Oxidative Balance Score, Colorectal Adenoma, and Markers of Oxidative Stress and Inflammation

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ABSTRACT (250 words)

Background: An oxidative balance score (OBS) that combines pro- and anti-oxidant exposures was previously reported to be associated with incident sporadic colorectal adenoma. We extend the previous analyses by assessing associations of the OBS and colorectal adenoma with circulating biomarkers of oxidative stress (F_2-isoprostanes [FIP] and fluorescent oxidation products [FOP]), and inflammation (C-reactive protein [CRP]).

Methods: Using pooled data from two previously conducted colonoscopy-based case-control studies of incident, sporadic colorectal adenoma (n=365), the OBS was constructed and divided into three approximately equal intervals, with the lowest interval used as the reference. Biomarker levels were dichotomized as "high" versus "low" based on the median values among controls. Multivariable logistic regression was used to calculate adjusted odds ratios (ORs) and 95% confidence intervals (CIs).

Results: For the OBS-adenoma association, the ORs (95% CIs) for the middle and highest (relative to the lowest) score intervals were 0.81 (0.46-1.43) and 0.39 (0.17-0.89), respectively. The corresponding OBS category-specific ORs (95% CIs) were 0.50 (0.25-1.01) and 0.25 (0.10-0.65) for FIP, 2.01 (1.13-3.75) and 3.48 (1.51-8.02) for FOP, and 0.57 (0.31-1.04) and 0.21 (0.09-0.49) for CRP. The ORs (95% CIs) reflecting associations of adenoma with high levels of FIP, FOP, and CRP were 1.89 (1.08-3.30), 1.82 (1.11-2.99) and 1.45 (0.88-2.40), respectively.

Conclusions: As hypothesized, the OBS was inversely associated with colorectal adenoma and circulating FIP and CRP levels. The explanation for the unexpected direct OBS-FOP association is unknown.

Impact: These data support the use of combined measures of pro- and anti-oxidant exposures in studies of colorectal neoplasia**.**

INTRODUCTION

A considerable body of evidence from basic science and animal studies supports the role of oxidative stress as both an initiator and promoter of carcinogenesis; however, epidemiological studies of associations between individual determinants of oxidative stress and cancer are conflicting (1-5). One potential explanation for this discrepancy is the complex and multi-factorial nature of mechanisms by which oxidative stress may affect cancer risk. The independent effects of individual oxidative balance-related exposures are difficult to ascertain because they may be small and highly correlated and because of the likely biological interactions involving multiple pro- and anti-oxidant factors (6). Therefore, it was suggested that a combined measure that takes into account multiple pro- and anti-oxidant exposures might be a more accurate indicator of the overall oxidative stress burden of an individual (7, 8). We and others previously proposed an oxidative balance score (OBS) as a measure of combined pro- and anti-oxidant exposure status (8, 9). We illustrated this approach using data from previously conducted case-control studies of incident, sporadic colorectal adenoma (10-12).

Many known pro- and anti-oxidants have been found to act through a variety of pro- and anti-carcinogenic mechanisms that may be independent of oxidative stress. Experimental biology evidence demonstrates that antioxidant nutrients may exert anti-proliferative effects on cells (13) and regulate gene expression (14) and immune response (15). Similarly, smoking, in addition to acting as pro-oxidant, has direct carcinogenic effects in many tissues and organ systems (16). These examples illustrate that the reported associations between the OBS and health outcomes (8-11) may or may not be attributable to changes in oxidative stress. For this reason it is important to assess how the OBS, which is designed to measure modifiable pro- and anti-oxidant exposures, may be related to biomarkers of oxidative stress or oxidative damage.

Currently, F2-isoprostanes (FIP) are considered to be the best available biomarker of oxidative stress *in vivo* (17-19). However, FIP measure only lipid peroxidation and may not reflect oxidative damage of

proteins and DNA. Moreover, measuring FIP is expensive and requires careful sample handling and rapid processing. Thus, the use of FIP may not be practical in very large epidemiological studies and is probably not suitable for analyses of archived samples that may have been affected by *in vitro* oxidation (20, 21).

A possible alternative to FIP as a biomarker of oxidative stress is plasma fluorescent oxidation products (FOP). FOP measure oxidation products from several sources, including lipids, proteins, and DNA, and thus may serve as a more global indicator of oxidative stress (21, 22). Previously used in the food industry and *in vitro* studies to detect oxidation (23-25), FOP are now being proposed as potential biomarkers of oxidative stress that can be used in clinical and epidemiologic studies. An additional advantage of FOP is that they are relatively easy to measure and are stable and can be assessed in samples with variable handling and storage protocols (26). Recently, a nested case-control study (22) and a small prospective study (27) reported that plasma FOP significantly and independently predicted risk of coronary heart disease. Yet, there have been no reported studies that measured plasma FOP in relation to cancer risk. Moreover, no previous studies assessed associations of FOP with measures of pro- and antioxidant exposures or the correlation between FOP and FIP.

It is important to emphasize that oxidative stress is closely related to inflammation and that these two processes should probably be assessed together. Chronic inflammation is associated with elevated oxidative stress levels; conversely, oxidative stress has pro-inflammatory effects through activation of nuclear factor-kappa B (NF-kB), a transcription factor that increases expression of cytokines, chemokines, and cell adhesion molecules (28-30). Thus, inflammation may be seen as both a cause and consequence of oxidative stress. For all of the above reasons an examination of an association between oxidative stress-modifying exposures and biomarkers of oxidative stress may be better informed by also taking into consideration the level of inflammation, which is commonly assessed by measuring serum C-reactive protein (CRP).

CRP is an acute-phase reactant that is produced in response to inflammatory stimuli (31). As one of relatively few well-characterized, reliable biomarkers of inflammation (32), CRP has been found to be closely

related to oxidative stress (33). Several measures of oxidative stress, including circulating levels of oxidized low density lipoproteins, free-oxygen radical test (FORT) results, and urine concentrations of FIP, have been reported to be positively correlated with serum CRP (34, 35); however, a CRP-OBS association has not been reported.

In this study, we extend our previous analysis of an OBS and adenoma (16) by examining whether the OBS is associated with FIP and FOP and by assessing the association of the OBS with inflammation as measured by serum CRP. We further explore associations of the three markers (FIP, FOP, and CRP) with risk of incident sporadic colorectal adenoma.

MATERIALS AND METHODS

Study Population

We used pooled data from two previously conducted colonoscopy-based case-control studies of incident, sporadic colorectal adenoma in two different US states by the same principal investigator (RMB). The first study, Markers of Adenomatous Polyps I (MAP I), was conducted in community gastroenterology practices in Winston-Salem and Charlotte, North Carolina. The second study, Markers of Adenomatous Polyps II (MAP II), identical in design to MAP I, was conducted at Consultants in Gastroenterology, PA, a large, private practice in Columbia, South Carolina.

Participants for these two case-control studies included patients who were 30-74 years of age with no prior history of colorectal neoplasms who were scheduled to undergo outpatient, elective colonoscopy at one of the study sites. Assessment of initial participant eligibility was identical in both studies. Cases (n=235) were first incident cases of colon or rectal adenomatous polyps at the time of elective outpatient colonoscopy, and controls (n=391) were free of all polyps at colonoscopy. The detailed study methods for MAP I (36, 37) and MAP II (38, 39) were previously published.

Data Collection

In both the MAP I and the MAP II studies, a modified 153-item Willett Food Frequency Questionnaire was administered to obtain information on usual dietary and nutritional supplement intakes (40, 41). Data were also collected on demographics, family history, lifestyle and body size characteristics, and medical history, including medications such as aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs). Total intakes of micronutrients (iron, vitamin C, β-carotene, and α-tocopherol) were calculated based on the sum of the total average daily dietary and supplement intakes.

For both studies, blood was collected, handled, and stored in a manner to allow measurements of pro-/anti-oxidants, FIP, FOP, and CRP. The samples were drawn into red-coated, pre-chilled Vacutainer tubes, plunged into ice and shielded from light and immediately delivered to the laboratory where the blood was centrifuged under refrigeration. Plasma and serum were separated; aliquotted into O-ring-capped, amber-colored cryopreservation vials; the air in the vials was displaced with inert gas (nitrogen in MAP I and argon in MAP II); and then immediately frozen at -70^{O} C until analysis. Plasma lycopene, α-carotene, β- carotene, lutein, β-cryptoxanthin, and α-tocopherol levels from both studies were measured using high-performance liquid chromatography (HPLC) (42, 43). Plasma free FIP was measured by a gas chromatography-mass spectrometry (GCMS) method (44) by the Molecular Epidemiology and Biomarker Research Laboratory (MEBRL) at the University of Minnesota (Minneapolis, MN). This method, considered the gold standard for measuring FIP, measures a well-defined set of F_2-isoprostane isomers. The FIP were extracted from participants' samples using deuterium (4)-labeled 8-iso-prostaglandin F_2 alpha as an internal standard. Unlabeled, purified F_2-isoprostane was used as a calibration standard.

The modified method from Shimasaki (24) was used to measure FOP. The procedures were described in detail previously (26). Briefly, 0.2 mL of plasma was extracted with ethanol/ether (3:1 v/v) and vigorously mixed on a vortex mixer. The mixed solution was centrifuged for 10 minutes at 3,000 rpm, and 1 mL of supernatant was added to cuvettes for spectrofluormetric readings. The fluorescence was determined as

relative fluorescence intensity units per milliliter of plasma at 360/430 nm wavelengths (excitation/emission) by a spectrofluorometer. Quinine sulfate diluted in 0.1 N H_2SO_4 was used for calibration. Due to the limited amount of plasma samples available, about 22% of the population's FOP were measured using serum samples instead of plasma; however, analyses of a subset of patients with both types of samples available indicated that the two sets of values were highly correlated ($r = 0.9$; $p < 0.001$). High sensitivity CRP was measured by latex-enhanced immunonephelometry on a Behring nephelometer II (BN-II) analyzer (inter-assay CV 4%; Behring Diagnostics, San Jose, CA).

Oxidative Balance Score

The oxidative balance score (OBS) was calculated by combining information from *a priori* selected pro- and anti-oxidant factors, which are summarized in Table 1. The blood levels of pro-oxidant (iron) and antioxidant (lycopene, α-carotene, β-carotene, lutein, β-cryptoxanthin, α-tocopherol) nutrients were divided into low, medium, and high categories based on study-specific tertile values among the controls. We did not include plasma γ-tocopherol in the OBS because circulating levels of this anti-oxidant are not a direct measure of its intake, but rather a reflection of metabolic response to oxidative stress and inflammation (45). Nevertheless, because γ-tocopherol is the major form of vitamin E in the US diet (46), we constructed two alternative score versions: with and without plasma γ-tocopherol.

The tertile cutoffs for FFQ-derived variables (polyunsaturated fat, vitamin C, and alcohol) were study- and sex-specific. The participants with low (1^{st} tertile) pro-oxidant exposures were awarded 2 points, those with medium (2^{nd} tertile) exposures received 1 point, and those with high (3^{rd} tertile) exposures received 0 points. For alcohol consumption, non-drinkers, moderate drinkers (below median), and heavy drinkers (above median) received 2, 1, and 0 points, respectively. For antioxidants, low, medium, and high levels were assigned 0, 1, and 2 points, respectively. Similarly, for categorical variables, smoking status was categorized as never (2 points), former (1 point), and current (0 points); and for selenium supplement, aspirin, and NSAID

use, 0 points were assigned to participants with no regular use, 1 point to those with unknown or missing data, and 2 points to those with regular use. The overall OBS was then calculated by summing the points assigned to each participant.

Statistical Analyses

The overall OBS was treated as a continuous as well as an ordinal variable with all categories representing an approximately equal interval and the lowest interval used as the reference category. The use of equal intervals instead of quantiles (*e.g.,* tertiles or quartiles) allows comparing extremes of the distribution. Unconditional logistic regression was used to examine three types of associations. First, we examined the association between the OBS and incident, sporadic colorectal adenoma, adjusting for age, race, sex, total energy intake, BMI, plasma cholesterol, hormone replacement therapy (among women), physical activity, dietary fiber intake, study, and family history of colorectal cancer in a first degree relative.

To assess the impact of individual OBS components on the overall results we removed each component from the overall score and included that component as a covariate in the model. The association between colorectal adenoma and the OBS in each alternative model was then compared to the association between colorectal adenoma and the *a priori*-defined OBS in the original analysis.

Next, we examined the associations between the OBS and the markers of oxidative stress (FIP and FOP) and inflammation (CRP), which were dichotomized based on the study- and sex-specific medians among the controls, adjusting for the same potential confounding factors as in the first analysis. Finally, we examined the associations between the dichotomized markers of oxidative stress and inflammation and incident sporadic colorectal adenoma. The models for the third analysis included the same covariates as in the analysis of the association between the OBS and adenoma. Correlations among FIP, FOP, and CRP were assessed using Pearson correlation coefficients. We also conducted several sensitivity analyses to evaluate possible differences in results when 1) OBS quartiles were used instead of equal intervals; 2) using biomarker

quartiles to assess the biomarker-adenoma associations; and 3) for the association between the OBS and each biomarker when both former and never smokers were assigned 2 points while current smokers were assigned 0 points to consider the possibility that biomarkers may only be affected by current smoking status. The results of the logistic regression analyses were expressed as adjusted odds ratios (ORs) with corresponding 95% confidence intervals (CIs).

All models were assessed for collinearity and goodness of fit. A two-sided p-value < 0.05 was considered statistically significant. Statistical analyses were performed with SAS version 9.2 (SAS Institute, Cary, NC) statistical software package.

RESULTS

A total of 150 (64%) cases and 215 (69%) controls in the pooled MAP studies had sufficient information for calculating the OBS. Selected characteristics of the cases and controls, by study, are shown in Table 2. Cases and controls did not differ considerably with regard to most risk factors; however, in MAP I, cases were more likely to be male, current smokers, and less likely to have a history of a first-degree relative with colorectal cancer. When the MAP studies were pooled, the mean plasma concentrations of α-carotene and β-cryptoxanthin were statistically significantly higher in the controls. The OBS ranged between 2 and 24 points. When the OBS was treated as a continuous variable, each additional score point was associated with a statistically significant lower risk of incident colorectal adenoma after multivariable adjustment (OR = 0.93, 95% CI: 0.88 – 0.99). Relative to those in the lowest OBS interval, risks for adenomas among those in the middle and the highest OBS intervals were statistically significantly 19% and 61% lower, respectively (p-trend = 0.04) (Table 3). When plasma levels of γ-tocopherol were added to the OBS, the results were essentially unaffected (Table 3).

The associations of the OBS with different markers of oxidative stress and inflammation are shown in Table 4. There was a statistically significant inverse higher OBS-FIP association. After adjusting for

confounding factors, the ORs (95% CIs) for the middle and the highest OBS intervals (again using the lowest interval as reference) were 0.50 (0.25 – 1.01) and 0.25 (0.10 – 0.65), respectively (p-trend <0.01). The corresponding results for FOP were in the opposite direction; compared to the reference category, those in the middle and highest OBS intervals had adjusted ORs (95% CIs) of 2.01 (1.13 – 3.75) and 3.48 (1.51 – 8.02), respectively (p-trend < 0.01).

The results for CRP were similar to those observed for FIP. Those in the middle and highest OBS interval groups were at approximately 40% and 80% lower risk, respectively, for having elevated CRP levels (p-trend < 0.01) (Table 4).

We further examined the associations of markers of oxidative stress and inflammation with incident, sporadic colorectal adenoma (Table 5). Elevated levels of both markers of oxidative stress (FIP and FOP) were statistically significantly associated with about 80% higher risk of colorectal adenoma; the adjusted ORs were 1.89 (95% CIs 1.08 – 3.30) for FIP and 1.82 (95% CI: 1.11–2.99) for FOP. The CRP-adenoma association was in the same direction as those for FIP and FOP, but it was not statistically significant (OR = 1.45; 95% CI: 0.88 – 2.40).

We also assessed correlations among FIP, FOP, and CRP. The Pearson correlation coefficients were 0.06, 0.09, and 0.08 between FOP and FIP, FOP and CRP, and FIP and CRP, respectively (p > 0.05 for all).

All sensitivity analyses are presented in supplemental tables. The results of the sensitivity analyses in which the observed association between colorectal adenoma and the original *a priori*-defined OBS (treated as a continuous variable) was compared to the corresponding results after each OBS component was removed from the score and included in the model as a covariate are shown in Supplemental Table 1. These sensitivity analyses produced a range of ORs from 0.91 (after exclusion of lycopene) to 0.96 (after exclusion of smoking). All OR estimates in the sensitivity analyses remained within 5% of the original OR of 0.94. When OBS quartiles were used instead of equal intervals the results for the OBS-adenoma association remained essentially the same (Supplemental Table 2). In the sensitivity analyses in which biomarker quartiles were

used instead of binary (high vs. low) categories, the estimates reflecting the associations between the biomarkers and adenoma were similar, but less stable and with wider confidence intervals (Supplemental Table 3).

DISCUSSION

While oxidative stress is thought to play a prominent role in many human diseases, there is no definitive evidence linking pro- and antioxidants to specific human health outcomes (47). This discrepancy between biological plausibility and the lack of established epidemiological associations is likely explained by inadequate methods of assessing oxidative stress in humans.

Previously, we and others used a score approach to measure combined pro- and anti-oxidant exposure status in relation to risk of several cancers including colorectal, prostate, and lung (6-11, 48). The current study extends our previous analyses by assessing associations between an OBS and markers of oxidative stress and inflammation and by assessing the possible relations of various biomarkers to each other and to colorectal adenoma risk. We found a rather strong and statistically significant inverse association between the OBS and plasma FIP, and a significant direct association between FIP and colorectal adenoma risk. These associations were in the hypothesized directions and are in agreement with evidence from other studies.

FIP are prostaglandin-like compounds formed non-enzymatically as products of free radical-mediated lipid peroxidation (19). Among various currently available markers of oxidative stress, FIP are considered the "gold-standard" in humans (18, 44). Current literature also supports the use of FIP in studies of human diseases (19, 49). Elevated levels of FIP were found to be directly associated with a wide variety of conditions, including cardiovascular, pulmonary, neurological, and renal diseases (50-53). Previously reported associations between FIP and individual anti- or pro-oxidant factors, however, have been inconsistent. Block *et al.* examined several physiologic and behavioral factors, including diet, for their

individual contributions to oxidative damage, as measured by plasma FIP (33). While they found statistically significant inverse correlations between plasma FIP and plasma ascorbic acid and several carotenoids, there were no associations with α-tocopherol, alcohol, or smoking. By contrast, Morrow *et al.* found significantly higher circulating plasma FIP in smokers than in the non-smokers (54).

In a randomized, placebo-controlled trial of the effects of a combination of vitamin E and carotenoids on markers of antioxidant status and lipid peroxidation over 11 weeks among healthy persons (55), the group given supplemental 111 mg of α-tocopherol and 1.24 mg of carotenoids daily had a 15% reduction in plasma total $F_{2\alpha}$-isoprostanes concentrations. In our study, we observed approximately 75% lower levels of plasma FIP in those with the highest relative to those with the lowest OBS, suggesting that the composite measure of OBS is more strongly associated with FIP than is any individual anti- or pro-oxidant factor.

Plasma FOP were relatively recently introduced into human population-based studies as biomarkers of oxidative stress, but no reported studies used FOP in relation to neoplasia outcomes. Measurement of FOP was first developed by Dillard and Tappel (56) in 1971, and modified by Shimasaki in 1994 (24). FOP are thought to measure oxidation products from several sources, including lipids, proteins, and DNA, and thus are thought to serve as a global indicator of oxidative balance (22). Moreover, FOP are relatively unaffected by specimen quality and storage conditions, an important, practical consideration for epidemiologic field studies.

In two previous studies, high levels of FOP were statistically significantly directly associated with the incidence of cardiovascular (57) and coronary heart diseases (22). In another recent study (21), FOP were statistically significantly, positively associated with variables linked to systemic oxidative balance, including smoking, hypertension, and reduced renal function.

The findings for FOP in this study were unexpected. On the one hand, elevated FOP, like FIP, were associated with higher risk for colorectal adenoma. On the other hand, unlike FIP, a higher OBS was significantly associated with higher FOP concentrations. Moreover, although FOP and FIP are both presumed to reflect oxidative damage there was no correlation between the two markers. Taken together, these

results suggest that different components of the OBS may affect different processes; e.g., lipid peroxidation, inflammation, or some other process that is independent of lipid peroxidation, but is related to oxidative stress (see hypothetical diagram shown in Supplemental Figure 1). The degree of lipid peroxidation is reflected by FIP, inflammation by CRP, and, hypothetically, non-lipid peroxidation component(s) of oxidative stress by FOP. If we assume that different components of the OBS exert different effects on lipid peroxidation and other oxidative stress mechanisms, then it is possible that the associations of the OBS with FOP and FIP will be in the opposite directions. As shown in Supplemental Table 4 this explanation is plausible because several OBS components were oppositely associated with FOP vs. FIP concentrations.

While the oxidative stress pathway is closely related to inflammation, most studies of biomarkers of oxidative stress do not consider markers of inflammation. The role of inflammation as both a cause and a result of oxidative stress is supported by a considerable body of evidence. Oxidative stress may play a role in inflammation by up-regulating the production of pro-inflammatory cytokines such as interleukin (IL)-6 and acute phase proteins such as C-reactive protein (CRP) through activating redox-sensitive transcription factors such as nuclear factor κB (NF-κB) (58, 59). We found a statistically significant inverse association between the OBS and CRP, which was comparable to the corresponding association between the OBS and FIP.

A distinguishing feature of this study was the use of biomarker-based measurements for most OBS components. Food frequency questionnaires may not capture all sources of each nutrient, do not account for bioavailability, and are subject to recall bias, particularly in case-control studies in which exposure is assessed retrospectively (60). For these reasons, biochemical indicators are being used with increasing frequency. Unlike questionnaires, biomarkers are independent of recall and social desirability, and because blood levels reflect an individual's absorption and delivery to the circulation, may provide better estimates of the relevant tissue doses (61, 62). On the other hand, biomarker-based measurements represent relatively recent exposures that may not reflect long-term patterns.

In addition to the general problems that are applicable to most case-control studies, our study has several limitations that are specific to the current analyses. First, the OBS was limited to dietary/lifestyle exposures and included no endogenous measures of antioxidant cell function. Although oxidative balance is affected by modifiable factors, such as those included in the OBS, oxidative balance is also determined by enzymatic mechanisms (63). Endogenous factors that influence DNA damage, cell growth, and cell death contribute to carcinogenesis through modulating gene expression (64). Another limitation of the current analysis is the assumption that individual pro- and anti-oxidant exposures have equal weights. An equal weighting approach might not represent the real relative biological contributions of the individual oxidative stress-related exposures. It has been shown, for example, that ascorbate (vitamin C) has a lower redox potential than α-tocopherol and, thus, relative contributions of vitamin C and vitamin E may be different (65). On the other hand, we previously found that an OBS-colorectal adenoma association was very little affected by various weighting methods (12).

In conclusion, our findings suggest that an OBS may serve as a composite measure of oxidative stress- and inflammation-related exposures. It is, however, unclear whether or how these exposures affect FOP, and what biochemical processes are reflected by plasma FOP concentrations. The lack of correlation between FOP and FIP also requires further study. Nevertheless, these data support the use of combined measures of pro- and anti-oxidant exposures in studies of colorectal neoplasia.

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Table 1. Oxidative Balance Score (OBS) assignment scheme

Oxidative Balance Score (OBS) Components	Assignment Scheme†
1. PUFA intake	0 = High (3rd tertile), 1 = Medium (2nd tertile), 2 = Low (1st tertile)
2. Serum ferritin	0 = High (3rd tertile), 1 = Medium (2nd tertile), 2 = Low (1st tertile)
3. Total* vitamin C intake	0 = Low (1st tertile), 1 = Medium (2nd tertile), 2 = High (3rd tertile)
4. Plasma lycopene	0 = Low (1st tertile), 1 = Medium (2nd tertile), 2 = High (3rd tertile)
5. Plasma α-carotene	0 = Low (1st tertile), 1 = Medium (2nd tertile), 2 = High (3rd tertile)
6. Plasma β-carotene	0 = Low (1st tertile), 1 = Medium (2nd tertile), 2 = High (3rd tertile)
7. Plasma lutein	0 = Low (1st tertile), 1 = Medium (2nd tertile), 2 = High (3rd tertile)
8. Plasma β-cryptoxanthin	0 = Low (1st tertile), 1 = Medium (2nd tertile), 2 = High (3rd tertile)
9. Plasma α-tocopherol	0 = Low (1st tertile), 1 = Medium (2nd tertile), 2 = High (3rd tertile)
10. Selenium supplements	0 = No supplement, 1 = Unknown (missing data), 2 = Supplement
11. Smoking history	0 = Current smoker, 1 = Former smoker, 2 = Never smoker
12. Regular aspirin use	0 = No regular use, 1 = Unknown, 2 = Regular Use
13. Regular NSAID use	0 = No regular use, 1 = Unknown, 2 = Regular Use
14. Alcohol consumption	0 = Above median 1 = Below median 2 = Non-drinker

Abbreviations: PUFA = polyunsaturated fatty acid; NSAID = non-steroidal anti-inflammatory drug

†Low, intermediate, and high categories correspond to study-specific tertile values among controls

*Total intake = dietary intake + supplemental intake

Table 2. Selected baseline characteristics of participants in the MAP I & II case-control studies of incident, sporadic colorectal adenomas

Characteristics	MAP I		MAP II		Pooled Analysis	
	Cases (n=106) mean (SD)	Controls (n=106) mean (SD)	Cases (n=33) mean (SD)	Controls (n=92) mean (SD)	Cases (n=139) mean (SD)	Controls (n=201) mean (SD)
Age, years	57.4 (8.9)	56.1 (10.2)	55.4 (7.3)	55.5 (7.9)	56.9 (8.6)	55.9 (9.2)
Male (%)	54.7	32.1[b]	57.6	44.6	55.4	37.8[a]
Body mass index, kg/m^2	27.8 (6.1)	27.1 (5.7)	28.5 (5.2)	28.6 (6.7)	27.9 (5.9)	27.8 (6.2)
Physical activity, MET-hours/week	216.8 (143.4)	196.1 (127.3)	163.7 (116.9)	176.5 (125.2)	204.2 (139.1)	187.1 (126.4)
Family history of colorectal cancer[+] (%)	17.0	33.0[b]	21.1	19.6	18.0	26.9
HRT user (women only) (%)	62.5	54.1	78.6	70.6	66.1	60.8
Regularly take an NSAID (%)	21.2	32.1	33.3	34.8	24.1	33.3
Regularly take aspirin (%)	34.9	35.8	45.5	41.3	37.4	38.3
Current smoker (%)	34.0	20.2[b]	24.2	13.0	31.7	16.9[b]
Alcohol, drinks/week	20.8 (25.6)	14.6 (20.2)	9.4 (9.1)	13.4 (16.3)	16.3 (21.4)	13.9 (17.8)
Dietary intakes per day						
Total energy, kcal	2,061.3 (851.8)	2,172.6 (2493.7)	1,831.3 (765.3)	1,648.0 (647.8)	2,006.7 (835.1)	1,932.5 (1902.0)
Total PUFA, gm	14.0 (6.3)	14.4 (14.5)	15.5 (8.9)	14.1 (10.4)	14.3 (7.0)	14.2 (12.8)
Dietary fiber, gm	22.8 (9.4)	25.5 (26.6)	16.6 (6.7)	15.3 (6.7)	21.3 (9.2)	20.9 (20.7)
Total° vitamin C, mg	286.6 (388.5)	302.1 (354.6)	237.5 (273.6)	298.9 (369.4)	275.0 (364.2)	300.7 (360.6)
Plasma levels						
Plasma lycopene, µg/dL	26.3 (14.3)	25.8 (13.3)	21.7 (11.4)	24.6 (10.8)	25.2 (13.8)	25.2 (12.2)
Plasma α-carotene, µg/dL	2.7 (2.9)	3.6 (4.8)	2.6 (2.6)	3.5 (3.1)	2.7 (2.8)	3.5 (4.1)[a]
Plasma β-carotene, µg/dL	15.3 (22.5)	16.4 (15.5)	12.6 (11.4)	16.3 (13.0)	14.6 (20.4)	16.4 (14.4)
Plasma lutein, µg/dL	16.8 (7.2)	18.1 (10.3)	17.7 (6.2)	15.7 (6.3)	17.0 (6.9)	17.0 (8.7)
Plasma β-cryptoxanthin, µg/dL	6.0 (4.7)	6.9 (5.8)	6.1 (4.1)	8.1 (7.2)	6.0 (4.5)	7.5 (6.5)[a]
Plasma α-tocopherol, mg/dL	1.2 (0.5)	1.1 (0.5)	1.1 (0.3)	1.2 (0.6)	1.1 (0.5)	1.2 (0.5)
Plasma γ-tocopherol, mg/dL	0.2 (0.1)	0.2 (0.1)	0.2 (0.1)	0.2 (0.1)	0.2 (0.1)	0.2 (0.1)
Plasma ferritin, mg/dL	146.1 (135.2)	148.8 (185.9)	144.5 (108.3)	130.8 (127.5)	145.7 (129.0)	140.6 (161.7)
Plasma total cholesterol, mg/dL	203.4 (35.8)	206.3 (39.5)	194.8 (32.4)	199.3 (39.5)	201.4 (35.1)	203.1 (39.6)
Biomarker levels						
FIP, pg/mL	94.0 (41.8)	88.8 (38.4)	76.0 (25.0)	78.0 (28.9)	90.1 (39.3)	84.4 (35.1)
FOP, avg. std. ref. adj.‡	0.06 (0.03)	0.05 (0.02)	0.03 (0.01)	0.04 (0.01)	0.05 (0.11)	0.05 (0.13)
CRP, µg/mL	6.1 (6.1)	7.5 (23.8)	3.7 (5.0)	4.6 (6.2)	5.5 (6.0)	6.2 (18.0)

SD = standard deviation; PUFA = polyunsaturated fatty acid; NSAID = non-steroidal anti-inflammatory drug; FIP = F_2-isoprostanes; FOP = fluorescent oxidation products; CRP = C-reactive protein

[a] $P < 0.05$ based on t-test for continuous variables and chi-square test for categorical variables; [b] $P < 0.01$ based on t-test for continuous variable and chi-square test for categorical variables

[+] In a first degree relative; ° Total = dietary + supplemental; ‡Unit for FOP measurement is "average standard reference adjusted", in which samples were calculated against a 1 ppm fluorescent reference standard quinine in 0.1 N sulfuric acid

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Table 3. Association between OBS (with and without inclusion of γ-tocopherol) and incident, sporadic colorectal adenoma

OBS without γ-tocopherol (Range 2 – 24)	**Cases (n)***	**Controls (n)***	**OR (95% CI)†**	**p-trend**
Interval 1 (OBS 2 – 9)	44	43	1.0	0.04
Interval 2 (OBS 10 – 16)	81	114	0.81 (0.46 – 1.43)	
Interval 3 (OBS 17 – 24)	14	44	0.39 (0.17 – 0.89)	
OBS as continuous variable	139	201	0.93 (0.87 – 0.99)	
OBS with γ-tocopherol (Range 2 – 25)	**Cases (n)***	**Controls (n)***	**OR (95% CI)†**	**p-trend**
Interval 1 (OBS 2 – 9)	34	31	1.0	0.04
Interval 2 (OBS 10 – 17)	88	126	0.76 (0.40 – 1.43)	
Interval 3 (OBS 18 – 25)	17	44	0.40 (0.17 – 0.97)	
OBS as continuous variable	139	201	0.93 (0.88 – 0.99)	

Abbreviations: OBS = oxidative balance score; OR = odds ratio; CI = confidence interval

†Adjusted for age, race, sex, body mass index (BMI), total energy intake, plasma cholesterol, and family history of colorectal cancer in a first degree relative, hormone replacement therapy (among women), dietary fiber, physical activity, and study (MAP I or MAP II)

*Total number of subjects in the model is lower due to missing covariate data

Table 4. Associations between OBS and markers of oxidative stress and inflammation

OBS	Biomarkers‡		OR (95% CI)†	p-trend
	High	Low		
		FIP		
Interval 1 (OBS 2 – 9)	51	20	1.0	<0.01
Interval 2 (OBS 10 – 16)	91	68	0.50 (0.25 – 1.01)	
Interval 3 (OBS 17 – 24)	17	27	0.25 (0.10 – 0.65)	
Continuous	159	115	0.87 (0.81 – 0.94)	
		FOP		
Interval 1 (OBS 2 – 9)	33	45	1.0	<0.01
Interval 2 (OBS 10 – 16)	107	77	2.01 (1.13 – 3.75)	
Interval 3 (OBS 17 – 24)	36	19	3.48 (1.51 – 8.02)	
Continuous	176	141	1.10 (1.03 – 1.17)	
		CRP		
Interval 1 (OBS 2 – 9)	56	31	1.0	<0.01
Interval 2 (OBS 10 – 16)	108	87	0.57 (0.31 – 1.04)	
Interval 3 (OBS 17 – 24)	19	39	0.21 (0.09 – 0.49)	
Continuous	183	157	0.88 (0.82 – 0.94)	

Abbreviations: OBS = oxidative balance score; OR = odds ratio; CI = confidence interval; FIP = F_2-isoprostanes; FOP = fluorescent oxidation products; CRP = C-reactive protein

†Adjusted for age, race, sex, body mass index (BMI), total energy intake, plasma cholesterol, and family history of colorectal cancer in a first degree relative, hormone replacement therapy (among women), dietary fiber, physical activity, and study (MAP I or MAP II)

*Total number of subjects in the model is lower due to missing covariate data

‡Each biomarker was dichotomized into "high" and "low" based on study- and sex-specific median values among controls

Table 5. Associations of markers of oxidative stress and inflammation with incident, sporadic colorectal adenoma

Biomarker‡	Cases	Controls	OR (95% CI)†	p-value
FIP				
Low	39	76	1.0	0.03
High	80	79	1.89 (1.08 – 3.30)	
Log (continuous)	119	155	1.38 (0.79 – 2.38)	
FOP				
Low	44	97	1.0	0.02
High	82	94	1.82 (1.11 – 2.99)	
Log (continuous)	126	191	1.32 (0.94 – 1.87)	
CRP				
Low	55	102	1.0	0.14
High	84	99	1.45 (0.88 – 2.40)	
Log (continuous)	139	201	1.14 (0.97 – 1.33)	

Abbreviations: OBS = oxidative balance score; OR = odds ratio; CI = confidence interval; FIP = F_2-isoprostanes; FOP = fluorescent oxidation products; CRP = C reactive protein

†Adjusted for age, race, sex, body mass index (BMI), total energy intake, plasma cholesterol, and family history of colorectal cancer in a first degree relative, hormone replacement therapy (among women), dietary fiber, physical activity, and study (MAP I or MAP II)

*Total number of subjects in the model is lower due to missing covariate data

‡Each biomarker was dichotomized into “high” and “low” based on sex-specific median values among controls

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