Vitamin D Activity and Colorectal Neoplasia: A Pathway Approach to Epidemiologic Studies

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The relationship of vitamin D with colorectal and other cancers is a rapidly expanding field of study. The pathway through which vitamin D exerts transcriptional effects is complex and involves the action of other nutrients. Recent epidemiologic work underscores the importance of considering the joint effects of calcium and vitamin D in studies of colorectal neoplasia (1, 2). A key feature of vitamin D is its role in maintaining calcium homeostasis, which further highlights the interrelationship of these nutrients. However, the action of a vitamin A derivative, 9-cis retinoic acid and its receptor, the retinoid X receptor (RXR), has seldom been investigated in epidemiologic studies of vitamin D, despite the importance of RXR to the transcriptional activity of the vitamin D receptor (VDR; ref. 3). The intricate biological relationship among these nutrients makes it difficult to assess their individual roles in the development of colorectal neoplasia. In this commentary, we present a pathway that outlines the independent and interactive effects of nutrients that impact vitamin D activity in the colorectum. Although the pathway that we present is relativley simplified, our purpose is to highlight the various gene-nutrient relationships that should be considered when conducting studies of vitamin D and colorectal cancer. In this context, we specifically emphasize the actions of 9-cis retinoic acid and RXR, two neglected factors in this pathway. Based on these actions, we recommend that future epidemiologic investigations consider the interrelationships of these nutrients and associated genetic polymorphisms, in addition to studying the effects of each individually.

As a brief introduction to the epidemiologic data for the action of vitamin D and related nutrients, there is epidemiologic support for a protective effect of vitamin D on risk of colorectal neoplasia (2, 4); however, the data are equivocal (5). For calcium, there are a wealth of prospective and clinical investigations consider the interrelationships of these nutrients and associated genetic polymorphisms, in addition to studying the effects of each individually. For calcium, there are a wealth of prospective and clinical investigations consider the interrelationships of these nutrients and associated genetic polymorphisms, in addition to studying the effects of each individually.

The calcium-sensing receptors may regulate the amount of calcium available to intestinal cells, and variation in the amount or activity of calcium-sensing receptors may have implications for colorectal carcinogenesis. Indeed, polymorphisms of this gene have been associated with risk of advanced stage rectal cancer (28). The vitamin D-binding protein is important for the transport of the two major forms of circulating vitamin D, 25-(OH)D and 1,25-(OH)2D. Various chemopreventive properties have been suggested for calcium and include the binding of bile acids (9, 10), decreased fecal water cytotoxicity (11), inhibition of cellular proliferation (12, 13), induction of apoptosis (14), promotion of the tumor suppressor gene, E-cadherin (15), and inhibition of β-catenin (16), a proto-oncogene that has been implicated in several stages of colorectal carcinogenesis (16). For vitamin D and its analogues, the proposed mechanisms include antiproliferative effects (17), increased expression of the cyclin-dependent inhibitor proteins, p27Kip1 (18, 19) and p21waf1 (18, 20), promotion of colorectal carcinoma cell differentiation by induction of E-cadherin (21), and inhibition of β-catenin (16, 21). Furthermore, analogues of 1,25-dihydroxyvitamin D3 [1,25-(OH)2D3] act as inducers of apoptosis, and have shown the ability to inhibit the expression of bcl-2, a suppressor of apoptosis, in HL-60 cells (22). Investigations of the effects of 9-cis retinoic acid in the colon have been relatively sparse. Until recently, the role of RXR as an important regulatory component has been largely overshadowed by the potent effects of its heterodimer partners, including the peroxisome proliferator-activated receptor-γ (23) and VDR (24). Nonetheless, 9-cis retinoic acid has been shown to inhibit growth of breast and bladder cancer cell lines (25, 26). In colon cancer cell lines, 9-cis retinoic acid has been shown to modify the antiproliferative response of 1,25-(OH)2D, exhibiting an increased antiproliferative response in Caco-2 cells but blocking it in HT-29 cells (17). The reasons for these differential responses are unclear, but the data support a role for 9-cis retinoic as an important modulator of vitamin D activity. In addition to the pathways that describe the downstream biological activities induced by vitamin D, calcium, and 9-cis retinoic acid, the activity of related receptors and binding proteins for these nutrients must also be considered (Fig. 1).

The calcium-sensing receptor is necessary for the detection and maintenance of extracellular calcium levels by influencing parathyroid hormone secretion and calcium reabsorption (27). Calcium-sensing receptors may regulate the amount of calcium available to intestinal cells, and variation in the amount or activity of calcium-sensing receptors may have implications for colorectal carcinogenesis. Indeed, polymorphisms of this gene have been associated with risk of advanced stage rectal cancer (28).

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1,25-(OH)₂D₃ (29). Although this protein has been shown to be highly polymorphic, there have been few studies of its genetic variation and cancer. Following vitamin D transport to target tissues via vitamin D-binding protein, the VDR is critical to the action of 1,25-(OH)₂D₃ (3). After binding its ligand, VDR must heterodimerize with the RXR to exert transcriptional effects on target genes (24).

There are three isoforms of RXR (α, β, and γ), with abundant RXRα expressed in normal and neoplastic colorectal tissue (30) and colorectal cancer cell lines (17). In addition, recent investigations have indicated an important role for RXRα in colorectal pathogenesis, both independently and in conjunction with its heterodimer partners. RXR has been shown to have a role in decreasing colonic inflammation in mouse models (31). In addition, RXRα may exert chemopreventive or chemotherapeutic effects in the colon via the regulation of β-catenin (32). Dysregulation of β-catenin is a common outcome of mutations observed in colorectal cancer, resulting in higher concentrations of β-catenin and ultimately increased activation of oncogenes (32). RXR agonists have been shown to enhance interaction between RXRα and β-catenin, resulting in more efficient β-catenin degradation and subsequent antiproliferative effects (32). The present work.

Alterations in the concentration or function of the receptors, binding proteins, or ligands presented in Fig. 1 could have major implications on actions within the cell. Polymorphic variation has been observed in several nuclear receptors (33, 34), including VDR, and has been shown to affect transcriptional activity (35). In addition, VDR polymorphisms have been associated with colorectal adenoma formation (36), as well as with risk of several types of cancer (37-39), although results have been equivocal (1, 2). Recently, polymorphic variation has been described in the gene for RXRβ (34), a subtype of RXR expressed in several human tissues. As has been observed with VDR polymorphisms, variation in the gene for RXRβ may elicit functional changes that are important for colorectal cancer risk. Therefore, investigations to identify the functional effects of genetic variation in RXR and its role in the vitamin D pathway will be critical to further the understanding of the mechanism of action of vitamin D.

In summary, the involvement of several nutrients and genes in altering vitamin D activity strongly indicates the need for a pathway approach to the study of its biological effects, including greater emphasis on the activity of 9-cis retinoic acid and RXR. Study of the biological effects of RXR is an especially rich area for research, given its role as a heterodimer partner for several steroid nuclear receptors (40), including peroxisome proliferator–activated receptor-γ (23), a molecule that has itself been shown to have implications for colorectal carcinogenesis (41). We believe that examining vitamin D and/or VDR alone in epidemiologic studies, without consideration of additional key factors involved in the proposed pathway, may result in misleading or incomplete mechanisms of action. We have presented a simplified pathway to facilitate further discussion of well-known interactions among the nutrients and genes discussed. However, the vitamin D pathway is clearly more complex. Because this is a rapidly evolving field of cancer research, future studies will undoubtedly continue to uncover additional gene-gene and gene-nutrient interactions that will need to be considered along with factors proposed in the present work.

References
8. Jacobs ET, Martinez ME, Alberts DS. Research and public health implications of the intricate relationship between calcium and vitamin D.
D in the prevention of colorectal neoplasia. J Natl Cancer Inst 2003;95:
1736 – 7.
9. Newmark HL, Wargovich MJ, Bruce WR. Colon cancer and dietary fat, 
phosphatase, and calcium: a hypothesis. J Natl Cancer Inst 1984;72:
1323 – 5.
11. Lapre JA, De Vries HT, Van der Meer R. Cytotoxicity of fecal water is 
dependent on the type of dietary fat and is reduced by supplemental 
12. Lipkin M, Newmark H. Effect of added dietary calcium on colonic 
epithelial-cell proliferation in subjects at high risk for familial colorectal 
13. Pence BC. Role of calcium in colon cancer prevention: experimental and 
components associated with high or low risk of colon cancer on apoptosis in 
calcium and calcium sensing receptor function in human colon carcinomas: 
promotion of E-cadherin expression and suppression of β-catenin/TCF 
16. Wong NA, Fignatelli M. β-Catenin—a linchpin in colorectal carcinogenesis? 
17. Kane KF, Langman MJ, Williams GR. Antiproliferative responses to two 
human colon cancer cell lines to vitamin D3 are differently modified by 9-
18. Scaglione-Sewell BA, Bissonnette M, Skarosi S, Abraham C, Brasitus TA. A 
vitamin D₃ analog induces a G₁-phase arrest in CaCo-2 cells by inhibiting 
cdk2 and cdk6; roles of cyclin E, p21Waf1, and p27Kip1. Endocrinology 
19. Wang QM, Jones JB, Studzinski GP. Cyclin-dependent kinase inhibitor p27 
as a mediator of the G₁-S phase block induced by 1,25-dihydroxyvitamin D₃ 
20. Jersm SS, Madsen MW, Lukas J, Binderup L, Bartek J. Inhibitory effects of 
calcium and calcium sensing receptor function in human colon carcinomas: 
21. Pence BC. Role of calcium in colon cancer prevention: experimental and 
22. Zhang NA, Pignatelli M. Role of calcium in colon cancer prevention: experimental and 
23. Pence BC. Role of calcium in colon cancer prevention: experimental and 
24. Pence BC. Role of calcium in colon cancer prevention: experimental and 
25. Pence BC. Role of calcium in colon cancer prevention: experimental and 
26. Pence BC. Role of calcium in colon cancer prevention: experimental and 
27. Pence BC. Role of calcium in colon cancer prevention: experimental and 
28. Pence BC. Role of calcium in colon cancer prevention: experimental and 
29. Pence BC. Role of calcium in colon cancer prevention: experimental and 
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38. Pence BC. Role of calcium in colon cancer prevention: experimental and 
39. Pence BC. Role of calcium in colon cancer prevention: experimental and 
40. Pence BC. Role of calcium in colon cancer prevention: experimental and 
41. Pence BC. Role of calcium in colon cancer prevention: experimental and 
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