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. 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, 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 relatively 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 clinicalologic support for a protective effect of vitamin D on risk of colorectal neoplasia (5-7). In a clinical trial conducted (5). For calcium, there are a wealth of prospective and clinical

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Vitamin D and Colorectal Neoplasia

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 RXRs 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).

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 RXRα 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

Figure 1. The intricate relationship between the effects of vitamin D, calcium, and 9-cis-retinoic acid on tissues of the colorectum. Abbreviations: 25-OHD, 25-dihydroxyvitamin D; DBP, vitamin D binding protein; 1,25-(OH)2D3, 1,25-dihydroxyvitamin D3; 9-cis RA, 9-cis retinoic acid; VDR, vitamin D receptor; RXR, retinoid X receptor; VDRE, vitamin D response element; CaSR, calcium sensing receptor.


17. Kane KF, Langman MJ, Williams GR. Antiproliferative responses to two 16.


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

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