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Dairy consumption and the prevention of colon cancer: is there more to the story than calcium?^{1,2}

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Sporadic colon cancer is a complex disease with well-characterized clinical and molecular features. Platz et al (1) estimated that >70% of colon cancer risk is preventable through a combination of dietary and lifestyle changes. Over the past decade, a number of studies reported that colon cancer risk is reduced by high dietary calcium consumption; eg, an intervention trial conducted in patients from whom a colorectal adenoma had recently been removed found that supplementation with 1200 mg calcium/d reduced the risk of advanced colorectal lesions (2). Other studies, including a study of early risk markers (3) and meta-analyses such as the Pooling Project of Prospective Studies of Diet and Cancer (4), indicate that calcium-rich dairy foods are also chemoprotective against colon cancer.

In this context, the article by Larsson et al (5) in the current issue of the Journal aims to expand our understanding of the relation between calcium or dairy intake and colon cancer. Their study is part of the ongoing Cohort of Swedish Men trial, which was established in 1997 to study lifestyle-disease interactions. This is a powerful study with a large population that is linked to well-maintained and complete health records. As a result, the use of high-quality and cross-validated food-frequency questionnaires in this study group has provided Larsson et al with the opportunity to make a significant contribution to the area of dietary modulation of colon cancer.

The most interesting aspect of this study is that it attempts to dissect the dairy intake–colon cancer interaction previously reported by others. Specifically, the authors try to determine whether the consumption of different dairy products provides site-specific protection from colon cancer. This may be critical for relating dietary factors to the distinct molecular pathology that differentiates proximal from distal colon cancer. For example, whereas distal colon cancer is characterized by a series of genetic changes in specific oncogenes (eg, *Ki-ras*, *p53*, *SMAD4*, and *APC*) resulting from chromosomal instability, the molecular signature of proximal colon cancer is characterized by microsatellite instability and may be independent of these changes (6). Thus, the use of location by Larsson et al may be a useful proxy for the molecular pathology of different colorectal cancers.

As did other investigators, Larsson et al found that colorectal cancer is influenced by both dietary calcium intake and total dairy food consumption [low- compared with high-intake group multivariate rate ratios (RRs) were 0.68 and 0.46, respectively]. They also confirmed that milk was the individual dairy food with the strongest influence on colorectal cancer risk and that the


distal colon is the segment most strongly influenced (low- compared with high-intake group multivariate RR = 0.53). The only other effect to reach significance was a reduction in distal colon cancer risk by cream or sour cream consumption (multivariate RR = 0.72), and a trend toward reduced proximal colon cancer risk was also seen for hard cheese consumption. Curiously, although total colorectal cancer risk was reduced by both high calcium and high total dairy food intakes, the segment-specific influence of calcium (reduced risk for rectum and trend for reduced risk in proximal colon) was different from that of total dairy consumption on cancer risk (reduced risk for proximal colon, distal colon, and rectum). This is one of several pieces of evidence that suggest the effect of dairy intake on colon cancer risk is not solely due to the calcium content and may be due to other factors. Another piece of evidence is that, even though calcium intake was closely correlated to total dairy ($r = 0.68$) or milk ($r = 0.50$) intake, control for total calcium intake in the analysis attenuated but did not eliminate the effect of milk or dairy intake on colorectal cancer. The authors suggest that these other factors might be dairy-associated factors, such as conjugated linoleic acid (CLA), sphingolipids, and milk proteins; their consumption has been linked to a reduction in colon cancer in animal models. However, no attempts were made by the authors to estimate the consumption of these dietary factors, nor did they discuss how milk or dairy intake provides protection in the distal colon that is not afforded by calcium alone.

Although this study offers some new insight into the dietary modulation of colon cancer, one is still likely to feel that this story has a lot more to reveal and that the article by Larsson et al only begins to address these gaps. For example, other studies suggest that the benefit to calcium consumption is maximal at <1100 mg/d (4, 7), but the study by Larsson et al suggests that the benefit may require 1400 mg calcium/d. This is a discrepancy that should be resolved before public health recommendations are made, especially in light of reports implicating high dietary calcium as a risk factor for advanced prostate cancer (8). One is also left to wonder whether there is something unique about the diet of this population. The men in the study by Larsson et al had a high

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dietary calcium consumption, even though calcium supplementation was low (2.1%), and there was a relatively weak relation between milk and calcium intakes ($r = 0.5$ compared with 0.78 in other populations), which suggests that other sources of calcium were unaccounted for.

A final missing feature in the current study is the impact of vitamin D status on the interaction between calcium intake, dairy intake, and colon cancer risk. Animal studies showed that dietary calcium and vitamin D status were comodulators of colon cancer and that vitamin D deficiency abolished the protective effects of calcium on tumor formation (9). Although many population studies have assessed dietary vitamin D intake, recent evidence suggests that dietary intake does not adequately meet the physiologic needs in certain population subgroups (eg, elderly or dark-skinned persons) and geographic regions ($>37^\circ\text{N}$ or S latitude) (10). Because dietary vitamin D intake is not the only contributor to vitamin D status, one would need to assess vitamin D status directly (eg, by measuring serum 25-hydroxyvitamin D concentrations) or at least incorporate estimates of sunlight exposure to determine the contribution of vitamin D to colon cancer risk. Even still, Cho et al (4) presented data suggesting that the benefit of higher calcium intake may depend on high vitamin D intake. Given that the interaction between vitamin D status and calcium metabolism is well established and that vitamin D status appears to modulate the effect of calcium on colon cancer risk, future studies on calcium or dairy intakes and cancer risk should not ignore it. 

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