Can Selenium Prevent Colorectal Cancer? A Signpost From Epidemiology

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The limited epidemiology published heretofore on associations between selenium and colorectal adenomas or cancer has been mixed, inconclusive, and based predominantly on small studies. The epidemiology studies have been about evenly split between those showing a statistically significant (1–5) or suggestive (6,7) protective association and those showing a null (8–11) or suggestive harmful (12,13) association between selenium and colorectal adenomas or cancer. The strongest (and only clinical) previous support for a possible protective effect of selenium intake came from a large, randomized controlled trial of selenium in preventing nonmelanoma skin cancer (14). This trial showed a statistically significant reduction of colorectal cancer as a secondary endpoint (relative risk [RR] = 0.58, 95% confidence interval [CI] = 0.18 to 0.95) that attenuated after longer follow-up (RR = 0.45, 95% CI = 0.19 to 1.08) (15). A marginally statistically significant overall reduction in colorectal adenomas, which became stronger in association with the lowest tertile of baseline selenium, was also observed again, as a secondary endpoint in the trial (16).

In this issue of the Journal, Jacobs et al. report their pooled analysis of three randomized clinical trials of dietary or nutrient interventions in preventing colorectal adenomas (17). Individual-level data from each of the Wheat Bran Fiber (WBF) Trial (18), the Polyp Prevention Trial (PPT) (19), and the Polyp Prevention Study (PPS) (20) were statistically reanalyzed to provide a more precise estimate of the association between plasma selenium concentration and adenoma risk than would be possible from any of the three studies alone. None of the trials tested selenium as an intervention. This pooled analysis, the largest epidemiologic investigation of the role of selenium in preventing colorectal neoplasia, indicates that individuals in the highest quartile of plasma selenium concentration (median 150 ng/mL) (plasma collected at enrollment for PPT and PPS and 1 year after randomization) of plasma selenium (median 113 ng/mL). Plasma selenium concentrations were not statistically significantly associated with adenoma size, location, or histology in the pooled analysis. There was a trend, however, of fewer advanced adenomas (≥1 cm in diameter and/or villous histology) in persons within the highest quartile of plasma selenium. This suggestion of activity in higher–cancer risk, advanced adenomas supports the promise of selenium for reducing colorectal cancer risk. The association of selenium with colorectal cancer development (and mortality) will be assessed as a pre-specified secondary endpoint of the Selenium and Vitamin E [prostate] Cancer Prevention Trial (SELECT) currently under way in more than 35,000 men (21).

Although the three source studies were mutually independent and executed prior to the pooling project, they had similar designs and outcomes that strengthened the pooled analysis. All participants were at high adenoma risk after recent colonoscopic adenoma resection; each of the three trials assessed colorectal adenoma endpoints in over 85% of its patients, at year 1 and either year 3 (WBF) or year 4 (PPT and PPS) after randomization; and each intervention did not statistically significantly alter the adenoma risk. The pooled analysis also had limitations, however, which were adequately discussed by the authors and included the possibility that some events (new adenomas) detected at year 1 were not actual events but preexisting adenomas missed at the index colonoscopy, varied blood collection times, and different methodologies used to determine plasma selenium concentrations.

The biologic plausibility of the pooled analysis and earlier secondary clinical data is provided by consistent animal studies showing the activity of selenium in colorectal neoplasia (22–28) and by other data that address relevant selenium mechanisms. Selenium has effects on key cellular events of tumorigenesis, such as cell proliferation and apoptosis, and the possible complex mechanisms underlying these effects are emerging in increasing numbers (28–30). Important relevant selenium mechanisms may involve gene promoter methylation and polyunsaturated fatty acid metabolism. Cancer cells commonly have aberrant methylation patterns characterized by global hypomethylation coupled with hypermethylation of CpG islands that appear to contribute importantly to tumorigenesis (31). The enzyme DNA cytosine methyltransferase 1 (DNMT1) is increased in tumor progression in association with regional hypermethylation (31). Preclinical studies suggest that selenium inhibits DNMT1 in various cell lines, including the HCT116 and HT-29 human colonic carcinoma cell lines (22,32–34).

Oxidative metabolism of the n-6 polyunsaturated fatty acids arachidonic and linoleic acids contributes importantly to colonic tumorigenesis (35), and current data suggest that selenium and arachidonic and linoleic acid metabolism are linked in colonic tumorigenesis. Selenomethionine inhibited growth in four hu-
man colon cancer cell lines (HCA-7, HT-29, Caco-pcDNA, and Caco-60) in a time- and concentration-dependent manner (36). Selenomethionine also decreased cyclooxygenase 2 (COX-2) protein and prostaglandin E$_2$ (PGE$_2$) levels in HCA-7 cells, and the growth inhibition effects of selenomethionine reversed with PGE$_2$ treatment, suggesting that selenomethionine-induced cell growth inhibition may be mediated in part by COX-2–dependent mechanisms (36). The synthetic inorganic selenium compound p-XSC (1,4-phenylene bis[methylene] selenocyanate) statistically significantly decreased the rate of small-intestine tumor formation and colon tumors in APC$^{min}$ mice in a dose-dependent manner and in association with statistically significantly lower levels of membrane-bound β-catenin and COX-2 activity in polyps (37). Unlike selenomethionine in HCA-7 cells, p-XSC did not affect COX-2 protein expression, suggesting that p-XSC modulates COX-2 activity at the posttranslational rather than at the transcriptional or translational levels. Docosahexaenoic acid (DHA, an n-3 polyunsaturated fatty acid) appears to act synergistically with p-XSC in inhibiting COX-2 and the growth of colon cancer cells in vitro (38).

Recent data indicate that the link between selenium and the oxidative metabolism of linoleic and arachidonic acids extends beyond COX-2 to the lipoxygenases (LOXs), another metabolic enzyme family involved in colorectal tumorigenesis (39–41). 15-LOX-1, which has anti–colorectal tumorigenic effects, and COX-2, which has pro–colorectal tumorigenic effects (35), exert opposing effects on the selenoprotein thioredoxin reductase, which is overexpressed in colorectal and other human cancers (42) and inhibited in vivo by selenium supplementation (43), in modulating cell growth and apoptosis (44).

In an intriguing study involving 11 patients with adenomatous polyps, the expression of the selenoproteins gastrointestinal glutathione peroxidase (GI-GPX) and selenoprotein-P (SelP), which are expressed abundantly in the colorectal mucosa of healthy individuals (44), were regulated differentially during colorectal carcinogenesis (45). SelP mRNA expression was markedly reduced, whereas GI-GPX mRNA expression was increased in colorectal adenomas, compared with the expression in adjacent normal mucosa (45). Future studies, including investigations into the functional relevance of polymorphisms in the SelP and GI-GPX genes (46), should assess a potential mechanistic relationship of decreased SelP expression with reduced GI-GPX expression in colorectal adenomas and whether levels of locally available selenium may affect this relationship. One interesting hypothesis is that the downregulation of SelP frees up locally available selenium for binding to GI-GPX, thus strengthening a premalignant cell’s defense against reactive oxygen species (ROS)–inducible DNA damage.

The completed randomized, controlled trial of selenium mentioned earlier (14,15), which led to the present pooled analysis, is far better known (to date) for a secondary reduction in prostate cancer (30) than it is for its secondary data on a selenium-associated reduction in colorectal cancer. Even though the colorectal association attenuated over time (15), the pooled analysis reinforces the earlier secondary clinical data on selenium in the colon–rectum and should intensify interest in ongoing or planned prospective translational trials of selenium, either alone or combined with other promising agents, in preventing colorectal adenomas. The correlative laboratory studies within these trials will advance our understanding of colorectal carcinogenesis and selenium mechanisms (e.g., those discussed above), activity, and pharmacogenomics—and will potentially lead to the development of new, promising interventions. These translational trials, combined with the prespecified colorectal analyses of SELECT, are likely to have the greatest impact on our understanding of the public health role of selenium in colorectal cancer prevention, since logistics make a phase III trial of selenium or another agent highly unlikely in this setting.

REFERENCES


