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EDITORIAL

New insights into calcium, dairy and colon cancer

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Abstract

This paper is to review recent information about the relationship of calcium and dairy foods to colon cancer. The review focuses on primary prevention, discusses the potential components in dairy foods that might be anti-neoplastic, reviews the epidemiologic information and describes intervention studies demonstrating efficacy of calcium and vitamin D in reducing colorectal polyp recurrence. Since vitamin D is important in cancer prevention, pertinent data is discussed and potential mechanisms of actions presented. Calcium and vitamin D are important agents for the primary prevention of colorectal neoplasia.

Key words: Colorectal cancer; Dairy foods; Calcium; Vitamin D; Colorectal polyp recurrence; Colon cancer prevention

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INTRODUCTION

Colorectal cancer is a common and lethal disease in the Western World and the incidence and mortality is increasing dramatically in the rest of the world. In the United States, colorectal cancer is the second most common cause of cancer deaths, with an incidence of around 130 000 cases a year and a mortality rate of approximately 55-60 000[1]. The World Health Organization statistics for colorectal cancer incidences worldwide in 1996 showed about 875 000 cases with a mortality of over 500 000. The incidence of this tumor in the less well developed countries of the world is increasing dramatically so that the death rate for this tumor far exceeds the 7.2% of all cancer deaths reported by the WHO. Incidence and mortality rates differ markedly across countries with the highest rates reported from Australia and Northern Great Britain and the lowest rates in Southern Africa. This 30-fold difference in incidence underscores the importance of environmental factors in inducing this cancer.

Although the treatment of established colorectal cancer has improved remarkably over the last half century, mortality rates still are high, particularly in our aging population. Therefore, a major focus of the management of this tumor has been in the area of cancer prevention which is better termed "cancer risk reduction". There are three modalities of cancer prevention; tertiary prevention is when efforts are made to lower the risk of a second cancer once a primary tumor has been diagnosed. A good example of this is the use of tamoxifen for risk reduction of breast cancer in women who have had one breast cancer and the use of retinoid acting agents to lower the risk of second squamous cancers of the aero-digestive tract. Secondary prevention involves the abolition of pre-cancerous neoplastic lesions, thus lowering the risk of the later development of cancer. For the colorectum, secondary prevention by detection of neoplastic colorectal adenomas and adenoma polypectomy has become an established preventive technique and has been demonstrated to be effective in lowering the incidence of this tumor[2]. Primary prevention aims to reduce the development of a cancer before tissue pre-neoplastic changes occur. This is the approach where calcium and dairy products appear to have an important role in lowering the risk of colorectal cancer. It must be emphasized that in order to advocate a primary cancer prevention modality which is likely to be applied to large numbers of the population, it must have an excellent benefit to risk ratio. The term "chemoprevention" which is better called "risk reduction" has been applied to these approaches. Chemoprevention involves the use

of an agent to slow the progress, to reverse or inhibit the process of carcinogenesis. Such agents may act at different levels modulating cancer production at the level of the cell, at the molecular level, at the whole tissue level or potentially at the whole patient clinical level.

There are many components of dairy foods that have been shown experimentally to have protective effects against colon cancer. These components include calcium and vitamin D for which there is most evidence and (which will be discussed below), conjugated linoleic acid[3], sphingolipids[4] and the potential of butyric acid formed by colonic lactobacilli from milk products. Clearly if one includes bacterial cultures, i.e. probiotics added to dairy products, there is an increasingly important literature that suggests that such agents may be beneficial in reducing the risk of colorectal neoplasia[5].

EPIDEMIOLOGY

There have been numerous epidemiologic studies that have suggested that calcium or dairy products may lower the risk of colorectal neoplasia. The data for many of these have been reviewed recently[6]. An important prospective epidemiologic study was performed in over 45 000 Swedish men, aged 45 to 79 years[7]. In this study, calcium intake was determined from food frequency questionnaires and there was a mean follow up of between 6 and 7 years. The data on colorectal cancer incidence, when analyzed for the highest versus the lowest quartile for calcium intake, showed a statistically significant reduction in colon cancer development with a mean odds ratio of 0.68 and for dairy intake a mean odds ratio of 0.46. Using multivariate analysis, the data from this study suggested that there might be a threshold effect at about 1200 mg to 1400 mg of calcium per day[7].

CALCIUM

At the present time, the gold standard for measuring risk reduction by an intervention in colorectal cancer uses determination of the incidence of recurrence of adenomatous polyps following removal of all colonic polyps by polypectomy. This approach was originally developed by Baron JA (Baron JA, Beach M, Mandel JS, van Stolk RU, Haile RW, Sandler RS, Rothstein R, Summers RW, Snover DC, Beck GJ, Bond JH, Greenberg ER. Calcium supplements for the prevention of colorectal adenomas. Calcium Polyp Prevention Study Group. *N Engl J Med* 1999; 340: 101-107) and his co-workers to analyze the beneficial effects of calcium for adenomatous polyp reduction[8]. Subsequent analyses have evaluated reduction of total adenomatous polyps and reduction of advanced polyps as defined by size and the presence of severe dysplasia. Calcium supplementation of 1200 mg per day reduced total adenomas by approximately 20%[8], but advanced adenomas by about 45%[9]. If one translates these data into numbers of adenomas that would be reduced in the United States by increased calcium intake this would total approximately 26 000 cases of adenomas with a more important impact on the advanced lesions. Subsequent analyses by Baron's group showed that most of the effect of calcium in lowering the incidence of recurrent adenomas occurred in individuals who had baseline levels of serum 25 hydroxy vitamin D above the median (about 29 ng per mL) with little effect in individuals with lower levels[10]. These data strongly suggest that it is the combination of calcium and vitamin D which is important in altering adenoma recurrence. A prospective US national study is ongoing to examine the relative effects of calcium, vitamin D or the combination of calcium plus vitamin D on colorectal adenoma recurrence. In a further recent publication, Baron JA and coworkers have followed calcium supplemented subjects for ten years after completing the ongoing study[11]. These data suggested that the beneficial effect of calcium upon adenoma recurrence persisted for five years even in subjects who were not taking supplemental calcium after stopping the formal study and showed 40% less adenoma recurrence when compared to control placebo treated subjects. After 5 years after no further beneficial effect of calcium administration was demonstrated[11].

The classical hypothesis for the beneficial effects of calcium derived from an original physiochemical hypothesis by Newmark and colleagues in which they suggested that fatty acids and bile acids in the colon may be detrimental to the epithelium and important in the initial steps of colorectal carcinogenesis and that calcium could bring bile acids and fatty acids out of solution in the colonic lumen and, thus, reduce the cytotoxicity of these agents[12]. A number of studies by Van der Meer's group subsequently were consistent with this hypothesis even in *in-vivo* studies[13,14].

However, calcium is known to have manifold cellular effects in colonic epithelial cells suggesting that these must be important in the action of this compound upon colorectal carcinogenesis. Two recent areas of research suggest that other mechanisms may well be crucial in the cellular effects of calcium. The human parathyroid calcium sensing receptor which senses minor changes in extra-cellular calcium concentrations is expressed in differentiated cells of the human colonic crypt. The receptor is partially or completely lost during colon carcinogenesis[15]. The calcium sensing receptor has two promoters with vitamin D response elements. *In vitro*, calcium and vitamin D stimulate the calcium sensing receptor promoter activity in colonic cells to reduce E-cadherin expression and inhibit TCF4. Thus, this receptor may function to regulate epithelial differentiation and be anticarcinogenic[15]. In addition, evidence suggests that the cardiac L-type calcium channel is present in colon tissue and may play a role in determining calcium influx into colonic epithelial cells[16].

Vitamin D stores of the body derive from photolysis of 7 dehydrocholesterol in the skin to form pre-vitamin D_3 which rapidly isomerizes at body temperature to form vitamin D_3 and then passes into the circulation.

Dietary vitamin D_2 and vitamin D_3 is absorbed from the intestinal lumen in micellar form and after transfer into intestinal lymph passes into the circulation where it is bound to a vitamin D binding protein. Vitamin D from both cutaneous and intestinal sources is taken up by the liver and converted to 25 hydroxy vitamin D (25 OHD_3). The circulating levels of serum 25 OHD_3 reflect the body stores of this vitamin. 25 OHD_3 is transported to the periphery and converted to calcitriol, (1,25 dihydroxy vitamin D3 1,25 $(OH)_2D_3$), mainly in the kidney but also in many peripheral tissues by the action of the enzyme 1 alpha hydroxylase (CYP 27 B2). 1,25 $(OH)_2D_3$ is bound to vitamin D receptors present in many tissues and has pleiomorphic actions in bone, the gastrointestinal tract and uterus, etc.

Epidemiologic studies of vitamin D effects upon human health have included evaluation of effects of sunlight (ultraviolet) exposure, analysis of dietary and supplemental vitamin D intake as well as measurement of serum 25 hydroxy vitamin D levels.

There is abundant epidemiologic data to show that exposure to sunlight results in a reduction in the incidence of many cancers, but most clearly reduced colorectal cancer. The original observations of Cedric Garland[17] which followed upon a forgotten report in 1941[18] showed a distinct North to South latitude difference in colorectal cancer development. More recently, several studies have shown not only a lowering of colorectal cancer incidence, but also that for breast, ovary and prostate[19] accompanied by the expected increased non-melanoma skin cancer formation. Other studies have also pointed to beneficial changes of sunlight in esophageal, renal and bladder cancer as well as non-Hodgkins lymphoma[20].

Many investigators have analyzed the relationship of colorectal cancer prevalence with vitamin D body stores, i.e. measurement of circulating 25 OHD_3. A metanalysis of vitamin D intake studies using dose response gradient analysis showed a reduction in colorectal cancer of approximately 20%[21]. In 2006, Garland analyzed positive and negative studies comparing serum 25 OHD levels and the development of colorectal, breast and prostate cancer. Six of seven studies of colorectal cancers showed a significant reduction of cancer and one was borderline, whereas for breast cancer only one was significant and one showed no effect with similar negative results for prostate cancer[22]. Further evidence for the beneficial effect of higher levels of 25 OHD were shown in the distal colon of older women (OR = 0.45)[23] and in black men[24], because of lower action of sunlight in pigmented skin to form this vitamin. A prospective 7.75 year study of serum levels of vitamin D showed a 55% reduction in cancer development in the highest compared to the lowest quartile[25].

MECHANISMS OF ACTION OF VITAMIN D

The cellular activity of vitamin D is dependent on the action of calcitriol principally through interaction with a high affinity binding protein (VDR). VDR is a member of the steroid receptor superfamily ligand dependent transcription factor and the binding of calcitriol to VDR induces a configurational change in the receptor. The receptor then heterodimerizes with the retinol receptor (RxR) and the VDR-RxR complex binds to vitamin D response elements in the nucleus. This interaction induces gene transcription which results in cell cycle arrest through the regulation of CDK2, p21, p27, p53, KI67 and E-cadherin. In addition there are effects on differentiation and apoptosis, the latter through changes in BcL-2, BcL-x_L, Mcl-1, etc. Furthermore, there are non-receptor dependent actions of vitamin D upon the cell which include activation of calcium channels at least in the small intestine and colon[26].

The clinical effects of vitamin D are also dependent on polymorphisms in the vitamin D receptor. Such polymorphisms can occur at the 3' end of the receptor and includes Bsm1, Taq1 and at the 5' end FoK1. It is known that such polymorphisms are functionally associated with differences in bone density and in serum calcitriol levels, but whether they affect the action of vitamin D upon the colon is unclear[27]. However, high dairy intake effects upon colon adenoma recurrence has been restricted to individuals with the Apal aA/AA genotype[28].

One small, but unique study has described the effects of 6 mo supplemental calcium (1200 mg) plus vitamin D (400 IU) to subjects with adenomatous polyps which were transected with one half tattooed and left *in situ*. Calcium plus vitamin D reduced proliferation indices in the remaining polyps and flat mucosa, but also dramatically down-regulated polyp mucin 5AC (MUC5AC)[29]. These data suggest that the combination alters important cellular processes both in the adenoma and the flat colorectal mucosa.

Turning to other studies of dairy products upon colon neoplasia formation, Cho *et al* (Cho E, Smith-Warner SA, Spiegelman D, Beeson WL, van den Brandt PA, Colditz GA, Folsom AR, Fraser GE, Freudenheim JL, Giovannucci E, Goldbohm RA, Graham S, Miller AB, Pietinen P, Potter JD, Rohan TE, Terry P, Toniolo P, Virtanen MJ, Willett WC, Wolk A, Wu K, Yaun SS, Zeleniuch-Jacquotte A, Hunter DJ. Dairy foods, calcium, and colorectal cancer: a pooled analysis of 10 cohort studies. *J Natl Cancer Inst* 2004; 96: 1015-1022) published pooled data of dairy product intake from 10 cohort studies and reported a 12% reduction in colon cancer risk with each 500 mL increase in milk intake. There also was a significant and 17% reduction in colorectal cancer incidence with the ingestion of ricotta cheese greater than 25 mg per day[30]. An important study that has received a large amount of attention was the Women's Health Initiative Dietary modification study (WHI study) in which women 50-79 years of age received supplemental 1100 mg calcium plus 400 IU vitamin D with meals. Some of these women also participated in a study of the effects of estrogen replacement therapy upon colon cancer development.

This prospective study had a mean follow up of 7.0 ± 1.4 years and had colorectal cancer as an end point[31]. There was no significant difference between the development of colorectal cancer in women taking the calcium plus vitamin D when compared to controls (OR = 1.08) (0.86-1.34). There clearly were a number of issues related to this study which have resulted in some considerable criticism. Such issues included the fact that the mean age of the women in the study was 62 and the increase in colon cancer in women occurs only after age 60, they had a high basal dietary intake of calcium of approximately 1100 mg to 1200 mg per day and relatively adequate vitamin D intake approaching 400 IU per day. There was low compliance with the intervention with only 70% of subjects consuming more than 50% of the pills and in addition the subjects were permitted to continue to take calcium and/or vitamin D supplements separately from study drugs. It also was felt that the duration of the study was too short for a cancer end point and the amount of vitamin D provided in the intervention was relatively low. Importantly however, women who showed a low serum 25 hydroxy vitamin D level at base line demonstrated a 2.5 fold increased risk of colorectal cancer compared to the top quartile of serum 25 hydroxy vitamin D levels ($P < 0.02$)[31].

VITAMIN D AND CANCER MORTALITY

A unique study by Lappe prospectively evaluated the development of any cancer in approximately 1200 postmenopausal women who received calcium 1500 mg/d with or without vitamin D 1100 IU per day. The unadjusted relative risk for the development of any cancer with calcium administration was 0.53 and for vitamin D plus calcium 0.40. Serum 25 hydroxy vitamin D also was a significant predictor of decreased cancer development[32]. A recent meta-analysis of 18 studies of effects of vitamin D on overall mortality by Philippe Autier showed an 8% reduction in overall mortality in subjects who received vitamin D[33].

ANIMAL STUDIES

Over the past decade Martin Lipkin's group have been evaluating the effects of a Western style diet (WD) relatively high in fat content (20%) and relatively low in vitamin D and calcium upon carcinogenic changes in the colon of mice. This represented the first demonstration of diet-induced colorectal tumor formation in the absence of a carcinogen[34]. When folic acid also was reduced in the WD over a period of 18-24 mo, adenomas and carcinomas developed with increases in both the percent of mice developing tumors as well as in tumor frequency. The addition of calcium and vitamin D to the diet dramatically reduced or eliminated most of these tumors[35]. It also is of interest that this Western style diet in mice produced hyperproliferation in mammary duct epithelial cells[36], pancreatic epithelial cells[37] and prostate cells[38] and that calcium and vitamin D suppressed such hyperproliferation. The molecular underpinnings of these observations are presently under study.

CONCLUSION

Epidemiologic intake and intervention studies have shown that calcium administration lowers colorectal adenomatous polyps as well as cancer rates and this effect may be prolonged. Most evidence suggests that the effect of calcium is dependent or partially related to simultaneous vitamin D intake. Vitamin D may also reduce colon cancer risk independent of the presence of increased amounts of calcium or dairy products in the diet. Few studies have been performed with dairy products alone, but the data generally supports the positive effects shown with calcium and vitamin supplementation as well. Understanding the cellular effects of calcium and vitamin D in humans' *in-vivo* is crucial to make further progress in this field.

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