RESEARCH ARTICLE

Obesity and increased risk of cancer: Does decrease of serum 25-hydroxyvitamin D level with increasing body mass index explain some of the association?

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Received: October 23, 2009
Revised: February 12, 2010
Accepted: February 22, 2010

Low levels of vitamin D and excess body weight are both factors associated with increased risk of cancer. The increased risk seems to be proportional to the increase in BMI, and to decrease in serum 25-hydroxyvitamin D (25(OH)D) level. Our earlier investigations suggest that serum 25(OH)D levels decrease with increasing BMI. Although the connection between cancer risk, BMI and vitamin D status might be arbitrary, it has not been discussed in the literature so far. In this study, we analyze data published in current meta-analysis, prospective studies, and systematic reviews on cancer-specific risk attributed to high BMI and low vitamin D status. The contribution of low 25(OH)D levels associated with high BMI to increased cancer risk was calculated for 13 vitamin-D-sensitive cancers with a focus on colorectal and breast cancer as the most frequently studied vitamin-D-sensitive cancer types. Our study suggests that a low vitamin D status may explain at least 20% of the cancer risk attributable to high BMI. The contribution of low 25(OH)D to the increased cancer risk with increasing BMI may be different for different cancer types. Thus, we find 40% for breast cancer, and 26 and 75% for colorectal cancer in men and women, respectively.

Keywords:
25-Hydroxyvitamin D / BMI / Cancer incidence / Obesity / Vitamin D

1 Introduction

Excess body weight is a well-known risk factor for colorectal and breast malignancies [1]. Additionally, increased BMI is associated with esophageal adenocarcinomas, gall bladder, endometrial, thyroid and renal cancers, as well as with multiple myeloma, leukemia, and non-Hodgkin's lymphoma [2].

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Abbreviation: VDR, vitamin D receptors

Both cancer incidence and mortality rates attributable to excess body weight have increased significantly during the last decades, along with an increased prevalence of overweight and obesity [1, 2]. Thus, it has been calculated that just between 2002 and 2008 the cancer risk attributable to excess BMI increased from 2.5 to 3.2% in men and from 4.1 to 8.6% in women [2]. Such a 65% increase in the number of new cases was observed for the incidence of endometrial, postmenopausal breast, and colorectal cancers [2].

Although the mechanisms linking excess body weight and cancer risk are not fully understood, a number of factors have been identified that may contribute to an increase in cancer incidence in overweight (BMI 25 to 29.9 kg/m^2), and obese (BMI 30 kg/m^2 or larger) individuals. Among these

are insulin resistance, dysfunction of adipose tissue, altered serum levels of adipokines, and endogenous sex steroids [3].

The levels of vitamin D steroids are also related to BMI, decreasing with increasing BMI [4]. The reason for this is probably that vitamin D is lipophilic, and that 25-hydroxyvitamin D can be stored in adipose tissue. Thus, decreased vitamin D bioavailability due to the volume-distribution effect in persons with excess body weight is likely to be the main reason for vitamin D deficiency in this category of patients. Meanwhile, high prevalence of vitamin D deficiency is often found in cancer patients, which may suggest that a low vitamin D level might be an independent risk factor for cancer. Thus, our main goal in this study was to estimate the fraction of the increase of cancer risk with increasing BMI that can be attributed to the decrease in vitamin D levels.

2 Materials and methods

Data on serum 25(OH)D levels, (nmol/L), and BMI, (kg/m^2), in 867 persons (161 men and 706 women) were provided by a Metabolic and Medical Lifestyle Management Clinic in Oslo, Norway, as described in an earlier publication [4]. Linear regression analysis was performed to calculate the average decrease in serum 25(OH)D concentration *per* $5\,kg/m^2$ BMI increase separately for men and women.

3 Results

3.1 Data sources

The relationships between BMI and cancer and between vitamin D level and cancer were obtained from recently published systematic reviews and meta-analyses of epidemiological studies [2, 5–8].

Gender-specific risk estimates for 13 cancer types, expressed as increase *per* $5\,kg/m^2$, were extracted from the study conducted by Renehan *et al.* on incident cases registered in 30 European countries [2]. The cancers of interest were those previously shown to be vitamin D sensitive [9–11]. Among those are: esophageal, colon, rectal, gall bladder, pancreas, renal, thyroid, prostate and postmenopausal breast cancers, leukemia, multiple myeloma, malignant melanoma, and non-Hodgkin's lymphoma.

The contribution of low vitamin D status to cancer incidence was calculated based on the results of two large meta-analyses [5–7] and a prospective study on cancer incidence and mortality in men [8].

Using the data extracted from these studies [2, 4–8], we estimated the cancer incidence rates attributable to the decrease of serum 25(OH)D levels in patients with excess body weight.

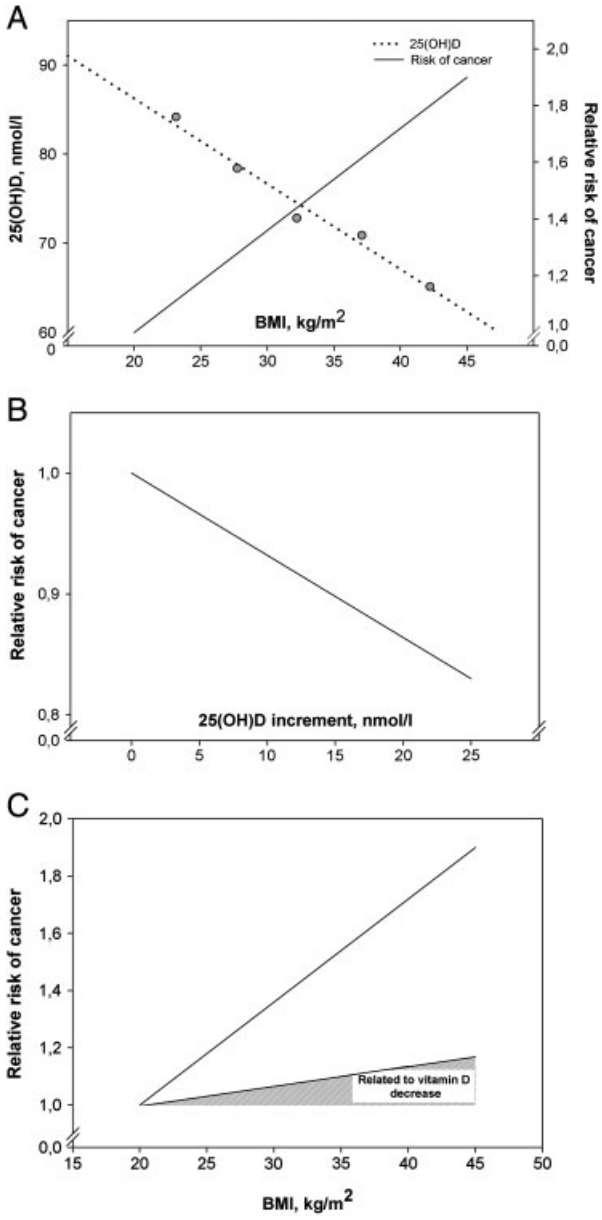

Figure 1. Relative risk of cancer, according to BMI (A, C) and serum 25(OH)D concentrations (B). Across 30 European countries the cancer risk increases by 18% with $5\,kg/m^2$ BMI increases (A, C) [2]. Under the assumption that the correlation between BMI and cancer risk is linear, that would result in almost two times higher risk for cancer in individuals with BMI close to $45\,kg/m^2$ compared to those with BMI around $20\,kg/m^2$ (A, C). At the same time, serum 25(OH)D levels decrease with increasing BMI (A) [4]. Thus, an increase of BMI from 20 to $45\,kg/m^2$ is associated with a 25 nmol/L decrease in serum 25(OH)D (A). According to Giovannucci *et al.* [8] an increment of 25 nmol/L in serum 25(OH)D is related to 17% decrease in cancer risk (B). Consequently, almost 20% of the effect of excess body weight on cancer risk may be explained by changes in vitamin D status (C).

Table 1. Summary of studies of the association between serum 25(OH)D levels and BMI

Study	25(OH)D (±SD) (nmol/L)	Age (±SD) (years)	BMI range (kg/m^2)	Gender	25(OH)D decrease[a)]	*p*-Value
McGill *et al.* [12]	62.2 (22.7)	47.6 (±11.6)	28–50	Women, men	0.7 nmol/L	0.002
Rodrigues–Rodrigues *et al.* [13]	56.5	27.8 (±4.6)	24–35	Women	1.2 nmol/L	<0.05
Stein *et al.* [14]	44.9 (22)	39 (12)	35–65	Women, men	1.3 nmol/L	<0.01
Lagunova *et al.* [4]	72.3 (24.9)	47 (14,5)	18–67	Women, men	1 nmol/L	<0.01

a) *Per* 1 kg/m2 BMI increase.

3.2 Excess body weight and vitamin D level

The prevalence of vitamin D deficiency is much higher in overweight and obese persons than in normal weight persons [4, 12–14]. We have also observed a linear decrease in serum 25(OH)D and 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) levels with increasing BMI [4]. The average decrease of 25(OH)D levels was about 1 nmol/L *per* kg/m^2 BMI increase (Fig. 1). These findings are in agreement with other studies, where an increase of $1\,kg/m^2$ in BMI was found to be associated with 0.74–1.3 nmol/L 25(OH)D decrease (Table 1) [12–14]. When the data were analyzed separately for men and women ≥50 years (Fig. 3A), the average decrease of 25(OH)D concentration *per* $5\,kg/m^2$ was 5.5 and 4.5 nmol/L for men and women, respectively.

3.3 Cancer and excess body weight

On an average, a $5\,kg/m^2$ increase in BMI was found to be associated with an increase of 18% in incidence of all cancers. If one assumes that the association between cancer risk and BMI is linear, one might expect to find a twice as high rate of cancer incidence in persons with BMI $>45\,kg/m^2$ as in normal weight individuals (Fig. 1A). A similar increase in BMI is related to 25 nmol/L decrease in serum 25(OH)D concentrations (Fig. 1A). Furthermore, an increase of 25 nmol/L may reduce total cancer risk by 17% (Fig. 1B). When these three parameters are brought together, the contribution of low vitamin D status to BMI-attributed cancer risk seems to be around 20% (Fig. 1C).

According to this analysis, a low vitamin D status may also explain about 40% of the effect of obesity on breast cancer risk (Fig. 3B), 75% of the effect on colon cancer risk in women (Fig. 3C), and 26% on colorectal cancer risk in men (Fig. 3D). The contribution of low 25(OH)D concentrations to colorectal cancer seems to be much smaller in men than in women, although men have slightly larger decrease of serum 25(OH)D with increasing BMI (Fig. 3A). This may be due to three to four times higher BMI-attributed colorectal cancer risk for men than for women (1.15 for men *versus* 1.04 for women *per* $5\,kg/m^2$ BMI increase) [2].

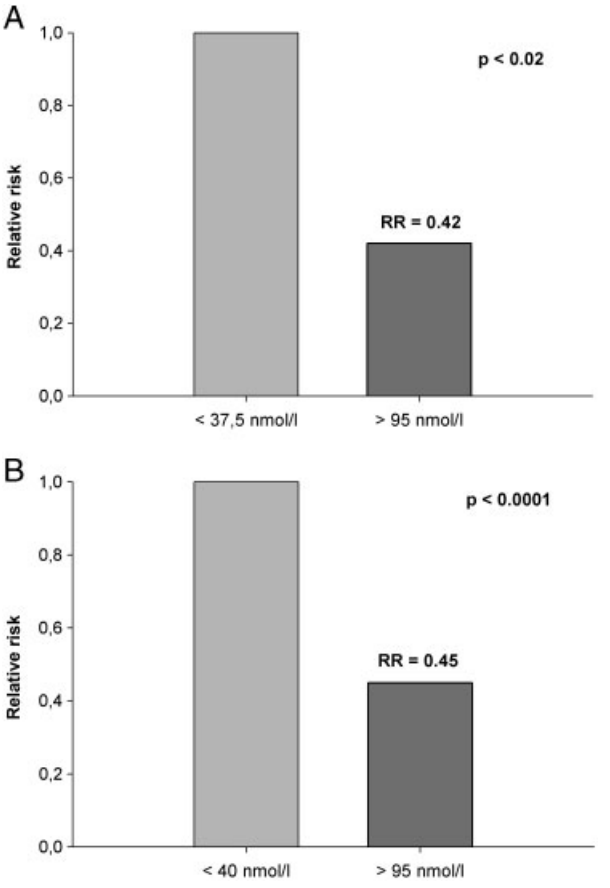

Figure 2. Relative risk of breast (A) and colorectal (B) cancers, for different serum 25(OH)D concentrations (data from [5–7]). An increment of 25 nmol/L in serum 25(OH)D is corresponding to a 20% reduction of breast cancer risk and an 18% reduction of colorectal cancer risk.

4 Discussion

This study suggests that lower serum 25(OH)D levels often found among persons with a high BMI may explain a significant fraction of the increased cancer risk associated with overweight and obesity.

The low vitamin D status among overweight and obese persons may be related to the volume-distribution effect, and the low bioavailability of fat-soluble vitamin D and

25(OH)D stored in the adipose tissue [15]. Thus, persons with excess body weight probably need a higher vitamin D intake or a larger UV-B exposure to achieve an optimal vitamin D status than persons with normal BMI [15]. However, a recent cross-sectional study on vitamin D intake has shown that obese persons consume less vitamin D than nonobese persons at all ages [16]. Moreover, a low vitamin D status among overweight and obese persons may be attributed to low sun exposure and low outdoor activity [17].

The role of vitamin D and its derivatives in cancer prevention and progression has been the topic of numerous recent investigations. Active vitamin D derivatives seem to affect cancer cell proliferation, differentiation, apoptosis as well as angiogenesis, and capacity to metastasize [18]. Thus, by a number of mechanisms vitamin D metabolites may contribute to reduced risk, progression, and metastasis of several types of cancer. Many organs have 1-α hydroxylase [19], which permits them to convert 25(OH)D to $1,25(OH)_2D$, the most active vitamin D metabolite. The effects of vitamin D metabolites are mediated through nuclear and/or membrane vitamin D receptors (VDRs), and thus involve activation of both genomic and nongenomic signaling pathways [20–22]. Recently, genetic variations of VDR have been associated also with risk and prognosis of several malignancies, including skin, prostate, breast, colon, ovary, kidney, and bladder cancers [20]. Furthermore, in some cases these associations may be modified by adiposity or excess body weight [23]. This may, at least in part, explain the possible effect of vitamin D status on BMI-related cancer risk.

The expression of VDR may be upregulated by circulating estrogen levels, which are higher for persons with high BMI, since adipose tissue is a source of endogenous estrogens [24, 25]. The effects of high estrogen levels and use of postmenopausal hormone replacement therapy are mainly mediated through estrogen receptor β and result in decreased BMI-attributed risk of colon cancer. These effects may clarify a gender difference in contribution of the low 25(OH)D concentrations to colorectal cancer incidence (Fig. 3). Other factors such as diet and cigarette smoking may influence this gender difference as well [26].

Serum 25(OH)D concentrations may be important determinants of circulating leptin levels [27], inflammatory

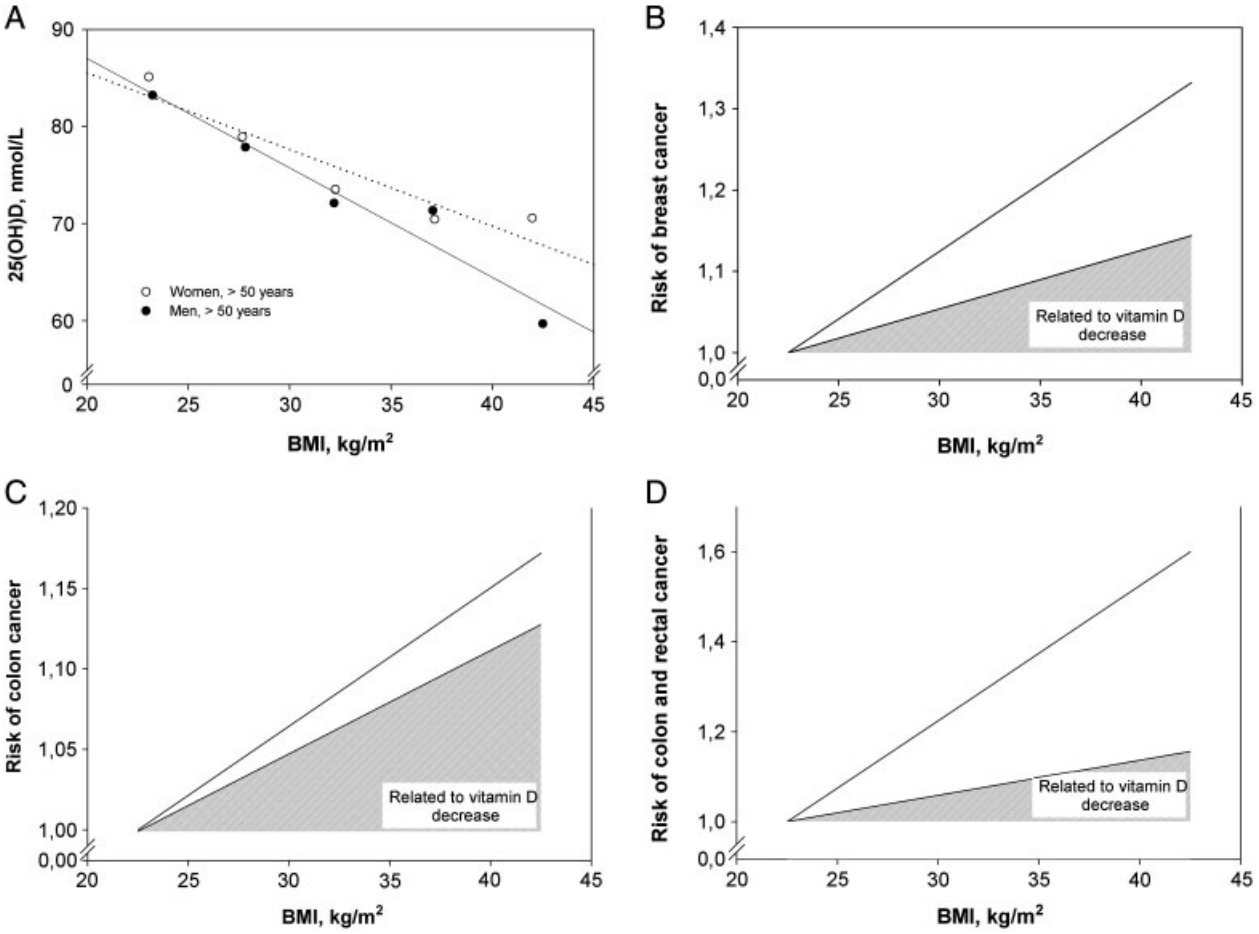

Figure 3. Relative risk of breast (B) and colorectal cancer (C, D), for different values of BMI [2]. The effect of vitamin D is calculated separately for men (colon and rectum) and women (colon) based on meta-analysis of cancer incidence [5–7] and gender-specific decay in serum 25(OH)D levels (A) [4].

markers [28, 29], glucose intolerance, and insulin resistance [30–32], which are factors contributing to increased risk of cancer in overweight and obese persons [33]. Additionally, low serum $1,25(OH)_2D$ levels, common among this group of patients, were recently linked to excess midterm mortality in patients with coronary heart disease, hypertension, diabetes, heart, and renal failure [29, 34].

Ecological studies support the hypothesis that the influence of serum 25(OH)D on cancer risk may be similar for many vitamin-D-sensitive cancers [9–11]. In a multifactorial ecological study of cancer mortality rates in the United States, UVB fluence rates in July, a surrogate measure of the vitamin D status, had nearly the same association with breast, colon, rectal, esophageal, renal, stomach, gall bladder, pancreas, prostate cancers as well as with multiple myeloma, and non-Hodgkin's lymphoma [11], even though these cancers have different risk factors. This allows us to assume that the effect of low 25(OH)D levels is similar for all vitamin-D-sensitive cancers and act together with other risk factors.

Low or nonexistent vitamin D photosynthesis during the winter may explain the seasonal variation in cancer prognosis we have demonstrated in a number of publications [35–39]. Sun exposure habits and vitamin D intake may certainly influence this variation [36, 38].

Based on cancer incidence and mortality rates in the 'Health Professionals Follow-up Study', it was estimated that an increase of 25 nmol/L would result in a 17% reduction of total cancer incidence (multivariable relative risk (RR) = 0.83, 95% confidence interval (CI) = 0.74–0.92) (Fig. 1B) [8]. These findings are in agreement with recent observational studies. According to a large meta-analysis, individuals with serum 25(OH)D concentrations larger than 95 nmol/L had 55 and 58% lower risk of colorectal and breast cancers, respectively, compared with individuals with 25(OH)D levels less than 40 nmol/L (Fig. 2) [6]. This corresponds to an 18–20% cancer risk reduction for every 25 nmol/L increase (Fig. 2).

In contrast to that, the results of a meta-analysis of prostate cancer risk and vitamin D status suggest no effect of a 25 nmol/L serum 25(OH)D increase on prostate cancer incidence [40]. This study focussed on ten case–control and cohort studies and revealed no evidence for any association between low vitamin D status and risk for prostate cancer. However, it supported a role of vitamin D as a potential marker of disease progression and associated mortality [40, 41]. This is in agreement with the seasonal variations found for cancer prognosis [35–39].

Currently, there are no meta-analyses published of the association between serum 25(OH)D and risk of other cancer types. However, according to recent cohort and case–control studies circulating 25(OH)D levels may play an important role in the development of pancreatic, lung, endometrial, ovarian, and other cancers [8, 42–47].

A randomized controlled trial on vitamin D and calcium supplementation for postmenopausal women living in Nebraska showed a 77% reduction in all cancer incidence between the ends of the first and fourth years for those taking 1100 IU/day of vitamin D and 1450 mg/day of calcium [48]. The risk reduction for those taking only calcium was 40%, implying about a 35% reduction in cancer risk for serum 25(OH)D increasing from 72 to 96 nmol/L.

Other clinical trials have failed to reveal any correlation between vitamin D intake and cancer risk or invasiveness [49, 50]. The dose of 400 IU/day of vitamin D supplementation used in these studies appeared to be inadequate for cancer prevention, and, according to Gorham *et al.*, should be increased up to 2000 IU/day [6]. It has been calculated that this vitamin D intake may result in 25–27% reduction in incidence of breast and colorectal cancers [6]. Persons with excess body weight may possibly require even higher vitamin D intake to achieve optimal vitamin D status [51].

This study relies on two types of ecological and observational studies, one for the relation between indices for vitamin D and risk of cancer, and the other for the relationship between BMI and serum 25(OH)D levels. There is only one RCT supporting the role of vitamin D in reducing the risk of cancer and none for BMI and serum 25(OH)D [48]. In addition, there are no studies relating to the effect of vitamin D and cancer risk as a function of BMI. We have kept in our mind the ''ecological fallacy'', *i.e.* finding a link between risk-modifying factors and disease outcome that could be due to unconsidered, confounding factors. As discussed in this study, the role of vitamin D in cancer risk reduction is well supported, and, in addition, can be considered causal as discussed in a paper reviewing the evidence in relation to Hill's criteria for causality in a biological system [52]. The association of higher BMI with lower serum 25(OH)D is strong, based on similar findings in at least four studies (Table 1). This study suggests that lower serum 25(OH)D for persons with higher BMI is one of the factors that contribute to higher risk of cancer. This is a testable hypothesis.

This study suggests that low serum 25(OH)D levels associated with high body mass indices may be responsible for 20% of the effect of excess body weight on total cancer risk, and, probably, up to 40% of breast cancer risk in postmenopausal women, and 75% on the colon cancer risk in women.

This study generates a hypothesis that should be tested. One way to do this would be to investigate prediagnostic serum 25(OH)D levels as well as BMI with respect to cancer incidence and/or mortality in an existing cohort study.

Our data suggest that individuals with high BMI may benefit from boosted vitamin D levels, not only with respect to cancer risk but also possibly other chronic diseases.

W. B. G. receives funding from the UV Foundation (McLean, VA), the Vitamin D Society (Canada), the Sunlight Research Forum (Veldhoven), and Bio-Tech-Pharmacal (Fayetteville, AR). The other authors have nothing to disclose.

The authors have declared no conflict of interest.

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