Published in final edited form as:

Ann Epidemiol. 2014 June ; 24(6): 475–478.e4. doi:10.1016/j.annepidem.2014.02.015.

Oxidative balance score and risk for incident prostate cancer in a prospective U.S. cohort study

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Abstract

Purpose—Oxidative stress is defined as an imbalance between pro-oxidants and antioxidants. Previous research found that a single comprehensive oxidative balance score (OBS) that includes individual pro-and anti-oxidant exposures may be associated with various conditions (including prostate cancer) in the absence of associations with the individual factors. We investigated an OBS-incident prostate cancer association among 43,325 men in the Cancer Prevention Study II Nutrition Cohort.

Methods—From 1999–2007, 3386 incident cases were identified. Twenty different components, used in two ways (unweighted or weighted based on literature reviews), were incorporated into the OBS, and the resulting scores were then expressed as three types of variables (continuous, quartiles, or six equal intervals). Multivariable-adjusted rate ratios were calculated using Cox proportional hazards models.

Results—We hypothesized that the OBS would be inversely associated with prostate cancer risk; however, the rate ratios (95% confidence intervals) comparing the highest with the lowest OBS categories ranged from 1.17 (1.04–1.32) to 1.39 (0.90–2.15) for all cases, 1.14 (0.87–1.50) to 1.59 (0.57–4.40) for aggressive disease (American Joint Committee on Cancer stage III/IV or Gleason score 8–10), and 0.91 (0.62–1.35) to 1.02 (1.02–1.04) for nonaggressive disease.

Conclusions—Our findings are not consistent with the hypothesis that oxidative balance–related exposures collectively affect risk for prostate cancer.

Keywords

Oxidative stress; Prostatic neoplasms; Cohort study

Introduction

Prostate cancer is the second leading cause of cancer death among men in the United States [1]. Migration studies [2] strongly suggest that environmental factors play a role in prostate carcinogenesis. One proposed mechanistic link is oxidative stress [3]. Oxidative stress is an imbalance in pro- and anti-oxidants, which results in macromolecular damage and disruption of redox signaling and control [4]; this can lead to mutagenesis and subsequent carcinogenesis [5].

Environmental exposures such as smoking and alcohol consumption act as pro-oxidants and can increase reactive oxygen species (ROS) generation and inflammation [6]. Antioxidants, such as vitamin E, act as free radical scavengers [7]. Other nutrients indirectly reduce oxidative stress through anti-inflammatory properties (omega-3 fatty acids) [8].

Although antioxidants can reduce cell proliferation and oxidative DNA damage *in vivo* and *in vitro*, findings from observational epidemiologic studies that investigated individual antioxidants and prostate cancer risk have been inconsistent [7], and clinical trials of antioxidants as chemopreventive agents have produced null results [9]. Other studies found that nutrients act synergistically, and combined factors can be more strongly associated with disease risk than are individual nutrients [10] leading us to believe that multiple pro- and antioxidant exposures incorporated into a composite measure of oxidative balance may be more strongly associated with prostate cancer risk than would be any single factor [11].

In the present study, in follow-up to our pilot case-control study in which we found an inverse association between oxidative balance score (OBS) and prostate cancer risk [11], we investigated the association in a large prospective U.S. cohort study.

Methods

The men in this analysis were participants in the Cancer Prevention Study II Nutrition Cohort, designed to assess associations of dietary and lifestyle factors with cancer incidence [12]. For the present study, follow-up was from 1999 until the date of diagnosis of prostate cancer, death, date of the last returned survey, or June 30, 2007. Our analysis begins with 1999 because this was when a more comprehensive 152-item semiquantitative modified Willet Food Frequency Questionnaire (FFQ) was administered. Participants reported diet in the previous year. Follow-up questionnaires were sent every 2 years to update exposure information. After excluding participants with no dietary information ($n = 9518$), were lost to follow-up ($n = 1570$), had a history of prostate cancer ($n = 6100$) or cancer other than nonmelanoma skin cancer ($n = 5468$) at before 1999, had incomplete or improbable FFQ data or did not report lifestyle OBS components ($n = 3668$), and those with unverified self-reported prostate cancer ($n = 82$), a total of 43,325 men were available for analysis. We identified and verified 3386 incident cases of prostate cancer between 1999 and June 30,

2007. This included cases verified via medical records ($n = 2720$) or linkage to cancer registry data ($n = 666$).

The OBS comprised 20 components, selected based on *a priori* knowledge about their relation to oxidative stress. These included dietary antioxidants alpha- and beta-carotene, beta-cryptoxanthin, zinc, lutein, lycopene, vitamins C and E, omega-3 fatty acids, flavonoids and glucosinolates, and selenium (supplements); dietary pro-oxidants omega-6 fatty acids, iron, and saturated fat, as well as lifestyle or medication-related antioxidant (physical activity and nonsteroidal anti-inflammatory drugs use) and pro-oxidant (smoking, alcohol and overweight/obesity) factors. The OBS component assignment scheme is shown in Supplementary Table 1. The points assigned to each component were summed to create the overall OBS. In the analyses of associations with prostate cancer, the score was used in several ways as (1) a continuous variable, (2) quartiles, and (3) equal interval categories. The cutoffs were determined using the distribution of the OBS within the analytical cohort (specific cutoffs in Tables 2 and 3). Assessing the OBS using quartiles and equal interval categories allowed for examination of particularly low and high scores.

OBS components were included in the score using the following two approaches: (1) equal weights and (2) weighted according to the reported associations with prostate cancer risk. For each OBS component, we identified comprehensive reviews or meta-analyses that summarized the magnitude of their associations with prostate cancer. If no published reviews were found, we conducted our own meta-analysis of published studies of nutrients and prostate cancer.

The weights for pro-oxidants were the pooled adjusted relative risks derived from published studies, whereas weights for the antioxidant OBS components were calculated using the inverse adjusted relative risks estimates (Supplementary Table 1).

Multivariable-adjusted rate (hazard) ratios (HRs) and their corresponding 95% confidence intervals (CIs) were calculated using Cox proportional hazards models. All models were tested for proportional hazards assumption violations using the likelihood ratio test. Models were examined for collinearity among independent variables. Interactions between OBS and each covariate were assessed using the likelihood ratio test. All analyses were conducted using SAS statistical software version 9.2 (SAS institute, Cary, NC).

The association between the OBS and prostate cancer risk was examined using each OBS version after adjusting for age, total energy intake, total (dietary plus supplemental) calcium intake, total vitamin D intake, total folate intake, race (white, black, and other), education (less than high school, high school graduate, some college, college graduate, and missing), family history of prostate cancer in a first-degree relative (no and yes), cholesterol lowering drug use (never, former, current, and missing), finasteride use (never, former, current, and missing), and history of prostate cancer screening (ever, never, and unknown). These potential confounders were selected based on evidence in the literature and other *a priori* considerations.

Associations with the OBS were also examined separately for aggressive and nonaggressive prostate cancer, after adjusting for the same covariates. Prostate cancer was classified as

aggressive based on either an advanced stage (American Joint Committee on Cancer stage III/IV) or high grade (Gleason score of 8–10) as reported previously [13]. In addition, a series of sensitivity analyses examined the impact of individual OBS components by removing each component from the score and controlling for it in the model as a covariate.

Results

The baseline characteristics of all participants by OBS quartile are presented in Table 1. There were no significant differences at baseline in age, race, family history of prostate cancer in a first-degree relative, total energy intake, or finasteride use by OBS quartile. The proportion of participants who were college educated, had undergone Prostate-specific antigen screening, and was currently using cholesterol-lowering drugs increased with an increasing OBS score. Total calcium, vitamin D, and folate intake also increased with an increasing OBS score.

Table 2 shows the association between prostate cancer risk and the OBS with equally weighted and weighted components. For equally weighted components, after adjusting for covariates, a statistically significant, but modest, positive association was found when the OBS was assessed as a continuous variable (HR = 1.008 95% CI, 1.002–1.013). Prostate cancer incidence was 17% higher in the highest versus the lowest OBS quartiles (HR = 1.17; 95% CI, 1.04–1.32; $P_{\text{trend}} = .01$). A similar analysis using equal interval categories yielded a corresponding HR of 1.39 (95% CI, 0.90–2.15; $P_{\text{trend}} = .007$; Table 2).

The results of the weighted analyses were essentially identical to those obtained without weighting: the HRs were 1.007 (95% CI, 1.002–1.012) for the OBS treated as a continuous variable, 1.15 (95% CI, 1.03–1.30) when comparing the lowest with the highest OBS quartile ($P_{\text{trend}} = .02$), and 1.41 (95% CI, 0.90–2.21) when comparing the lowest with the highest category in the equal interval analyses ($P_{\text{trend}} = 0.01$).

Table 3 shows that the associations for aggressive and nonaggressive tumors were similar to that for all prostate cancer cases combined (Table 2). The weighted results were not substantially different from the unweighted results (data not shown). In the sensitivity analyses assessing the impact of individual OBS components, (by removing each component from the score and including it as a covariate) all Odds Ratio estimates were within 5% of the original model result (data not shown, available on request).

Discussion

The results from this prospective cohort study provide no evidence that an OBS is inversely associated with prostate cancer risk. In fact, the data suggest that persons with a higher OBS may be at increased risk of developing (or being diagnosed with) prostate cancer. Separating aggressive and nonaggressive prostate cancer cases did not appreciably change the observed associations. These results are not consistent with the hypothesis that a presumably beneficial balance of pro- and anti-oxidant exposures protects against prostate carcinogenesis.

Other studies examined the association between OBS and prostate cancer, with conflicting results. In the Markers of Prostate Cancer case control study, two different methods were used to measure OBS components, a FFQ-based method [11] and a combined FFQ and biomarker-based method [14]. For both methods, a higher OBS was inversely associated with prostate cancer, although a statistically significant trend was found with the biomarker-based method [11,14]. In the large Canadian Study of Diet, Lifestyle, and Health cohort study, Agalliu *et al.* [15] found no association between an OBS and prostate cancer risk with increasing OBS quintiles. Among these three studies and the present study, different categorizations of the components for inclusion into the OBS were used, and, although unlikely, may be related to the discrepant findings across the studies.

Our study examined a more comprehensive list of OBS components than did previous studies, which did not include α -carotene, zinc, flavonoids, or glucosinolates, all of which may act as antioxidants [16,17]. Our OBS also included physical activity and body mass index. While strenuous physical activity increases ROS production (short term), moderate physical activity promotes antioxidant gene expression by activating Nrf2 [18]. Obesity increases ROS production and adipocytokine expression, inducing inflammation, a cause and a consequence of oxidative stress [19,20]. A growing body of evidence suggests that physical activity and obesity are potential modifiable risk factors for prostate cancer [21,22]. The Agalliu *et al.* and Goodman *et al.* studies used all polyunsaturated fats as a pro-oxidant, whereas we examined the various polyunsaturated fatty acids separately. Omega-3 fatty acids were categorized as antioxidants because they promote the transcription of antioxidant enzymes, whereas omega-6 fatty acids were considered pro-oxidants because they serve as precursors to proinflammatory eicosanoids [23,24]. Furthermore, unlike in the Agalliu study, our analyses were adjusted for family history of prostate cancer, and in contrast to all of the above-referenced previous studies, we also controlled for statin use.

The most distinguishing feature of this study was the number of ways the OBS was constructed and assessed. None of the previous studies compared the results of a weighted and unweighted OBS in relation with prostate cancer risk. The unweighted OBS assumes that each component is equally associated with prostate cancer. Although the literature-based weights account for the different strengths of association, the range of component weights was quite narrow (0.9–1.2), making the weighted and the unweighted results similar.

There may be other methods of weighting OBS components such as weighting OBS based on the effects of these components on oxidative stress measures. Such alternative weighting could be based on associations of OBS components with biomarkers of oxidation such as isoprostanes or disruption of thiol redox circuits as measured by plasma levels of glutathione redox [25].

Other limitations of our study also should be considered. Carcinogenesis is a multiyear process, and it may be that the OBS at the time of measurement may not be related to cancer risk. Although our OBS is the most comprehensive of those used in the three previous prostate cancer studies, it included only extrinsic factors. Intrinsic factors that affect oxidative stress, such as cellular antioxidant enzymes [17], were not included. Moreover,

this cohort included a high proportion of health conscious participants, suggesting that there was insufficient variability in lifestyle to detect an association between the OBS and prostate cancer. Additionally, participants with missing dietary data were excluded from this analysis, which may have led to possible selection bias.

Despite the study limitations and apparent inconsistency with mechanistic evidence, our study affirms that at a population level, pro- and anti-oxidant exposures are unlikely to explain differences in prostate cancer incidence. Prostate cancer is a difficult disease to study, and after much research no modifiable, well-accepted risk factors have been identified. This study, like many before, underscores the enigmatic nature of this disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1
Baseline characteristics of Cancer Prevention Study II men ($n = 43,325$) by OBS quartile

Characteristics	OBS quartile 1	OBS quartile 2	OBS quartile 3	OBS quartile 4
Age at 1999 interview, y, mean (SD)	69.84 (5.69)	70.22 (5.73)	70.45 (5.45)	70.45 (5.77)
Caucasian (%)	98.15	98.06	97.74	97.57
College education or higher (%)	36.83	48.11	55.38	64.82
Family history of prostate cancer in a first-degree relative (%) [*] missing 5680	14.06	13.56	13.77	14.59
Current cholesterol-lowering drug use (%)	23.03	27.72	30.11	32.45
Prostate-specific antigen screening (%)	77.20	82.50	85.65	87.88
Total energy intake, mean (SD) (kcal/d)	1936.11 (604.96)	1901.33 (578.14)	1892.49 (573.93)	1856.77 (551.58)
Total calcium intake, mean (SD) (mg/d) [†]	752.93 (330.55)	857.43 (372.79)	946.68 (408.20)	1112.69(473.24)
Total vitamin D intake, mean (SD) (IU/d) [†]	278.30 (201.74)	363.89 (227.98)	427.07 (242.43)	502.37(253.17)
Total folate intake, mean (SD) (mcg/d) [†]	439.36 (203.33)	567.95 (239.81)	661.92 (260.78)	794.47 (280.46)
Finasteride use (%)	2.15	2.55	2.73	3.20

Note: All nutrients adjusted for total energy intake.

^{*} Self-reported history of recent Prostate-specific antigen screening.

[†] Diet plus supplements.

Table 2
Associations of OBS comprised equally weighted and literature-weighted components with incident prostate cancer in the Cancer Prevention Study II Nutrition Cohort (1999–2007)

OBS Categories	Equally weighted OBS components			Components weighted by literature reviews		
	Number of cases/total	Age-adjusted HR (95% CI)	Multivariable HR* (95% CI)	Number of cases/total	Age-adjusted HR (95% CI)	Multivariable HR* (95% CI)
Continuous Quartiles [†]	3386/43,325	1.008 (1.003–1.012)	1.008 (1.002–1.013)	3386/43,325	1.007(1.003–1.011)	1.007 (1.002–1.012)
1	810/11,570	1.00	1.00	758/10,831	1.00	1.00
2	919/11,678	1.12(1.02–1.23)	1.12(1.01–1.24)	843/10,830	1.11 (1.00–1.22)	1.11 (0.99–1.23)
3	954/9442	1.12 (1.02–1.24)	1.12(1.01–1.26)	875/10,832	1.14(1.03–1.25)	1.14(1.03–1.28)
4	903/10,635	1.18(1.08–1.30)	1.17(1.04–1.32)	910/10,832	1.17(1.06–1.29)	1.15(1.03–1.30)
$P_{trend}^{\S}$		<.001	.01		.002	.02
Equal intervals [‡]						
1	92/1303	1.00	1.00	65/956	1.00	1.00
2	595/8586	0.97(0.78–1.21)	0.98 (0.77–1.23)	536/7924	1.00 (0.77–1.29)	1.03 (0.78–1.36)
3	1189/15,430	1.08 (0.87–1.33)	1.07 (0.85–1.34)	1188/15,141	1.15 (0.90–1.48)	1.19(0.91–1.55)
4	1073/12,955	1.14(0.92–1.41)	1.15 (0.91–1.45)	1108/13,598	1.18(0.92–1.51)	1.21 (0.92–1.60)
5	403/4703	1.17(0.943–1.46)	1.13 (0.88–1.46)	452/5318	1.22 (0.94–1.58)	1.22 (0.92–1.66)
6	34/348	1.36(0.91–2.01)	1.39 (0.90–2.15)	37/388	1.39 (0.93–2.08)	1.41 (0.90–2.21)
$P_{trend}^{\S}$		<.001	.01		<.001	.01

* Adjusted for age, race, sex, education, family history of prostate cancer in a first degree relative, prostate cancer screening, nonsteroidal anti-inflammatory drugs/aspirin use, total calcium intake, total vitamin D intake, total energy intake, cholesterol-lowering drug use, and finasteride use.

[†] Quartile cutoffs: equally weighted (first = 8–25, second = 26–31, third = 32–36, and fourth = 36–55); weighted (first = 8.1–27.0, second = 27.1–33.2, third = 33.3–39.4, and fourth = 39.5–60.0).

[‡] Equal interval cutoffs: equally weighted (first = 8–16, second = 17–24, third = 25–32, fourth = 33–40, fifth = 41–48, and sixth = 49–55); weighted (first = 8.1–16.9, second = 16.9–25.7, third = 25.8–34.5, fourth = 34.6–43.3, fifth = 43.3–52.1, and sixth = 52.2–60.0).

[§] P_{trend} assessed using category median.

Table 3
Associations of OBS comprised equally weighted components with incident aggressive* and nonaggressive prostate cancer in the Cancer Prevention Study II Nutrition Cohort (1999–2007)

OBS categories	Aggressive		Nonaggressive	
	Number of cases/total	Multivariable HR [†] (95% CI)	Number of cases/total	Multivariable HR [†] (95% CI)
OBS continuous	657/43,325	1.010 (0.991–1.020)	2729/43,325	1.001 (0.995–1.007)
OBS quartiles				
8–25	169/11,570	1.00	649/11,570	1.00
26–31	170/11,678	1.06 (0.84–1.35)	744/11,678	1.06 (0.94–1.19)
32–36	144/9442	0.93 (0.72–1.20)	602/9442	1.00 (0.88–1.13)
36–55	174/10,635	1.14(0.87–1.50)	734/10,635	1.02 (1.02–1.04)
$P_{\text{trend}}^{\ddagger}$		.47		.85
OBS five categories				
8–16	21/1303	1.00	71/1303	1.00
17–26	169/12,116	1.00(0.62–1.61)	686/12,116	0.79 (0.61–1.03)
27–36	293/19,271	0.98 (0.61–1.58)	1238/19,271	0.84 (0.64–1.09)
37–46	164/9801	1.12 (0.67–1.86)	674/9801	0.82 (0.62–1.09)
47–55	10/834	1.59 (0.57–4.40)	60/834	0.91 (0.62–1.35)
$P_{\text{trend}}^{\ddagger}$		.39		.77

* Prostate cancer was classified as aggressive based on either an advanced stage (American Joint Committee on Cancer stage III/IV) or high grade (Gleason score of 8–10).

[†] Adjusted for age, race, sex, education, family history of prostate cancer in a first degree relative, prostate cancer screening, nonsteroidal anti-inflammatory drugs/aspirin use, total calcium intake, total vitamin D intake, total energy intake, physical activity, cholesterol-lowering drug use, and finasteride use.

[‡] P_{trend} assessed using category medians.