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Editorial

Calcium in the prevention of colorectal cancer

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In a year from now, 200 years will have passed, since calcium was discovered. Although calcium is one of the most common elements, our information regarding its role in biology is relatively recent. The size and electronic configuration of calcium ion makes it capable of bonding with a variety of organic and inorganic molecules. Taking into consideration its ability to form bonds with nitrogen and oxygen, one can appreciate its' biochemical importance, both intracellular as well as extracellular.

From a biological standpoint, three main roles can be attributed to calcium: structural, electrical and as an information carrier.[1] The last of these roles is the least studied, but serious research it is in progress all over the world. It is this precise role that correlates calcium with the tumorigenic mechanisms and the effort to reveal them is the natural extension of the aforementioned research. Broadening the therapeutic manipulations is the expected end-point of these efforts.

Colorectal cancer's relationship with calcium has constituted an area of intense research for some years now. Garland et al, were among the first to report increased colorectal cancer incidence in a population with low dietary calcium intake.[2] Ever since, bibliography on this subject has been expanding rapidly. In general,relative literature can be divided in two broad categories; studies investigating the role of calcium in colorectal cancer at cellular and molecular level and studies exploring the epidemiology of calcium intake in preventing the development of colorectal cancer or polyps.

The conclusions of various epidemiological studies are somewhat inconsistent. Larsson et al, reported recently the results of an epidemiological study of 45,306 men, 45-79 years old who were enrolled and followed up in a prospective manner for 7 years.[3] The multivariate rate ratio of colorectal cancer in men of the highest quartile of calcium dietary intake compared to those of the lowest was 0.68 (95% CI: 0.51, 0.91). Kesse et al, also reported reduced incidence of colorectal cancer among subjects of the highest quartile of calcium intake, compared to those of the lowest.[4] On the contrary, Jarvinen et al, after completing a 24 years follow up of 9,959 subjects aged 15 years old or more, were unable to demonstrate any relationship between calcium dietary intake and colorectal cancer.[5]

To complicate matters more, a number of studies tried to explore the potentials of calcium in reducing the incidence of colorectal polyps or cancer with the results being once again inconsistent. A prospective controlled study conducted by Peters et al, demonstrated reduction in the incidence of colorectal polyp in the distal colon for patients receiving calcium supplements.[6] On the contrary Ireland et al, reported no reduction in colorectal cancer incidence among patients on high calcium and vitamin D supplementary intake.[7] According to Fletcher et al, supplementary calcium intake cannot protect postmenopausal women from colorectal cancer. [8] Similar findings were reported by Lin et al.[9] They prospectively observed 40,000 women aged 45 years or more for 10 years. Multivariate analysis failed to demonstrate any protective role for colorectal cancer among women with high calcium intake (dietary and supplementary).

Given the prolonged time required for colorectal cancer to move from the cellular to the clinical stage, prolonged observation of subjects constitutes a huge obstacle in carrying out well designed studies. This may in part explain the inconsistency observed in medical literature. Conduction of studies attempting to evaluate the role of calcium intake in reducing osteoporosis incidence in postmenopausal women has made matters easier since colorectal cancer incidence could be evaluated in parallel. In addition to this, the inclusion of a large number of subjects in these study makes them appealing. Interpretation of this kind of study poses a significant dilemma since extrapolation of their results to include the whole population is a step in the wrong direction as selection bias for age and sex is evident. In parallel to calcium, vitamin D is also under investigation in many studies. Although the role of vitamin D in calcium metabolism is given, inclusion of this aspect in these studies makes interpretation of data a difficult task for vitamin D is acting as a confounding factor.

Weingarten et al, conducted a meta-analysis of well designed prospective double-blind controlled studies in their effort to shed more light on the issue of calcium as a chemopreventive agent for colorectal polyps.[10] Only two studies fulfilled their inclusion criteria. They concluded that calcium supplementary intake contributes moderately in the prevention of colorectal polyps, but as they state "this does not constitute sufficient evidence to recommend the general use of calcium supplements to prevent colorectal cancer". Reviewing the medical literature Grau et al, introduce calcium as a very promising method in preventing colorectal cancer, but due to lack of sufficient evidence they

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cannot recommend it for common practice.[11]

At cellular level calcium binds to a variety of molecules that participate in many cellular processes including differentiation, division and apoptosis. Free intra-cellular calcium concentration elevates as a result of a variety of interactions. Changes in cytosolic free calcium serve as an intracellular second messenger that activates diverse cellular processes.[12] Endoplasmic reticulum is the source of most of the intracellular calcium. The presence of high endoplasmic calcium concentrations are of uttmost importance in the process of protein synthesis, especially those participating in cell proliferation and apoptosis. Chung et al, demonstrated mutations in genes regulating endoplasmic calcium concentration and they correlated this with poor outcome in colorectal cancer patients.[13] Clusterin poses a dual role in a cell's life span; antiapoptotic when cytosolic concentration is high and apoptotic when nuclear concentration is high. According to Pajac et al, calcium-dependent cellular retention of clusterin positively correlates with cell survival, whereas nuclear translocation of this protein promotes cell death in calcium-deprived cells.[14] Miller et al, applied logistic regression to evaluate apoptosis of normal rectal epithelium in patients with and without rectal polyps with respect to dietary calcium intake. They concluded that increased calcium intake correlates with increased apoptotic index only in patients with rectal adenomas [OR: 3.4 (CI), 0.9-12.9].[15] Ohmachi et al, reported overexpression of TROP2 gene that encodes for a signal-transduction calcium-dependent protein.[16] According to Manning et al, loss of expression of the calcium sensitive receptor is accompanied by abnormal differentiation and progression of colorectal carcinoma.[17]

The precise protective mechanisms of calcium in colorectal cancer, if present, are still unknown. In fact, based on the knowledge gathered so far, only hypotheses can be made. According to some investigators calcium exerts its protective role by binding to biliary and fatty acids thus making them ineffective in irritating colorectal epithelium, while for others calcium stabilizes cellular processes especially those associated with proliferation and apoptosis.

Of our understanding of calcium's role in colorectal cancer has changed over the years and it's still evolving. The reports of numerous studies concerning the relationship of calcium and colorectal cancer are indicative but not conclusive for recommendations to be made. Conducting interventional trials comprises a challenge, given the population that must be enrolled as well as the prolonged follow up period required, but this may be the only way forward.

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