Inflammation Modifies the Association of Obesity with Circulating 25-Hydroxyvitamin D Levels in Cancer Survivors

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Objective: Obesity, inflammation, and circulating 25-hydroxyvitamin D (25-OHD) have distinct roles in cancer prognosis. The interplay of these factors was investigated by evaluating the associations of body mass index (BMI) with circulating 25-OHD levels in cancer survivors and determining whether associations were modified by inflammation, defined by C-reactive protein (CRP) levels.

Methods: Data on cancer survivors were aggregated from the US National Health and Nutrition Examination Survey (2001–2010). Multivariable linear regression models were used to evaluate the associations of BMI with circulating 25-OHD. Analyses were stratified by CRP levels: low (< 1.0 mg/L), moderate 1.0-3.0 mg/L, and high > 3.0-9.9 mg/L.

Results: Among 1,305 cancer survivors (mean age = 60.8 years, mean BMI = 28.0 kg/m²), circulating 25-OHD levels were 8.74 nmol/L lower (95% CI: 4.71 to 12.77) in cancer survivors with BMI ≥ 30.0 kg/m² compared with those with BMI < 25.0 kg/m². This association was, however, limited to those with moderate CRP (−9.90 nmol/L, 95% CI: −16.45 to −3.36) and high CRP (−11.61 nmol/L, 95% CI: −18.71 to −5.05), but not among those with low CRP levels (−5.31 nmol/L, 95% CI: −12.66 to 2.04).

Conclusions: A greater understanding of the interplay between 25-OHD and inflammation in cancer survivors with obesity should allow for targeted secondary prevention and help improve prognosis in these patients.

Introduction

The growing aging population contributes to an increasing cancer incidence globally (1), while advances in cancer prevention, diagnosis, and treatment have contributed to an overall reduction in cancer mortality (2). Thus, the increasing prevalence and reduced mortality are expected to result in a growing number of survivors. There are currently more than 15.5 million cancer survivors in the United States, and the number is expected to rise to 20 million by 2026 (3). Identifying modifiable factors that improve prognosis in this rapidly expanding demographic group, and how these factors interact, is of high priority.

Emerging evidence suggests that vitamin D status may be associated with improved cancer prognosis and survival, particularly colorectal and breast cancers (4-7). On the other hand, obesity is associated with poor prognosis in many cancers (8) and with low circulating 25-hydroxyvitamin D (25-OHD) levels in both cancer-free individuals and cancer survivors (9-11). There is emerging evidence that individuals with obesity who are metabolically normal may be protected from the adverse effects of obesity (12,13). Thus, when evaluating the associations of obesity with health outcomes, it is important to consider the metabolic status so that interventions to reduce the adverse effects of obesity can be targeted toward individuals at the highest risk of detrimental health outcomes.

Although there are no unified criteria to define metabolically healthy obesity, previous studies have shown that individuals with metabolically healthy obesity have a favorable inflammation profile (12,14). Further, it has been shown that an individual’s inflammatory status could mediate the effect of obesity on health outcomes, including cancer (15), and could thus be used to identify individuals who may be at the highest risk of adverse health outcomes related to obesity. However, no studies have evaluated whether inflammation modifies the effect of obesity on circulating 25-OHD levels in cancer survivors.
To fill this knowledge gap, we evaluated the associations of body mass index (BMI) with circulating 25-OHD levels among cancer survivors using data from the US National Health and Nutrition Examination Survey (NHANES). Further, we determined whether this association is modified by inflammation, as determined C-reactive protein (CRP) levels.

**Methods**

**Study population**

NHANES was designed to provide cross-sectional estimates on the prevalence of health, nutrition, and potential risk factors among the civilian noninstitutionalized US population up to 85 years old (16). In brief, NHANES surveys a nationally representative, complex, stratified, multistage, probability-clustered sample of about 5,000 participants each year in 15 counties across the country. NHANES obtained approval from the National Center for Health Statistics Research Ethics Review Board, and participants provided written consent.

We extracted demographic information, measures of adiposity, smoking history, time of blood draw, circulating CRP and 25-OHD levels, cancer diagnosis, and vitamin D supplementation use and combined these into a single data set for data collection from 2001-2002 to 2009-2010. Participants were considered as cancer survivors if they answered “yes” to the question “Have you ever been told by a doctor or other health professional that you had cancer or a malignancy of any kind?” We excluded participants who had nonmelanoma skin cancer. This interview question was given to males and females 20 years or older, and subsequently restricted the analyzed sample to adult cancer survivors. We aggregated five waves’ data and excluded those who were never diagnosed with cancer or were pregnant (Figure 1).

**BMI**

Weight and height were measured in a mobile examination center (MEC) or in the participant’s home at the time of physical examination. The measurements followed standard procedures and were carried out by trained technicians using standardized equipment. BMI was calculated as weight in kilograms/(height in meters)². We categorized study participants into BMI categories: underweight (<18.5 kg/m²), normal weight (18.5-24.9 kg/m²), overweight (25.0-29.9 kg/m²), and obesity (≥30.0 kg/m²). For analytic purposes, we combined underweight and normal weight into one category (<25.0 kg/m²).

**Circulating 25-OHD levels**

The process of blood collection is detailed in the NHANES Laboratory/Medical Technologist Procedures Manual (17). The NHANES blood collection excluded participants who received chemotherapy within the preceding 4 weeks. Blood samples were collected, processed, stored, and shipped to the University of Washington in Seattle for testing. The lab methods for measuring 25-OHD for 2007-2010 changed from 2005-2006 and earlier in NHANES, and has been described previously (18). Briefly, circulating 25-OHD concentrations were measured at the National Center for Environmental Health, Centers for Disease Control and Prevention, Atlanta, Georgia, using the DiaSorin RIA kit (Stillwater, Minnesota) between 2001 and 2006. NHANES provided regression to convert the 2001-2006 measures to equivalent 25-OHD measurement from a standardized liquid chromatography-tandem mass spectrometry method, which was used in the analysis of 25-OHD in NHANES 2007-2010 data (19). This standardization procedure therefore ensures that 25-OHD data are comparable between 2001-2006 and 2007-2010.

**Circulating CRP**

CRP levels were determined from blood samples. The process of blood collection is detailed in the NHANES Laboratory/Medical Technologist Procedures Manual (17). Circulating CRP was quantified by latex-enhanced nephelometry with a Behring Nephelometer Analyzer System (Siemens Healthcare Diagnostics, Inc., New Castle, Delaware). CRP levels were categorized to low (<1.0 mg/L), moderate (1.0 –3.0 mg/L), and high (>3.0 mg/L) (20). Cancer survivors with CRP levels ≥10.0 mg/L were excluded, as this may represent an acute infective episode.

**Season of blood draw**

Blood samples were collected at the same time as weight and height. Season of blood draw was determined from the month of physical examination. Months were documented in two groups: November 1st through April 30th, or May 1st through October 31st, and classified into winter or summer, respectively (21).

**Dietary vitamin D supplement use**

Information on dietary vitamin D supplement was retrieved from the 30-day dietary supplement data. For 2001-2006 data, information on individual products for participants who reported taking vitamin supplements was obtained and linked to the Dietary Supplements...
Ingredient Database (22). Products’ ingredients that contained vitamin D were aggregated for each participant and categorized into a binary variable (yes/no) for dietary vitamin D supplement use assessment. In 2007-2010 data, aggregated information on dietary supplement use (including vitamin D supplement use) was readily available and was used to determine participants’ dietary vitamin D supplement use (yes/no).

**Sociodemographic characteristics**

Information on age, sex, race and ethnicity, and smoking status were extracted. Based on self-reported race and ethnicity, participants were classified into one of three racial/ethnic groups: non-Hispanic white, non-Hispanic black, and Hispanic and others. For smoking status, we classified participants into three groups: never smokers (did not smoke 100 cigarettes and not currently smoking), former smokers (smoked 100 cigarettes in life and not currently smoking), and current smokers (smoked 100 cigarettes in life and currently smoking).

**Statistical analyses**

Survey analysis procedures were used to account for the sample weights (MEC exam weight), stratification, and clustering of the complex sampling design to ensure nationally representative estimates. Information on sociodemographic characteristics, weight, height, season of blood draw, and CRP was complete among cancer survivors who had available data on circulating 25-OHD levels. We calculated the descriptive statistics for participants’ characteristics and CRP levels by quintiles of 25-OHD. We summarized weighted means and standard errors for continuous variables and weighted proportions for categorical variables.

We estimated the linear associations of BMI categories with circulating 25-OHD, adjusted for sociodemographic characteristics (age, sex, race, and smoking status), season of blood draw, vitamin D supplement use, and CRP levels. A cross-product term with BMI and CRP categories was entered into the multivariable linear regression with the main effect terms. A statistical significant interaction
Results

There were 1,305 cancer survivors in the five NHANES waves who had data on circulating 25-OHD and CRP levels. The prevalent cancer sites were breast (19.6%), prostate (19.6%), cervix (10.0%), and colon (8.9%). Participants’ mean age was 60.8 years at the time of examination, and their mean BMI was 28.0 kg/m². We observed statistically significant differences in circulating 25-OHD levels for most characteristics, except for age and sex (Table 1). Cancer survivors with BMI ≥ 30.0 kg/m², non-Hispanic blacks, smokers, and who reported no vitamin D supplement use had lower 25-OHD levels than those with BMI < 25.0 kg/m², non-Hispanic whites/Hispanics, nonsmokers, and those who reported vitamin D supplement use, respectively.

Associations between obesity and circulating 25-OHD levels

Table 2 summarizes both the nonadjusted and adjusted associations between BMI categories and circulating 25-OHD in linear regression models. Circulating 25-OHD levels were 8.74 nmol/L (95% CI: 4.71-12.77) lower among cancer survivors with BMI ≥ 30.0 kg/m² compared to cancer survivors with BMI < 25.0 kg/m².

Table 3 summarizes analyses stratified by CRP categories. We observed an interaction (P < 0.001) as the associations of BMI categories with circulating 25-OHD levels differ in each strata of CRP. In cancer survivors with low CRP level group, there were no statistically significant associations between BMI and circulating 25-OHD (−1.33 nmol/L, 95% CI: −9.33 to 6.67) in cancer survivors with BMI ≥ 30.0 kg/m²; −5.31 nmol/L, 95% CI: −12.66 to 2.04) in cancer survivors with BMI ≥ 30.0 kg/m². Among those with...
One unit increase in BMI was associated with a reduction in 25-OHD levels (−0.57 nmol/L, 95% CI: −0.23 to 0.23) in the overall analyses (data not shown). The obesity prevalence was higher in non-Hispanic black cancer survivors than in non-Hispanic white survivors (46.1% non-Hispanic blacks with BMI ≥ 30.0 kg/m² vs. 30.6% non-Hispanic whites with BMI ≥ 30.0 kg/m², and 28.3% Hispanics with BMI ≥ 30.0 kg/m²). Similarly, racial/ethnic differences were observed for CRP levels (mean CRP levels were 3.25 mg/L among non-Hispanic blacks vs. 2.63 mg/L among non-Hispanic whites, and 2.77 mg/L among Hispanics; data not shown).

### Discussion

In a US nationally representative sample of 1,305 cancer survivors, higher BMI was associated with lower circulating 25-OHD levels. Nevertheless, this association was modified by the inflammation status. In analyses stratified by CRP categories, the association of higher BMI with lower circulating 25-OHD persisted among cancer survivors with elevated levels of CRP, yet attenuated to null among those with low CRP levels.

Our finding of an estimated 0.57 nmol/L (95% CI: 0.23 to 0.9) lower circulating 25-OHD with each unit increase of BMI in the

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**TABLE 4** Overall and CRP level stratified associations between BMI and circulating 25-OHD from unadjusted and multivariable-adjusted linear regression models among breast cancer survivors aged 20 years or older from NHANES 2001-2010 (n = 256)

| BMI (kg/m²) | Circulating 25-OHD (nmol/L) | Unadjusted beta coefficient (95% CI) | Adjusted* beta coefficient (95% CI) |
|-------------|-----------------------------|-------------------------------------|-------------------------------------|
| <25.0       |                             | reference                           | reference                           |
| 25.0-29.9   | −6.66 (−14.50 to 1.19)      | −5.21 (−12.09 to 1.68)              |
| ≥30.0       | −8.52 (−16.15 to −0.89)     | −8.75 (−16.78 to −0.72)             |
| P trend     | 0.03                        | 0.03                                |
| Low risk CRP level (<1.0 mg/L), n = 70 |
| BMI (kg/m²) |                             | reference                           | reference                           |
| <25.0       | −3.23 (−13.55 to 7.08)      | −3.67 (−14.82 to 7.47)              |
| 25.0-29.9   | −5.81 (−23.27 to 11.65)     | −4.26 (−20.39 to 11.88)             |
| P trend     | 0.46                        | 0.52                                |
| Moderate risk CRP level (1.0-3.0 mg/L), n = 97 |
| BMI (kg/m²) |                             | reference                           | reference                           |
| <25.0       | −6.48 (−20.50 to 7.53)      | −2.79 (−13.15 to 7.56)              |
| 25.0-29.9   | −5.10 (−19.02 to 8.67)      | −9.64 (−18.88 to −0.40)             |
| P trend     | 0.41                        | 0.06                                |
| High risk CRP level (3.1-9.9 mg/L), n = 89 |
| BMI (kg/m²) |                             | reference                           | reference                           |
| <25.0       | −12.23 (−29.94 to 5.48)     | −10.46 (−24.65 to 3.72)             |
| 25.0-29.9   | −13.39 (−30.51 to 3.74)     | −14.87 (−29.77 to 0.03)             |
| P trend     | 0.16                        | 0.08                                |

*Adjusted for age, race, smoking status, season of blood draw, dietary vitamin D supplement use, and CRP in the overall analysis.

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**Table legend:**

- CRP: C-reactive protein
- BMI: Body mass index
- 25-OHD: Circulating 25-hydroxyvitamin D
- NHANES: National Health and Nutrition Examination Survey
- CI: Confidence interval

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**Notes:**

- Moderate CRP levels, cancer survivors with BMI ≥ 30.0 kg/m² (−9.90 nmol/L, 95% CI: −16.45 to −3.36), but not those with 25.0 kg/m² ≤ BMI < 30.0 kg/m² (−1.64 nmol/L, 95% CI: −7.86 to 4.58), had low 25-OHD levels. Among those with high CRP levels, cancer survivors with BMI ≥ 25.0 kg/m² ≤ BMI < 30.0 kg/m² (−8.63 nmol/L, 95% CI: −14.33 to −2.92) and those with BMI ≥ 30.0 kg/m² (−11.61 nmol/L, 95% CI: −18.17 to −5.05) both had low 25-OHD levels.

- We conducted further analyses among breast (n = 256) and prostate cancer survivors (n = 255), because these were the two most prevalent cancer types among study participants (Tables 4 and 5). We observed similar trends in associations as we did in the overall analyses, especially for breast cancer, but the stratified analyses, though highly suggestive, were not statistically significant, likely due to the small sample size.

- Breast cancer survivors with BMI ≥ 30.0 kg/m² had low 25-OHD levels (−8.75, 95% CI: −16.78 to −0.72). Among those with high CRP levels, although breast cancer survivors with BMI ≥ 30.0 kg/m² had low 25-OHD levels (−14.87, 95% CI: −29.77 to -0.03), the trend test was not statistically significant likely as a result of the reduced sample size (n = 89).

- Our findings were similar when using BMI as a continuous variable. One unit increase in BMI was associated with a reduction in 25-OHD levels (−0.57 nmol/L, 95% CI: −0.23 to 0.23) in the overall analyses (data not shown). The obesity prevalence was higher in non-Hispanic black cancer survivors than in non-Hispanic white survivors (46.1% non-Hispanic blacks with BMI ≥ 30.0 kg/m² vs. 30.6% non-Hispanic whites with BMI ≥ 30.0 kg/m², and 28.3% Hispanics with BMI ≥ 30.0 kg/m²). Similarly, racial/ethnic differences were observed for CRP levels (mean CRP levels were 3.25 mg/L among non-Hispanic blacks vs. 2.63 mg/L among non-Hispanic whites, and 2.77 mg/L among Hispanics; data not shown).
TABLE 5 Overall and CRP level stratified associations between BMI and circulating 25-OHD from unadjusted and multivariable-adjusted linear regression models among prostate cancer survivors aged 20 years or older from NHANES 2001-2010 (n = 255)

| Circulating 25-OHD (nmol/L) | Unadjusted beta coefficient (95% CI) | Adjusted\* beta-coefficient (95% CI) |
|-----------------------------|-------------------------------------|-------------------------------------|
| All prostate cancer survivors, n = 255 | | |
| BMI (kg/m²) | | |
| <25.0 | reference | reference |
| 25.0-29.9 | 5.59 (−2.41 to 13.59) | −0.76 (−7.89 to 6.38) |
| ≥30.0 | 3.69 (−4.38 to 11.75) | −4.02 (−11.52 to 3.47) |
| P trend | 0.41 | 0.27 |
| Low risk CRP level (<1.0 mg/L), n = 74 | | |
| BMI (kg/m²) | | |
| <25.0 | reference | reference |
| 25.0-29.9 | 8.70 (−3.27 to 20.67) | 3.19 (−9.01 to 15.40) |
| ≥30.0 | 7.39 (−3.01 to 17.79) | 2.71 (−12.05 to 17.47) |
| P trend | 0.15 | 0.72 |
| Moderate risk CRP level (1.0-3.0 mg/L), n = 95 | | |
| BMI (kg/m²) | | |
| <25.0 | reference | reference |
| 25.0-29.9 | 4.87 (−9.38 to 19.12) | −1.74 (−15.06 to 11.57) |
| ≥30.0 | 2.51 (−12.30 to 17.32) | −7.30 (−20.91 to 6.32) |
| P trend | 0.71 | 0.28 |
| High risk CRP level (3.1-9.9 mg/L), n = 86 | | |
| BMI (kg/m²) | | |
| <25.0 | reference | reference |
| 25.0-29.9 | 2.66 (−11.49 to 16.82) | −3.12 (−13.37 to 9.14) |
| ≥30.0 | 1.87 (−9.79 to 13.54) | −7.73 (−18.75 to 3.29) |
| P trend | 0.87 | 0.22 |

\*Adjusted for age, race, smoking status, season of blood draw, and dietary vitamin D supplement use, and CRP in the overall analysis.

Overall analyses is consistent with previous studies. Using a hospital sample, Vashi and colleagues (10) found a similar trend of lower circulating 25-OHD levels with each increase in BMI among cancer survivors of mixed cancer sites. The magnitude of the decrease in that study was slightly larger (−0.42 ng/mL, 95% CI: −0.56 to −0.28, which translates to −1.05 nmol/L, 95% CI: −1.40 to −0.70) than what we found, probably due to the limited number of confounding factors (age and gender) adjusted in their multivariable linear regression model. Likewise, Friedman et al. (9) reported that the vitamin D deficiency rate was three-fold higher (aOR = 3.05, 95% CI: 1.72 to 5.41) in postmenopausal breast cancer survivors with obesity compared to those with normal weight. However, none of the aforementioned studies had included any inflammation assessment.

To the best of our knowledge, our study is the first to investigate the associations of obesity with circulating 25-OHD levels by strata of inflammation status. Our findings suggested that CRP modifies the association between obesity and circulating 25-OHD. Adipose tissue is a metabolically active endocrine organ that is involved in whole-body tissue homeostasis. Obesity is characterized by a state of chronic inflammation and adipose tissue hypoxia resulting in dysregulation in adipokine production and activation of pro-inflammatory pathways (23), which can promote tumor progression (24-26). Nevertheless, although the majority of individuals with obesity are metabolically unhealthy with evidence of low-grade systemic inflammation, it has been shown that up to 28% of individuals with obesity are metabolically healthy (27) and have no evidence of systemic inflammation. Metabolically healthy individuals with or without obesity have lower circulating CRP concentrations compared to metabolically unhealthy individuals (28). After stratifying cancer survivors by CRP levels in our study, we observed that among cancer survivors with BMI ≥ 30.0 kg/m², only those with moderate and high CRP levels, but not those with low CRP, had low circulating 25-OHD levels. Similar associations have been reported among noncancer individuals. In a large study among individuals with obesity, participants who were classified as having metabolically healthy obesity (classified using CRP and other biomarkers) had higher circulating 25-OHD levels compared with those who were classified as having metabolically unhealthy obesity (29). This is in line with a recent review of mechanistic studies (30) that pointed to the potential mediator role of inflammation in vitamin D and cancer prognosis. It has been suggested that vitamin D status may modulate the favorable inflammatory profile among metabolically healthy cancer survivors with obesity because of vitamin D’s role in regulating chronic inflammation (29,30). This needs to be
investigated in a longitudinal setting with repeated measures of vitamin D and inflammation biomarkers in cancer survivors.

The main strength of this analysis is pooling a considerable size of adult cancer survivors from a US nationally representative sample. In addition, we controlled for a range of factors that are known to affect circulating 25-OHD levels. Furthermore, we were able to compare associations of BMI with circulating 25-OHD by CRP categories, thereby providing further insight into the interplay between circulating 25-OHD and inflammation among cancer survivors with obesity.

There are a number of limitations to this study. First, intervention studies and Mendelian randomization analyses supported a causal relationship between obesity and low circulating 25-OHD levels (31-33). The cross-sectional nature of this study makes it impossible to determine a causal association between circulating 25-OHD and inflammation. It is unclear if correcting vitamin D levels could effectively lower inflammation among cancer survivors with obesity and evident systematic inflammation (34). Second, season, an important determinant of 25-OHD levels, was only available in two categories. Solar radiation is required for skin to synthesize vitamin D, yet it is weaker in winter compared to summer. Although the NHANES study collected blood samples in the southern states during winter and in the northern states during summer, higher circulating 25-OHD levels were seen in the Northern States. Third, apart from breast and prostate cancers, we were not able to conduct analyses stratified by other cancer type and disease stage because of the limited number of individual cancers. Finally, participants who received chemotherapy within the last 4 weeks were excluded from blood collection when they enrolled in the NHANES study. Given the documented chemotherapy-associated reduction of circulating 25-OHD level (35-37), our findings might not be generalizable to patients currently receiving chemotherapy.

To date, inflammation has been rarely considered in prospective studies investigating the impact of circulating 25-OHD on cancer prognosis (38). As evidence emerges of potential associations between low circulating 25-OHD levels and prognosis in cancer patients, secondary prevention efforts might be best served if interventions to correct low 25-OHD levels are directed towards cancer survivors with obesity and high CRP levels.

Conclusion

Obesity is associated with lower circulating 25-OHD levels in cancer survivors. This appears, however, to be limited to those with evidence of systemic inflammation. Further studies are needed to elucidate the causal relationship between circulating 25-OHD and inflammation in cancer prognosis, particularly among cancer survivors with obesity. Findings from such studies could open up opportunities to prioritize interventions to correct 25-OHD by stratifying cancer survivors with obesity based on their metabolic profile or inflammation markers.

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