
MINI-REVIEW

Milk Components as Cancer Chemopreventive Agents

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Abstract

Since milk and dairy products constitute very important ingredients of the western style diet, a large number of epidemiological studies have been conducted to determine effects of their consumption on neoplastic development. However, reflecting the variety of included components, the data are to some extent equivocal. It has been proposed that whereas fats in general might promote tumour development, individual milk fats like conjugated linoleic acid and glycosphingolipids could exert inhibitory effects. There is also considerable evidence that calcium in milk products protects against colon cancer, while promoting in the prostate through suppression of circulating levels of 1,25 dihydroxyvitamin D. Whey protein may also be beneficial, as shown by both animal and human studies, and experimental data have demonstrated that the major component bovine lactoferrin (bLF), inhibits colon carcinogenesis in the post-initiation stage in male F344 rats treated with azoxymethane (AOM) without any overt toxicity. Results in other animal models have provided further indications that bovine lactoferrin might find application as a natural ingredient of milk with potential for chemoprevention of colon and other cancers.

Key words: milk components - lactoferrin - whey proteins - preventive agents

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Introduction

Dietary factors clearly have a major impact on cancer development, as well as other chronic diseases (World Cancer Research Fund, American Institute for Cancer Research], 1997) and one of the most important components of diet, especially in the Western world, but increasingly also in Asia, is milk or dairy products like butter, cheese and yogurt. Cow's milk is the most frequently encountered, although there is considerable geographical variation, with goat, sheep and camel milk consumed in the Middle East and the water buffalo as a traditional source in Asia. Milk contains something in the region of 3g of protein, 4g of fat and 5g of lactose and other sugars per 100g. Other important ingredients include calcium, riboflavin, vitamin B12 and retinoids, all of which are of potential significance for tumor development.

Epidemiological Studies

A large number of epidemiological studies have been performed aimed at assessing the influence of milk intake

on cancer development but the data are generally equivocal, in line with the complex mixture of ingredients. The World Cancer Research Fund (1997) concluded possible increased risk for kidney and prostate cancer for milk and dairy products, but not for any other site.

Relatively extensive data are available for squamous cell carcinoma of the mouth and pharynx, but despite some indications of protection (La Vecchia et al., 1991), they are inconsistent, while two of four studies of the cervix demonstrated decreased risk and the others no association (La Vecchia et al., 1988; Verrault et al., 1989; Ziegler, et al., 1990; 1991). Buttermilk may protect, also in the oesophagus (Notani and Jayant, 1987) while skimmed rather than whole milk may be beneficial in general for squamous epithelium (Tuyns et al., 1987). There may be a link between adolescent intake and testicular cancer (Davies et al., 1996).

Regarding sites of adenocarcinoma development, the results have only pointed to weak associations for milk alone, and none for cheese in the pancreas (Farrow and Davis, 1990; La Vecchia et al., 1990, Webb et al., 1998). There may be protective effects against colon like Seventh Day Adventists (Phillips, 1975) and in France and Italy (Macquart-Moulin

et al., 1986; Centonze et al., 1994). Although an increased risk of rectal but not colon cancer has been noted in Spain (Benito et al., 1990), in the breast, the majority of studies have pointed to no effect or increase and a meta-analysis, conducted in 1993, concluded a weak increase in risk (Boyd et al., 1990). Similarly, a promoting effect has been suggested for the kidney and the prostate, with a possible role for the included fat suggested by case-control studies, although one large cohort study in America did not reveal any link to advanced prostate malignancy (Giovannucci, et al., 1993).

Milk Components

The difficulty with all these epidemiological studies is that it is exceedingly difficult to distinguish between effects of the various ingredients. There appears to be a general link between calorific intake and cancer and milk products are high in fat, significant correlations being found between site-specific cancer mortality and dairy fat intake for breast, prostate, rectum, colon and lung, perhaps with a link to ischemic heart disease mortality (Kesteloot et al., 1991).

Milk Fats

However, individual milk fat components are also potential anticarcinogenic agents, including conjugated linoleic acid, ether lipids, butyric acid and sphingomyelin (Parodi 1997). These and certain vitamins have recently been reviewed by Parodi (1999), conjugated linoleic acid inhibiting development of rat mammary gland tumors as well as proliferative activity in the breast epithelium (Ip et al., 1994). This may be related to morphological development and differentiative status of the mammary gland, so that the sensitivity to carcinogen is reduced, although post-initiation inhibition has also been described (Ip et al., 1995). Glycosphingolipids are reported to inhibit colonic cell proliferation and aberrant crypt formation (Schmelz et al., 2000). The milk phospholipid, sphingomyelin, could exert an antiproliferative influence via its biologically active metabolites, sphingosine and ceramide, while butyrate in milk triacylglycerols has general potential for prevention of colon cancer (for reviews see Parodi, 1999; Moore et al., 1998). Clearly other potential protective agents could be transferred into milk by ruminants, like antioxidants present in plant feed.

Calcium

Calcium has long attracted attention as a component abundant in milk, and both clinical and experimental studies have pointed to an inverse link between intake and colon cancer development. Supplements have been reported to decrease ornithine decarboxylase activity and the colonic epithelial hyperproliferation induced by bile and fatty acids, as well as nutritional stress and enteric resection (Pence, 1993). Calcium was also emphasized to be a protective factor in the colon in a review by McIntosh (1993). In one study in volunteers, transfer from a dairy-product-rich to dairy-product-free diet was associated with significant decrease

in calcium intake and an increase in an accepted cytotoxicity-associated risk factor for colon cancer (Glinghammar et al., 1997). Although a randomized controlled trial in outpatients demonstrated a reduction in colonic epithelial cell proliferative activity, a shift towards acidic mucins, and nuclear size towards normal with low fat dairy products (Holt et al., 1998), in another study, no change in rectal mucosal cell proliferation was noted with change in consumption in milk and dairy products (Karagas et al., 1998). Nonfat dried milk as a source of calcium was found in one rat model to be associated with decrease in lesion development when given together with a high fat diet (Pence et al., 1996). The data thus appear to be relatively consistent for calcium protection in the colon but at least in one other organ the opposite may be the case. Recently it has been proposed that 1,25 dihydroxyvitamin (1,25(OH)₂D) is protective for prostate cancer, and high serum levels of calcium and phosphorus, to a large extent from dairy products, can cause a reduction in circulating 1,25(OH)₂D (Giovannucci, 1998). Epidemiological evidence has been obtained in support of this hypothesis that this may explain the observed positive association between milk products and prostate cancer (Chan et al., 1998).

Milk Proteins

The major milk proteins, caseins, whey proteins and membrane structures, might all exert preventive effects (Bounous et al., 1988; 1991). In addition to protecting the mammary gland against carcinogen exposure (Hakkak et al., 2000, in colon cancer models in rats, whey protein concentrate was found to be protective relative to other protein sources (Bounous et al., 1988; McIntosh, 1993) this being associated with an increase in the intracellular levels of glutathione, whey being a prime source of precursors McIntosh et al., 1995). An importance for elevated GSH synthesis has also been argued by Bounous et al. (1991). Compared to Purina diet, whey protein administration to DMH-treated mice in the post-initiation stage resulted in a decrease in the colon tumor burden and prolongation of survival (Papenberg et al., 1990), perhaps related to a boost to the immune system McCormick et al., 1991). Milk treatment of rats initiated with DMBA or IQ has also been reported to potentiate the protective effects of tea on tumor development in the mammary as well as the colon (Weisburger et al., 1997). Uninoculated skim milk or skim milk fermented with *Bifidobacterium* sp. may act against development of aberrant crypt foci (ACF), putative preneoplastic lesions in the colon (Balansky et al., 1999), in association with decrease in cecal beta-glucuronidase activity (Abdelali et al., 1995). Protection has also been described for the mammary glands (Rice et al., 1995). Consumption of fermented milk products may protect against cancer and it has been reported that cultures of *Bifidobacterium* lactic bacteria themselves can inhibit preneoplastic lesion development in a rat model (Kulkarni and Reddy, 1995).

The whey fraction is actually composed of a large number of ingredients, the most important of which are alpha-



Figure 1. Structure of Lactoferrin

lactalbumin, beta-lactoglobulin, immunoglobulin, bovine serum albumin and lactoferrin. Very little is known about their individual effects, although multimeric alpha-lactalbumin has been shown to be a potent Ca^{++} -elevating and apoptosis-inducing agent (Hakansson et al., 1995). We have concentrated attention on lactoferrin (bLF) (see Figure 1), an 80kDa siderophilic protein which has two iron-binding sites per molecule and is well known to have bacteriostatic properties (Lonnerdal and Iyer, 1995). In addition to sequestration of the ferric ion necessary for microbes to grow, it activates NK cells (Nishiya and Horwitz, 1992) and neutrophils (Gahr et al., 1991), induces colony stimulating activity (Sawatzki and Rich, 1989), stimulates LAK cells (Shau et al., 1992) and augments macrophage cytotoxicity (McCormick et al., 1991). It is present in large amounts in mammalian secretions like tears, saliva and seminal fluid as well as being particularly abundant in colostrum (Levay and Viljoen, 1995).

However, despite extensive studies of its anti-microbial properties there is only little information available regarding the influence of lactoferrin on disease processes. This is unfortunate since Bezault et al. (1994) have pointed to a protective influence against growth of solid tumors and development of experimental metastases in mice. They argued that the action of lactoferrin might have been mediated by NK cells, in line with its stimulation of NK and LAK cell activity in vitro and in vivo. Furthermore, neoplastic transformation of the human endocervix has been shown to be associated with down-regulation of lactoferrin expression, accompanied by a pronounced elevation in cell proliferation (Farley et al., 1997). We have therefore conducted a number of investigations of its influence on experimental carcinogenesis, primarily in the colon.

In a first study in Fischer 344 male rats bLF significantly reduced the incidence and the multiplicity of carcinomas (Sekine et al., 1997a). In addition, 2% bLF caused significant reduction in incidences and multiplicities of total tumor (adenomas + carcinomas). Inhibition of initiation and early stage development of ACF was also found with concomitant administration of bLF and AOM (Sekine et al., 1997b). In a second experiment, possible prevention of intestinal polyposis in the Apc^{Min} mouse was assessed. Among bLF effects are anti-inflammatory actions (Britigan et al., 1994) and significant suppression of the polyp number in the jejunum was observed with bLF at the 2% dose (Ushida et al., 1998). Recent findings have indicated a more widespread organ spectrum of inhibitory potential, including the tongue, oesophagus, lung and bladder (Masuda et al., 2000; Tanaka et al., 2000; Ushida et al., 1999). It may also protect against development of pepsinogen-negative pyloric glands in Mongolian gerbils infected with *Helicobacter pylori* (Shimizu et al., 2000). Indeed, lactoferrin is well known to act against bacteria and stimulate the immune response. It further activates intestinal mucosal immunity in tumor-

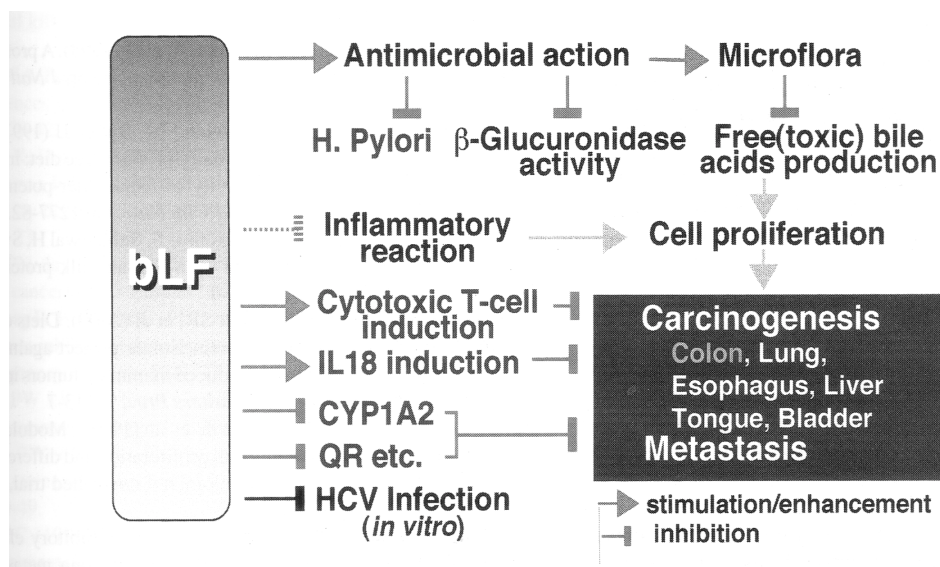


Figure 1. Possible Mechanisms of Inhibitory Effects of Lactoferrin on Carcinogenesis

bearing mice (Wang et al., 2000). This latter might be of importance regarding the mechanisms underlying the observed inhibition of carcinogenesis, and more particularly of metastasis (Iigo et al., 1999; Yoo et al., 1997).

As discussed earlier (Tsuda et al., 2000), for the practical employment of chemopreventive agents, it is important to know whether their action is limited to only inhibition. Therefore, use of chemopreventive agents should follow appropriate indications based on reliable information regarding beneficial (preventive) and adverse (promoting or toxic) effects. With this regard, a chemopreventive agent which could be recommended for high risk second primary cancer patients could certainly not be introduced for general consumption because the agent may possess adverse effects which are accepted due to its efficacy in this particular situation. For high risk populations, information regarding organotropism is particularly important to cancel out the promoting effects of known adverse environmental exposure. Exact follow up of patients or populations during and after administration of chemopreventive agents is obviously necessary for effective assessment and conclusions to be drawn. For general public use, agents require safety approval based on a long-term toxicity/carcinogenicity testing. Further development of appropriate in vivo animal assay systems to provide reliable information regarding organotropism and adverse effects is also critical for this purpose. To this regard, use of naturally occurring compounds is advantageous because most of them are ingested routinely as food components. Fiber, unsaturated fatty acid, carotenoids, flavonoids, phenolic compounds, especially polyphenols, and now bLF could be promising compounds in this respect.

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Main Areas of Research Interest

1. Chemical carcinogenesis using gene-engineered rodents
2. Cancer chemoprevention
 - 1) Search for chemopreventive agents from natural elements in plants and foods
 - 2) Mechanisms of cancer chemoprevention