Original Article

Vitamin D Status and Biomarkers Correlation in Thai Cancer Patients

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Background: The serum vitamin D level has been reported as a potential agent in cancer prevention by modulating innate and adaptive immune responses. Insufficient serum vitamin D is related to risks of cancer incidence, progression and mortality.

Objective: To analyze vitamin D status with anthropometric, biochemical and tumor markers at the first cancer diagnosis among Thai cancer patients.

Materials and Methods: A total of 106 patient's medical records at King Chulalongkorn Memorial Hospital were retrospectively reviewed. The body mass index as an anthropometric marker, biomarkers included diabetes status, hematological parameters, albumin level, lipid profiles, kidney and liver functions, C-reactive protein, and tumor markers were recorded. Level of serum circulating vitamin D was categorized into three groups: 1) vitamin D deficiency, <20 ng/mL; 2) insufficiency, 20 to 30 ng/mL; 3) sufficiency, >30 ng/mL. All parameters were analyzed using SPSS with the significance level of *p*-value at 0.05.

Results: The results revealed that the prevalence of serum circulating vitamin D deficiency, insufficiency and sufficiency were 49%, 49%, and 2% respectively. Interestingly, colon cancer patients showed significantly lower mean serum circulating vitamin D which was 17.4 ng/mL, while the mean serum circulating vitamin D level of the other cancer group was 20.3 ng/mL with *p*-value of 0.036. Additionally, five markers including BMI, diabetes, low Hb, low Hct, and high ALP levels showed significantly low serum circulating vitamin D when compared to normal reference range group.

Conclusion: The present study strongly revealed that 98% of cancer patients had low serum circulating vitamin D levels and the prevalence of vitamin D deficiency was 49% which commonly found in colon cancer patients. This finding suggests that vitamin D deficiency is an important indicator related to colon cancer prognosis.

Keywords: Biochemical markers, Cancer, Vitamin D deficiency, Vitamin D status, Tumor markers

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Cancer is the second leading cause of death worldwide, accounting for 9.6 million deaths in 2018. The most common causes of cancer deaths are those of the lung (1.76 million), colorectum (862,000), stomach (783,000), liver (782,000), and breast (627,000)[1]. The four major risk factors of cancer are tobacco, alcohol, unhealthy diet, and physical inactivity. Avoiding these risk factors can prevent 30 to 50% of the cancers. Early detection and effective management can reduce the burden of cancer[2].

Vitamin D (VD) acts like hormone by turning on or off genes and processes related to maintaining human body functions[3]. Previous studies have reported that VD deficiency (<20 ng/mL) is common among cancer patients[4]. In advanced cancer, prevalence of VD deficiency ranged from 47% to 64%[5]. Colorectal cancer related to serum circulating vitamin D (cVD) has been reported[5]. Levels of 10 ng/mL (25 nmol/L) of cVD has been associated with 29% reduction in cancer-related mortality and 17% reduction in cancer incidence[7-9]. In Thailand, approximately 60% of the cancer burden is due to five types i.e. breast, cervix, colorectal, liver and lung with 63.1% mortality and 54.3%, 5-year prevalence in 2012[10,11]. However, no data about VD status and its association with medical condition among Thai cancer patients have been reported. Therefore, this study aims to investigate the VD status of Thai cancer patients at the first diagnosis, and its correlations with anthropometric, biochemical and tumor markers.

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Materials and Methods

Ethics statement

Ethics approval for this research was obtained

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from the Institutional Review Board of the Research affairs, Faculty of Medicine, Chulalongkorn University.

Data collection

A total of 106 patients' medical records with cancer diagnosis since 2012 and follow up at the OPD Cancer Clinic, King Chulalongkorn Memorial Hospital, Bangkok, Thailand during April to August 2017 were retrospectively reviewed. All available data of cVD, anthropometric, biochemical and tumor markers recorded at the first diagnosis of cancer were collected. A cVD of less than 20 ng/mL, 20 to 30 ng/mL and more than 30 ng/mL were used as cutoff values for VD deficiency, insufficiency and sufficiency, respectively. Patients were grouped into colon and other cancers. Anthropometric, biochemical and tumor markers data were categorized as normal and abnormal levels. Mean values of cVD levels were then analyzed. These included cutoff points at BMI ≥23 kg/m^2, FBS ≥126 mg/dl, Hb <12 g/dL, Hct <39%, RBC <5 x10*6/ul , WBC <5 x10*3/ul, platelet <150 x10*3/ul, albumin <3.5 g/dl, TC ≥200 mg/dL, LDL-c ≥130 mg/dL, HDL-c <35 mg/dL, TG ≥150 mg/dL, BUN ≥20 mg/dL, Cr ≥1 mg/dL, Phosphate ≥2.5 mg/dL, Calcium ≥11 mg/dL, SGOT ≥35 U/L, SGPT ≥40 U/L, ALP >120 U/L, CRP ≥5 mg/L, CEA >5 ng/mL, CA15-3 >30 IU/mL, CA125 >30 IU/mL, and PSA >4 ng/mL.

Statistical analysis

Prevalence of VD deficiency, insufficiency, and sufficiency were estimated with 95% confidence interval (CI) and compared the mean difference by a series of t-tests. All variables were described using mean and standard error (SE). Statistical significance level (*p*-value) at 0.05 was set as threshold.

Results

Demographic characteristics and prevalence of Vitamin D deficiency, insufficiency and sufficiency

Of the 106 medical records, only 100 provided complete data qualification. Of the 100, 28%, 30%, 13% and 29% were colon, breast, lung and other cancers, respectively (Table 1). Patient characteristic data showed mean age of 63 years old, half of which had normal BMI (51.4%). One-third were overweight and obese (36.4%). The prevalence of VD deficiency, insufficiency and sufficiency were 49%, 49% and 2% respectively.

Baseline VD status stratified by age groups

The data clearly demonstrated that patients aged more than 60 years old tended to have higher prevalence of VD deficiency when compared to the younger groups (Figure 1).

Baseline VD status stratified by cancer types

Figure 2 shows that the proportion of VD deficiency and insufficiency among the cancer types range from one-third to more than one-half. Of the cancer types in

Table 1. Summary of patient characteristics

Parameters	Female	Male	Total
Age groups, n (%) mean age of 63 years old	(n = 69)	(n = 31)	(n = 100)
<40	5 (7.2)	0	5 (5)
40 to 49	4 (5.8)	0	4 (4)
50 to 59	21 (30.4)	7 (22.6)	28 (28)
60 to 69	24 (34.8)	11 (35.5)	35 (35)
≥70	15 (21.8)	13 (41.9)	28 (28)
Types of cancer, n (%)	(n = 69)	(n = 31)	(n = 100)
Colon	17 (24.6)	11 (35.5)	28 (28)
Breast	30 (43.5)	0	30 (30)
Lung	8 (11.6)	5 (16.1)	13 (13)
Others	14 (20.3)	15 (48.4)	29 (29)
BMI groups, n (%)	(n = 50)	(n = 24)	(n = 74)
Underweight, BMI <18.5 kg/m^2	6 (12)	3 (12.5)	9 (12.2)
Normal, BMI 18.5 to 22.9 kg/m^2	28 (56)	10 (41.6)	38 (51.4)
Overweight, BMI 23.0 to 24.9 kg/m^2	8 (16)	3 (12.5)	11 (14.8)
Obese I, BMI 25.0 to 29.9 kg/m^2	7 (14)	7 (29.2)	14 (18.9)
Obese II, BMI ≥30 kg/m^2	1 (2)	1 (4.2)	2 (2.7)
Vitamin D status, n (%)	(n = 69)	(n = 31)	(n = 100)
Deficiency, 25(OH)D <20 ng/mL	33 (47.8)	16 (51.6)	49 (49)
Insufficiency, 25(OH)D 20 to 30 ng/mL	35 (50.7)	14 (45.2)	49 (49)
Sufficiency, 25(OH)D >30 ng/mL	1 (1.5)	1 (3.2)	2 (2)

BMI = Body mass index

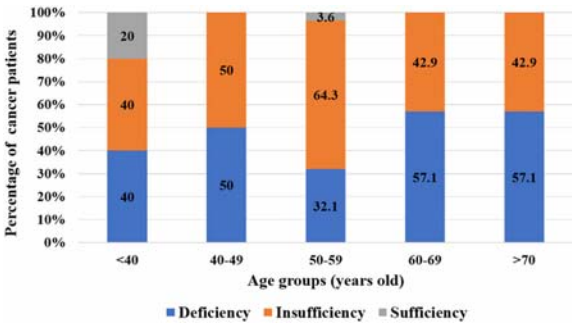

Figure 1. Baseline VD status stratified by age groups (n = 100).

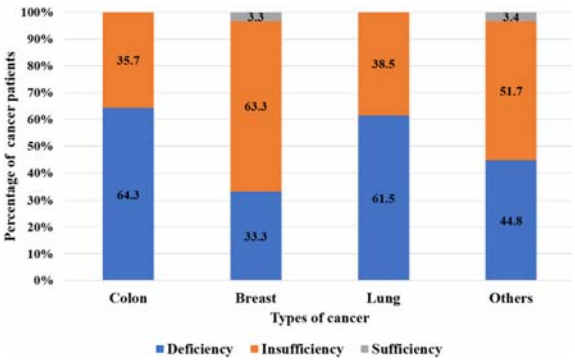

Figure 2. Baseline VD status stratified by cancer types (n = 100).

Figure 2, that of the colon had the highest prevalence of VD deficiency (64.3%).

Relationship between mean cVD and markers in Thai cancer patients

As shown in the Table 2, significant mean cVD of the colon cancer group (p<0.036) was elucidated. Overweight and obese, DM, low Hb, low Hct and high ALP levels were significant lower mean cVD levels compared to the normal marker groups (p<0.05). They were 17.2, 16.1, 16.8, 18.4 and 15.6 ng/mL, respectively. However, no statistically significant correlation between cVD and RBC, WBC, albumin, lipid profiles (TC, HDL-c, LDL-c), kidney and liver functions (BUN, Cr, Phosphate, Calcium, SGOT, SGPT), CRP and tumor markers in all cancers was observed.

Discussion

In the present study, 98% of patients had low cVD levels. High prevalence of VD deficiency was reported in elderly cancer patients[12-14], which may be due to less sun exposure and decreasing in VD synthesis in the skin[15].

We found that high prevalence of VD deficiency was dominant in colon cancer patients. Statistically significant low cVD level was reported in cancer patients compared to healthy controls[16]. Previous studies reported that VD deficiency could increase the risk of cancer development, particularly in colon cancer, suggesting that cVD levels could have an important role for cancer detection[16,17]. cVD level more than 33 ng/mL or 82 nmol/L could decrease the colorectal cancer incidence risk to 50%[18].

Associations of VD deficiency with diabetes status, Hb, Hct, ALP and BMI were found. Overweight and obese cancer patients were found to have significantly lower mean of cVD levels when compared to non-overweight group as well as increasing BMI significantly decreased cVD level[19]. Overweight condition or obesity have been found to be important risk factor of cancer in men and women[20]. Thus, our findings suggest that maintaining healthy BMI (18.5 to 22.9 kg/m^2) may reduce the risk for cancer.

Low serum cVD levels were found in diabetic cancer patients. Significant prevalence of VD deficiency in non-cancer type 2 diabetes mellitus patients was reported as 39.3%, while 51.2% was found in healthy control group[21]. Despite, the absence of reports on low serum cVD level in diabetic cancer patients, it might be related to cancer pathophysiology itself regardless of diabetes status.

Significant low mean cVD levels were found in patients with low Hb and Hct. A study reported that 49% of VD deficient subjects (25(OH)D <30 ng/mL) presented anemia compared to 36% of normal VD subjects (p<0.01)[22]. This demonstrated an association between VD deficiency and a greater risk of anemia; though the mechanism is unknown. VD modulates the levels of systemic cytokine production, reducing the inflammatory micro-environment, leading to anemia in chronic diseases[22]. The active form of VD reduces cytokine production both in vivo and in vitro studies[23]. Another possible mechanism is that erythroid precursors are directly activated by high local concentrations of an active form of VD in hematopoietic tissues in a paracrine fashion. VDR have been found in numerous non-renal target tissues including the bone marrow, and they affect bone marrow function[24,25]. Moreover, the active form of VD levels in bone marrow are several hundred-fold higher compared with plasma[23]. Cancer itself can suppress hematopoiesis through bone marrow infiltration or production of cytokines, that lead to iron sequestration, or by reducing the production of RBC. Moreover, treatment of cancer may also be a major cause of anemia[26]. Based on the findings of an association between VD deficiency and anemia, evaluating whether there is a direct causal effect of VD deficiency on anemia needs to be conducted. If erythropoiesis can be improved by VD, then correction of VD deficient status may lead to improvement of anemia in cancer patients.

Our finding of significantly low cVD levels in the high ALP group may render the essential marker role of elevated serum ALP level for the diagnosis of VD deficiency. Thus, monitoring of ALP level may be helpful in checking the progress of treatment for patients with VD deficiency[27].

The advantage of the present study is that cVD level was used to be one of relevant factor for cancer incidence and development at the first of cancer diagnosis. Moreover,

Table 2. Relationship between mean cVD and markers in Thai cancer patients

Variables	Serum 25(OH)D, ng/mL, mean (SE)	Mean difference (95% CI)	*p*-value*
Cancer types			
Colon (n = 28)	17.4 (0.99)	-2.90 (-5.63, -0.18)	0.036
Others (n = 72)	20.3 (0.76)		
BMI status			
Overweight and obese (n = 27)	17.2 (0.93)	-3.89 (-6.79, -0.98)	0.009
Non-overweight (n = 47)	21.1 (0.96)		
DM status			
Diabetes (n = 7)	16.1 (1.2)	-5.16 (-9.95, -0.37)	0.035
Non-diabetes (n = 43)	21.2 (0.94)		
Hematological markers			
Hb <12 g/dL (n = 28)	16.8 (1.23)	3.84 (1.15, 6.53)	0.006
Hb ≥12 g/dL (n = 68)	20.6 (0.71)		
Hct <39 g/dL (n = 52)	18.4 (0.88)	2.53 (0.02, 5.03)	0.048
Hct ≥39 g/dL (n = 44)	20.9 (0.89)		
RBC <5x10*6/ul (n = 88)	19.5 (0.68)	0.08 (-4.53, 4.69)	0.970
RBC ≥5x10*6/ul (n = 8)	19.4 (2.02)		
WBC <5x10*3/ul (n = 29)	18.9 (1.05)	0.69 (-1.99, 3.38)	0.612
WBC ≥5x10*3/ul (n = 66)	19.6 (0.77)		
Platelet <150x10*3/ul (n = 14)	18.8 (1.94)	-0.85 (-4.46, 2.75)	0.640
Platelet ≥150x10*3/ul (n = 82)	19.6 (0.67)		
Albumin (mg/dL)			
Albumin <3.5 (n = 7)	16.4 (1.75)	3.52 (-1.12, 8.15)	0.136
Albumin ≥3.5 (n = 86)	19.9 (0.65)		
Lipid profiles, mg/dL			
TC <200 (n = 30)	19.1 (1.04)	0.60 (-2.67, 3.87)	0.713
TC ≥200 (n = 21)	19.7 (1.26)		
HDL <35 (n = 1)	11.5	-7.64 (-21.44, 6.14)	0.265
HDL ≥35 (n = 27)	19.1 (1.27)		
LDL <130 (n = 19)	19.7 (1.44)	-1.19 (-6.89, 4.49)	0.669
LDL ≥130 (n = 8)	18.5 (2.54)		
TG <150 (n = 41)	20.1 (0.96)	-1.44 (-5.50, 2.63)	0.482
TG ≥150 (n = 12)	18.7 (1.81)		
Kidney function, mg/dL			
BUN <20 (n = 83)	19.3 (0.67)	0.47 (-3.74, 4.68)	0.826
BUN ≥20 (n = 10)	19.8 (2.63)		
Cr <1 (n = 43)	18.1 (0.89)	3.26 (-2.46, 8.98)	0.243
Cr ≥1 (n = 13)	21.4 (2.53)		
Phosphate <2.5 (n = 5)	15.3 (2.43)	4.16 (-1.53, 9.84)	0.150
Phosphate ≥2.5 (n = 78)	19.4 (0.71)		
Calcium <11 (n = 90)	19.5 (0.67)	NA	NA
Calcium ≥11 (n = 0)	NA		
Liver function, U/L			
SGOT <35 (n = 77)	19.7 (1.50)	-0.38 (-3.62, 2.86)	0.816
SGOT ≥35 (n = 18)	19.3 (0.71)		
SGPT <40 (n = 80)	19.3 (0.66)	1.31 (-2.26, 4.89)	0.469
SGPT ≥40 (n = 13)	20.6 (1.90)		
ALP ≤120 (n = 83)	20.3 (0.69)	4.74 (0.68, 8.79)	0.023
ALP >120 (n = 10)	15.6 (1.37)		
C-reactive protein (CRP), mg/L			
CRP <5 (n = 20)	20.1 (1.28)	-1.69 (-8.75, 5.38)	0.625
CRP ≥5 (n = 5)	18.4 (1.47)		
Tumor markers			
CEA ≤5 ng/mL (n = 67)	19.9 (0.83)	1.02 (-3.08, 5.12)	0.621
CEA >5 ng/mL (n = 12)	18.9 (1.49)		
CA15-3 ≤30, IU/mL (n = 32)	22.6 (1.15)	6.38 (-3.20, 15.97)	0.185
CA15-3 >30, IU/mL (n = 2)	16.3 (2.85)		
CA125 ≤35, IU/mL (n = 8)	19.2 (1.76)	-5.95 (-16.07, 4.17)	0.212
CA125, >35, IU/mL (n = 2)	25.2 (6.05)		
PSA ≤4, ng/mL (n = 7)	20.5 (3.63)	7.54 (-17.58, 32.66)	0.490
PSA >4, ng/mL (n = 1)	13.0		

* Threshold for statistical significance is $p<0.05$.
BMI = body mass index, DM = diabetes mellitus, Hb = hemoglobin, Hct = hematocrit, RBC = red blood cell, WBC = white blood cell, TC = total cholesterol, HDL-c = high-density lipoprotein cholesterol, LDL-c = low-density lipoprotein cholesterol, TG = triglyceride, BUN = blood urea nitrogen, Cr = creatinine, SGOT = serum glutamic oxaloacetic transaminase, SGPT = serum glutamic pyruvate transaminase, ALP = alkaline phosphatase, CRP = C-reactive protein, CEA = carcinoembryonic antigen, CA15-3 = carcinoma antigen 15-3, CA125 = carcinoma antigen 125, PSA = prostate-specific antigen

the study is the first report of VD status in Thai cancer patients, resulting its association with some anthropometric and biochemical markers related to health status of cancer patients in a clinical practice setting.

Conclusion

There are three important findings of this study: (i) the high prevalence (98%) of cancer patients with low cVD level; (ii) colon cancer group showed greater prevalence of VD deficiency and significantly lower cVD level compared to the other cancer group; (iii) an anthropometric marker i.e. BMI and certain biomarkers such as diabetes status, hematological parameters (Hb and Hct) and ALP showed their associations with mean cVD level. Therefore, these findings suggest that early determination of VD status can be helpful in providing integrative care for Thai cancer patients.

What is already known on this topic?

The serum vitamin D level has been reported as a potential agent in cancer prevention by modulating innate and adaptive immune responses. Insufficient serum vitamin D is related to risks of cancer incidence, progression and mortality. Previous studies revealed that serum vitamin D deficiency is commonly found in cancer patients. Advanced cancer patients showed high prevalence of serum vitamin D deficiency, varying from 47% to 64%. However, no data about VD status and its association with health status among Thai cancer patients have been reported.

What this study adds?

The results revealed that the prevalence of serum circulating vitamin D deficiency, insufficiency and sufficiency were 49%, 49%, and 2% respectively. Interestingly, colon cancer patients showed significantly lower mean serum circulating vitamin D which was 17.4 ng/mL, while the other cancer type group was 20.3 ng/mL with *p*-value of 0.036. Additionally, among other observed biomarkers, five of them including diabetes, overweight, low Hb, low Hct, and high ALP levels showed significantly low serum circulating vitamin D when compared to normal referent range group. Therefore, the present study strongly revealed that 98% of cancer patients were low serum circulating vitamin D level, especially in colon cancer group. These findings suggest that serum circulating vitamin D level is crucial for prevention, treatment and care of colon cancer patients.

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Author's contributions

PC collected and analyzed the data, and wrote manuscript. SS concepted and designed of the study, critical and final revision of the manuscript. JP advised for statistical analysis. NV advised for VD status in cancer patients.

Potential conflicts of interest

The authors declare no conflict of interest.

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ภาวะวิตามินดีกับความสัมพันธ์ต่อตัวชี้วัดทางชีวภาพในผู้ป่วยมะเร็งคนไทย

ภนิตา จตุรวิทย์, โสภิดา สุขประเสริฐ, จรรยา ภัทรอาชาชัย, นรินทร์ วรวุฒิ

ภูมิหลัง: ระดับวิตามินดีในเลือดจัดเป็นตัวชี้วัดที่มีประสิทธิภาพต่อการป้องกันโรคมะเร็ง โดยเข้าไปควบคุมการตอบสนองของระบบภูมิคุ้มกันทั้งระบบภูมิคุ้มกันโดยกำเนิดและแบบจำเพาะ ระดับวิตามินดีในเลือดที่ไม่เพียงพอเกี่ยวข้องกับความเสี่ยงต่ออุบัติการณ์ของการเกิดโรคมะเร็ง การดำเนินโรค และการตายของผู้ป่วยมะเร็ง

วัตถุประสงค์: เพื่อวิเคราะห์ภาวะวิตามินดีและความสัมพันธ์ของระดับวิตามินดีในเลือดต่อตัวชี้วัดด้านสัดส่วนของร่างกาย ชีวเคมีและสารบ่งชี้มะเร็งในผู้ป่วยมะเร็งคนไทย ณ วันที่ได้รับการวินิจฉัยโรคเป็นครั้งแรก

วัสดุและวิธีการ: ทบทวนแฟ้มผู้ป่วยมะเร็ง 106 รายที่เข้ามาติดตามการรักษา ณ คลินิกมะเร็งผู้ป่วยนอกโรงพยาบาลจุฬาลงกรณ์ในระหว่าง เดือนเมษายน ถึง เดือนสิงหาคม พ.ศ. 2560 โดยรวบรวมข้อมูลตัวชี้วัดต่าง ๆ เพื่อหาความสัมพันธ์กับระดับวิตามินดีในเลือด ได้แก่ ดัชนีมวลกาย ภาวะโรคเบาหวาน ค่าโลหิตวิทยา ระดับอัลบูมิน ระดับไขมันในเลือด ค่าการทำงานของตับและไต ค่าบ่งบอกการอักเสบในร่างกาย และสารบ่งชี้มะเร็งที่เกี่ยวข้อง โดยแบ่งภาวะวิตามินดีเป็น 3 กลุ่ม ตามระดับวิตามินดีในเลือด ได้แก่ กลุ่มที่ขาดวิตามินดี คือ มีระดับวิตามินดีในเลือดน้อยกว่า 20 ng/mL กลุ่มที่ระดับวิตามินดีไม่เพียงพอ คือมีระดับวิตามินดีในเลือดระหว่าง 20 ถึง 30 ng/mL และกลุ่มที่มีระดับวิตามินดีเพียงพอ คือมีระดับวิตามินดีในเลือดมากกว่า 30 ng/mL วิเคราะห์ข้อมูลทั้งหมดโดยใช้โปรแกรมสำเร็จรูป SPSS กำหนดนัยสำคัญทางสถิติที่ระดับ $p<0.05$

ผลการศึกษา: พบความชุกของผู้ป่วยมะเร็งที่อยู่ในภาวะขาดวิตามินดี 49% ภาวะที่ระดับวิตามินดีไม่เพียงพอ 49% และภาวะที่ระดับวิตามินดีเพียงพอ 2% โดยผู้ป่วยมะเร็งลำไส้ใหญ่มีค่าเฉลี่ยของระดับวิตามินดีในเลือด (17.4 ng/mL) น้อยกว่าผู้ป่วยมะเร็งชนิดอื่น ๆ (20.3 ng/mL) อย่างมีนัยสำคัญทางสถิติ (p = 0.036) นอกจากนี้ยังพบว่าผู้ป่วยมะเร็งในกลุ่มที่เป็นเบาหวาน น้ำหนักตัวเกิน มีระดับ Hb และ Hct ต่ำกว่าเกณฑ์ และมีค่าเอนไซม์ ALP สูงกว่าเกณฑ์มีค่าเฉลี่ยของระดับวิตามินดีในเลือดน้อยกว่ากลุ่มที่มีค่าตัวชี้วัดดังกล่าวในระดับปกติอย่างมีนัยสำคัญทางสถิติ

สรุป: ผลการศึกษาแสดงให้เห็นว่า 98% ของผู้ป่วยมะเร็งมีระดับวิตามินดีในเลือดต่ำกว่าเกณฑ์ปกติ และ 49% ของผู้ป่วยมะเร็งอยู่ในภาวะขาดวิตามินดี โดยพบมากในผู้ป่วยมะเร็งลำไส้ใหญ่ การค้นพบในครั้งนี้แสดงให้เห็นว่าภาวะขาดวิตามินดีนับเป็นตัวบ่งชี้ที่สำคัญ ซึ่งสัมพันธ์กับการพยากรณ์โรคมะเร็งลำไส้ใหญ่