Short Communication

Cancer Epidemiology, Biomarkers & Prevention

Plasma 25-Hydroxyvitamin D and Risk of Colorectal Cancer after Adjusting for Inflammatory Markers

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Abstract

Despite the substantial epidemiologic evidence on the inverse association between circulating 25-hydroxyvitamin D [25(OH)D] and colorectal cancer, it remains controversial whether this relationship is causal or due to confounding by inflammation. We reevaluated the association between plasma 25(OH)D and colorectal cancer risk by additionally accounting for inflammatory markers in a prospective case–control study nested within the Nurses' Health Study and Health Professionals Follow-up Study (615 cases and 1,209 matched controls). Conditional logistic regression was used to estimate relative risk (RR) and 95% confidence interval (CI) of colorectal cancer in relation to quartiles of plasma 25(OH)D. Results were compared before and after adjusting for inflammatory markers in the multivariable model. Plasma 25(OH)D was associated with reduced risk of colorectal cancer (multivariable RR comparing extreme quartiles = 0.71; 95% CI, 0.52–0.97; $P_{trend} = 0.01$). Additional adjustment for C-reactive protein, IL6, soluble tumor necrosis factor receptor 2, or a composite inflammatory score did not change the results [multivariable (including inflammatory score) RR = 0.72; 95% CI, 0.53–0.98; $P_{trend} = 0.02$). Our findings suggest that confounding by inflammation, as reflected by circulating inflammatory markers, does not appear to account for the inverse association between plasma 25(OH)D and colorectal cancer. *Cancer Epidemiol Biomarkers Prev; 23(10); 2175–80. ©2014 AACR.*

Introduction

The effect of vitamin D on a wide variety of nonskeletal health outcomes, including colorectal cancer, has been the subject of considerable debate (1). High vitamin D has been associated with reduced risk of colorectal cancer in observational studies evaluating dietary intake (2, 3), circulating 25-hydroxyvitamin D [25(OH)D] (2, 4, 5), and predicted 25(OH)D (6). A recent meta-analysis of observational data reported a 26% lower risk of colorectal cancer [95% confidence interval (CI), 11%–37%) per 10 ng/mL increment in blood 25(OH)D levels (4). Possible mechanisms include antiproliferative, proapoptotic, prodifferentiating, and anti-inflammatory actions by the physiologically most active molecular form of vitamin D, formed locally 1α,25-dihydroxyvitamin D_3 [1,25 $(OH)_2D_3$] (7).

Despite the preponderance of observational and mechanistic evidence, no benefit was reported for vitamin D supplementation against colorectal cancer occurrence in several randomized trials (1), including the Women's Health Initiative (WHI; ref. 8), the largest trial in this regard. However, these data are far from conclusive given critical limitations of the WHI, including poor adherence, inadequate vitamin D dose and duration, complex factorial design, and low baseline risk of the study population. Each of these factors may have contributed to the null findings (9–11).

Recently, Autier and colleagues summarized the observational and experimental findings on vitamin D and nonskeletal disorders with a special emphasis on colorectal cancer, which is the only cancer related to low 25(OH)D in observational studies but not in randomized trials in their analyses (1). Considering the potential link between inflammation, vitamin D, and colorectal cancer, they hypothesized that low 25(OH)D is just a marker of ill health, with inflammation, measured by elevated concentrations of circulating C-reactive protein (CRP), IL6, and TNFα, acting as a confounding factor in the observed inverse association of 25(OH)D and colorectal cancer (1).

To assess the hypothesis of Autier and colleagues (1) and to assess the robustness of our prior findings on the association between plasma 25(OH)D and colorectal cancer risk (5), we performed an updated analysis with simultaneous adjustment for inflammatory markers in two large ongoing cohorts, the Nurses' Health Study (NHS) and the Health Professionals Follow-up Study (HPFS).

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Materials and Methods

Study population

The NHS enrolled 121,701 female nurses aged 30 to 55 years in the United States in 1976. The HPFS enrolled 51,529 male health professionals aged 40 to 75 years in the United States in 1986. Details of the two cohorts have been described elsewhere (12, 13). Briefly, in both cohorts, follow-up questionnaires were administered biennially to collect and update medical and lifestyle information; validated food frequency questionnaires were completed every 4 years to update dietary data. Both cohorts have a follow-up rate of approximately 90% in each 2-year cycle. The study protocol was approved by the institutional review board of the Brigham and Women's Hospital (Boston, MA).

Ascertainment of cases and controls

Self-reported diagnoses of colorectal cancer were obtained in biennial questionnaires, and participants who reported a diagnosis of colorectal cancer were asked for permission to acquire their medical records and pathologic reports. We identified deaths with more than 96% sensitivity through the National Death Index and next-of-kin. For all colorectal cancer deaths, we requested permission from next-of-kin to review medical records. A study physician, blinded to exposure information, reviewed records to confirm colorectal cancer diagnosis and to extract information on anatomic location, stage, and histologic type of cancer.

A blood specimen was returned from 32,826 women in the NHS between 1989 and 1990 and from 18,225 men in the HPFS between 1993 and 1995. Among these participants, we documented 360 incident colorectal cancer cases in the NHS during follow-up through October 1, 2008 and 287 colorectal cancer cases in the HPFS through January 1, 2008. Among participants who provided plasma samples, we randomly selected up to 2 controls for each colorectal cancer patient matched on age (within 2 years) and on year (same year) and month (within 1 month) of blood donation from those who were alive and free of cancer at the time of diagnosis of the colorectal cancer case. A total of 706 and 550 controls were selected in the NHS and in the HPFS, respectively.

Laboratory assays

We used the radioimmunoassay method to measure plasma 25(OH)D, a highly sensitive immunoturbidimetric assay (Denka Seiken Co) to measure CRP, an ultra-sensitive ELISA (R&D Systems) to measure IL6, and an ELISA (R&D Systems) to measure soluble TNF receptor 2 (sTNFR2, also known as TNF receptor superfamily member 1B, TNFRSF1B), as previously described (5, 14, 15). Samples from cases and their matched controls were handled together and analyzed in the same batch. Quality control samples were randomly interspersed among the case–control samples. Personnel blinded to quality control and case–control status conducted all assays. For 25(OH)D, the mean intra-assay coefficient of variation from blinded quality control samples was less than 15% for all batches. For inflammatory markers, the intra-assay coefficients of variations in the NHS and HPFS were as follows: CRP, 2.2% and 7.8%; IL6, 10.6% and 12.1%; sTNFR2, 6.7% and 10.1% (14, 15). We excluded plasma samples that failed any of the four laboratory assays from 19 cases and 28 controls in the NHS, and 13 cases and 19 controls in the HPFS.

Statistical analyses

We corrected biomarker concentrations for measurement batch using the average batch correction method (16), with adjustment for age, body mass index (BMI), physical activity and case control status. We employed principal component analysis to construct a composite inflammatory score based on log-transformed CRP, IL6, and sTNFR2 concentrations among control participants. The first principal component explaining 57.5% of variance in women and 57.6% in men was extracted and the score was calculated as a linear combination, weighted by eigenvectors, of the three markers (all standardized to have a mean of zero and SD of one). Age-adjusted Spearman correlation coefficients were calculated between biomarkers, BMI, and physical activity among control participants. We calculated quartiles of 25(OH)D based on the distribution among control participants within each cohort and used conditional logistic regression to estimate relative risk (RR) and 95% CI of colorectal cancer. In the multivariable model, we adjusted for several confounding factors that are generally considered as important risk factors for colorectal cancer (see footnote of Table 3). We used SAS version 9.3 (SAS Institute, Inc) for analyses. All statistical tests were two-sided and $P < 0.05$ was considered statistically significant.

Results

After excluding samples that failed laboratory assays, a total of 341 cases and 678 controls from the NHS and 274 cases and 531 controls from the HPFS were included in the present analysis (Table 1). Plasma 25(OH)D levels were lower among colorectal cancer patients than controls ($P < 0.001$ in women and $P = 0.08$ in men). In the cross-sectional assessment, plasma 25(OH)D was not significantly correlated with inflammatory markers except a weak inverse association with IL6 among women ($r = -0.08$; $P = 0.04$). High BMI and low physical activity were inversely associated with 25(OH)D and positively associated with inflammatory markers in both men and women (Table 2).

Table 3 shows the association between plasma 25(OH)D and colorectal cancer with and without adjusting for inflammatory markers. High 25(OH)D was associated with decreased risk of colorectal cancer in both women and men after adjusting for multiple confounding factors, although the trend test was not statistically significant in men. In the pooled cohorts, participants in the highest quartile had a 29% reduced risk of colorectal cancer compared with those in the lowest quartile with a 95%

Table 1. Baseline characteristics of study participants in the NHS (women) and HPFS (men)[a]

	Women		Men	
Variable	**Cases ($n = 341$)**	**Controls ($n = 678$)**	**Cases ($n = 274$)**	**Controls ($n = 531$)**
Age at blood draw, year	59.0 (6.7)	59.0 (6.7)	65.8 (8.3)	65.9 (8.5)
Body mass index, kg/m^2	25.9 (4.9)	25.4 (4.7)	26.3 (3.4)	25.5 (3.0)
Physical activity, MET-h/wk	16.8 (19.2)	17.1 (21.4)	31.9 (26.9)	30.9 (25.1)
Pack-year of smoking before age 30	3.9 (5.5)	3.7 (5.5)	5.6 (6.7)	4.9 (6.8)
Current smoker, %	13.9	12.7	4.92	4.75
Family history of colorectal cancer, %[b]	23.2	18.1	22.6	15.3
History of previous endoscopy, %	35.2	38.8	53.7	63.7
Current multivitamin use, %	35.2	39.5	47.5	51.8
Regular aspirin use, %[c]	37.8	45.3	42.0	48.4
Regular NSAID use, %[d]	15.9	16.6	11.4	12.0
Postmenopausal, %	88.0	87.9	—	—
Current hormone use, %[e]	32.9	41.5	—	—
Alcohol consumption, g/day	5.7 (9.7)	5.6 (9.5)	12.4 (16.2)	12.3 (15.1)
Folate intake, μg/day	425 (260)	453 (239)	513 (257)	544 (281)
Calcium intake, mg/day	987 (544)	1073 (558)	931 (441)	946 (424)
Total fiber intake, g/day	18.6 (5.8)	19.0 (5.7)	22.9 (7.5)	23.3 (7.2)
Dietary DASH score	23.7 (4.1)	24.3 (4.3)	24.2 (4.6)	24.7 (4.5)
Time between blood draw and colorectal cancer diagnosis, y	9.3 (5.1)	—	6.3 (3.6)	—
Plasma biomarker concentrations, median (interquartile range)				
25(OH)D, ng/mL	23.9 (17.8–30.1)	26.0 (19.6–31.6)	27.5 (22.4–33.4)	28.6 (22.7–34.1)
CRP, mg/L	1.47 (0.50–3.07)	1.52 (0.60–3.48)	1.36 (0.68–2.62)	1.11 (0.59–2.17)
IL6, pg/mL	1.03 (0.56–1.62)	0.94 (0.54–1.61)	1.60 (0.99–2.65)	1.39 (0.93–2.25)
sTNFR2, pg/mL	2,732 (2,335–3,216)	2,666 (2,249–3,155)	2,746 (2,346–3,232)	2,723 (2,342–3,339)

Abbreviations: DASH, Dietary Approaches to Stop Hypertension; MET, metabolic equivalent = (caloric need/kilogram body weight per hour activity)/(caloric need/kilogram body weight per hour at rest); NSAID, nonsteroidal anti-inflammatory drug.

[a]Numbers in parenthesis indicate SD for means unless otherwise specified.

[b]Defined as having a diagnosis of colorectal cancer among parents or siblings.

[c]A standard tablet contains 325 mg aspirin, and regular users were defined as those who used at least 2 tablets per week.

[d]Regular users were defined as those who used at least 2 tablets per week.

[e]Percentage is among postmenopausal women.

CI of 3.0%–48% ($P_{trend} = 0.01$). After additionally adjusting for CRP, IL6, and sTNFR2 in our multivariable model, the association between 25(OH)D and colorectal cancer was minimally altered. The RR comparing the highest to the lowest quartile of 25(OH)D was 0.72 (95% CI, 0.53–0.98; $P_{trend} = 0.02$) when inflammatory score was included in the model. For colon cancer alone, the multivariable RRs comparing extreme quartiles of 25(OH)D were 0.67 (95% CI, 0.47–0.95; $P_{trend} = 0.01$) and 0.68 (95% CI, 0.48–0.97; $P_{trend} = 0.01$) in the pooled cohorts before and after adjusting for inflammatory score, respectively (data not shown).

Because geographic location is an important determinant of vitamin D levels, in the sensitivity analysis, we additionally adjusted for this variable (defined according to the state of residence; categorized as South, North, Midwest, and West, as previously described; ref. 17) and the results remained essentially unchanged (comparing the extreme quartiles: multivariable RR = 0.72; 95% CI, 0.53–0.99; $P_{trend} = 0.02$). We also considered the possibility that the inverse association may be related to reverse causation due to clinically undetected disorders at the time of blood collection, and thus conducted a stratified analysis by time interval. Plasma 25(OH)D was associated, in a similar magnitude, with colorectal cancer cases that were diagnosed within and after 6 years of blood draw with a RR of 0.61 (95% CI, 0.33–1.12) and 0.74 (95% CI, 0.52–1.07), respectively, thus arguing against the reverse causation explanation.

Because the first principal component used to create the inflammatory score only explained less than 60% of the variance of inflammatory markers, we additionally extracted the second principal component and created the new inflammatory scores based on the first two principal components, which cumulatively explained 80.0% of variance in women and 83.0% in men. We adjusted for the scores in the multivariable model and the results remained the same with the RR of colorectal cancer of

Table 2. Age-adjusted Spearman correlation coefficient between plasma biomarkers, body mass index, and physical activity at blood draw among control participants of women (in white) and men (in gray), respectively

Variable	25(OH)D	CRP	IL6	sTNFR2	Inflammatory score[a]	BMI	Physical activity (METs-h/wk)
25(OH)D	—	−0.05	−0.08[b]	0.05	−0.04	−0.17[c]	0.21[c]
CRP	−0.008	—	0.45[c]	0.28[c]	0.79[c]	0.38[c]	−0.18[c]
IL6	−0.06	0.48[c]	—	0.35[c]	0.75[c]	0.22[c]	−0.08[b]
sTNFR2	0.02	0.23[c]	0.26[c]	—	0.67[c]	0.28[c]	−0.06
Inflammatory score[a]	−0.02	0.78[c]	0.80[c]	0.60[c]	—	0.38[c]	−0.14[c]
BMI	−0.15[c]	0.20[c]	0.15[c]	0.11[b]	0.20[c]	—	−0.16[c]
Physical activity (METs-h/wk)	0.23[c]	−0.10[b]	−0.14[d]	−0.13[d]	−0.16[c]	−0.13[d]	—

Abbreviations: MET, metabolic equivalent = (caloric need/kilogram body weight per hour activity)/(caloric need/kilogram body weight per hour at rest).

[a]Inflammatory score was created by principal component analysis using plasma CRP, IL6, and sTNFR2 levels among controls.

[b]$P < 0.05$.

[c]$P < 0.001$.

[d]$P < 0.01$.

0.71 (95% CI, 0.52–0.97; $P_{trend} = 0.01$) comparing the extreme quartiles of 25(OH)D.

Discussion

Using data from two large cohorts, we assessed the hypothesis of Autier and colleagues that confounding by inflammation, as reflected by elevated levels of circulating inflammatory markers, explains the observed inverse association between 25(OH)D and colorectal cancer in epidemiologic studies. CRP, IL6, and sTNFR2, which is a surrogate for TNFα, have been shown to mediate inflammatory response and are sensitive to dysregulation in inflammatory processes (18). Through further adjustment for these markers, we did not find any meaningful change in the association between 25(OH)D and colorectal cancer. It is possible that the inflammatory markers we measured did not fully reflect inflammatory factors that contribute to colorectal cancer pathogenesis. However, if the hypothesis of Autier and colleagues is correct, our findings would suggest that low 25(OH)D is a superior marker for inflammation than these three well-accepted inflammatory markers, which seems unlikely, especially given the little correlation between plasma 25(OH)D and inflammatory markers observed in the current study.

In addition, the hypothesis of Autier and colleagues builds on the postulations that systemic inflammation is the common underlying factor for both low 25(OH)D and increased colorectal cancer risk. However, animal and human studies have suggested a potential anti-inflammatory effect of vitamin D (19). A recent study in mice found that increased dietary vitamin D intake reduced inflammation and colon cancer incidence, possibly through suppression of MAPK and NFκB signaling (20). Human vitamin D supplementation has been found to reduce inflammatory marker levels, especially among patients with autoimmune disease or other chronic conditions (e.g., chronic kidney disease, heart disease, type 2 diabetes, and osteoporosis), who are more likely to have vitamin D deficiency (21). Regarding the association between general markers of systemic inflammation and colorectal cancer risk, the evidence remains inconclusive with a positive relationship reported in some studies (22, 23) but not in others (15, 24). Therefore, on the basis of the current evidence, it seems implausible that the inflammatory process acts as a predominant confounding factor and explains the increased colorectal cancer risk associated with low vitamin D status.

Our study has some limitations. First, we assessed 25(OH)D and inflammatory markers from plasma collected at the same time and in a single measurement that may not represent long-term concentrations. However, these inflammatory markers have been shown to be generally stable over time and any misclassification of 25(OH)D should be nondifferential, which should have biased the results towards unity. Second, given the observational nature of our study, residual confounding cannot be excluded. However, the robust adjustment for a host of colorectal cancer–related lifestyle factors makes it unlikely that residual confounding from major risk factors of colorectal cancer explains our findings.

The strength of the current study is the prospective design within the two large well-established cohorts, which have both laboratory data on biomarkers and detailed information on a variety of lifestyle factors, therefore providing us the unique opportunity to examine the relationship between plasma 25(OH)D and colorectal cancer while accounting for inflammatory markers and other potential confounders.

Table 3. RR and 95% CI of colorectal cancer by plasma 25(OH)D levels accounting for inflammatory markers in the NHS (women), the HPFS (men), and the pooled cohorts

	Quartile of plasma 25(OH)D levels				
	1	2	3	4	P_{trend}[a]
Women					
No. of cases/controls	118/184	91/174	72/173	60/147	
Median (interquartile range), ng/mL	15.8 (12.8–18.3)	23.5 (21.8–25.2)	29.2 (27.7–30.7)	38.7 (35.3–44.5)	
Age-adjusted RR (95% CI)[b]	1.00 (reference)	0.81 (0.57–1.15)	0.62 (0.43–0.90)	0.59 (0.40–0.88)	0.005
Multivariable RR (95% CI)[c]	1.00 (reference)	0.84 (0.58–1.20)	0.67 (0.45–0.98)	0.64 (0.42–0.98)	0.02
Multivariable + CRP[d]	1.00 (reference)	0.86 (0.60–1.23)	0.66 (0.45–0.98)	0.65 (0.43–1.00)	0.03
Multivariable + IL6[d]	1.00 (reference)	0.85 (0.59–1.23)	0.67 (0.45–0.98)	0.63 (0.41–0.97)	0.02
Multivariable + sTNFR2[d]	1.00 (reference)	0.82 (0.57–1.18)	0.67 (0.45–0.99)	0.62 (0.40–0.95)	0.02
Multivariable + inflammatory score[e]	1.00 (reference)	0.82 (0.57–1.17)	0.68 (0.46–1.00)	0.64 (0.42–0.99)	0.03
Men					
No. of cases/controls	75/131	80/131	60/135	59/134	
Median (interquartile range), ng/mL	18.6 (14.9–20.8)	25.7 (24.5–27.1)	31.3 (29.9–32.9)	38.9 (36.6–43.1)	
Age-adjusted RR (95% CI)[b]	1.00 (reference)	1.07 (0.72–1.60)	0.78 (0.51–1.20)	0.74 (0.47–1.14)	0.10
Multivariable RR (95% CI)[c]	1.00 (reference)	1.05 (0.69–1.61)	0.80 (0.51–1.26)	0.80 (0.50–1.28)	0.22
Multivariable + CRP[d]	1.00 (reference)	1.03 (0.67–1.58)	0.79 (0.50–1.25)	0.77 (0.47–1.24)	0.18
Multivariable + IL6[d]	1.00 (reference)	1.13 (0.73–1.73)	0.86 (0.54–1.36)	0.82 (0.51–1.32)	0.28
Multivariable + sTNFR2[d]	1.00 (reference)	1.07 (0.70–1.64)	0.79 (0.50–1.25)	0.77 (0.48–1.24)	0.18
Multivariable + inflammatory score[e]	1.00 (reference)	1.05 (0.68–1.60)	0.81 (0.51–1.27)	0.81 (0.50–1.30)	0.25
Pooled cohorts					
Age-adjusted RR (95% CI)[b]	1.00 (reference)	0.91 (0.70–1.19)	0.68 (0.51–0.90)	0.65 (0.48–0.87)	0.001
Multivariable RR (95% CI)[c]	1.00 (reference)	0.94 (0.71–1.23)	0.72 (0.54–0.97)	0.71 (0.52–0.97)	0.01
Multivariable + CRP[d]	1.00 (reference)	0.93 (0.71–1.22)	0.72 (0.53–0.96)	0.70 (0.51–0.95)	0.01
Multivariable + IL6[d]	1.00 (reference)	0.96 (0.73–1.25)	0.74 (0.55–0.99)	0.71 (0.52–0.97)	0.01
Multivariable + sTNFR2[d]	1.00 (reference)	0.94 (0.71–1.23)	0.72 (0.54–0.97)	0.69 (0.51–0.95)	0.009
Multivariable + inflammatory score[e]	1.00 (reference)	0.93 (0.71–1.22)	0.73 (0.55–0.98)	0.72 (0.53–0.98)	0.02

[a]Test for trend was performed using the median value of each quartile of plasma 25(OH)D as a continuous variable in the regression model.

[b]Conditional logistic regression adjusted for matching factors (age [within 2 years], year [same year], and month [within 1 month] of blood collection).

[c]In addition to matching factors (age and time of blood draw), multivariable conditional logistic regression adjusted for family history of colorectal cancer, history of endoscopy, pack-years of smoking before age 30, BMI, physical activity, multivitamin use, regular aspirin/NSAID use, alcohol consumption, and DASH score.

[d]Additional adjustment for plasma inflammatory marker levels (in quartile).

[e]Inflammatory score was created by principal component analysis using plasma CRP, IL6, and sTNFR2 levels among controls.

In conclusion, the inverse association between plasma 25(OH)D and colorectal cancer persisted after adjustment for inflammatory markers, therefore highlighting the continuing priority for further research on vitamin D and colorectal cancer prevention.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

Certain data used in this publication were obtained from the DPH. The authors assume full responsibility for analyses and interpretation of these data.

Authors' Contributions

Conception and design: K. Wu, C.S. Fuchs, E.L. Giovannucci
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References

1. Autier P, Boniol M, Pizot CPM. Vitamin D status and ill health: a systematic review. Lancet Diabetes Endocrinol 2014;2:76–89.
2. Touvier M, Chan DS, Lau R, Aune D, Vieira R, Greenwood DC, et al. Meta-analyses of vitamin D intake, 25-hydroxyvitamin D status, vitamin D receptor polymorphisms, and colorectal cancer risk. Cancer Epidemiol Biomarkers Prev 2011;20:1003–16.
3. Garland C, Shekelle RB, Barrett-Connor E, Criqui MH, Rossof AH, Paul O. Dietary vitamin D and calcium and risk of colorectal cancer: a 19-year prospective study in men. Lancet 1985;1:307–9.
4. Ma Y, Zhang P, Wang F, Yang J, Liu Z, Qin H. Association between vitamin D and risk of colorectal cancer: a systematic review of prospective studies. J Clin Oncol 2011;29:3775–82.
5. Wu K, Feskanich D, Fuchs CS, Willett WC, Hollis BW, Giovannucci EL. A nested case control study of plasma 25-hydroxyvitamin D concentrations and risk of colorectal cancer. J Natl Cancer Inst 2007;99:1120–9.
6. Giovannucci E, Liu Y, Rimm EB, Hollis BW, Fuchs CS, Stampfer MJ, et al. Prospective study of predictors of vitamin D status and cancer incidence and mortality in men. J Natl Cancer Inst 2006;98:451–9.
7. Feldman D, Krishnan AV, Swami S, Giovannucci E, Feldman BJ. The role of vitamin D in reducing cancer risk and progression. Nat Rev Cancer 2014;14:342–57.
8. Wactawski-Wende J, Kotchen JM, Anderson GL, Assaf AR, Brunner RL, O'Sullivan MJ, et al. Calcium plus vitamin D supplementation and the risk of colorectal cancer. N Engl J Med 2006;354:684–96.
9. Holick MF. Calcium plus vitamin D supplementation and the risk of colorectal cancer. N Engl J Med 2006;354:2287–8.
10. Giovannucci E. Calcium plus vitamin D supplementation and the risk of colorectal cancer. N Engl J Med 2006;354:2287–8.
11. Forman MR, Levin B. Calcium plus vitamin D3 supplementation and colorectal cancer in women. N Engl J Med 2006;354:752–4.
12. Colditz GA, Manson JE, Hankinson SE. The Nurses' Health Study: 20-year contribution to the understanding of health among women. J Womens Health 1997;6:49–62.
13. Rimm EB, Giovannucci EL, Willett WC, Colditz GA, Ascherio A, Rosner B, et al. Prospective study of alcohol consumption and risk of coronary disease in men. Lancet 1991;338:464–8.
14. Chan AT, Ogino S, Giovannucci EL, Fuchs CS. Inflammatory markers are associated with risk of colorectal cancer and chemopreventive response to anti-inflammatory drugs. Gastroenterology 2011;140:799–808.
15. Song M, Wu K, Ogino S, Fuchs CS, Giovannucci EL, Chan AT. A prospective study of plasma inflammatory markers and risk of colorectal cancer in men. Br J Cancer 2013;108:1891–8.
16. Rosner B, Cook N, Portman R, Daniels S, Falkner B. Determination of blood pressure percentiles in normal-weight children: some methodological issues. Am J Epidemiol 2008;167:653–66.
17. Bertrand KA, Giovannucci E, Liu Y, Malspeis S, Eliassen AH, Wu K, et al. Determinants of plasma 25-hydroxyvitamin D and development of prediction models in three US cohorts. Br J Nutr 2012;108:1889–96.
18. Hussain SP, Harris CC. Inflammation and cancer: an ancient link with novel potentials. Int J Cancer 2007;121:2373–80.
19. Krishnan AV, Feldman D. Mechanisms of the anti-cancer and anti-inflammatory actions of vitamin D. Annu Rev Pharmacol Toxicol 2011;51:311–36.
20. Meeker S, Seamons A, Paik J, Treuting PM, Brabb T, Grady WM, et al. Increased dietary vitamin D suppresses MAPK signaling, colitis and colon cancer. Cancer Res. 2014 Jun 17. [Epub ahead of print].
21. Shab-Bidar S, Neyestani TR, Djazayery A, Eshraghian MR, Houshiarrad A, Kalayi A, et al. Improvement of vitamin D status resulted in amelioration of biomarkers of systemic inflammation in the subjects with type 2 diabetes. Diabetes Metab Res Rev 2012;28:424–30.
22. Erlinger TP, Platz EA, Rifai N, Helzlsouer KJ. C-reactive protein and the risk of incident colorectal cancer. JAMA 2004;291:585–90.
23. Otani T, Iwasaki M, Sasazuki S, Inoue M, Tsugane S. Plasma C-reactive protein and risk of colorectal cancer in a nested case-control study: Japan Public Health Center-based prospective study. Cancer Epidemiol Biomarkers Prev 2006;15:690–5.
24. Zhang SM, Buring JE, Lee IM, Cook NR, Ridker PM. C-reactive protein levels are not associated with increased risk for colorectal cancer in women. Ann Intern Med 2005;142:425–32.