Published in final edited form as:
Ann Epidemiol. 2010 December ; 20(12): 955–957. doi:10.1016/j.annepidem.2010.08.011.

Combined measure of pro- and anti-oxidant exposures in relation to prostate cancer and colorectal adenoma risk: an update

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Keywords

prostate cancer; colorectal adenoma; oxidative balance score

Introduction

The role of oxidative stress as both initiator and promoter of carcinogenesis is supported by a considerable body of basic science literature,[1, 2] but the associations with individual pro- and antioxidant agents are generally weak and inconsistent.[3] We previously proposed an oxidative stress score (OSS) in which high and low pro-oxidant exposures were assigned values of 0 and 1, respectively, and high and low antioxidant exposures were assigned values of 1 and 0, respectively.[4] Individual points for all exposures were then summed to calculate the overall OSS.

We illustrated this approach by using data from two previously-conducted case-control studies of two different neoplasms – sporadic colorectal adenoma and prostate cancer – both repeatedly linked to oxidative stress in mechanistic studies.[5–8] Using an OSS of <2 as reference, the multivariate-adjusted odds ratio (OR) for colorectal adenoma was 0.64 with a 95% confidence interval from 0.33 to 1.24 for a score of 3–6, and 0.45 (95% CI, 0.21–0.99) for a score of >7. The corresponding ORs (95% CIs) for prostate cancer were 0.29 (0.12–0.71) for an OSS of 3–6 and 0.28 (0.28–0.82) for an OSS of >7. Analyses using OSS as a continuous variable yielded findings of a borderline significant 10% decrease in risk for each additional OSS point in both studies: OR of 0.90 (0.79–1.01) for colorectal adenoma and 0.90 (0.77–1.04) for prostate cancer.[4]

In the present study we extend our previous analysis by substituting questionnaire-based measures with systemic biomarkers of pro- and anti-oxidant exposures. As reviewed elsewhere,[9] there are three main reasons for using nutritional markers instead of self-reports:

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1) markers of nutrient status can be measured with less error; 2) for some nutrients, dietary data are inadequate because of limitations in food-composition data; and 3) unlike nutritional intake estimates from questionnaires, biomarkers serve as integral measures of intake, absorption, and metabolism of the nutrients.[9]

Methods

As in our previous publication,4 for the current analysis we used data from two previously conducted, methodologically different case-control studies: a colonoscopy-based study of incident, sporadic colorectal adenoma (Markers of Adenomatous Polyps, or MAP), and a population-based study of incident prostate cancer (Markers of Prostate Cancer, or MPC). These studies were described in detail previously.10–13 Both studies administered food frequency questionnaires (FFQ). In addition to questionnaires, the MPC data included α-tocopherol and β-carotene plasma levels, which were used in the original score.

Herein we now use the term 'oxidative balance score' (OBS) as proposed by van Hoydonck *et al.* (2002)14 to reflect the hypothesized beneficial effect of higher score values. Whenever possible we use biomarkers instead of questionnaire data; however, compared to the previous analyses the new score has three notable changes. First, in keeping with our more recent study (using unrelated data),15 the values were divided into tertiles instead of a high-low dichotomy. Second, we were able to include α- and β-carotene (instead of total carotenes) and α- and γ-tocopherol (instead of only α-tocopherol or total vitamin E) as separate OBS components. Third, we followed the recommendation of Mayne *et al.* (2007) that only polyunsaturated fatty acids (PUFA) rather than saturated fat be included in the score.[16]

The OBS for the MAP study included the following components. From questionnaires we used data on PUFA and vitamin C intakes; use of aspirin, selenium supplements, and non-aspirin non-steroidal anti-inflammatory drugs (NSAIDs); and smoking history. Biomarker-based measures included serum ferritin (indicator of iron intake) and plasma concentrations of α- and β-carotene, lutein/zeaxanthin, β-cryptoxanthin, lycopene, and α- and γ-tocopherol. We included the same OBS components for the MPC study except that we used 1) FFQ-based iron intake since there were no serum samples available for ferritin analysis, and 2) urinary selenium concentrations since, unlike the MAP study, urine samples were available on most participants.

Continuous variables were divided into high, medium, and low categories based on tertile values among the controls. Participants whose exposure to a particular pro-oxidant (*e.g.*, serum ferritin) was low (1st tertile) were assigned two points, and those whose exposure to the same pro-oxidant was medium (2nd tertile) or high (3rd tertile) received one or zero points, respectively. For anti-oxidant exposure variables, two points were awarded for the 3rd tertile, one point for 2nd tertile, and zero points for the 1st tertile.

Smoking status was categorized as never (2 points), former (1 point), or current (zero points). For selenium supplements (MAP only), NSAIDs, and aspirin, zero points were assigned to participants who reported no regular use, one point to those with missing data, and two points to those who reported regular use.

The associations between OBS and each outcome were examined using logistic regression models to calculate ORs and 95% CIs. All models controlled for age, race, total energy intake, blood cholesterol, body mass index (BMI), and family history of prostate cancer (MPC) or colorectal cancer (MAP). In addition, the MAP study analyses controlled for sex and (among women) for hormone replacement therapy.

Results

A total of 111 cases and 115 controls in the MAP study, and 97 cases and 226 controls in the MPC study had sufficient information for a full score. The OBS ranged from 1 to 22 among MAP participants and from 3 to 23 among MPC subjects. When OBS was treated as a continuous variable the adjusted OR (95% CIs) for each additional score point after rounding were the same (OR=0.90; 0.83–0.97) for each study. In the categorical analyses in which the OBS was divided into three approximately equal intervals, using the lowest interval as reference (Table 1) the adjusted ORs (95% CIs) for the middle and the highest intervals in the MAP study were 0.62 (0.28–1.38) and 0.34 (0.13–0.88), respectively (p-trend = 0.02). The corresponding results in the MPC study were very similar with an OR of 0.60 (0.31–1.16) for the median interval and 0.34 (0.14–0.86) for the highest interval (p-trend = 0.02). When the OBS variable was dichotomized into approximately equal categories (1–11 versus 12–22 for MAP and 3–12 versus 13–23 for MPC) the adjusted ORs for the higher categories were 0.50 (0.27–0.92) and 0.46 (0.27–0.79) in MAP and MPC, respectively. To assess the impacts of individual OBS components, we re-analyzed the data by removing one factor (e.g., smoking, vitamin C, blood α-tocopherol, or NSAID use) from the score and then including that factor by itself in the model along with the revised OBS. The results showed no evidence that any particular factor alone could completely explain the associations between OBS and the outcomes of interest.

Conclusion

Despite previously discussed limitations of case-control studies such as these,[4, 15] our analyses provide support for the stated hypothesis that combined measures of pro- and anti-oxidant exposures may be associated with oxidative stress-related conditions such as prostate cancer and colorectal neoplasia. Although we are unable to perform a direct side-by-side comparison of associations using questionnaire-based and biomarker-based scores because of the differences in the number and categorization of individual score components, the associations we found for biomarker-based measures of exposure were consistent with those we previously reported for questionnaire-based measures.

Acknowledgments

The funding for this publication was provided by the National Cancer Institute (grant R01 CA116795-01) and by the Woodruff Health Sciences Fund

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Table 1

Multivariable-adjusted associations[1] of oxidative balance score (OBS) with incident, sporadic colorectal adenoma (MAP study) and incident prostate cancer (MPC study)

MAP study				
OBS (range 1 – 22)	**Cases (n)**	**Controls (n)**	**OR[2]**	**95% CI[3]**
1 – 7	28	15	1.0	ref
8 – 14	60	60	0.62	0.28 – 1.38
15 – 22	23	40	0.34	0.13 – 0.88
			P-trend = 0.02	
MPC study				
OBS (range 3 – 23)	Cases (n)	Controls (n)	OR[2]	95% CI[3]
3 – 9	24	37	1.0	ref
10 – 16	62	145	0.60	0.31 – 1.16
17 – 23	11	44	0.34	0.14 – 0.86
			P-trend = 0.02	

[1] All results adjusted for age, race, body mass index (BMI), total energy intake, blood cholesterol; MAP results also adjusted for sex, hormonal replacement therapy (in women), and family history of colorectal cancer in a first degree relative; MPC results also adjusted for family history of prostate cancer

[2] OR, odds ratio

[3] 95% CI, ninety-five percent confidence interval