Emerging role of vitamin D in colorectal cancer

Wonmo Kang, Sujin Lee, Eunyi Jeon, Ye-Rang Yun, Kook-Hyun Kim, Jun-Hyeog Jang

INTRODUCTION

Cancer of the colon or rectum is called colorectal cancer. It is a common cancer and the fourth leading cause of cancer-related death in the world. Colorectal cancer is also the third most common cancer in men and the second in women worldwide. It counted for an estimated, 1.2 million new cases and 0.6 million deaths in 2008[1]. In addition, colorectal cancer is the second leading cause of cancer death in the United States. Colorectal cancer incidence rates are rapidly increasing in several historically low risk areas including Spain, and a number of countries within Eastern Asia and Eastern Europe[2]. The risk factors for colorectal cancer are age, family history, and lifestyle, such as food habits and physical activities.

Vitamin D is associated with bone growth. Vitamin D insufficiency causes abnormal bone growth, while sufficiency prevents rickets and osteomalacia, as well as osteoporosis. Vitamin D enhances the immune system[3]. In addition, vitamin D is known to prevent cancer[4] and cardiovascular diseases[5]. Vitamin D and its analogues have the ability to prevent cancer in vitro and in animal models. However, the anti-cancer effect of dietary vitamin D remains controversial. Recently, a study reported that vitamin D is not effective in preventing cancer and cardiovascular diseases[6]. Of vitamin D forms, 1,25(OH)2D3 (calciferol) induces biological effects by binding to the vitamin D receptor (VDR). The activation of VDR leads...
to the maintenance of calcium and phosphorus levels in the blood as well as of bone content. Vitamin D is also involved in cell proliferation and differentiation.

For more than 20 years, epidemiological, experimental and clinical studies have shown that vitamin D has significant protective effect against the development of cancer[6]. The mechanism of vitamin D works through several molecular pathways, such as growth-factor signaling, and transforming growth factor-β-SMAD signaling. The anti-cancer activities of vitamin D exerted by 1,25(OH)\(_2\)D\(_3\): are produced by regulating the cell cycle, apoptosis, and adhesion, as well as by cellular differentiation and proliferation. Interestingly, vitamin D reduces the incidence of colorectal cancer, when vitamin D intake, the plasma level of 25(OH)D\(_3\) and UV exposure is particularly high. In addition, the combination of vitamin D with other anti-cancer agents efficiently controls the development of colorectal cancer growth[7].

Here, the function and mechanism of vitamin D is briefly introduced, and the beneficial effect of vitamin D on colorectal cancer is discussed.

CLASSIFICATION AND MOLECULAR GENETICS OF COLORECTAL CANCER

The molecular pathogenesis of colorectal cancer has been one of the most prominent study areas in recent years. Colorectal cancer exhibits two major forms: sporadic colorectal cancer and inherited colorectal cancer.

First, sporadic cancer occurs in people who have no family history or very little of the disease. Although cancer sometimes has a hereditary or familial component, it is not common. Approximately 70%-75% of colorectal cancer is sporadic cancer. Second, inherited colorectal cancer comprises familial and hereditary cancer. Familial and hereditary cancer occurs in families who have a faulty gene inherited from the father or mother. Generally, 5% of colorectal cancer is familial cancer. Familial adenomatous polyposis and hereditary nonpolyposis colorectal cancer are the two forms of inherited colorectal cancer[8].

Ten to thirty percent of cases are attributed to familial risk and the rest to sporadic cancer. The majority of cancers are considered to be sporadic cancer. As stated above, most colorectal cancers are sporadic cancer, and only 5%-10% are inherited cancers.

FUNCTIONS OF VITAMIN D

Vitamin D exerts its various functions through molecular pathways. Vitamin D pathways are highly complex. The factors, affecting the vitamin D pathway, are P21, P27, CDKs, P53, BRCA-1-2, β-catenin and c-myc. Depending on which factor, vitamin D is involved in cell adhesion, apoptosis, differentiation and division[9]. Primarily, vitamin D plays an important role in muscle and bone health. Vitamin D deficiency results in impaired bone mineralization and leads to bone softening diseases including rickets and osteomalacia[10]. Further, vitamin D deficiency is involved in high bone turnover[11]. Vitamin D deficiency can also play a role in the pathogenesis of auto-immune diseases such as multiple sclerosis, diabetes type 1, cancer[12] and cardiovascular disease[13]. Conversely, vitamin D deficiency increases parathyroid hormone levels leading to mobilization of calcium from bone, thereby compromising bone development in the adolescent[14]. In contrast, vitamin D supplementation enhances bone density[15]. Next, vitamin D exerts an anti-cancer activity[16]. These activities of vitamin D functions are regulated by circulating vitamin D forms, the increasing concentration of 25(OH)D\(_3\) and increasing activity of 1,25(OH)\(_2\)D\(_3\). Vitamin D induces cellular proliferation, differentiation, and apoptosis of cancer and normal cells through the regulatory mechanism[17-19]. These studies show that low intake levels of vitamin D increase the risk of colorectal cancer. Some studies show vitamin D exerts growth-restraining, anti-carcinogenic effects on colorectal cancer[20,21]. In addition, vitamin D affects growth factors, regulation of cell division, cytokine synthesis, signaling, cell cycle control, and apoptosis pathways[22]. In a study in vitro, a similar result was reported. When LOVO cells were treated for 8 d with various concentrations of 1,25(OH)\(_2\)D\(_3\), cell proliferation was inhibited significantly[23]. Table 1 summarizes the anti-cancer effects of vitamin D in vivo in mice and rats.

MECHANISM OF VITAMIN D IN COLORECTAL CANCER

Vitamin D and its metabolites reduce the incidence of various cancers by inhibiting cancer angiogenesis, stimulating normal cells[33-37] and also by promoting the inhibition of proliferation. Vitamin D metabolites also help to maintain a standard calcium gradient in the various colonic epithelial cells. High levels of blood serum 25(OH)D\(_3\) are associated with a noticeable decrease in proliferation of non-cancerous cells[18,19]. The anti-proliferative effect of vitamin D is attained by inducing G1 cell-cycle arrest, which is probably mediated by up-regulation of cell cycle inhibitors. Vitamin D modulates the activation of these cell cycle related genes by various mechanisms. Vitamin D also exerts anti-carcinogenic effects by interfering with the synthesis of growth factors and cytokines and by modulating their signaling pathways. In addition to the growth inhibitory effects, vitamin D induces the differentiation of colon cancer cells. The 1,25(OH)\(_2\)D\(_3\) and its analogs exert anti-carcinogenic activities in human colon cancer cells by inhibition of proliferation and induction of differentiation and apoptosis[22]. The 1,25(OH)\(_2\)D\(_3\) significantly increases the expression and activity of alkaline phosphatase, a marker of colonic differentiation. VDR activation by 1,25(OH)\(_2\)D\(_3\) produces changes in cell junction integrity, increases differentiation and reduces oncogenic cell signaling. Induction of these genes affects cell oncogenesis, and tissue development. Thus, treatment with 1,25(OH)\(_2\)D\(_3\) suppresses oncogenic genes in
colon cancer cells. Finally, VDR genotypes are associated with anti-cancer activity in colorectal cancer. There are several VDR genotypes. For example, the most important VDR genotype is Bsm I, which has 3 variants: BB, Bb, and bb in America. The bb genotype is associated with lower concentrations of circulating 1,25(OH)₂D₃, leading to an increased incidence of colorectal cancer [40,41]. Taken together, these observations demonstrate that vitamin D exerts anti-cancer activity in colon cancer.

Figure 1 describes the mechanisms of vitamin D in various tissues. In the figure, the dotted arrow shows a newly discovered function of vitamin D.

### SUMMARY AND CONCLUSIONS

Previous research has shown the efficacy of taking vitamin D for reducing cancer risk [42]. There is strong evidence that vitamin D can change and inhibit the development of colon cancers [22]. These protective effects are likely due to the regulatory effects of 1,25-dihydroxyvitamin D₃ (calciferol) on cellular mechanisms involved in cancer development, including apoptosis, cell adhesion, cell cycle control, regulation of cellular differentiation and proliferation. A clinical study group will set up guidelines for vitamin D intake and develop models to define levels of serum 25(OH)D₃ that prevent the growth of cancer. Elevation of vitamin D levels may protect against diverse cancers. Many studies show that vitamin D assists in prevention and therapy of cancer [29]. The new guidelines will lead to more effective physical condition policies, resulting in substantially fewer cases of cancer of the colon in the future [5].

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