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EDITORIAL

Calcium and vitamin D in the serrated neoplastic pathway: Friends or foes?

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Abstract

Sessile serrated adenoma/polyps (known as SSA/Ps) may play an important role in the development of interval colorectal cancer (CRC). These lesions are more difficult to detect with conventional endoscopy and they may quickly turn into CRC, especially when dysplasia has developed. Therefore, primary or secondary chemoprevention may be an appealing strategy at a population level. Calcium and vitamin D have been shown in epidemiological studies to reduce the risk of CRC and conventional adenomas, but the evidence regarding their effect on SSA/Ps is controversial. In this editorial we comment on the results of a recent randomized controlled trial investigating the effect of calcium and vitamin D on the development of serrated lesions, summarizing the possible antineoplastic mechanisms of calcium and vitamin D, and discussing the differences found with previous observational reports.

Key words: Serrated polyps; Sessile serrated polyp; Vitamin D; Calcium; Colorectal cancer

Core tip: Calcium and vitamin D have been shown in epidemiological studies to reduce the risk of colorectal cancer and adenomas, but the evidence regarding their effect on sessile serrated adenomas/polyps (SSA/P) is controversial - some studies showing no effect and others showing some degree of risk reduction. Recently, a randomized controlled trial with calcium and

vitamin D supplements was published, concluding that the relative risk of developing a SSA/P was increased in patients taking calcium and vitamin D/calcium. In this editorial we try to place these surprising results into context, describing the limitations of this and previous studies on this topic.

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INTRODUCTION

Serrated polyps (SPs), and particularly sessile serrated adenoma/polyps (SSA/Ps), are precursor lesions of colorectal cancer (CRC). Some authors have affirmed that the so-called "serrated neoplastic pathway" is the route through which 10% to 30% of CRCs develop[1]. SSA/Ps are more difficult to detect with conventional endoscopy[2] and they may quickly turn into CRC, especially when dysplasia has developed[3]. Therefore, SSA/Ps may play an important role in the development of interval cancer. In this situation, primary or secondary chemoprevention may be an appealing strategy at a population level.

Calcium and vitamin D have been shown to exert their anticancer properties by stimulating differentiation, reducing proliferation and inducing apoptosis. The majority of epidemiologic studies support a reduction of the risk of CRC and adenomas by almost 30% when comparing high to low intake of both calcium and vitamin D. For instance, a dose-response meta-analysis of observational studies found that an intake of supplemental calcium could reduce the risk of CRC at a rate of 9% for each 300 mg/d increase[4]. Calcium supplementation has also been shown in a randomized trial to reduce the recurrence of colorectal adenomas[5].

Based on this idea, interest has been focused in recent years on the effect of calcium and vitamin D on SPs' development. Several large pooled studies and meta-analyses have been published on the topic, with disparate results. Some have shown no effect of calcium supplementation on SPs[6], others have shown a nonsignificant reduction in SP risk in individuals consuming the highest levels of calcium but no effect of vitamin D[7], and in other reports no effect of calcium was shown but vitamin D intake was found to be inversely associated with SPs, especially for polyps in the distal colon[8].

Despite the inclusion of hundreds of thousands of patients, these studies have some limitations that make it difficult to draw firm conclusions. Many studies were published years ago, prior to the classification of SPs into different subtypes. Current knowledge includes the different subtypes of SPs [hyperplastic polyp (HP), SSA/P, traditional serrated adenoma] being biologically different, posing different risks of developing a CRC, and possibly having different behaviors regarding dietary factors. Some of the included studies are based on sigmoidoscopies and, as we know, SSA/Ps are generally located in proximal segments of the colon[9]. Assessing possible risk factors in observational cohort studies may be difficult when there is a low prevalence of the disease - SSA/Ps in this case - while the prevalence of SSA/Ps in several studies is at most 8%[10]. In order to detect weak associations and describe possible long-term effects, follow-up should be long enough; however, most prospective studies have a relatively short follow-up, between 1 to 6 year[5,7]. Finally, risk factors often overlap in dietary epidemiological studies and, in regards to the specific case of calcium and vitamin D; many studies do not assess them separately.

Recently, a colonoscopy-based case-control study analyzing data from more than 7000 patients and controls was published[11]. In this study, an expert pathologist classified all serrated lesions according to subtype. Among other lifestyle and dietary factors, calcium intake was associated with a reduced risk of HP and adenomas but not with a statistically significant reduction in the risk of SSA/Ps. Vitamin D intake was not considered. Although designed following up-to-date knowledge, this study again has some limitations that do not allow the definite ruling out of a possible influence of calcium intake on SP development. Based on surveys, recall bias cannot be excluded. Moreover, only those individuals who answered some surveys were included, representing only 51% of the initial candidates. Sample size could also be seen as an issue, since patients with SSA/Ps accounted for around only 7% of the entire case group. Finally, in this study only dietary calcium, and not supplements, was evaluated.

All together, these observational and case-control studies are a very useful tool for detecting possible associations and formulating hypothesis, but casualty has to be confirmed in clinical trials. This is the reason why the results of a well-designed randomized controlled trial have been eagerly awaited.

A randomized, multicenter, double-blind, placebo-controlled chemoprevention trial with calcium and vitamin D supplements was recently published. Crockett *et al*[11] analyzed the risk of SPs among participants in the Vitamin D/Calcium Polyp Prevention Study. Participants with at least one adenoma in a baseline colonoscopy were included and distributed in four treatment arms (calcium, vitamin D, both or placebo). Individuals were treated for 3-5 year (treatment phase, *n* = 2058 patients), until the next surveillance colonoscopy, enabling a complete follow-up of at least 3 more year (observation phase, *n* = 1108 patients). A total of 1111 SPs (955 of HP and 132 of SSA/P) and 607 SPs (498 of HP and 79 SSA/Ps) were detected at the end of the treatment phase and the observation phase, respectively. There was no difference in the risk of developing a SP in patients taking vitamin D, calcium

or vitamin D plus calcium during the treatment phase. However, during the observation phase, relative risk of developing a SSA/P had increased in patients taking calcium and vitamin D plus calcium [crude relative risk: 2.72 (1.47-5.03) and 4.09 (1.6-10.5), respectively]. This risk was further increased in women and smokers.

This study shows surprising results, as they go against previous findings, and they also seem to contradict current knowledge regarding the role of vitamin D in cancer prevention. This latter aspect is particularly intriguing. Why has vitamin D been related to an anti-neoplastic activity? Skin-produced vitamin D_3 goes through two-cytochrome P450-mediated hydroxylation steps, first in the liver and then in the kidney, to yield calcitriol. Calcitriol - besides its critical role in regulating mineral homeostasis - through its binding to the nuclear vitamin D receptor (VDR), modulates the expression of many genes, thereby regulating multiple signaling pathways affecting inflammation, cell differentiation and proliferation, apoptotic mechanisms, invasion and metastasis[12]. The CYP27B1 enzyme, responsible for the second step of hydrolization in the kidney, has been shown to be present in several extra-kidney tissues and in cancer cells as well. Modulation of signaling pathways at this level could be responsible for vitamin D anticancer properties.

In the case of CRC, these properties are mainly driven by the modulation of the Wnt-β-catenin pathway[12]. Among other mechanisms, VDR binds to β-catenin, inhibiting its nuclear translocation. Wnt activation has been demonstrated in 93% of CRC[13]. Therefore, its inhibition could be keying in the anticancer properties of vitamin D. However, the role of this VDR-mediated mechanism in the modulation of SPs development is not so clear. The Wnt pathway has been related to the transition to dysplasia in SPs, according to β-catenin immunostaining being more prevalent in dysplastic lesions[14]. Therefore, the Wnt pathway does not seem to be essential in the earlier steps of the serrated pathway, and its inhibition could not therefore affect the overall incidence of SPs.

And, what about the main molecular mechanisms involved in the serrated pathway? These mechanisms are aberrant promoter hypermethylation of CpG islands (CIMP phenotype), microsatellite instability (MSI), and alteration of the mitogen-activated protein kinase pathway (*BRAF* and *KRAS* mutations). Few studies have assessed the relationship between vitamin D and calcium and these molecular alterations, but a consistent effect of these nutrients has not been shown. For instance, there is a study showing how VDR over-expression was significantly associated with *KRAS* mutation but not with *BRAF* mutation, CIMP or MSI[15]. In another study, calcium intake was not associated with CIMP status[16]. In a case-control study, neither calcium nor vitamin D was related to the MSI status[17]. Evidence for the effect of calcium in other putative molecular alterations of SPs is even weaker.

It is hard to explain the difference between the results of Crockett *et al*[11] and those of previous reports. Unlike most observational studies, the effect of vitamin D and calcium could be separately assessed. Moreover, supplements of both nutrients were given in this therapeutic trial, and their effect could be different from that of daily intake. Another reason may be that this trial assesses the effect of calcium and vitamin D on incidental polyps, while observational studies assess the effect on prevalent ones. Inherent limitations of this trial should be also taken into account. The study is a secondary analysis of the Vitamin D/Calcium Polyp Prevention Study, initially designed to evaluate the risk of adenomas. The final sample size of SSA/Ps was small and many of the subgroup analysis may be under-powered, as the authors acknowledge. Another limitation is that only 53.8% of patients in the treatment phase provided enough information to be evaluated in the observation phase.

CONCLUSION

In conclusion, this study raises more questions than it provides answers. Just as the use of calcium and vitamin D as chemopreventive agents could not be recommended on the basis of the results of observational studies, its avoidance in certain groups to decrease the incidence of SSA/Ps should not be recommended either. At the moment, we cannot decide if calcium and vitamin D are friends or foes, but this study reminds us that, albeit necessary, observational studies do not give us the same level of evidence as a well-designed randomized controlled trial does. Calcium and vitamin D supplements are widely used at a population level. Lessons learned from this trial should prompt the design of more powerful, multicenter, randomized trials to finally clarify whether their use should be recommended or discouraged.

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