

I. COLON POLYPS' PREVALENCE AND SURROGATE MARKER STATUS

The American Cancer Society (ACS) estimated that in 2001 almost 139,000 Americans were diagnosed with colorectal cancer and that over 57,000 Americans will die from this cancer (Smith, et al., 2001). ACS also reported that without preventative measures, about 5.6% of Americans will develop colorectal cancer at some time during their lives. Most (>95%) colorectal cancer develops from adenomatous polyps (Bond, 2000). About 25% of adults at age 50 years will have colorectal adenomas (Smith, et al., 2001). The main focus of colorectal cancer control relies on methods to reliably detect and remove adenomas before they become malignant. The FDA and experts in the field recognize colon polyps as surrogate markers for colon cancer, as adenomas are established risk factors for colorectal cancer. Since adenomas are so very common among the U.S. population, recommending calcium provides the public with a simple, safe and inexpensive method of helping to reduce their risk of developing recurrent adenomas.

The Health Claim Petition for Calcium and Various Cancers provided a summary of the scientific literature pertaining to the effects of calcium on various aspects of colon cancer. The review addressed the importance of maintaining normal colorectal epithelium, the conversion of normal epithelium to neoplastic epithelium, the effect of bile acid solubility on epithelium, the effects of calcium on chemically induced colorectal cancer in animal models, and the effects of calcium on colorectal cell proliferation and apoptosis. It also included an extensive section on the direct effect of dietary calcium on colorectal cancer in humans. We have concluded that this information, as submitted in the 10/09/03 Petition, is a comprehensive review of the available scientific literature. We, however, believe that additional information regarding the particular colon cancer risk factor of recurrent colon polyps should be reviewed and evaluated.

II. PROPOSED HEALTH CLAIM LANGUAGE

We support the following health claim regarding calcium and colon cancer:

Calcium may reduce the risk of recurrent colon polyps

In addition, we respectfully request that FDA approve a modified version of this health claim:

Calcium may reduce the risk of recurrent colon polyps, a major risk factor for colon cancer

We believe this statement is more indicative of the scientific support for calcium and colon polyps. The totality of the scientific evidence supports the effectiveness of calcium in reducing recurrent colon polyps, an established surrogate endpoint for colon cancer.

The statement also provides a more comprehensive public health message and more effectively explains the importance of calcium to the general public in the context of promoting long-term health. In light of these benefits, we are seeking FDA approval of this modified claim, as we recognize that only the exact claim language set forth in an FDA letter of enforcement discretion may be used in labeling.

III. QUALIFIED EXPERT ASSESSMENTS

A. Digestive Disease Societies – Polyp Guideline: Diagnosis, Treatment, and Surveillance For Patients with Colorectal Polyps

The current practice guideline, Polyp Guideline: Diagnosis, Treatment, and Surveillance for Patients with Colorectal Polyps, is based on the science as determined by qualified experts in the field of colon cancer prevention. The Polyp Guideline was developed under the auspices of the American College of Gastroenterology and its Practice Parameters Committee following a rigorous formal process of an extensive review of the literature and counsel from a committee of experts. In addition, these guidelines were also approved and endorsed by the governing boards of the other major Digestive Disease Societies (DDS) including the American Gastroenterology Association, the American Society for Gastrointestinal Endoscopy, and the American Association for the Study of Liver Disease.

The Polyp Guideline recommends 3 grams of calcium carbonate (1200 mg of elemental calcium) daily to prevent the recurrence of adenomas. The recommendation is primarily based on the results of the Calcium Polyp Prevention Study by J.A. Baron et al, which involved six clinical centers.

The Polyp Guideline has a specific section on Primary Prevention of Colorectal Adenomas, that states:

“To prevent initial or recurrent colorectal adenomas, a diet that is low in fat and high in fruits, vegetables, and fiber is recommended. Normal body weight should be maintained, and smoking and excessive alcohol use should be avoided. Daily dietary supplementations with 3 g calcium carbonate may reduce the recurrence of adenomas. Other chemopreventive measures (i.e., supplementation with aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs), selenium, or folic acid), supported by indirect data, cannot be recommended pending the results of ongoing clinical trials showing both efficacy and a good risk-benefit ratio.” (Emphasis added)

It is important to note that it is very unusual for a scientific body, such as the Digestive Diseases Societies, to adopt a practice guideline that makes this type of recommendation. Thus, this guideline recommendation provides substantial evidence that significant

scientific agreement exists about the validity of the scientific evidence supporting the use of 3 grams of calcium carbonate (1200mg of elemental calcium) for the prevention of recurrent colorectal adenomas.

B. Additional Comments From Qualified Experts

We asked four individual experts in the field of colon cancer prevention to review the totality of the publicly available scientific data regarding calcium and colon health. Additionally, we asked these experts to provide a professional opinion as to the strength of the relationship of increased calcium intake to the recurrence of colorectal polyps and to the risk of colon cancer.

The four experts providing assessments and opinion are:

1. Martin Lipkin, MD
Director of Clinical Research
Professor of Medicine
Strang Cancer Prevention Center
Cornell University Medical College
2. Peter R. Holt, MD
Former Chair of Gastroenterology at St. Luke's /
Roosevelt Hospital Center
Professor Emeritus, Columbia University
Senior Scientist at the Institute of Cancer Prevention
3. Phillip P. Toskes, MD
Professor of Medicine
College of Medicine
Department of Medicine
Division of Gastroenterology, Hepatology and Nutrition
University of Florida
4. Richard S. Rivlin, MD
Senior Vice President Medical Affairs
Naylor Dana Chair in Nutrition
American Health Foundation
Professor of Medicine
Weill Medical College of Cornell University

The curricula vitae for these experts are included in section VII.

Their comments are summarized briefly here and their complete summaries are provided in section VI.

1. **Dr. Lipkin of the Strang Cancer Research Laboratory** stated:

“Based on the evidence described below my opinion is that calcium helps to prevent recurrent colonic polyps which are a major risk factor and cause of colon cancer.”

Dr. Lipkin then provides a summary of the relevant data supporting his conclusion, in particular, human studies of effects of calcium on colon cancer and mechanisms of effects of calcium on colon tumor development.

2. **Dr. Holt, former Chair of Gastroenterology at St. Luke’s/Roosevelt Hospital** concluded:

“In my opinion, the weight of the scientific evidence described above thoroughly supports the contention that calcium lowers the recurrence of colorectal polyp (adenoma) formation as well as early markers of increased risk for cancer formation.”

In his letter, Dr. Holt describes his extensive background in the field and then proceeds to succinctly summarize the relevant scientific data regarding the effects of calcium on the risk of colon cancer from animal models, mechanistic studies, epidemiological studies and, human clinical intervention trials.

3. Regarding primary and secondary prevention of colon cancer, **Dr. Phillip Toskes, Professor of Medicine, University of Florida**, stated:

“At the present time the most appropriate primary prevention modality appears to be calcium”

More specifically, he states:

“The use of calcium to prevent polyp formation has strong basic science support in experimental animals and humans, solid evidence from clinical trials, and virtually no evidence of side effects whatsoever with 1200 mg of calcium per day.”

4. **Dr. Richard Rivlin, Senior Vice President for Medical Affairs, Institute for Cancer Prevention**, reported:

“It is my conclusion after a thorough review of the relevant medical literature that the scientific evidence to date overwhelmingly favors the recommendation of calcium on a daily basis for all adult Americans to help prevent colorectal adenomas.”

“The scientific evidence in favor of calcium comes from a large number of independent reports, including the results of basic research studies in animals, and cell-free systems as well as clinical interventional. Of the recent interventional studies, the most significant is that of Baron et al published in the New England Journal of Medicine in 1999. In this report a major reduction in the recurrence of colonic adenomas was observed in subjects receiving 1200 mg/day of elemental calcium compared to controls receiving placebos.”

“In summary, for all these reasons, I am of the strong opinion that calcium intake has a very firm relationship to supporting colorectal health, including colorectal cancer and polyps, the precursor lesion to colorectal cancer.”

IV. HEALTH CLAIM CRITERIA

Consistent with claim criteria for the calcium and osteoporosis health claim set forth in 21 CFR 101.72 (c), we are requesting that FDA establish eligibility requirements for the proposed calcium and colon polyps health claims, specifically:

- a. The food or dietary supplement product meets or exceeds the requirements for a “high” level of calcium or 20% of the RDI.
- b. The calcium content of the product is bioavailable;
- c. The food or total daily recommended dietary supplement intake does not contain more phosphorus than calcium on a weight per weight basis.

Additionally, due to its integral role in the absorption of calcium, we also recommend that the eligible food or dietary supplement product meets or exceeds the requirements for “good source” of vitamin D or 10% of the RDI.

V. SUMMARY

Given that the Polyp Guideline was approved by the Digestive Disease Societies and is consistent with the opinions of all four eminently qualified experts, we conclude that there is significant scientific agreement that 3 grams daily of calcium carbonate (1200 mg/day calcium) may reduce the recurrence of colorectal adenomas which is a recognized risk factor for colon cancer.

We propose that two health claims related to colon polyps, **“Calcium may reduce the risk of recurrent colon polyps”**, and **“Calcium may reduce the risk of recurrent colon polyps, a major risk factor for colon cancer,”** be approved based on the weight of the body of scientific evidence and the strong support of the scientific community. It is important to note that since adenomas are a common and growing concern among the U.S. population, recommending calcium intake provides a necessary public health message for a simple, safe and inexpensive method to help reduce consumer risk of developing recurrent polyps.