of endogenous cholesterol biosynthesis by reducing the level of HMG-CoA reductase. This rate-limiting enzyme in the cholesterol biosynthetic pathway converts HMG-CoA to mevalonate, which is required for DNA synthesis and cell proliferation.

Potential cancer chemopreventive agents from products of vegetable origin are actively being evaluated. It is feasible that some of these compounds may be transferred to milk by feeding products such as vegetable or cannery waste and spent brewers grains to dairy cows. These compounds, and those outlined in this review, may act either by themselves, cooperatively or synergistically to prevent cancer.

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