Editorial Commentary

The role of vitamin D and calcium in preventing recurrence of colon adenomas: is precision medicine the answer?

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Colorectal cancer (CRC) is the third most common cause of cancer worldwide and the second leading cause of mortality according to the World Health Organization GLOBOCAN database in 2020 (1).

Dietary composition is a widely accepted risk factor for the development of CRC. Consumption of red or processed meat, a high-fat diet, or alcohol are some of the most clearly established dietary risk factors (2,3). Conversely, diets high in fiber, as well as the consumption of whole grains or dairy products have been shown to protect against the development of colorectal cancer (2,4).

The mechanism by which dairy products prevent colonic carcinogenesis is not clearly established, but their high calcium and vitamin D content is among the components potentially involved. Calcium may intervene in the early stages of carcinogenesis by sequestering fatty acids and bile acids in the intestinal lumen, thus reducing the carcinogenic effect of these substances, which has been observed in animal models. In addition to this indirect effect, calcium appears to act directly with an antiproliferative and proapoptotic action on transformed cells (5). On the other hand, vitamin D appears to act on carcinogenesis through multiple mechanisms, including inhibition of tumor cell proliferation and migration, sensitization to apoptosis, regulation of autophagy, induction of cell differentiation, and inhibition of angiogenesis (6).

With all this evidence, one might think that calcium and vitamin D supplementation will protect against the development of CRC. However, the clinical evidence for calcium and vitamin D supplementation in the prevention of CRC and colorectal adenoma recurrence remains controversial.

On the one hand, multiple observational studies have been published with favorable results for the supplementation of these substances. For example, Lopez-Caleya *et al.* (7) have recently published a meta-analysis of 37 case-control studies showing a reduction in the risk of CRC of 6% for every 300 mg of calcium ingested daily and 4% for every 100 UI/day of vitamin D. Similar results regarding the protective effect of calcium were obtained in a meta-analysis of prospective cohort studies published up to 2013. However, the results for the association between vitamin D intake and CRC risk were more inconsistent (8).

On the other hand, the results of RCTs on this topic have been disappointing so far. For instance, a study comparing an arm of 18,176 women receiving calcium carbonate plus vitamin D with an arm of 18,106 women treated with a placebo could not find any significant difference in the incidence of CRC during follow-up (hazard ratio 1.08, 95% CI: 0.86–1.34) (9). A meta-analysis published in 2010,

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which included this trial, again showed no effect of calcium plus vitamin D supplementation on the incidence of CRC [risk ratio (RR) 1.08, 95% CI: 0.87–1.34]. However, a mild reduction in the adenoma recurrence was shown in patients with a personal history of adenomas who were treated with calcium 1,200 to 2,000 mg/day (RR 0.8, 95% CI: 0.69–0.94) (10).

More recent reports do not seem to confirm reduction in the adenoma recurrence rate. For instance, the Vitamin D/Calcium Polyp Prevention Study, published in 2015, included 2,259 patients with newly diagnosed colorectal adenoma that were randomized into 4 groups: 1,200 mg calcium, 1,000 IU vitamin D, both or placebo, although women were allowed to choose to receive calcium and to be randomized to vitamin D *vs.* placebo. After follow-up with colonoscopy at 3 or 5 years, this trial failed to demonstrate a protective action of either calcium or vitamin D or the combination of both on the recurrence of colorectal adenomas (11). In the same sense, the VITAL trial, over a sample of 25,871 patients, found no differences in the rate of occurrence of adenomas when comparing the administration of vitamin D with a placebo (12). Other clinical trials that sought to demonstrate the effect of the combination of vitamin D, calcium and aspirin also found no protective effect (13).

Why did the better-designed studies fail to show a consistent protective effect of calcium or vitamin D on adenoma and CRC development? A recent study may shed some light on this situation. Gibbs *et al.* (14) have recently published a secondary analysis of the Vitamin D/Calcium Polyp Prevention Study, evaluating the effect of interventions based on the vitamin D-binding protein (DBP) isoform. DBP is a serum protein primarily responsible for the binding, solubilizing, and transporting vitamin D and its metabolites (15). DBP is a highly polymorphic protein with the DBP1f, DBP1s, and DBP2 isoforms (also referred to as Gc1f, Gc1s, and Gc2 in the literature) being the most common in the population. The difference between these isoforms is due to two missense mutations: rs4588*C>A, which distinguishes between DBP2 and DBP1 isoforms (1s and 1f), and rs7041*G>T, which differentiates between DBP1s and DBP1f isoforms. The importance of this distinction lies in the fact that patients with the DBP2 isoform appear to have lower baseline levels of vitamin D, but they achieve the highest increases in response to vitamin D treatment (16). The study analyzed data from 1,604 non-Hispanic white patients who had their DBP gene genotyped and had completed the follow-up. The primary and secondary endpoints were any histologically verified adenoma and advanced adenoma, respectively, diagnosed at the follow-up colonoscopies. In the subgroup of 735 patients with at least one DBP2 isoform allele, a statistically significant protective effect for adenoma recurrence was found for calcium (RR 0.83; 95% CI: 0.70–0.99) and the combination of calcium and vitamin D supplementation (RR 0.76, 95% CI: 0.59–0.98). The protective effect of isolated vitamin D supplementation almost reached statistical significance (RR 0.84, 95% CI: 0.72–1.00). Moreover, when analyzing the RR of adenoma recurrence stratified by the number of DBP2 coding alleles, the protective effect of supplementation was found to increase progressively in patients with additional copies of the DBP2 allele, especially in the combined supplementation group (one copy: RR 0.81, 95% CI: 0.61–1.09; two copies: RR 0.57, 95% CI: 0.31–1.08). Regarding the secondary endpoint (advanced adenoma occurrence), no statistically significant differences were found for any of the subgroups, although this could be due to a lack of statistical power because of the low number of advanced adenomas in the sample.

Lower levels of vitamin D have been found in patients with the BPD2/Gc2 isoforms in some case-control studies, and have been related to a higher risk of incident colorectal adenomas (17,18). This relationship gives biological plausibility to the higher effect of vitamin D and calcium supplementation on this subgroup of patients. However, before recommending universal DPB2 genotyping, some limitations of this study should be noted. Firstly, the study included only non-Hispanic white patients. Circulating levels of both vitamin D and DBP appear to differ according to the patient's ethnicity, and so do the frequency of polymorphisms on the vitamin *DBP* gene (19). Therefore, the results may not be generalizable to other populations. Secondly, some studies suggest that the protective effect of both vitamin D and calcium may be dose-dependent (20), thus greater effects could be expected with higher doses. Thirdly, the chemoprotective effect of calcium and vitamin D may have a greater influence at later stages of carcinogenesis. If so, the influence should be noted on the incidence of advanced adenomas. However, in this study, the incidence of advanced adenomas was too low to draw conclusions. And finally, there are many factors influencing the development of adenomas and advanced adenomas, like diet, physical activity, obesity, tobacco, and alcohol consumption. To accurately evaluate the effect of vitamin D or calcium supplementation on adenoma recurrence those variables should be controlled.

The possible effect of vitamin D and calcium supplementation on the development of serrated lesions of the colon has to be also taken into account before recommending supplementation. Sessile serrated lesions are a known precursor of CRC and may be responsible for more than 15% of CRC through the serrated pathway of carcinogenesis (21). A secondary analysis of the Vitamin D/Calcium Polyp Prevention Study found an increased risk of sessile serrated lesions in the groups of patients that had received both calcium supplementation and the combination of calcium and vitamin D (22).

Despite these limitations, this study nicely shows that a standard therapy may not be suitable for everyone and that identifying those individuals who may benefit the most from it should be a first step even in preventive medicine. This is the relatively new and very fashionable concept of precision medicine, a discipline that aims to adapt prevention and treatment strategies to the individual particularities of each patient (in our case genetics but also epigenetics, environment, or lifestyle). This individualized approach holds great promise and is expected to lead to significant advancements in multiple fields, with particular relevance to oncology (23). Although in recent years there has been a real revolution in the treatment of advanced cancer with the use of immunotherapy, it is through prevention and early diagnosis that we will probably be able to obtain the greatest benefit at a population level. Given that the process of carcinogenesis is long and is influenced by multiple genetic and environmental factors, there is a window of opportunity to act before the onset of the disease (24). An individualized approach may allow us to identify those susceptible individuals with an increased risk of developing cancer and to act before the development of cancer with effective preventive measures.

The study from Gibbs *et al.* (14), shows how a genetic characterization of patients with a moderate risk of CRC (patients with previous colorectal adenomas) could allow us to tailor a simple and safe preventive therapy to the subgroup of patients where it is effective. It is to be expected that the identification of more individual characteristics will allow a more precise prescription of preventive measures for the most prevalent cancers, helping us—in the long term—to win the battle against this dreadful disease.

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