Editorial
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The Association of Vitamin D Deficiency with Colorectal Cancer: A Wake-up Call for Physicians and Health Authorities

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Abstract

Although there is evidence that vitamin D deficiency leads to the development of several cancers, including colorectal cancer, research has shown gaps in establishing a relationship between hypovitaminosis D and the incidence of colorectal cancer. There are controversial reports and inadequate scientific evidence about the role of age and race-specific dosage of vitamin D supplementation for chemoprevention. This editorial sheds light on the current evidence on the association of vitamin D deficiency and colorectal cancer, the role of vitamin D supplementation, and the future action plans to establish the needs analysis and goal setting about this area of research.

Keywords: Colorectal cancer, Vitamin D, Apoptosis, Vitamin D supplementation, Chemoprevention

Introduction

There has been a staggering upsurge in the incidence of colorectal cancer (CRC) and the magnitude of mortality rates from CRC varies widely up to 10-fold worldwide. Although there is substantial geographical variation, research has estimated a projected increase of the incidence of CRC by 60% to more than 2.2 million new cases and 1.1 million deaths by 2030.[1] At the same time, research has convincingly shown an escalating incidence of CRC that affects the younger population under 40 years of age as well as a reported change in the subsite distribution of CRC towards the right-sided colon.[2,3]

In addition to the established confounding factors for CRC such as Western lifestyle, colonic polyps, family history and the use of processed meat, recently, a number of new risk factors have been identified that include type 2 diabetes mellitus,[4] vitamin D deficiency,[5] exogenous insulin,[6] and statins.[7] Further exploration of the carcinogenic role of vitamin D deficiency has shown that the body of available research work demonstrated a growing evidence of association between hypovitaminosis D and several

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cancers, including CRC, breast,[8] lung,[9] and thyroid.[10]

Vitamin D deficiency, defined as concentrations <20 ng/mL, is an epidemic challenge to the healthcare authorities with an estimated figure of 1 billion people who suffer from this deficiency worldwide.[11] Geographically, only in the USA, approximately 25%–58% of adolescents and adults are found to have low serum concentrations of vitamin D.[12] On the other side of the continuum, the prevalence of vitamin D insufficiency in cancer patients has been found to approach 90%.[13] The serum level of a precursor of the physiologically active form of vitamin D, 25(OH)D, depends upon exposure of the skin to sunlight, dietary intake of vitamin D, as well as age, skin pigmentation, and obesity. Physiologically, vitamin D has the ability to inhibit cell proliferation and thus lead to increased cellular apoptosis *in vitro*. This inhibitory effect of vitamin D, paralleled by the action of the locally produced physiologically active form of vitamin D, has been shown to exhibit anticarcinogenic properties.[14] Several cell types, including colorectal epithelial cells, contain vitamin D receptors that can convert the circulating 25(OH)D into active 1,25(OH)2 vitamin D metabolites that, in turn, bind to the cells' own vitamin D receptors. The end-product of this physiological pathway provides an autocrine effect by inducing cell differentiation and inhibiting proliferation, invasiveness, angiogenesis, and metastatic potential.[15] The deeper understanding of this mechanism sheds light on the oncogenetic potential of vitamin D deficiency in various human systems.

On a serious note, the inverse relationship between vitamin D concentrations and CRC incidence has been studied from another perspective. Niv et al. investigated the varying serum levels of vitamin D with cancer stage and deduced that "serum 1,25(OH)2D3 decreased with advancing stage: 73±18, 48±16, 39±12, 34±13, and 75±20 pg/mL in stages I, II, III, IV, and controls, respectively".[16] This research underpinned the premise that the most active physiological precursor of vitamin D, vitamin D3, inhibits the proliferation of colonic epithelial cells and exerts a putative role in chemoprevention of CRC. Thus a subnormal serum level of vitamin D3 would certainly influence the biological cascade and lead to uninhibited growth of colonic epithelial cells. Kane et al. have proposed that 1,25(OH)2D3 regulates target gene transcription via a specific nuclear vitamin D receptor that mediates hormone action presumably as a heterodimer with 9-cis-retinoic acid receptors.[17] The investigators have argued that the 1,25(OH)2D3-responsive gene, referred as 25-hydroxyvitamin D3 24-hydroxylase, can induce the actions of 1,25(OH)2D3 in attenuating the anticarcinogenic actions of vitamin D.

Interestingly, vitamin D supplementation has been shown to reduce CRC related mortality; thus reaffirming the significance of optimizing vitamin D concentrations for cancer prevention and reduction of cancer mortality.[18] Zhou et al. argued that bringing the serum concentrations of vitamin D within a range of 32-100 ng/ml could potentially reduce CRC risk and mortality.[19] The researchers have deduced that a daily vitamin D intake of 1000 IU is sufficient to reduce CRC risk and mortality.[19] Several other randomized controlled trials and interventional studies have endorsed these findings.[20-22] Unfortunately, owing to a substantial disparity in vitamin D concentrations reflected by the individuals' skin pigmentations seriously challenges the attempts to standardize the dosage for vitamin D supplementation in cancer prevention. Compared with Caucasians, the African Americans are reported to carry one half concentrations of 25(OH)D, essentially due to low vitamin D synthesis in skin with a greater melanin content.[23] Henceforth, while initiating an optimal dose of vitamin D supplementation, the specific race and region should be considered by physicians. In contrast, other original studies and meta-analyses have challenged the effectiveness of 1000 IU of vitamin D supplementation for cancer prevention, thus envisaging this issue as controversial and debatable.[24,25]

To conclude, the presented data prompts the

researchers by providing a great impetus for future evidence-based studies that can endorse or discard the available findings, in particular the role of vitamin D supplementation in CRC prevention and reduction of CRC mortality. There is a need to determine other cancers that may be directly associated with vitamin D deficiency, a set of standards for the dosage of vitamin D supplementation, and a unified protocol to measure the concentrations of vitamin D in normal people or those with precancerous stage that will help reduce the cancer incidence and mortality. Hence, a simple laboratory test can facilitate vitamin D supplementation with clear advantages of chemoprevention and reduction of cancer burden on healthcare authorities. Such efforts are urged to be generated and advocated by a national level multidisciplinary cohesive action that can bring collaborative work among physicians from endocrinology, surgery, oncology, laboratory medicine, and institutional leadership fields.

Conflict of Interest

No conflict of interest is declared.

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