



# Relationship between 25(OH)D and Colorectal Cancer Prevalence at Dr. Moewardi Hospital Surakarta-Indonesia: A Cross-Sectional Study

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## Abstract

**BACKGROUND:** Colorectal cancer is a malignancy of the colon and/or rectum. Vitamin D has a role as an inhibitor of tumor progression, namely, through the process of influencing cellular differentiation and proliferation. Vitamin D receptor (VDR) affects cell differentiation by upregulating brush boundary enzymes and improving morphological microvilli.

**AIM:** This study seeks to determine the relationship between 25(OH)D levels and colorectal cancer in Dr. Moewardi Hospital, Surakarta, Indonesia.

**METHODS:** A cross-sectional design study with quantitative-analytical observation was conducted. All patients had symptoms of colorectal cancer, either undiagnosed or previously diagnosed. 25(OH)D samples were taken from a total of 50 patients at Dr. Moewardi Surakarta and subsequent diagnostic measures from the results of histopathology were assessed. The parameters assessed were 25(OH)D levels and a diagnosis of colorectal malignancy. Statistical analysis of 25(OH)D levels and colorectal diagnosis using the Chi-square test.

**RESULTS:** The prevalence of colorectal cancer is higher in respondents with 25(OH)D deficiency and insufficiency compared to respondents with normal 25(OH)D concentrations who tend to have non-colorectal cancer. Based on the Chi-square test result, the significance value was 0.004, marking a statistically significant association.

**CONCLUSION:** This study shows a significant relationship between deficiency and insufficiency of 25(OH)D concentrations with the occurrence of colorectal malignancy

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## Introduction

Colorectal cancer is a malignancy of the colon and/or rectum and is widely found in Western countries, with 12% of yearly cancer deaths being caused by this cancer [1]. Ranked as third-highest cancer in Indonesia, colorectal cancer is becoming an emerging public health problem [2]. Several factors that contribute to the rise of this cancer are evolving lifestyle and limited colonoscopy screening [2]. In recent decades, genetic and environmental factors have grown into the factors of interest in colorectal carcinogenesis [2]. Previous studies have shown that colorectal cancer takes place through three main mechanisms, which are inflammation, chromosomal instability, and microsatellite instability [2].

In the past decade of research, Vitamin D has a role as an inhibitor of tumor progression through the process of influencing cellular differentiation

and proliferation [3]. Vitamin D receptor (VDR) affects cell differentiation by upregulating brush border enzymes and improving the morphology of microvilli by influencing the maturation of the apical microvilli membrane in colorectal cancer cell cultures and then forming a well-differentiated tumor morphology [4], [5]. Steroid hormone calcitriol precursor, Vitamin D, has wide-ranging functions throughout the body [3]. Calcitriol itself controls many cellular pathways that contribute to the risk and prognosis of cancer [3]. Despite inconsistency in initial and epidemiological clinical trials, there are also no randomized controlled trials in humans to convincingly prove a favorable role of Vitamin D. Preclinical and clinical research have suggested that one of the high risks of developing cancer is lack of Vitamin D [6], [7], [8], [9]. Preventing the lack of Vitamin D levels and consuming it as a supplement may be the most beneficial way to decrease the cancer incidence and improve its prognosis.

## Methods

A cross-sectional design study with quantitative-analytical observation was conducted to establish the relation between 25(OH)D levels and colorectal cancer prevalence. Data were collected from May 2021 to July 2021 at the Digestive Surgery Sub-division of Dr. Moewardi Hospital in Surakarta, Indonesia.

A purposive random sampling technique was employed, in which the subjects were selected based on certain considerations, with the characteristics of the population that are considered to have a close relationship with the characteristics of the previously known population. The inclusion criteria were all patients aged 20–85 years, with signs, symptoms, and/or imaging indicative of colorectal cancer, either undiagnosed or previously diagnosed via diagnostic testing. Patients who have previously been tested for serum Vitamin D levels outside of Moewardi hospital, patients who consumed Vitamin D supplementation, and patients who did not give consent were excluded from this study.

Elecsys Vitamin D was used to obtain 25(OH)D concentrations and then categorized into insufficiency, deficiency, and normal. The Elecsys test is a tool for measuring linearity and functional sensitivity at three test sites. The results were then compared with the liquid chromatography-tandem mass spectrometry (LC-MS/MS), the high-performance liquid chromatography, and the Link 25 (OH) Vitamin D Total immunoassay methods (Diasorin).

The assay used was PreciControl Vitamin D total III for quality control of Elecsys Vitamin D total III immunoassays on a Cobas e immunoassay analyzer, using the reaction mixture being siphoned into the measuring cell where the electrode surface captured the microparticles. ProCell II M was used to remove unbound substances. Electrodes voltage then induced chemiluminescent emission as measured by a photomultiplier.

25(OH)D levels were categorized into deficiency, insufficiency, and normal levels based on cutoff values proposed by Pusparini (2014) [10]. The research variables include age, sex, 25(OH)D value, and colorectal cancer prevalence. Variables were collected as categorical data and presented in the distribution of frequency and percentage values. The relationship between variables was analyzed using Chi-square or Fisher's exact test. Statistical analysis program, Statistical Package for the Social Sciences (SPSS) version 22 was used for data processing and analysis.

## Results

From inclusion-exclusion data results and data collection by purposive sampling, 50 respondents aged

29–83 years were found to be eligible, 28 of whom had histopathology results and/or other diagnostic examinations with a diagnosis of colorectal cancer. Characteristics of study participants are shown in Table 1. In this study, two data were obtained, namely the concentration of 25(OH)D and cancer data: colorectal cancer vs no colorectal cancer. The data obtained were primary data, which were analyzed by the SPSS program and Chi-square calculation technique.

**Table 1: Characteristics of study participants**

Colorectal cancer	Median age (years)	Sex		Median Vitamin D (ng/mL)
		Male (%)	Female (%)	
Yes	55	14 (28)	14 (28)	16.855
No	60	10 (20)	12 (24)	24.64

Based on the data gathered, there were 20 (69.6%) and 7 (46.7%) respondents with 25(OH)D deficiency and insufficiency who also have colorectal cancer. One respondent (12.5%) with colorectal cancer had a normal 25(OH)D concentrations. The number of respondents who did not have colorectal cancer with 25(OH)D deficiency and insufficiency levels was 7 (30.4%) and 8 (53.3%), respectively. Meanwhile, 7 respondents (87.5%) without colorectal cancer had normal limits of 25(OH)D (Table 2).

**Table 2: Description of research data by colorectal cancer manifestation**

Vit-D category	Colorectal cancer				p-value
	No colorectal cancer		Colorectal cancer		
	n	%	n	%	
Deficiency	7	31.8	21	75	0.004
Insufficiency	8	36.4	6	21.4	
Normal	7	31.8	1	3.6	
Total	22	44	28	56	
Contingency coefficient	0.428				0.004

Remark: Chi-square/Fisher's exact test; \*significant if  $\alpha = 5\%$

Based on data analysis, the percentage of colorectal cancer is higher in respondents with low 25(OH)D concentration compared to respondents with normal 25(OH)D concentrations who tend to have non-colorectal cancer (Figure 1). Based on the Chi-square test result, the significance value was 0.004. Based on this value, because the  $p < 0.05$ , therefore 25(OH)D levels have a significant association with the incidence of colorectal cancer at Dr. Moewardi Hospital Surakarta.

## Discussion

We used Elecsys Vitamin D assay [11] to obtain 25(OH)D serum concentration, which was subsequently categorized into insufficiency, deficiency, and normal. Meanwhile, colorectal cancer status was obtained through the results of histopathology. A significance value of 0.004 was obtained with the Chi-Square test. Therefore, it can be concluded that 25(OH)D levels were linked to colorectal cancer at our center.

These results are in line with those from a study in Western Europe by Jenab *et al.*, which revealed a

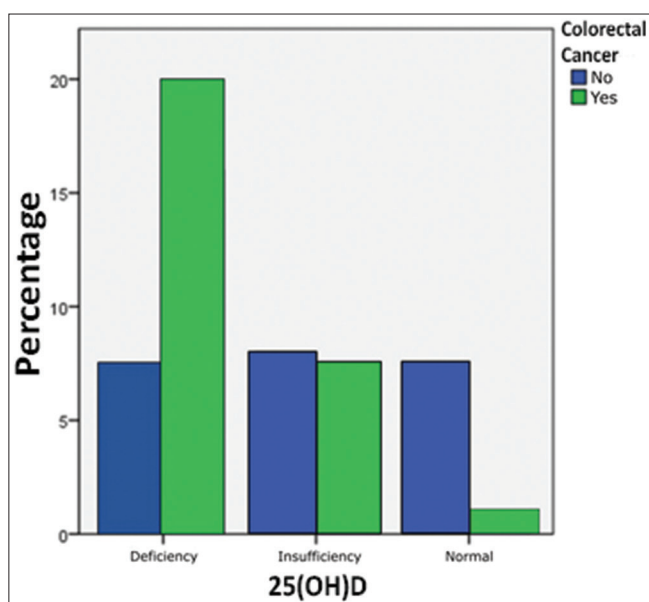


Figure 1: Colorectal cancer diagnosis in patients with 25(OH)D deficiency, insufficiency, and normal levels

negative relationship between prior diagnostic 25(OH)D concentrations and the risk malignancy of the colon and rectum [9]. The evidence associating lower 25(OH)D plasma concentrations with higher incidence of colorectal malignancy is strong. Two meta-analyses studies have reported a relationship between 25(OH)D and incidence of colorectal adenoma, a precancerous lesion that is a well established for the development of colorectal malignancy [12], [13]. A study conducted by Zhang *et al.* revealed a link between levels of circulating Vitamin D and colorectal cancer reduction in Asian countries [14]. Another study by Ekmekcioglu *et al.* in 2017 concluded that patients with higher 25(OH)D concentrations have a lower possibility of colorectal malignancy than patients with 25(OH)D deficiency [15].

Commonly used to assess Vitamin D levels, 25(OH)D is influenced by Vitamin D intake in diet and also endogenous production [16]. Vitamin D deficiency was described by most authors as a 25(OH)D serum/plasma amount under 75 nmol/L (or 30 ng/ml) [17], [18]. Levels of <25 or <30 nmol/L (or 10/12 ng/ml) is defined as severe Vitamin D deficiency [19]. A level of 25(OH)D with a range of 21–29 ng/ml (52–72 nmol/L) is stated as a relative Vitamin D insufficiency, while levels above 30 ng/ml are considered normal [10]. Besides its well-known role in mineral and bone metabolism, 25(OH)D also has a role in preventing hyperlipidemia, hypertension, T2 diabetes mellitus, and cardiovascular disease [18].

In various cells in the body, 1,25(OH)<sub>2</sub>D<sub>3</sub> binds to VDR. After that, VDR heterodimerizes with the retinoid X receptor and migrates to the nucleus in order to meet the Vitamin D<sub>3</sub> responsive element (VDRE) in the target gene promoter region to upregulate or downregulate its transcription [3], [7], [20]. When 1,25(OH)<sub>2</sub>D<sub>3</sub> is absent, the VDRE of the target gene and histone

deacetylation are blocked by corepressors to keep the dense configuration of chromatin [7]. After that, the 1,25(OH)<sub>2</sub>D<sub>3</sub>/VDR complex changes its conformation upon binding, leading to depleted corepressor and coactivator attraction that subsequently opens up the chromatin structure by causing the loss of corepressor and coactivator attraction, resulting in transcription of the target gene [7], [21]. In aggressive cancer cells, there is an increased expression of corepressors, which does not respond to 1,25(OH)<sub>2</sub>D<sub>3</sub> treatment and its antiproliferative effect [22].

VDR and 1- $\alpha$ -hydroxylase are known to be expressed in colon cancer cells, which convert serum 25(OH)D to 1,25(OH)<sub>2</sub>D [23]. In noncancerous cells the expressed VDR is extremely receptive to 1,25(OH)<sub>2</sub>D. When bound by 1,25(OH)<sub>2</sub>D, VDR performs as a transcription factor, reduces the proliferation of epithelial cells, and induces colorectal neoplasia differentiation and apoptosis [23]. When there is deficiency of Vitamin D, cell proliferation [5], blood vessels formation [20], and metastasis likelihood [23] are increased, whereas survival rate is decreased [24].

Previous studies have documented that decreased amount of Vitamin D is common in colorectal cancer patients [3], [7], [9], [23]. From 515 subjects with advanced colorectal cancer obtained from clinical trials across the United States and Canada, the 25(OH)D levels ranging from 2.3 to 75.4 ng/mL, with the median value of 20 ng/mL; showed that 82% of subjects suffered Vitamin D insufficiency (<30 ng/mL) and 50% had deficiency (<20 ng/mL) [23]. In CALGB 89803, 1,016 stage III colorectal cancer patients were enrolled. The mean predicted 25(OH)D level before adjuvant chemotherapy was 27.6 ng/mL (range, 16.0–36.4 ng/mL) [8]. A consistent report of 25(OH)D levels at diagnosis and overall survival in stage III and IV colorectal cancer patients association has been documented [24].

This study showed significant data from the comparison between patients with colon cancer who had 25(OH)D deficiency and subjects with normal 25(OH)D levels. In addition, this research also investigates patients with an insufficiency amount of 25(OH)D. Thus, the information on colon cancer patients with insufficiency levels of 25(OH)D was obtained.

The authors acknowledge the limitations of this study. The number of research subjects in this study was less due to the limited number of patients who met the inclusion requirements. Second, for this study, we chose a cross-sectional design because the aim is merely to find association. Consequently, this study does not attribute causation or correlation. Therefore, logistic regression to calculate odds ratio was also not performed. Lastly, an analysis of confounding risk factors for the occurrence of colon cancer such as smoking, age, physical activities, diet, and educational levels should have been performed. However, in addition to the limited sample size, most of the patients

that met the inclusion criteria were of a low income and low educational background, with a positive history of smoking. It is hoped that in the future, further and more massive studies can be carried out and comparisons of the aforementioned factors with 25(OH)D levels can be done to obtain comprehensive information on the degree of influence of these risk factors for colorectal cancer.

## Conclusion

Colorectal cancer is a disease that has a variety of risk factors that can increase the risk of manifestation. Among the risk factors, low levels of Vitamin D are commonly present in colorectal cancer patients. This study shows a significant relationship between deficiency and insufficiency of 25(OH)D with the occurrence of colorectal cancer.

## Disclosures

This study was part of a thesis for the General Surgery program at Universitas Sebelas Maret. The authors declare no conflicts of interest. This study received approval from the Health Research Ethics Committee of Dr. Moewardi Hospital, Surakarta.

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