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C-Reactive Protein, Lipid-soluble Micronutrients, and Survival in Colorectal Cancer Patients

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Abstract

Background—Identification of biomarkers associated with survival in cancer patients is important for elucidating the underlying mechanisms of cancer progression and identifying possible interventions to reduce cancer morbidity and mortality.

Methods—Using stored patient plasma samples from a multiethnic population-based case-control study of invasive colorectal cancer, we measured post-treatment blood levels of C-reactive protein (CRP) and lipid-soluble micronutrients. Patients (n=368) were followed after phlebotomy (mean of 8 years), during which time 47% died (25% colorectal cancer-specific). Hazard ratios (HR) were estimated by Cox proportional hazards regression with adjustment for stage, age at diagnosis, ethnicity, sex, smoking status, and month of blood draw.

Results—A positive association with overall risk of death was observed for CRP (HR for highest vs. lowest quintile: 1.80; 95% CI: 1.07-3.04; P_{trend}=0.01) whereas, inverse associations were generally observed for retinol and carotenoids (HRs for overall risk of death for the highest quintile ranging from 0.5-0.8); these associations were significant for retinol (P_{trend}=0.0002), α-carotene (P_{trend}=0.02), and total carotenoids (P_{trend}=0.02) and were generally consistent across subgroups (sex, ethnicity, cancer anatomical subtype, and stage). Hazard ratios for retinol and carotenoids were attenuated somewhat after adjustment for CRP. Similar trends for CRP were observed for colorectal cancer-specific deaths (HR for highest vs. lowest tertile: 2.06; 95% CI: 1.18-3.61; P_{trend}=0.01) as for deaths from all other causes ($P_{heterogeneity}$=0.78).

Conclusion—These observations are consistent with a direct relationship between circulating CRP and overall survival among colorectal cancer patients.

Impact—These results, if reproduced, suggest that reduction of inflammation should be explored as a potential complementary treatment strategy.

Keywords

Survival; colorectal cancer; carotenoids; coenzyme Q10; C-reactive protein

BACKGROUND

Colorectal cancer is a disease for which diet/nutrition and inflammation are considered to be key etiologic factors [1,2]. It is also a common cancer with relatively low survival

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probability, approximately 60% at five years [3]. While the role of nutritional status in the etiology of colon cancer has been extensively studied, its potential impact on survival has not been adequately examined. Risk of colon cancer is not only associated with chronic inflammatory disease states, such as Crohn's Disease and inflammatory bowel disease [4], but also with low-grade chronic inflammation which may increase levels of circulating inflammatory markers, such as C-reactive protein (CRP) [5]. Strong evidence for a protective effect of NSAID consumption further emphasizes the potential role of inflammation in colon cancer development [6,7] and the potential for prevention strategies. Excessive weight, decreased physical activity and smoking have also been implicated as causative factors [8, 9] while the protective effects of fruit and vegetable consumption, particularly with respect to individual dietary components, such as carotenoids, tocopherols and fiber, remain somewhat controversial [10]. Vitamin D and folate deficiencies are also postulated to play important roles in the development of colon cancer and other cancers [11,12], yet some evidence suggests that excessive levels may not be beneficial [13,14].

The 5-year survival probability for colon cancer patients has increased substantially over the last fifty years, rising from nearly 20% in the 1950's to approximately 60% by the turn of the century [3], largely through earlier detection and improved treatments. Factors beyond age and stage at diagnosis that have been associated with survival in patients diagnosed with colon cancer include serum albumin, plasma CRP, circulating Interleukin-6 (IL-6), BMI, physical activity, and smoking history [15-20]. Associations with improved survival have been reported for several lipophilic micronutrients, including vitamin D and colorectal cancer [11,21], retinol and carotenoids for various cancer types [22-24], α-tocopherol with all cause mortality [25], and coenzyme Q10 with melanoma [26]. Improved survival time for end-stage cancer patients after treatment with coenzyme Q10 and antioxidants has also been reported [27]. The positive associations for elevated circulating CRP and IL-6 levels with mortality from colorectal cancer [15,19], as well as other diseases [28], suggest a possible role for inflammation in determining survival. Studies specifically looking at colorectal cancer survival with multiple lipid phase micronutrients are limited, however a study by Ito, et al involving 16 colorectal cancer patients previously reported a significant inverse association between pre-diagnostic pro-vitamin A carotenoids and mortality [29]. The important contributions of lipophilic vitamins in the immune system [30,31], as well as in cell differentiation [32], suggests their potential benefit in controlling cancer recurrence and progression.

Although the epidemiological evidence for the associations of inflammation and micronutrient status and/or their circulating markers with survival is still limited, such studies are important as an initial step in developing biology-based models to predict disease outcome and potentially lead to low-risk interventions that may modify disease progression and mortality. Lipid-soluble micronutrients were chosen as a primary focus for this study because of their reported associations with cancer incidence and mortality [11,22-26] and their important role for immune function [30,31]. In particular, tocopherols, vitamin D, coenzyme Q_{10} (CoQ_{10}), carotenoids and retinol/vitamin A are essential physiologic molecules with broad effects on immune function and provide varying degrees of protection from oxidative damage that may impact survival. Using stored plasma samples obtained several weeks or months after completion of initial treatment from colorectal cancer patients in a population-based case-control study of large bowel cancer, we have measured a variety of lipid-soluble micronutrients and other biomarkers to test their associations with survival.

METHODS

Study Population

Data and plasma samples obtained as part of a population-based case-control study [33] conducted between 1994 and 1998 were used to carry out the current study. Cases were identified through the rapid reporting system of the Hawaii Tumor Registry (HTR), a member of the United States National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program. Cases consisted of Japanese-American, Caucasian, or Native Hawaiian residents (<85 years of age) of the island of Oahu, Hawaii, diagnosed with a primary adenocarcinoma of the colon or rectum during the study period. Blood samples were obtained from 548 cases (46% of the originally interviewed cases) and 516 were available for assessment of biomarkers. Data analyses were done on 455 of these cases who had complete data on the adjustment variables described below. Lastly, 87 cases with in-situ cancer were excluded, leaving 368 cases for this analysis of survival. In-person interviews were conducted at the subjects' homes at a median time of 4.5 months post diagnosis and at least 21 days after completion of any chemotherapy. The questionnaire included detailed information on demographics, smoking, family history of cancer, aspirin use, age, race, education, height and weight. Dietary information was obtained for each individual with a quantitative food frequency questionnaire as described previously [34]. A fasting blood sample was collected, processed and stored at -80°C. The study population of colorectal patients consisted of 58.7% males, 41.3% females, 59.1% Japanese American, 29.1% non-Hispanic White, and 12.8% Native Hawaiian. The percentages by stage of colorectal cancer were 25.8%, 34.0%, 36.7%, and 3.5% for stages I, II, III, IV, respectively. Deaths were identified from the HTR, based on linkages with vital status files from the state of Hawaii and the National Death Index. Informed consent was obtained from each subject and the study was approved by the University of Hawaii Institutional Review Board.

Analytical Methods

Analysis of lipid-phase micronutrients from plasma was carried out by HPLC with photo diode array detection and by mass spectra, as appropriate [35]. Assays were regularly validated for carotenoids, retinol, tocopherols, vitamin D, and CoQ_{10} through inclusion of external standards and by participation in quality assurance programs of the US National Institute of Standards and Technology [36]. For carotenoid, tocopherol, and retinol analyses, 0.20 mL of plasma was mixed with 0.20 mL ethanol containing butylated hydroxytoluene as antioxidant and 3 internal standards (tocol, retinyl laurate, and n-butyl-β-apo-8'-carotenoate) then partitioned into 1.0 mL hexane, evaporated under nitrogen and resuspended in 0.2 mL of HPLC mobile phase and analyzed by HPLC as described previously [37]. HPLC analysis of CoQ_{10} was by pre-column oxidation using a Coulochem III electrochemical detector with a coulometric 5021A cell (ESA Inc.; Chelmsford, MA) at +900mV followed by separation on a C18 reversed-phase Gemini analytical column (150mm × 2.0mm, 3 μM) coupled to a Gemini pre-column (4mm × 2.0mm, 3 μM) (Phenomenex; Torrance, CA) using an isocratic mobile phase of methanol/hexane/2-propanol/glacial acetic acid 695/275/15/15 (V/V) containing 15g sodium acetate trihydrate/liter (flow rate = 0.5 ml/min). CoQ10 was monitored at 275 nm and quantitated using area units with final values adjusted for internal standard recovery (tocol-monitored at 295 nm).

Vitamin D—Plasma levels of $25(OH)D_2$ and $25(OH)D_3$ were analyzed using liquid chromatography orbitrap mass spectrometry. Plasma (0.2 mL) was mixed with 0.01 mL of methanolic $25(OH)D_3$-d_6 (Medical Isotopes, Pelham, NH) and 0.2 mL methanol, gently vortexed, and incubated at room temperature for 15 minutes. After addition of 1.5 mL hexane, manual shaking and centrifugation, the hexane layer was removed and evaporated to dryness at room temperature under a stream of nitrogen. The residue was reconstituted in 0.1

mL methanol and 20 μL was injected into the HPLC instrument (model Accela, ThermoFisher, San Jose, CA) with an Ascentis Express C18 column (150 × 3.0 mm; 2.7 μm; Supelco, Park Bellefonte, PA) and a 0.2 μm pre-filter cartridge (2.1mm ID, ThermoFisher) at a flow rate of 0.65 mL/min using the following linear mobile phase gradient of water/methanol: 10/90 for 1.0 minute, then to 2/98 in 2.0 minutes and maintained for 4 minutes then returned to initial conditions in 0.1 minute with equilibration for 5 minutes. Analytes were quantitated after atmospheric pressure chemical ionization in positive mode by an orbitrap mass spectrometer (model Exactive, ThermoFisher) using exact masses (±5 ppm mass window): 25(OH)D_2 (m/z 413.33734), 25OH-D_3 (401.33731), 25(OH)D_3-d_6 (m/z 389.3647).

C-Reactive Protein (CRP) was measured in plasma with an automated chemical analyzer (Cobas MiraPlus, Roche Diagnostics, Switzerland). Kits based on latex immuno reactions followed by turbidimetric measurements were used from Pointe Scientific, Inc. (Canton, MI; www.pointescientific.com).

Statistical Analysis

The Cox proportional hazards regression model of mortality (both colorectal and all-cause deaths) was used to estimate hazard ratios (HR) and 95% confidence intervals (95% CI). Survival time was defined from the date of diagnosis until death or the last contact date, as of July 1, 2009. For colorectal cancer-specific survival analyses, deaths due to other causes were censored. Biomarker levels were categorized to quintiles (for all-cause mortality), quartiles (for all-cause mortality in stratified analyses), or tertiles (colorectal cancer-specific survival analyses) based on the distribution of the overall case population. Spline analysis was used to assess the relationship between mortality and biomarkers [38, 39]. When a linear relationship is appropriate, trend was assessed by the Wald test for a variable assigned the median value of the appropriate category (quintile, quartile or tertile). When it was found that the relationship was non-linear (quadratic), significance was assessed by the global 2 degree of freedom Wald test of a linear and a quadratic term. The proportionality assumption was met for all biomarker variables. The fully adjusted model included the following covariates: age of diagnosis (continuous), stage of disease at diagnosis according to TNM staging system (I, II, III, or IV) [40], race/ethnicity (Japanese American, White, or Native Hawaiian), sex (male or female), tobacco smoking status at blood draw (never, former, or current smoker), and month of blood draw to account for seasonal variation [41]. Models of micronutrients were additionally adjusted for log CRP to determine their independent associations. Other variables considered for adjustment included chemotherapy (yes or no), radiation (yes or no), BMI, and alcohol consumption; however, adjusting for these covariates did not materially change the risk estimates for the biomarkers. Stratified analyses were performed for subgroups defined by cancer sub-site (colon vs rectum), sex, ethnicity (Japanese American vs. White), and stage (I-IV). Heterogeneity across subgroups was tested by the Wald test of cross-product terms of the trend variables and subgroup membership. Spearman correlation coefficients were computed to determine the relationships between biomarkers. The Student's t-test was also used to compare mean plasma carotenoid levels between subgroups. SAS software (SAS Institute, Cary, North Carolina) was used for all analyses. All tests were two-sided, and $P < 0.05$ was used as the critical value for statistical significance.

RESULTS

Characteristics of the 368 colorectal cancer patients are shown in Table 1. Overall, 175 patients (47.6%) died during the follow-up period (mean observation time of 8.03 years after blood draw). Approximately 52.6% (92 cases) of the deaths were due to colorectal cancer. Other major causes of death included other cancers (10.8%), heart disease (8.0%), stroke

(5.1%) and respiratory/ pulmonary diseases (4.6%). Age, male sex, white or Native Hawaiian race/ethnicity, advanced stage at diagnosis, smoking, and alcohol consumption were associated with overall mortality. The survival advantage for Japanese Americans compared with whites remained after adjusting for age at diagnosis, sex, and stage (HR, 0.73; 95% CI, 0.52-1.02). All patients received surgery with a minority receiving chemotherapy and/or radiation. The increased percentage of deaths among those receiving these treatments (Table 1) probably reflects disease stage, as treatment was not positively associated with mortality after adjustment for stage.

Correlations between blood biomarkers are shown in Table 2. CRP was correlated inversely with carotenoids and retinol, and positively with γ-tocopherol. CoQ10 was positively correlated with 25(OH)D_3, tocopherols, retinol, and most carotenoids (β-carotene, β-cryptoxanthin, lutein/zeaxanthin, and lycopene). The coefficients for these correlations were all <0.45. Carotenoids were generally positively correlated with each other with correlation coefficients of 0.4-0.8. Pro-vitamin A carotenoids were positively correlated with α-tocopherol and negatively correlated with γ-tocopherol.

CRP was positively associated with all-cause mortality (Table 3), with an 80% increased risk of death for the highest vs. the lowest quintile of CRP. In contrast, a strong inverse association with all-cause mortality was observed for retinol, with an apparent threshold effect with decreased risk of death for those individuals above the lowest quintile. Weaker inverse associations were suggested for α-carotene, total carotenoids, lycopene and lutein/ zeaxanthin, whereas β-carotene, β-cryptoxanthin, tocopherols and 25-OH vitamin D_3 levels showed no significant association with subsequent risk of death. CoQ_{10} adjusted for age at diagnosis, race/ethnicity, sex, smoking status and month of blood draw was strongly inversely associated with all-cause mortality ($p = 0.01$); however, further adjustment for stage reduced the significance of this association ($P = 0.12$, Table 3). Further adjustment for CRP levels did not alter the observed significant inverse associations for retinol and carotenoids with mortality, but did attenuate the significance slightly. In contrast, adjustment for CRP level increased the significance of the inverse association observed for CoQ_{10} with mortality ($p = 0.05$).

As shown in Table 4, mortality from colorectal cancer as a specific cause of death (N=92) revealed an even stronger associations with CRP, with a two-fold increase in risk of death for patients in the upper tertile compared to those in the lower tertile of CRP. Inverse associations were also suggested for retinol, cryptoxanthins, lutein, lycopene and total carotenoids; however, these associations did not reach statistical significance possibly due to the reduced sample size in the stratified analyses.

In an analysis stratified by anatomical subsite, similar results were found for CRP and retinol for all-cause mortality among patients with colon or rectal cancer (Supplementary Table S1). For β-carotene, β-cryptoxanthin, and total carotenoids (Supplementary Table S1), inverse associations were suggested for rectal cancer patients only. However, we note that this subset analysis was based on small numbers of deaths.

Stratification by sex (Supplementary Table S2) yielded similar associations in men as in women (p's for interaction ≥ 0.08). Results were also similar for whites and Japanese-Americans (p's for interaction ≥ 0.30) (Supplementary Table S3). There was no evidence of strong heterogeneity of associations for biomarkers by stage (p's for interaction ≥ 0.26) (Supplementary Table S4). However, there were significant inverse associations observed for CoQ_{10}, cryptoxanthins, lycopene and total carotenoids with stage, with higher mean levels for patients with Stage I, compared to those with Stage II-V(Supplementary Table

S5). No significant differences in mean plasma levels were observed for CRP and retinol by stage.

DISCUSSION

The current study assessed associations of plasma CRP and various lipid-soluble micronutrients with overall and colorectal cancer-specific survival among a population-based, multiethnic series of colorectal cancer patients. Of the markers examined, CRP was observed to have the strongest and most consistent association with both all-cause and colorectal cancer-specific mortality across subgroups defined by sex, ethnicity, anatomical sub-site and stage of disease at diagnosis in agreement with previous reports [15, 16, 19]. Furthermore, Koike, et al. [19] reported that for Stage 2 colorectal patients with low CRP levels, survival was the same regardless of treatment, whereas in those patients with elevated CRP, chemotherapy conferred a significant survival advantage. Although the biological function of CRP is not established, it is an acute phase protein associated with immune response that represents a general marker of inflammation and is indicative of a variety of pathologies [42]. Tumor progression may in part be due to deficiencies in immune function [43] and restoration of the immune system through dietary or other means may therefore contribute to survival. Post-diagnostic use of aspirin, as assessed in this study, was not significantly associated with mortality. However, it was recently reported that a 35% improvement in survival was observed in aspirin users for colon, but not rectal cancer [44]. Previously it was also demonstrated that a mixture of CoQ_{10} (2 g/Kg diet) and vitamin E (250-1000 IU/kg diet) decreased CRP levels 70% in baboons [45]. Total carotenoids (r = -0.3) and retinol (r = -0.28) were significantly weakly inversely associated with CRP in the present study (Tables 2 and 3)

Evidence from the current study also suggests that low plasma levels of vitamin A, CoQ10, and various carotenoids may be associated with excess mortality in colorectal cancer patients independently of CRP. Inverse associations between dietary intakes or circulating levels of carotenoids and mortality have also been observed in previous studies [29, 46-50], suggesting the potential benefits of carotenoids (or other associated phytochemicals) for optimal health and disease prevention. However, associations for carotenoids and retinol in this study were not strongly monotonic and, for colorectal cancer-specific deaths, appeared to have threshold effects in which increased risk of death was primarily observed among those in the lowest tertile. Further, some associations for carotenoids with survival did not reach significance when stratified for colorectal-cancer specific deaths, indicating the need for replication in a larger study. Ultimately a determination of the mechanistic relationship distinguishing whether increased inflammation results in reduced levels of antioxidants and retinol, or decreased levels of antioxidants are the result of increased inflammation and associated increase in CRP will require further studies in humans. Our observations, if further reproduced, would be in agreement, however, with Shardell et al. [46] who reported that the incremental benefits of total carotenoids in relation to mortality diminished when their concentrations were greater than 1.0 μmol/L. Nonlinear relationships for some of the micronutrient biomarkers with mortality observed in the current study are consistent with observations for many micronutrients with mortality, including α-tocopherol [25], vitamin D [51], folate [13], and calcium [52] and may reflect the growing realization that optimal levels for various micronutrients may exist, and that the expectation of a continuous linear relationship is based on a false premise. The strong association with stage at diagnosis for CoQ_{10}, as well as its borderline significant association with mortality after adjustment for stage and CRP, requires further study to better define the possible relationship of CoQ_{10} with disease progression.

In addition to the population-based study design and the virtually complete follow-up conducted by our SEER registry, the strengths of the current study include a reasonably large sample size and relatively long follow-up time enabling us to determine significant associations between biomarkers and the risk of death prospectively. A limitation of our study was the lower power for some subgroup analyses, that should be reexamined in the future, as more deaths accrue in our study, and in other large cohorts. Although we previously showed in serial samples that plasma levels of lipid-soluble micronutrients are relatively stable over time in our population (41), future studies utilizing blood samples from multiple time-points in cancer patients before, during, and after diagnosis may provide important information clarifying the temporal relationship of biomarkers with cancer survival. In particular, samples for the current study were obtained after completion of chemotherapy, consequently no conclusions can be drawn as to the benefit or harm associated with increased antioxidant levels during therapy. Melichar, et al [53] did report, however, similar results for a small group of patients (N = 25) in which baseline levels of retinol and CRP prior to therapy were also predictive of poor prognosis. A further limitation of the current study is the inability to adjust for socioeconomic status, which may impact nutrition and mortality through multiple mechanisms.

In conclusion, our results suggest that the risk of mortality among colorectal cancer patients is positively associated with plasma CRP. Our data also provide more limited evidence for an inverse association with survival in these patients for plasma levels of CoQ10, retinol and carotenoids, as these associations remain after adjustment for CRP. However, the possibility of residual confounding cannot be ruled out. While the replication of our findings is warranted, our data are consistent with a possible reduction of all-cause mortality through the use of anti-inflammatory agents, such as NSAIDs, and, possibly, dietary modification and supplement use among colorectal cancer patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

CoQ10	Co-enzyme Q10
CRP	C-reactive protein
HR	Hazard Ratio
Carot	carotene
Crx	crptoxanthin
Zea	zeaxanthin
Toc	tocopherol
HPLC	High Performance Liquid Chromatography

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Table 1

Characteristics of colorectal cancer patients.*

	All Patients (N = 368)	Number of participants who died of all causes (N = 175)	Number of participants who died of colorectal Cancer (N = 92)
Age at diagnosis (years ± SD)	64.8 ± 11.2	67.1 ± 11.4	62.7 ± 11.8
Sex			
Female, n (%)	152 (41.3)	62 (35.4)	31 (33.7)
Male, n (%)	216 (58.7)	113 (64.6)	61 (66.3)
Ethnicity			
White, n (%)	107 (29.1)	57 (32.6)	47 (51.1)
Japanese-American, n (%)	214 (59.1)	91 (52.0)	28 (30.4)
Hawaiian, n (%)	47 (12.8)	27 (15.4)	17 (18.5)
Site‡			
Colon, n (%)	263 (71.7)	122 (69.7)	62 (67.4)
Rectum, n (%)	104 (28.3)	53 (30.3)	30 (32.6)
Stage (TNM)			
I, n (%)	95 (25.8)	29 (16.6)	6 (6.5)
II, n (%)	125 (34.0)	62 (35.4)	24 (26.1)
III, n (%)	135 (36.7)	73 (41.7)	51 (55.4)
IV, n (%)	13 (3.5)	11 (6.3)	11 (12.0)
Chemotherapy, n (%)‡			
No, n (%)	220 (60.0)	94 (53.7)	32 (34.8)
Yes, n (%)	147 (40.0)	81 (46.3)	60 (65.2)
Radiation, n (%)‡			
No, n (%)	321 (87.5)	146 (83.4)	73 (79.4)
Yes, n (%)	46 (12.5)	29 (16.6)	19 (20.6)
NSAID use, n (%)‡§			
No, n (%)	276 (75.4)	134 (76.6)	72 (78.3)
Yes, n (%)	90 (24.6)	41 (23.4)	20 (21.7)
Smoking status			
Never, n (%)	155 (47.1)	66 (37.7)	36 (39.1)
Former, n (%)	147 (40.0)	74 (42.3)	38 (41.3)
Current, n (%)	66 (17.9)	35 (20.0)	18 (19.6)
Alcohol drinking status			
Never, n (%)	167 (45.4)	67 (38.3)	38 (41.3)
Ever, n (%)	201 (54.6)	108 (61.7)	54 (58.7)
Family history of colorectal cancer among first-degree relatives			
No, n (%)	304 (82.6)	144 (82.3)	79 (85.9)
Yes, n (%)	64 (17.4)	31 (17.7)	13 (14.1)

Abbreviations: SD, standard deviation; NSAIDs, nonsteroidal anti-inflammatory drugs; TNM: T, primary tumor; N, regional lymph nodes; M, distant metastasis.

[*] Data are given as mean (SD) unless otherwise specified

[‡] 2 patients had missing data.

[§] Ever took NSAIDs at least twice a week for 3 months or more before diagnosis

Table 2

Correlations between blood biomarkers among the 516 participants.

	CRP†	CoQ10†	25(OH)D_3	α-Toc	γ-Toc	Retinol	α-Carot	β-Carot	α-Crx	β-Crx	Lutein/Zea	Lycopene	Total Carotenoids
CRP	1.00	0.13 (0.01)	0.04 (0.49)	-0.004 (0.95)	0.15 (0.004)	-0.24 (<0.0001)	-0.24 (<0.0001)	-0.20 (<0.0001)	-0.19 (0.0002)	-0.22 (<0.0001)	-0.26 (<0.0001)	-0.12 (0.02)	-0.26 (<0.0001)
CoQ10†		1.00	-0.02 (0.58)	0.37 (<0.0001)	0.21 (<0.001)	0.25 (<0.0001)	0.04 (0.36)	0.03 (0.54)	0.21 (<0.0001)	-0.002 (0.97)	0.30 (<0.0001)	0.30 (<0.0001)	0.17 (<0.0001)
25(OH)D_3			1.00	-0.002 (0.97)	-0.05 (0.34)	0.11 (0.03)	0.04 (0.44)	-0.01 (0.86)	0.06 (0.25)	-0.02 (0.64)	0.03 (0.59)	0.09 (0.08)	0.04 (0.40)
α-Toc				1.00	-0.37 (<0.0001)	0.36 (<0.0001)	0.22 (<0.0001)	0.37 (<0.0001)	0.11 (0.04)	0.23 (<0.0001)	0.18 (0.0004)	0.06 (0.27)	0.29 (<0.0001)
γ-Toc					1.00	-0.19 (0.0003)	-0.30 (<0.0001)	-0.47 (<0.0001)	-0.03 (0.63)	-0.25 (<0.0001)	-0.01 (0.78)	0.05 (0.35)	-0.27 (<0.0001)
Retinol						1.00	0.16 (0.0004)	0.18 (0.003)	0.16 (0.004)	0.15 (<0.0001)	0.24 (0.01)	0.13 (<0.0001)	0.22 (0.002)
α-Carot							1.00	0.78 (<0.0001)	0.53 (<0.0001)	0.59 (<0.0001)	0.51 (<0.0001)	0.42 (<0.0001)	0.79 (<0.0001)
β-Carot								1.00	0.40 (<0.0001)	0.57 (<0.0001)	0.41 (<0.0001)	0.30 (<0.0001)	0.80 (<0.0001)
α-Crx									1.00	0.39 (<0.0001)	0.65 (<0.0001)	0.57 (<0.0001)	0.66 (<0.0001)
β-Crx										1.00	0.53 (<0.0001)	0.23 (<0.0001)	0.75 (<0.0001)
Lutein/Zea											1.00	0.40 (<0.0001)	0.73 (<0.0001)
Lycopene												1.00	0.58 (<0.0001)
Total Carotenoids													1.00

* Data are given as SPEARMAN correlation coefficients (P value).

Abbreviations: CRP, C-reactive protein, CoQ10, Coenzyme Q10; 25(OH)D3, 25(OH)-vitamin D3; α-Toc, α-tocopherol; γ-Toc, γ-tocopherol; α-Carot, α-carotene; β-Carot, β-carotene; α-Crx, α-cryptoxanthin; β-Crx, β-cryptoxanthin; Zea, zeaxanthin.

Table 3

Multivariate hazard ratios (HR) and 95% Confidence Intervals (CI) for all-cause mortality by quintiles of blood biomarker.*

Blood Biomarker	Quintile					
	Q1 (Ref)	**Q2**	**Q3**	**Q4**	**Q5**	**P for trend**
CRP (mg/L)	< 0.4	0.4 – 0.9	1.0 – 1.8	1.8 – 4.0	> 4.0	
N	73	69	78	74	74	
Number of Deaths	27	25	37	44	42	
HR (95% CI)	1.00	0.85 (0.49-1.47)	1.28 (0.78-2.13)	1.68 (1.02-2.78)	1.80 (1.07-3.04)	0.01
Coenzyme Q_{10} (ng/mL)	< 828	828-1062	1063-1285	1286-1630	> 1630	
N	73	74	73	74	74	
Number of Deaths	38	37	37	31	31	
HR (95% CI)	1.00	0.83 (0.52-1.32)	0.80 (0.50-1.29)	0.70 (0.43-1.13)	0.70 (0.43-1.13)	0.12
HR# (95% CI)	1.00	0.84 (0.52-1.34)	0.74 (0.46-1.19)	0.65 (0.40-1.06)	0.64 (0.39-1.05)	0.0527
25(OH)-vitamin D_3 (ng/mL)	< 15.5	15.5 - 20.8	20.9 – 24.7	24.8 – 30.8	> 30.8	
N	73	74	73	74	74	
Number of Deaths	35	33	39	35	33	
HR (95% CI)	1.00	0.98 (0.60-1.61)	1.05 (0.64-1.72)	1.36 (0.83-2.24)	0.97 (0.59-1.61)	0.81
HR# (95% CI)	1.00	1.12 (0.68-1.83)	1.28 (0.78-2.10)	1.45 (0.88-2.39)	1.06 (0.64-1.75)	0.69
α-Tocopherol (μg/mL)	< 9.57	9.57 - 12.43	12.44 - 15.15	15.16 - 19.91	> 19.91	
N	73	74	73	74	74	
Number of Deaths	37	33	38	35	32	
HR (95% CI)	1.00	1.12 (0.68–1.84)	1.18 (0.73–1.89)	1.05 (0.64–1.71)	0.84 (0.51–1.38)	0.30
HR# (95% CI)	1.00	1.10 (0.67–1.80)	1.22 (0.75–1.96)	1.06 (0.65–1.73)	0.80 (0.49–1.32)	0.23
γ-Tocopherol (μg/mL)	< 0.96	0.96 - 1.79	1.80 - 2.60	2.61 - 3.70	> 3.70	
N	73	74	73	74	74	
Number of Deaths	35	32	37	34	37	
HR (95% CI)	1.00	0.93 (0.57–1.53)	1.21 (0.74–1.97)	1.01 (0.61–1.67)	1.12 (0.68–1.85)	0.61
HR# (95% CI)	1.00	0.96 (0.58–1.59)	1.18 (0.72–1.93)	1.03 (0.62–1.70)	1.06 (0.64–1.75)	0.81
Retinol (ng/mL)	< 532	532 - 637	638 - 732	733 - 841	> 841	

Blood Biomarker	Quintile					
	Q1 (Ref)	Q2	Q3	Q4	Q5	P for trend
N	73	74	73	74	73	
Number of Deaths	48	34	25	35	33	
HR (95% CI)	1.00	0.53 (0.34–0.83)	0.34 (0.20–0.56)	0.52 (0.33–0.82)	0.50 (0.31–0.80)	0.0002**
HR# (95% CI)	1.00	0.62 (0.39–0.99)	0.40 (0.24–0.66)	0.67 (0.41–1.09)	0.62 (0.38–1.01)	0.01**
α-Carotene (ng/mL)	< 19.0	19.0 – 31.5	31.6 – 43.6	43.7 – 67.6	> 67.6	
N	73	74	73	74	74	
Number of Deaths	43	40	32	27	33	
HR (95% CI)	1.00	0.81 (0.52 -1.26)	0.61 (0.38-0.99)	0.51 (0.30-0.86)	0.67 (0.40-1.10)	0.02**
HR# (95% CI)	1.00	0.78 (0.50 -1.22)	0.62 (0.38-1.01)	0.54 (0.32-0.91)	0.74 (0.44-1.23)	0.04**
β-Carotene (ng/mL)	< 79.0	79.0 – 128.8	128.9 – 208.9	209.0 – 368.8	> 368.8	
N	73	74	73	74	74	
Number of Deaths	38	39	32	30	36	
HR (95% CI)	1.00	1.00 (0.63-1.60)	0.94 (0.56-1.59)	0.53 (0.31–0.91)	0.90 (0.53-1.54)	0.54
HR# (95% CI)	1.00	1.02 (0.64-1.62)	0.98 (0.58-1.66)	0.60 (0.34–1.03)	0.92 (0.54-1.57)	0.59
α-Cryptoxanthin (ng/mL)	< 21.0	21.0 – 26.4	26.5 – 32.9	33.0 – 41.3	> 41.3	
N	73	74	73	74	74	
Number of Deaths	46	34	35	28	32	
HR (95% CI)	1.00	0.80 (0.50-1.26)	0.77 (0.49-1.21)	0.60 (0.36-0.98)	0.75 (0.47-1.20)	0.15
HR# (95% CI)	1.00	0.79 (0.50-1.26)	0.82 (0.52-1.28)	0.65 (0.39-1.07)	0.88 (0.54-1.43)	0.46
β-Cryptoxanthin (ng/mL)	< 100.6	100.6 – 152.4	152.5 – 234.4	234.5 – 369.9	> 369.9	
N	73	74	73	74	74	
Number of Deaths	39	36	33	33	34	
HR (95% CI)	1.00	0.91 (0.57–1.46)	1.00 (0.61–1.64)	0.88 (0.53–1.48)	0.92 (0.53–1.58)	0.78
HR# (95% CI)	1.00	1.04 (0.64–1.69)	1.07 (0.65–1.76)	1.06 (0.63–1.79)	1.14 (0.66–1.97)	0.66
Lutein/Zeaxanthin (ng/mL)	< 220.8	220.8 – 280.8	280.8 – 348.0	348.1 – 421.7	> 421.7	
N	73	74	73	74	74	
Number of Deaths	41	35	38	36	25	
HR (95% CI)	1.00	0.95 (0.59-1.52)	1.13 (0.71-1.79)	0.89 (0.56-1.43)	0.60 (0.35-1.01)	0.054

Blood Biomarker	Quintile					
	Q1 (Ref)	**Q2**	**Q3**	**Q4**	**Q5**	**P for trend**
HR[#] (95% CI)	1.00	1.17 (0.72-1.90)	1.22 (0.76-1.94)	1.05 (0.65-1.70)	0.74 (0.44-1.28)	0.24
Lycopene (ng/mL)	< 163.9	164.0 – 236.6	236.7 – 304.5	304.6 – 406.3	> 406.3	
N	73	74	73	74	74	
Number of Deaths	45	34	27	36	33	
HR (95% CI)	1.00	0.75 (0.48-1.19)	0.51 (0.31-0.83)	0.64 (0.40-1.00)	0.61 (0.38-0.97)	0.0505
HR[#] (95% CI)	1.00	0.79 (0.50-1.24)	0.59 (0.36-0.98)	0.74 (0.47-1.17)	0.70 (0.43-1.13)	0.22
Total Carotenoids (ng/mL)	< 794.5	794.5 – 1085.3	1085.4 – 1344.2	1344.3 – 1755.6	> 1755.6	
N	73	74	73	74	74	
Number of Deaths	42	38	33	27	35	
HR (95% CI)	1.00	0.89 (0.56-1.43)	0.80 (0.49-1.29)	0.55 (0.33-0.92)	0.80 (0.49-1.32)	0.02[**]
HR[#] (95% CI)	1.00	0.96 (0.59-1.54)	0.82 (0.50-1.33)	0.59 (0.35-1.00)	0.96 (0.57-1.60)	0.18[**]

[*] HR and 95% CI were estimated by Cox proportional hazards regression with adjustment for stage (I, II, III, or IV), age at diagnosis (continuous), race/ethnicity (Japanese American, white, or Native Hawaiian), sex, smoking status (never, former, current), and month of blood draw (January-February, March-April, May- June, July-August, September-October, November-December).

[#] HR is further adjusted for log CRP.

[**] Global test of linear and quadratic terms.

Table 4

Hazard ratios (HR) and 95% Confidence Intervals (CI) for colorectal cancer-specific mortality by tertiles of blood biomarkers.*

Blood Biomarker	Colorectal Cancer-specific Mortality Tertile			
	T1	T2	T3	P for trend
CRP (mg/L)	< 0.9	0.9-2.2	> 2.2	
N	116	125	127	
Number of deaths	22	32	38	
HR (95% CI)	1.00	1.32 (0.75-2.31)	2.06 (1.18-3.61)	0.01
Coenzyme Q_{10} (ng/mL)	< 979	979-1364	> 1364	
N	122	123	123	
Number of deaths	34	32	26	
HR (95% CI)	1.00	1.04 (0.62-1.73)	0.88 (0.52-1.48)	0.61
HR# (95% CI)	1.00	1.01 (0.60-1.69)	0.85 (0.50-1.43)	0.53
25(OH)-vitamin D_3 (ng/mL)	< 19.0	19.0-26.6	> 26.6	
N	122	123	123	
Number of deaths	36	29	27	
HR (95% CI)	1.00	0.89 (0.53-1.50)	0.98 (0.57-1.67)	0.92
HR# (95% CI)	1.00	0.96 (0.57-1.63)	1.01 (0.59-1.74)	0.97
α-Tocopherol (μg/mL)	< 11.5	11.5-16.3	> 16.3	
N	122	123	123	
Number of deaths	35	28	29	
HR (95% CI)	1.00	0.85 (0.49-1.45)	0.80 (0.46-1.39)	0.47
HR# (95% CI)	1.00	0.86 (0.50-1.47)	0.79 (0.45-1.36)	0.42
γ-Tocopherol (μg/mL)	< 1.45	1.45-2.93	> 2.93	
N	122	123	123	
Number of deaths	29	27	36	
HR (95% CI)	1.00	1.00 (0.57-1.77)	1.01 (0.58-1.74)	0.97
HR# (95% CI)	1.00	0.92 (0.52-1.63)	0.98 (0.56-1.70)	0.99
Retinol (ng/mL)	< 612	612-767	> 767	
Number of cases	122	123	123	
Number of deaths	37	27	28	
HR (95% CI)	1.00	0.69 (0.41-1.16)	0.68 (0.40-1.15)	0.24**
HR# (95% CI)	1.00	0.76 (0.44-1.29)	0.84 (0.48-1.48)	0.59**
α-Carotene (ng/mL)	< 26.8	26.8-49.1	> 49.1	
N	122	123	123	
Number of deaths	39	28	25	
HR (95% CI)	1.00	0.73 (0.43-1.23)	0.91 (0.51-1.62)	0.48**
HR# (95% CI)	1.00	0.77 (0.45-1.31)	1.05 (0.58-1.88)	0.50**

Blood Biomarker	Colorectal Cancer-specific Mortality Tertile			
	T1	T2	T3	P for trend
β-Carotene (ng/mL)	< 110.6	110.6-238.9	> 238.9	
N	122	123	123	
Number of deaths	44	22	26	
HR (95% CI)	1.00	0.69 (0.39-1.20)	0.63 (0.35-1.14)	0.16
HR[#] (95% CI)	1.00	0.77 (0.44-1.35)	0.69 (0.38-1.24)	0.24
α-Cryptoxanthin (ng/mL)	< 24.9	24.9-35.6	> 35.6	
N	122	123	123	
Number of deaths	44	24	24	
HR (95% CI)	1.00	0.65 (0.39-1.08)	0.69 (0.41-1.16)	0.15
HR[#] (95% CI)	1.00	0.67 (0.40-1.12)	0.79 (0.46-1.35)	0.35
β-Cryptoxanthin (ng/mL)	< 139.2	139.2-287.1	> 287.1	
N	122	123	123	
Number of deaths	42	30	20	
HR (95% CI)	1.00	0.77 (0.47-1.28)	0.62 (0.33-1.14)	0.12
HR[#] (95% CI)	1.00	0.82 (0.50-1.37)	0.68 (0.36-1.27)	0.23
Lutein/zeaxanthin (ng/mL)	< 262.2	262.2-369.1	> 369.1	
N	122	123	123	
Number of deaths	40	33	19	
HR (95% CI)	1.00	1.34 (0.81-2.19)	0.58 (0.32-1.04)	0.08
HR[#] (95% CI)	1.00	1.43 (0.87-2.36)	0.67 (0.37-1.22)	0.23
Lycopene (ng/mL)	< 211.9	211.9-327.4	> 327.4	
N	122	123	123	
Number of deaths	41	24	27	
HR (95% CI)	1.00	0.48 (0.28-0.82)	0.62 (0.37-1.05)	0.07
HR[#] (95% CI)	1.00	0.52 (0.30-0.90)	0.70 (0.41-1.20)	0.20
Total Carotenoids (ng/mL)	< 978	978-1468	> 1468	
N	122	123	123	
Number of deaths	44	27	21	
HR (95% CI)	1.00	0.48 (0.28-0.82)	0.62 (0.37-1.05)	0.16[**]
HR[#] (95% CI)	1.00	0.69 (0.41-1.15)	0.76 (0.42-1.36)	0.34[**]

[*] HR and 95% CI were estimated by Cox proportional hazards regression with adjustment for stage (I, II, III, or IV), age at diagnosis (continuous), race/ethnicity (Japanese American, white, or Native Hawaiian), sex, smoking status (never, former, current), and month of blood draw (January-February, March-April, May-June, July-August, September-October, November-December).

[#] HR is further adjusted for log CRP.

[**] Global test of linear and quadratic terms.