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Oxidative stress in prostate cancer patients: A systematic review of case control studies

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Abstract

Background: Prostate cancer (PCa) is the most common cancer in men in Western countries. In-vitro and in-vivo studies suggest that oxidative stress (OS) and antioxidants play a key role in the pathogenesis of chronic diseases including PCa, which is promoted by the production of reactive oxygen species and impaired antioxidant defense mechanisms. This study evaluates the association between OS and men with PCa.

Methods: A literature search was carried out on Medline, PubMed, and ScienceDirect databases, as well as manual searches from inception up to August 2015 using the keywords “Oxidative stress” or “Reactive oxygen species” or “Lipid peroxidation” AND “Prostate cancer.” All studies including data on the measurement of OS biomarkers in PCa were included.

Results: Twenty-three case control studies were retrieved with sample sizes ranging from 15 to 3,613 (6,439 participants in total). Markers of OS were significantly higher in patients with PCa compared with control groups in 21 studies. Two self-controlled case studies comparing OS between PCa cells and non-PCa cells in tissue biopsies found OS to be statistically higher in PCa cancer cells. Results on markers of antioxidant capacity (superoxide dismutase, catalase, glutathione, glutathione reductase, glutathione peroxidase, uric acid, lutein, lycopene, beta carotene, vitamin A, vitamin C, vitamin E, and total antioxidants) were not completely consistent in their association with PCa.

Conclusions: Upregulated OS profiles and impairment of antioxidant defense systems may play a role in men with PCa. To confirm these findings, robust clinical trials utilizing a personalized approach which monitors both OS and antioxidant markers during therapy are warranted.

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1. Introduction

Prostate cancer (PCa) is the most common malignancy and the second leading cause of cancer-related mortality in men in the Western world including Australia and the USA.1 PCa is a multifocal neoplasm, which forms solid tumors of glandular origin. The risk of PCa increases with age but the etiology and pathogenesis are poorly understood.2 Clinically localized PCa is managed with observation, surgery, or radiation treatment; the latter may be combined with androgen-deprivation therapy (ADT). Men with metastatic disease3 are managed almost exclusively with ADT and chemotherapy. The natural history of untreated PCa is still poorly understood, with a wide variation in outcomes in patients with apparently similar cancers based on standard staging and pathological grading.4 Being able to risk stratify individuals with regard to clinical risk is therefore necessary in order to personalize therapeutic strategies, with the aim of minimizing harm to those at low risk, and maximizing the therapeutic armament to those at highest risk. The most widely used biomarker to detect and monitor PCa is prostate-specific antigen. However, strong clinical and preclinical evidence for the role of elevated cellular reactive oxygen species (ROS) and impaired protective mechanisms as a driver of PCa susceptibility5,6 points to the potential clinical utility of these markers. The term oxidative stress has been used to refer to the imbalance between levels of ROS and the protective “antioxidant” mechanisms, resulting in an accumulation of molecular damage in DNA, proteins, and lipids.7

Several clinical studies have demonstrated that increased OS is related to PCa and that some antioxidants have the potential to protect men from PCa.6–8 Multiple in-vitro and in-vivo studies have attempted to elucidate the mechanisms of initiation and progression of PCa in relation to OS.9 Oxidative free radicals caused by multiple factors such as modulation of androgens, inflammation, vitamin D, tumor suppressor protein (p53), antioxidants, and age-related OS may initiate PCa.10 More specifically, in men with PCa it has been suggested that serum androgens promote ROS production and accumulation in PCa cells.10 Androgen-associated redox homeostasis is involved in the signal transduction network of multimeric redox-sensitive transcription factors, enzymes, and epigenetic modifications. Androgens have been shown to promote cancer by increasing reactive oxygen derivatives in tissue.11 Androgen-induced ROS levels in prostate epithelial cells play a critical role in PCa development, progression, and recurrence.12 Further, studies demonstrate that castration or estrogen therapy can lead to the regression of cancer in patients with metastatic PCa.13 Hence, it may be proposed that ADT combined with antioxidant agents may inhibit the progression of PCa.14

To date, no robust randomized controlled trials have been conducted to determine the impact of OS on the risk of developing PCa. A number of studies have attempted to examine the effect of exogenous antioxidants in preventing cancer recurrence and reducing the risk of developing cancer. These studies include lung,15 breast,16,17 colorectal,18 gastrointestinal,19 head and neck,20 leukemia,21 bladder cancer,22 and PCa.23,24 and findings have been inconsistent. Further, there have been reported risks of antioxidants instead of their protective effects. The major limitation of these studies is the lack of consideration of the redox imbalance between oxidation and antioxidants, and the double-edged effect of exogenous antioxidants. Supplementation of exogenous antioxidants in the long-term without monitoring the redox balance can result in beneficial as well as harmful effects depending on the concentration of ROS and the required amounts to maintain or re-establish redox homeostasis in each individual patient.25 Studies suggest that high doses of exogenous antioxidants could paradoxically act as a pro-oxidant by disrupting the redox balance. Thus, the balance between oxidation and antioxidants is a critical issue to consider in an individual patient when assessing the anticaner effect of antioxidants. To our knowledge, there have been no literature reviews examining the association between OS and men with PCa. Furthermore, none of the aforementioned studies have examined the effect of the redox balance in men with PCa. Thus, we conducted a systemic review to clarify the association between OS and men with PCa.

2. Materials and methods

2.1. Search strategy

A literature search was carried out on Medline, PubMed, and ScienceDirect databases from inception up to August 2015 using the keywords “Oxidative stress” or “Reactive oxygen species” or “Free radical” or “Lipid peroxidation” AND “Prostate cancer.” A manual search was also conducted from the retrieved articles. Inclusion criteria were articles that presented data on OS biomarkers, with the full article published in English. Acceptable study designs were case control, nested case control, prospective cohort, or randomized control trials. We excluded articles based on animal and cell models.

2.2. Quality assessment

The quality of each article included in this review was assessed using the Newcastle–Ottawa Scale following the Cochrane Collaboration recommendation.26,27 The Newcastle–Ottawa Scale was developed jointly by the University of Newcastle (Australia) and the University of Ottawa (Canada) to assess the quality of nonrandomized studies to be included in systematic reviews.26 It has been widely used since at least 2004.28 It and the results from several validation studies have been published.29,30 The total score ranges from 0 to 9, with a higher score indicating greater quality.

2.3. Data extraction

A review template was developed specifying the key information about each study (Tables 1 and 2). Two reviewers (B.O. and S.L.) independently applied the inclusion and quality assessment criteria. The two reviewers compared results and resolved any discrepancies in the published articles.

2.4. Statistical analysis for meta-analysis

The meta-analysis was conducted using a random-effects model, which assumes that the effect size has a distribution rather than a fixed value, i.e., the effect size varies within the population. The summary statistic of interest is the standardized mean difference; specifically, the difference in mean for PCa patients compared with healthy controls, divided by the standard deviation pooled across these groups. For each effect size we calculated a 95% confidence interval (CI). Restricted maximum likelihood estimation was used to estimate the model. Analyses were conducted using the metafor package in R 3.2.1 (R Foundation for Statistical Computing, Vienna, Austria). The relevant studies covered a range of oxidation and antioxidants, but these were dominated by malondialdehyde (MDA), superoxide dismutase (SOD), and glutathione peroxidase (GSH-Px), so to allow for comparisons of sufficient size and homogeneity, and to avoid the complication of including multiple outcomes per study, we chose to analyze only MDA, SOD, and GSH-Px. The results presented are an overall effect size and CI, as well as a forest plot. Heterogeneity of effects for each outcome was reported using $I^2$, which represents
| Author, y, country       | Study population | Study design | Sample size | Control group   | Sample collection | Outcome measurement & method | Clinical variables | Results & conclusion                                                                                                                                                                                                 |
|-------------------------|------------------|--------------|-------------|-----------------|------------------|--------------------------|---------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Klotz et al33 1988      | PCa and benign BPH | Case control study | 2 arms     | Total N = 26    | BPH              | Tissue specimens         | Nitric oxide: iNOS iNOS immunostaining | Age, clinical diagnosis | Positive iNOS immunostaining was detected in all sections from patients with prostate carcinoma. The malignant epithelial cells were highly positive. However, round cells in benign tissue stained negative for iNOS. Prostate carcinoma tissue had high iNOS expression, whereas benign tissue did not. Epithelial iNOS expression can be used as a specific immunohistochemical marker for prostate carcinoma. Positive iNOS immunostaining was detected in all samples from all patients; iNOS was detected in both basal epithelial cells and secretory cells of the glandular epithelium. High-grade PIN and prostatic carcinoma samples had more intense iNOS immunostaining than low-grade PIN and BPH samples. In all samples, smooth muscle cells showed weak or moderate iNOS immunoreactivity and endothelial cells showed moderate immunostaining. Nitric oxide generated by iNOS may be involved in prostate tumorigenesis and further studies with immunohistochemical and molecular biology are needed to determine the exact role of iNOS in the pathogenesis of prostatic carcinoma. No increase in either 8-iso-PGF2_ or 15-keto-dihydro-PGF2_ in the urine of patients with PCa compared with in historical normal controls. No increase in either of the eicosanoids during RT to the prostate gland. Plasma MDA levels were significantly higher and plasma vitamin E levels were significantly lower in the patients compared with control patients (P ≤ 0.001 and P ≤ 0.001, respectively). Plasma MDA levels were found to be significantly decreased after antiandrogenic supplementation (P < 0.05). There were no significant differences in erythrocyte GSH, GR, GSH-Px and plasma vitamin E levels before and after therapy. (continued on next page) |
| Baltaci et al34 2001    | High-grade prostatic intraepithelial neoplasia (PIN) | Case control study | 4 arms     | Total N = 80    | Tissue samples        | Nitric oxide: iNOS iNOS immunostaining |                      |                                                                                                                                                    |
| Camphausen et al31 2004 | PCa              | Case control study | 2 arms     | Total N = 15    | Historical data     | Urine sample            | Oxidative stress: 8-iso-PGF2 and 15-keto-dihydro-PGF2 Student t test | ND                   |                                                                                                                                                    |
| Iynem et al35 2004      | Metastatic PCa patients | Prospective case control study | 2 arms     | Total N = 41    | Healthy volunteer nonsmokers | Blood samples          | Oxidative stress: MDA Antioxidant status: GSH, GSH-Px, GR, GST, and Vit E | ND                   |                                                                                                                                                    |
Table 1 (continued)

| Author, y, country | Study population | Study design | Sample size | Control group | Sample collection | Outcome measurement & method | Clinical variables | Results & conclusion |
|--------------------|------------------|--------------|-------------|---------------|------------------|-------------------------------|-------------------|---------------------|
| Yilmaz et al36 2004 Turkey | Newly diagnosed PCa and Treated benign prostatic nodular hyperplasia (BPNH) patients | Case control study with 3 arms | Total N = 121 Case PCA (n = 21) 68 y BPNH (n = 50) 64 y Control (n = 50) 66 y | Age, sex, BMI matched healthy participants | Blood samples | Oxidative stress: MDA Antioxidant status: Cu, Zn, Cu-Zn SOD, and GSH-Px Data analysis: The Mann—Whitney U-test | PSA level, transrectal ultrasonography, and biopsy Gleson sum. | Erythrocyte GST activity was found to be significantly elevated after therapy when compared with baseline (P < 0.01). MDA levels were higher and the antioxidant activity and Zn levels lower in the PCA groups compared to healthy control and BPNH groups (P < 0.001). MDA levels were higher in the advanced PCA group compared to localized PCA group (P < 0.001). MDA and SOD were associated with Gleason score in PCA patients. MDA levels can be used in the diagnosis and follow-up of PCA. The ratio of urinary 8-OHdG-to-Cr (8-OHdG/Cr) was significantly higher in patients with PCA compared to controls (P < 0.05). Only age was significantly associated with 8-OHdG/Cr in PCA cases among several clinico-pathological factors including serum PSA, clinical T stage, metastasis and Gleason score. No significant differences in urinary 8-OHdG/Cr in 42 patients before and after radical prostatectomy. Urinary 8-OHdG/Cr in 40 patients was significantly lower (P < 0.05) after hormonal therapy compared with before hormonal therapy. Changes in PSA after initial treatment were not related to changes in urinary 8-OHdG/Cr. Oxidative stress may be involved in an early event in PCA development and androgen suppression without surgical removal of PCA is capable of decreasing oxidative DNA damage. Androgen ablation therapy combined with antioxidant agents could be a novel therapeutic strategy for inhibiting the progression of PCA. Significantly higher levels of MDA and GSTs activities were observed in the serum (P < 0.005) of PCA and BPH cases compared to controls. GSH concentration and GSH-Px activities were significantly lower in PCAs compared with controls (P < 0.05). |
| Miyake H37 2004 Japan | PCa limited to prostate stage (T1-T4) | Prospective case control study 2 arms | Total N = 115 Case (n = 82) Control (n = 33) | Age-matched healthy participants | Urine samples | Oxidative Stress: DNA damage: Urinary 8-OHdG and creatinine (Cr) Serum prostate Specific antigen (PSA) Data analysis: The Mann—Whitney U-test | Serum PSA, clinical stage, metastasis, biopsy, Gleason score | |
| Srivastava38 2005 India | PCa and benign BPH | Case control study 3 arms | Total N = 107 Case (n = 47) 62 y BPH (n = 55) 60 y Control (n = 25) 61 y | Healthy men | Blood samples | Oxidative stress: MDA Antioxidant status: GST from serum, GSH-Px and GSH Data analysis: One-way ANOVA | ND | |
and Linear regression model

**Oxidant–antioxidant imbalance may be one of the major factors responsible for the development of PCA and benign prostate hyperplasia.**

- PCA patients had higher concentrations of MDA ($P < 0.05$) and lower circulating concentrations of lutein ($P < 0.05$), lycopene ($P < 0.001$) and β-carotene ($P < 0.05$).
- Patients with metastatic PCAs, when compared to patients with localized disease, had a higher Gleason score ($P < 0.01$) and more hormonal treatment, but lower concentrations of PSA ($P < 0.05$), α-tocopherol ($P < 0.05$), retinol ($P < 0.01$), lutein ($P < 0.05$), and lycopene ($P < 0.01$).
- PCA PSA correlated with the concentrations of the lipid peroxidation product, MDA ($r_s = 0.353, P < 0.002$) in PCA cases.
- CRP was not correlated with the vitamin antioxidants or MDA.
- In contrast, there was a negative correlation between MDA concentrations and both lutein ($r_s = -0.263, P < 0.020$) and lycopene ($r_s = -0.269, P < 0.017$).
- The lower concentrations of carotenoids, in particular lycopene, reflect disease progression rather than the systemic inflammatory response in patients with PCA.
- Increased lipid peroxidation (TBARS) with a concomitant decrease in GSH-Px and CuZn-SOD activities in the PCA patients versus controls ($P < 0.001$) and versus BPH patients ($P < 0.05$). Zn levels were lower in PCA patients versus controls ($P < 0.01$) with no significant changes between BPH and the cancer group.
- No significant differences were observed in the erythrocyte CAT and Cu levels among any of the studied groups.

- Vitamin A, C, and E levels were significantly lower and MDA levels significantly higher ($P < 0.001$) in patients with PCAs compared with controls.
- Se and Zn levels were significantly lower, and levels of Ni, Co, and Cu were higher ($P < 0.001$) in patients with PCAs compared with controls.

(continued on next page)
| Author, y, country | Study population | Study design | Sample size | Control group | Sample collection | Outcome measurement & method | Clinical variables | Results & conclusion |
|-------------------|-----------------|--------------|-------------|---------------|-----------------|----------------------------|-------------------|---------------------|
| Surapanenet al\[^42\] | PCa | Case control study | 2 arms | Total N = 60 | Healthy men | Blood samples | Oxidative stress: MDA | ND |
| 2006 India | | | Case (n = 30) Control (n = 30) | | | | Antioxidant status: GSH, SOD, and GST | |
| | | | | | | Data analysis: Student t test | |
| Yossepowitch\[^43\] | PCa completed either radical prostatectomy or receiving androgen deprivation therapy | Case control study | 4 arms | Total N = 104 | Age matched healthy men | 12-h fasting blood sample | Oxidative stress: MDA | PSA, biopsy, Gleason score, age, smoking history, vitamin supplements, and lipid profiles |
| 2007 Israel | | | Case: (n = 79) Localized undergoing radical prostatectomy (N = 42) 63 y Metastatic disease receiving androgen deprivation therapy (n = 37) HRPC (n = 15) | HRPC (n = 22) 63 y Control (n = 25) 72 y | | | Antioxidant status: Uric acid, vitamin E (β-tocopherol), copper induced peroxidation (CucCl\(_2\)), nd Vmax (OD\(_{246}\)) OD\(_{max}\) | |
| | | | | | | Data analysis: ANOVA on log transformed data. Univariate binary logistic regression analyses | |
| | | | | | | Ordinal logistic regression model | |
| | | | | | | | Compared to control subjects, patients with localized PCa had no difference in oxidative stress indexes, whereas those with metastatic disease had a shorter lag preceding oxidation and increased MDA (P < 0.03), each reflecting a state of high oxidative stress. |
| | | | | | | | In patients with PCa, the probability of disease progression from localized to advanced state increased with a shorter lag preceding oxidation (P < 0.001), increased MDA (P < 0.03) and decreased uric acid (P < 0.04). |
| | | | | | | | Patients with advanced PCa had higher circulating markers of oxidative stress compared with controls, as determined by increased susceptibility of serum lipids to peroxidation. This association was not detected in patients with localized cancer and is not attributable to altered levels of β-tocopherol. |
| | | | | | | | Plasma MDA levels were significantly higher in patients with both BPH and carcinoma of prostate. |

\[^42\] Fe levels were not significantly different in patients compared with controls. 
\[^43\] The administration of vitamins A, C, and E, and Se and Zn may be beneficial in the prevention and treatment of human PCa. 
\[^44\] Erythrocyte MDA & SOD levels were significantly higher in patients with carcinoma of prostate compared with controls (P < 0.01 and P < 0.001 respectively). 
\[^45\] GSH levels were significantly lower in patients with carcinoma of prostate compared with controls (P < 0.01). 
\[^46\] No significant change was observed in GST compared with controls. 
\[^47\] Oxidative stress may be involved in PCa as evidenced by higher MDA levels and lower GSH levels. 
\[^48\] Increased activity of antioxidant enzyme may be a compensatory regulation in response to oxidative stress.
Prostate compared to controls ($P < 0.001$ and $P < 0.001$ respectively).

- **SOD activity in blood erythrocytes showed that increase in SOD activity was sharply manifested in BPH (~1.3 times, $P < 0.001$), compared with the control group, while in PCa, activity of the enzyme decreases versus control group (~1.6 times, $P < 0.0001$).**
- CAT activity remained unaltered in BPH and was slightly declined in PCa ($0.01$).
- Cp was increased in both kind of tumors, especially in PCa ($0.0001$), as well as GSH ($0.0001$) and GR ($0.0001$).
- GSH-Px was sharply increased in BPH and reduced in PCa ($0.0001$).

The development of BPH reflects relatively weakly on blood system as activity and content of antioxidant enzymes do not reveal marked changes. In contrast to PCa, which show the reduced functional state of blood antioxidant enzyme system.

**Akinloye et al.**

**PCa**

Case control study

4 arms

| Total N | Case | Healthy volunteers | Blood samples |
|---------|------|--------------------|---------------|
| 170     | 120  | PSA concentration  | PSA, ALT, AST, Total bilirubin |
|         |      | < 3.0 ng/mL        | Microsomal membrane |

Oxidative stress: SOD, CAT, reduced GSH, Uric acid and Vitamin C and E.

Data was analysis: One-way ANOVA followed by the post-hoc Duncan multiple range test for analysis of biochemical data.

Serum LPO, total bilirubin and alkaline phosphatase (ALP) were significantly elevated ($P < 0.05$) in patients with PSA >11 ng/mL. More specifically, total bilirubin, ALP and LPO levels were elevated by 75%, 60% and 107% in subjects with PSA at 11–20 ng/mL, and by 167%, 105%, 98% in patients with PSA >20 ng/mL, respectively.

- SOD and CAT activities were lower ($P < 0.05$) in all cancer patients.
- Subjects with a PSA level of 11–20 ng/mL and PSA >20 ng/mL had significantly lower uric acid and GSH levels ($P < 0.05$).
- A significant reduction ($P < 0.05$) in plasma vitamin C and E levels was observed in these patients. The levels of vitamins C and E decreased by 27% and 77% in subjects with PSA >20 ng/mL, and by 25% and 47% in subjects with a PSA level of 11–20 ng/mL, respectively.
- Depletion of antioxidants was found in PCa patients, and an inverse relationship between antioxidants and PSA values.
- A similar pattern of alteration in the oxidative/ nitrosative stress-related (continued on next page)
| Author, y, country | Study population | Sample size | Study design | Outcome measurement & method | Clinical variables | Results & conclusion |
|--------------------|------------------|-------------|--------------|-------------------------------|--------------------|---------------------|
| 2009 Turkey         | Case (n = 107)   |             | Control (n = 38) | NO2 - /NO3– and cGMP         | Smoking, family   | parameters was found in both, Macedonian and Turkish studied samples: higher MDA concentrations in PCA patients versus controls and BPH Groups (P < 0.001) and lower GSH-Px (P < 0.001) and CuZn-SOD (P < 0.01) activities in PCA patients versus controls and BPH groups. |
|                    | BPH (n = 167)    |             |              | Antioxidant status: CuZn-SOD, GSH-Px, and CAT | history of cancer, Gleason score and PSA |                   |
|                    |                  |             |              | Data analysis: ANOVA and Tukey –Kramer multiple comparisons test a posteriori or Kruskal–Wallis nonparametric test, Dunn's multiple comparisons test |                   |                   |
| 2010 USA           | PCa               | Biopsy negative | Biopsy and blood samples | Oxidative stress: Carboxyl | Age, race, education, physical activity, smoking, fruit intake, vegetable intake, and family history of PCA, and BMI |                   |
| Hoque et al        | Nested case-control design 2 arms | Total n = 3,613 |              |                   |                   | No significant associations between PCA risk nor its aggressiveness and serum levels of oxidized protein as measured by protein carbonyls. |
| Battist et al 2011 | PCA               | Age matched-healthy men | Blood sample | Oxidative stress: MDA and carboxylation Antioxidant status: CAT, SOD, Vitamin C and vitamin E | Metastasis, standard treatment, Gleason score, family history, smoking and alcohol intake |                   |
| Brazil             | Case control study 3 arms | Total N = 110 |              |                   |                   | • TBARS levels and serum protein carboxylation were higher (P < 0.005) in PCA patients than in controls. |
|                    | Case (n = 55) |              | Control (n = 55) |                   |                   | • CAT activity was decreased (P < 0.005) and SOD (P < 0.005) activity was higher in PCA patients when compared with controls. Nonprotein thiol levels were increased, however, serum vitamin C and vitamin E content were reduced (P < 0.05) in PCA patients when compared with controls. |
|                    | Metastatic (n = 23) |              |              |                   |                   | • Different parameters analyzed in PCA patients based on metastasis, treatment and Gleason score showed changes in oxidative stress biomarkers and antioxidant defenses. This may indicate an imbalance in the oxidant/antioxidant status, supporting the idea that oxidative stress plays a role in PCA, moreover, the oxidative profile appear to be modified by bone metastasis, treatment and Gleason score. |
|                    | Non-metastatic (n = 32) |              |              |                   |                   | • Adjusted geometric mean F2-isoprostane levels were higher in patients with PCA |
|                    | Control (n = 55) |              |              |                   |                   | |
| Patients with high grade prostatic | Case control study 3 arms | Total N = 500 | Confirmed biopsy negative | Oxidative stress: F2IP | BMI race, health history, family | |
|                    | HGPIN (n = 140) |              |              |                   |                   | |
Barocas et al 48 2011 USA intraepithelial neoplasia (HGPIN) and PCa 66 y PCa (n = 200) 68 y Control (n = 160) 67 y

Data analysis: Multivariable linear and logistic regression was used

- History and other risk factors (smoke), biopsy, DRE results, current use of NSAIDs and statins, and transrectal ultrasound prostate volume.

- The adjusted odds of high grade prostatic intraepithelial neoplasia (1.82, 95% CI 1.66−2.00) or high grade prostatic intraepithelial neoplasia (1.82, 95% CI 1.68−1.96) than in controls (1.63, 95% CI 1.49−1.78, P < 0.001), but were similar across Gleason scores (P < 0.511).

- Urinary F2-isoprostane provides a biomarker for the role for oxidative stress in prostate carcinogenesis. F2-isoprostanes may also serve to estimate the efficacy of interventions targeting oxidative stress mechanisms in PCa prevention or treatment.

Wozniak et al 49 2012 Poland PCa limited to prostate gland (T1ABCN0M0, T2ABCN0M0Gx, and T1ABCN0M0Gx) Prospective case control study 2 arms Total N = 90 Case (n = 60) 67 y Healthy men. Blood sample Oxidative stress: TBARS
Antioxidant status: GSH-Px, CAT, and SOD
Data analysis: ANOVA

- Erythrocyte GSH-Px in the patients was lower than in healthy subjects by 34% (P < 0.001), 50% (P < 0.001), 30% (P < 0.05), and 61% (P < 0.001), respectively, at all periods.

- No significant differences were found by comparing SOD and CAT in PCa patients with that of controls.

- After 2 y of treatment, the activity of studied enzymes demonstrated a decreasing tendency versus before therapy.

- Blood plasma TBARS concentration was higher than in controls at all periods, while erythrocyte TBARS decreased after 2 y compared with control levels.

- An imbalance of oxidant-antioxidant processes occurs in the course of PCa.

- The therapy did not alter the levels of oxidative stress markers, which may prove its applicability. Two y is too short a period to restore the oxidant–antioxidant balance.

PCa Case control study 2 arms Total N = 537 Case (n = 304) Healthy individuals Blood and urine samples. Oxidative stress: 8-isoPGF2a

- Age, PSA, Gleason score, TNM, hemoglobin (1.82, 95% CI 1.66−2.00) or high grade prostatic intraepithelial neoplasia (1.82, 95% CI 1.68−1.96) than in controls (1.63, 95% CI 1.49−1.78, P < 0.001), but were similar across Gleason scores (P < 0.511).

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- Urinary F2-isoprostane provides a biomarker for the role for oxidative stress in prostate carcinogenesis. F2-isoprostanes may also serve to estimate the efficacy of interventions targeting oxidative stress mechanisms in PCa prevention or treatment.

(continued on next page)
| Author, y, country | Study population | Study design | Sample size | Control group | Sample collection | Outcome measurement & method | Clinical variables | Results & conclusion |
|--------------------|------------------|--------------|-------------|---------------|-------------------|-------------------------------|-------------------|---------------------|
| Brys et al50        | 2013 Poland      |              | 61 y        | Control (n = 233) | 65 y              | Antioxidant status: Urac acid and glucose | hemoglobin, Prostate volume | - A statistically increased level of isoprostanes was present in urine of patients with PCa compared with control group (P < 0.001). |
|                    |                  |              |             |               |                   | Data analysis: Q-Dixon test, Mann–Whitney and Cox regression analysis |              | - The concentration of tested antioxidants (uric acid and glucose) in blood from patients with PCa was also higher than in healthy volunteers (P < 0.001). |
|                    |                  |              |             |               |                   |                              |              | - The correlation between increased amount of UA and lipid peroxidation exists in PCa patients (in all tested groups) (P < 0.001). |
|                    |                  |              |             |               |                   |                              |              | - Correlation between PCa risk and urinary isoprostanes level was analyzed, and a positive association was found (relative risk for highest vs. lowest quartile of urinary isoprostanes = 1.6; 95% confidence interval 1.2–2.4; p for trend = 0.03). |
| Pande et al51       | 2013 India       |              |              | Total N = 80 |                  | Venous blood collection, and the serum was used for various biochemical and hematologic investigations | Serum VEGF, cell proliferation, and oxidative stress levels were significantly higher in patients with prostate carcinoma compared with controls |
|                    |                  | Case control study | Case (n = 40) | Control (n = 40) | 64 y | Oxidative stress: 8-OHdG, protein carbonyls and MDA | Levels of 8-OHdG, protein carbonyls, and MDA were found to be significantly increased with the progression of disease as depicted by increased level in advanced PSA, stage, spread, and Gleason score (P < 0.0001). |
| Kosova et al52      | 2014 Turkey      | Prospective case control study | Total N = 40 | Case (n = 20) | Control (n = 20) | Age matched BPH | Oxidative stress: 8-OHdG and MDA | Serum VEGF level and cell proliferation index were significantly associated with PSA, stage, spread and Gleason score. |
|                    |                  |              |              |               |                   | Blood sample | Caspase-3 | VEGF and cell proliferation index correlated with increase in levels of oxidative stress markers. |
|                    |                  |              |             |               |                   |                              | Age, sex, weight, and height | All indexes of oxidative stress, angiogenesis, and cell proliferation share a significant negative correlation with total antioxidant status. |
|                    |                  |              |             |               |                   |                              |              | - In PCa patients, MDA and DNA damage levels were significantly higher but caspase-3 levels were significantly lower compared to levels in benign prostate hyperplasia (P < 0.05). |
|                    |                  |              |             |               |                   |                              |              | - Altered pro-oxidant, DNA damage levels may lead to an increase in oxidative damage and may consequently play an important role in prostate carcinogenesis. |
At baseline, cases had similar age, body mass index, proportion of family history of PCa, history of hypertension, history of diabetes, no. of smokers, and plasma glucose levels compared with controls. Levels of plasma CML were significantly higher in cases \( P < 0.05 \) than in controls (182 vs. 152 mg/mL, an increase in CML equivalent to 1 standard deviation was associated with an increased risk of incident PCa (relative risk, 1.79; 95% confidence interval, 1.00–3.21) and accounted for approximately 8% variance of PCa risk compared with controls. Levels of plasma CML were not associated with higher incidence of PCa.

3. Results

3.1. Study characteristics

Twenty-three case control studies were identified (Fig. 1). In 23 studies, the total number of participants was 6,377 of which 3,558 were PCa cases. Seven studies were undertaken in Turkey; three studies each in India and USA; two studies in Poland; one study each in Brazil, Georgia, Germany, Japan, Nigeria, Sweden, and the UK. All study participants were recruited from urology clinics. Sample sizes ranged from 15 to 3,163. \(^ {31,32} \) The mean age of participants ranged from 60 years to 74 years. Twenty-three studies were conducted using a case control study design, 19 were case control studies, two were prospective, one was nested, and one was a subset of the Nashville Men’s Health study.

Comparative and control groups varied. Two self-controlled case studies compared oxidation status with the biopsy specimens of PCa cells and non-PCa cells. \(^ {15,16} \) Twenty-one case control studies compared oxidation status between patients with PCa and healthy volunteers. Studies included two arms \((n = 11)\), three arms \((n = 7)\), or four arms \((n = 3)\). One study used historical data as the control group, two studies used men with benign prostate hyperplasia as the comparator, two studies used a negative biopsy, and 18 studies used age-matched healthy men as the control group.

3.2. Oxidative stress and antioxidant status in PCa

Of 23 studies, 21 studies reported at least one of the markers of OS to be significantly higher in patients compared with controls while two studies reported no significant difference. OS was analyzed on biopsy \((n = 2)\), urine \((n = 2)\), blood \((n = 16)\), and both urine and blood \((n = 3)\) samples of participants (Tables 1 and 2). Fifteen studies measured both OS and antioxidant values whilst eight studies measured OS only. OS value was measured based on lipid peroxidation \((n = 19)\), protein oxidation \((n = 9)\), and both lipid and protein peroxidation \((n = 5)\). Eight OS biomarkers were identified among 23 studies. Most studies \((n = 14)\) measured MDA while nine studies used different biomarkers including 8-hydroxy-2’-deoxyguanosine \((n = 8)\), uric acid \((n = 1)\); lycopene \((n = 2)\); vitamin C \((n = 1)\); beta-carotene \((n = 1)\); vitamin A \((n = 1)\); vitamin E \((n = 1)\); and total antioxidants \((n = 1)\). Twelve studies measured antioxidant values based on more than two indicators. Three studies measured antioxidant values based on only one indicator. Seven studies reported GSH-Px values to be low in patients with PCa. The values of six other antioxidant indicators \((\text{CAT}, \text{GSH}, \text{GR}, \text{SOD}, \text{uric acid}, \text{and vitamin E})\) were more variable, but tended to be lower in patients compared with the control group. Conversely, two antioxidant indicator values \((\text{GST} \text{ and bilirubin})\) were higher in patients.
|                          | Lipid peroxidation | Protein peroxidation | Antioxidant indicators | Exogenous antioxidant |
|--------------------------|--------------------|----------------------|------------------------|-----------------------|
|                          | MDA                | NO\(_2^\)\,NO\(_3^\)\,\, 8-OHdG | DNA damage | Carboxylation | Glycation (CML) | CAT | GSH | GR | GSH-Px | GST | SOD | Bilirubin | Uric acid | Lutein | Lycopene | Vit A | Vit C | Vit E | Total antioxidant (TAS) |
| Klotz et al 1988         |                    |                      |                        |                       |               |      |      |      |       |      |      |            |           |        |          |      |      |      |                      |
| Baltaci et al 2001       |                    |                      |                        |                       |               |      |      |      |       |      |      |            |           |        |          |      |      |      |                      |
| Camphausen et al 2004    |                    |                      |                        |                       |               |      |      |      |       |      |      |            |           |        |          |      |      |      |                      |
| Lynem et al 2004         |                    |                      |                        |                       |               |      |      |      |       |      |      |            |           |        |          |      |      |      |                      |
| Yilmaz et al 2004        |                    |                      |                        |                       |               |      |      |      |       |      |      |            |           |        |          |      |      |      |                      |
| Miyake H 2004            |                    |                      |                        |                       |               |      |      |      |       |      |      |            |           |        |          |      |      |      |                      |
| Srivastava et al 2005    |                    |                      |                        |                       |               |      |      |      |       |      |      |            |           |        |          |      |      |      |                      |
| Almushatet al 2006       |                    |                      |                        |                       |               |      |      |      |       |      |      |            |           |        |          |      |      |      |                      |
| Aydin A et al 2006       |                    |                      |                        |                       |               |      |      |      |       |      |      |            |           |        |          |      |      |      |                      |
| Ozmen et al 2006         |                    |                      |                        |                       |               |      |      |      |       |      |      |            |           |        |          |      |      |      |                      |
| Surapaneni et al 2006    |                    |                      |                        |                       |               |      |      |      |       |      |      |            |           |        |          |      |      |      |                      |
| Yossepowitch et al 2007  |                    |                      |                        |                       |               |      |      |      |       |      |      |            |           |        |          |      |      |      |                      |
| Kotrikadzet al 2008      |                    |                      |                        |                       |               |      |      |      |       |      |      |            |           |        |          |      |      |      |                      |
| Akinloye et al 2009      |                    |                      |                        |                       |               |      |      |      |       |      |      |            |           |        |          |      |      |      |                      |
| Arsova-Sarafinovsk et al 2009 | +                   |                      |                        |                       |               |      |      |      |       |      |      |            |           |        |          |      |      |      |                      |
| Hoque et al 2010         |                    |                      |                        |                       |               |      |      |      |       |      |      |            |           |        |          |      |      |      |                      |
| Battist et al 2011       |                    |                      |                        |                       |               |      |      |      |       |      |      |            |           |        |          |      |      |      |                      |
| Barocas DA et al 2011    |                    |                      |                        |                       |               |      |      |      |       |      |      |            |           |        |          |      |      |      |                      |
| Wozniak et al 2012       |                    |                      |                        |                       |               |      |      |      |       |      |      |            |           |        |          |      |      |      |                      |
| Bys et al 2013           |                    |                      |                        |                       |               |      |      |      |       |      |      |            |           |        |          |      |      |      |                      |
| Pande et al 2013         |                    |                      |                        |                       |               |      |      |      |       |      |      |            |           |        |          |      |      |      |                      |
| Kosova et al 2014        |                    |                      |                        |                       |               |      |      |      |       |      |      |            |           |        |          |      |      |      |                      |
| Yang et al 2015          |                    |                      |                        |                       |               |      |      |      |       |      |      |            |           |        |          |      |      |      |                      |

+ - significant increase in prostate cancer; - - significant decrease in prostate cancer; CAT, catalase; cGMP, cyclic guanosine monophosphate; CML, carboxymethyl-lysine; GR, glutathione reductase; GSH, glutathione; GSH-Px, glutathione peroxidase; GST, glutathione S-transferase; iNOS, inducible nitric oxide synthase; MDA, malondialdehyde; NS, not significant; SOD, superoxide dismutase; Vit, vitamin; 8-isoPGF2, 4-HNE, 4-hydroxy-2-nonenal.
3.3. Result of meta-analysis

Studies that reported data of sample size, mean value of OS, mean value of antioxidant, and standard deviation were included in the meta-analysis (Figs. 2–4). In studies included in this review, MDA, SOD, and GSX-Px were the most commonly used indicator for OS and antioxidants, respectively.

For the comparison of MDA (n = 9), the mean effect size was 2.47 [95% CI (1.42, 3.52)] indicating that MDA levels were significantly higher for PCa patients than controls. Heterogeneity for this outcome was high (I² = 96%). For the comparison of SOD (n = 13), the mean effect size was –0.62 [95%, CI (–1.73, 0.50)], indicating no differences between PCa patients and controls. Heterogeneity for this outcome was high (I² = 96%). For GSX-Px (n = 8), the mean effect size was –1.01 [95%, CI (–1.22, –0.80)], indicating GSX-Px levels were lower for PCa patients than controls. Heterogeneity for this outcome, as measured by I², was 0%.

3.4. Study quality

The overall quality of the studies included in this review, assessed using the Newcastle–Ottawa Scale, was moderate with an average score of 6.83 (standard deviation = 1.19, range, 4–8) on a nine-point scale. The main areas where quality was lacking were comparability of cases and controls on the basis of the design and analysis. Nonreporting of the nonresponse rates was a major factor for low scores in the provision of well-defined outcome measures.

4. Discussion

Over the last decades, epidemiological, experimental, and clinical studies have demonstrated that markers of OS are associated with the development and progression of cancer.9 The present study seeks to evaluate the association between PCa and OS and antioxidants. Overall, results of our review confirm that markers of OS are increased in PCa patients compared with healthy controls, with the strongest and most consistent circulating biomarker being MDA. To our knowledge, this is the first systemic review conducted to examine the association between OS and antioxidants in men with PCa.

The present study found that most OS biomarkers were significantly higher in patients with PCa than the control group. Of 23 studies, 21 studies reported at least one marker of OS to be higher in men with PCa, whereas two studies did not detect any significant differences between the two groups. These results are consistent with recent studies examining the correlation of OS and the risk of cancer in various tumor groups which reported significantly increased lipid peroxidation and DNA damage in breast,54,55 brain,56 colorectal,57 lung,58 liver,59 head and neck60 cancers, and oral squamous cell61 carcinoma.
The oxidation of lipid or lipid peroxidation is one of the most commonly reported indices of OS which is recognized as a pathological factor contributing to chronic disease including cancer and aging.62,63 The most frequently studied markers of lipid peroxidation are MDA and isoprostanes.64 Of 23 studies, 14 studies measured OS with MDA and reported OS to be associated with PCa. In those studies, high levels of OS in PCa were consistent, although, MDA was measured using different methods such as thiobarbituric acid test, thiobarbituric acid-reactive substances test, and chromatographic assays (high performance liquid chromatography-diode array detection-fluoro and Liquid chromatography–mass spectrometry-diode array detection). One study reported that MDA levels correlated with the Gleason score and progression of disease.36 However, another study43 observed an association between OS and advanced PCa but not localized PCa. To confirm this result will require further studies with an adequate sample size.

Four studies measured lipid peroxidation with isoprostanes, which are prostaglandin-like compounds formed from the free radical catalyzed peroxidation of arachidonic acid. Two studies48,50 reported urine F2-isoprostane generated by lipid peroxidation to be associated with PCa whilst two other studies did not.31,53 These two studies31,53 were likely hampered by the limitation of small sample sizes. Further, differences in study populations may also be a cause of divergent findings. One study53 was conducted in diabetic and hypoglycemia patients while the former two studies were conducted in nondiabetic patients.

To measure outcomes of protein oxidation, DNA damage with 8-OHdG and with NO₂ or NO₃⁻ are commonly used in cancer...
Three studies reported a difference of 8-OHdG between two groups while one study did not observe a difference. The latter study suggested that there was a need to improve the validated analytical procedure of measuring 8-OHdG using plasma or serum samples. The results of these three studies are similar to previous studies which demonstrated that higher DNA damage correlated with the risk of PCa.45,66

Three studies which measured protein oxidation with NO2 or NO3 showed OS to be consistently higher in PCa. These findings are in agreement with previous studies which suggested that ROS, including oxygen and nitrogen-free radicals, may cause specific oxidative DNA damage and play a leading role in initiation and promotion of carcinogenesis.47

CAT, SOD, and GSH related enzymes are considered primary endogenous antioxidants while vitamins C, E, and A (converted from beta-carotene) are considered exogenous antioxidants as they are directly involved in elimination of ROS.46,66 Both endogenous and exogenous antioxidants protect cells against ROS induced during metabolism in living organisms.46 For example, GSH-Px removes both H2O2 and lipid peroxides using GSH. SOD metabolizes and protects the cells against O2− mediated by lipid peroxidation, and CAT acts on H2O2 and decomposes it to H2O and OH−. The exogenous antioxidants (vitamins A, C, and E) at the molecular and cellular level are also considered to be effective in eliminating free radicals and prevent chronic diseases including cancer.48 Thus, our review further evaluated the relationship between antioxidants and men with PCa, in addition to OS.

Fifteen studies measured antioxidant indicators. SOD was measured in eight studies with erythrocytes or whole blood. Five studies reported low SOD levels in patients while two studies42,47 reported contrasting results, and one study49 found no differences. CAT was measured on erythrocytes and whole blood samples in six studies. Four studies44–46 reported lower CAT levels in patients and two studies40,49 found no differences. The main reason for the inconsistency in SOD and CAT values could be attributed to the progression of disease.49 This hypothesis is consistent with Battisit et al47 who observed that an alteration in CAT and SOD values existed between patients with localized disease and those with bone metastases.

Further, four studies reported lower GSH levels in patients whereas two studies reported conflicting results.44,47 All seven studies that measured GSH-Px showed GSH-Px values to be lower in patients. In contrast, GST values were higher in men with PCa. Overall, the GSH-dependent enzyme levels were either decreased or increased or unchanged. The reason for the inconsistency of GSH-dependent enzyme activities could be influenced by the prostate-specific antigen values, as suggested by several studies.45,51 Furthermore, GSH and GSH-dependent enzymes have been known to be of central importance in the detoxification of peroxides, hydroperoxides, xenobiotics, and drugs.45,51 Hence, modification of GSH-dependent enzyme activities can be explained by the interdependence and dynamics of the GSH enzyme family pathway. GSH is turned to glutathione disulfide by GSH-Px. Glutathione disulfide is reduced again by GR using nicotinamide adenine dinucleotide phosphate as a cofactor. GSH has the ability to directly scavenge cellular ROS nonenzymatically as well as serving as a cofactor for GSH-Px in the reduction of H2O2 and other peroxide species.45,51 GSH-Px is also responsible for detoxifying other lipid peroxides to the corresponding alcohol.51 GST catalyzes the conjugation of GSH to a wide variety of endogenous and exogenous electrophilic compounds. GSH conjugation is the first step in the mercapturic acids pathway that leads to the elimination of toxic compounds.71

Six studies measured exogenous antioxidant substances.35,39,41,43,45,47,51 Both vitamin A (including beta-carotene, lycopene, leutin) and vitamin C were found to be lower in patients with PCa. With regard to vitamin E, four studies found lower levels in patients whereas one study44 reported contrasting results. The authors44 attributed this difference to different study populations. Patients participating in this study received ADT whilst most other studies included patients who did not receive anticancer treatment. ADT may alter vitamin E levels. Future studies are needed to confirm this.

A major limitation of this review is the inability to control for potential confounding factors. It is possible that the risk of PCa is influenced by multiple factors such as radiation, pollution, alcohol, diet, smoking, anxiety and stress, inflammation, drugs, and chronic diseases, which can all modulate OS levels. Most papers included in this review did not report these variables. Despite this limitation, our results suggest that redox imbalance is more common in men with PCa which may be useful for designing future randomized controlled trials.

In conclusion, the results of our review suggest that dysregulation of redox balance occurs in patients with PCa. OS biomarkers MDA and 8OH-dg as well as antioxidant parameters SOD, CAT, GSH enzyme family, and vitamins C and E may be potentially predictive biomarkers of PCa. Robust studies are required to elucidate whether reduced antioxidant enzyme levels are caused by the counteraction to OS or enhanced oxidation, which occurs as a result of depleted antioxidants over a prolonged period of time.

Conflicts of interest

The authors declare no conflicts of interest.

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