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Impact of Oxidative Stress Biomarkers and Carboxymethyllysine (An Advanced Glycation End Product) on Prostate Cancer: A Prospective Study

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Abstract

Introduction—Biomarkers of oxidative stress and advanced glycation end products (AGE) have been linked to the development of prostate cancer, but evidence from human studies is either scarce or controversial.

Materials and Methods—We conducted a prospective nested case-control study among 48 men (24 prostate cancer cases and 24 controls) aged 48–76 years at baseline. The participants of our study were a part of the Fernald Community Cohort (FCC). Prostate cancer cases and controls were matched individually on age (± 3 years) with 1:1 ratio. Biomarkers included urine F2-isoprostanes (markers of lipid oxidation), plasma fluorescent oxidation products (FlOPs; markers of global oxidation) and carboxymethyllysine (CML; a major end-stage AGE).

Results—At baseline, cases had similar age, body mass index, proportion of family history of prostate cancer, history of benign prostatic hyperplasia, history of hypertension, history of diabetes, smokers and plasma glucose levels as compared to controls. Levels of plasma CML were significantly higher in cases than in controls (182 vs. 152 μg/ml, $P < 0.05$). In the conditional logistic regression model, an increase in CML equivalent to one standard deviation was associated with increased risk of incident prostate cancer (Relative risk = 1.79, 95% confidence interval =

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Conflicts of Interest

None declared.

1.00–3.21), and accounted for ~8% variance of prostate cancer liability. Urine F2-isoprostanes and plasma FlOPs were not associated with prostate cancer incidence.

Conclusion—Higher levels of plasma CML were associated with increased risk of prostate cancer. This suggests a potential new pathway for prostate cancer prediction and treatment.

Keywords

Advanced glycation end products; F2-isoprostanes; fluorescent oxidation products; carboxymethyllysine; prostate cancer

Introduction

Prostate cancer (PCa) is a very frequently diagnosed cancer in men, and remains the leading cause of cancer death in men worldwide.[1, 2] However, novel biomarkers that are able to accurately predict risk prostate cancer, and can be used as a treatment target for PCa are lacking.

One of the etiologic pathways related to PCa is oxidative stress. Oxidative stress occurs when the reactive oxygen species (ROS) overwhelm the capacity of antioxidant defense system. Excessive ROS cause DNA damage and mutation, cell and tissue damage, and further lead to cancer development.[3] There are several lines of evidence suggesting that oxidative stress is linked to the development of malignancy of prostate.[4–7] However, the relationship between oxidative stress and prostate cancer in human studies is still controversial. [8–12] Moreover, few human prospective studies have investigated the relationship between oxidative stress biomarkers and incident prostate cancer.

The F2-isoprostanes are the most commonly used oxidation marker; however, they are a marker of lipid oxidation, not for oxidation from carbohydrate, DNA and protein. Fluorescent oxidation products (FlOPs) are generated from many different oxidation pathways (lipid, protein and DNA), and have been used as a marker of global oxidation in our [13–16] and other studies.[17–19] As compared to malondialdehyde measured by colorimetric thiobarbituric acid assay, the FlOP assay is 10–100 times more sensitive in measuring oxidative stress.[17] FlOPs have been found to be a significant predictor for coronary heart disease;[13, 16] one type of FlOPs–FlOP_320 significantly predicted risk of breast cancer.[14]

Another biomarker that may be associated with prostate cancer is advanced glycation end products (AGE). AGEare constantly generated under a high level of glucose concentration (hyperglycemia) via nonenzymatic pathway; this reaction is called glycation. During glycation process, glucose can bind with proteins, making cells stiffer, less pliable and more subject to damage and premature aging. Heating and oxidative stress can accelerate the process of glycation. AGE are a type of maker for many chronic diseases such as diabetes, atherosclerosis and renal failure.[20, 21] Recently, it has been found that receptor of AGE (RAGE) has higher mRNA expression in prostate cancer cell lines than normal prostate.[22] Thus, higher levels of AGE are potentially involved in the development of prostate cancer. However, the association between pre-diagnosis plasma AGE and prostate cancers has not

been examined in a prospective study. Carboxymethyllysine (CML), a major end-stage AGE, is the most commonly used AGE marker.

Therefore, the aim of our current study was to investigate the associations of urine F2-isoprostanes, plasma FlOPs, and CML with the risk of prostate cancer in a prospective study.

Materials and Methods

Study setting and participants

The participants and their biospecimens for the present study were obtained from the Fernald Community Cohort (FCC), which has been reported previously.[23] The FCC is a result of the Fernald Medical Monitoring Program (FMMP), which was a voluntary ongoing medical surveillance program for 9782 community residents living within five miles from the perimeter of a former US Department of Energy uranium-processing site, located near Cincinnati, Ohio, U.S.. Members of the cohort (N = 9,778) received medical screening examinations every two or three years, over an 18 year period, from 1990 to 2008 when the program ended. Some of the members of this cohort were exposed to emissions from the Fernald plant but others were not. Extensive uranium dose reconstruction using the methods developed by the Centers for Disease Control and Prevention demonstrated that over 60% of the cohort had such minimal exposure to uranium and radon that their cumulative ionizing radiation exposure was less than 3.2% over lifetime background levels.[24]

At baseline, 8,496 adult participants provided blood and urine samples between 1990 and 1993. Detailed questionnaires, administered at baseline and yearly, collected information on age, smoking status (current and past smoker, or never smoked), family history of prostate cancer, history of benign prostatic hyperplasia (BPH), history of hypertension, history of diabetes and other demographic characteristics (www.uc.edu/fmmp). Height and weight were measured at interview and body mass index (BMI) was calculated. After the initial visit, a regular follow-up examination was performed every 2 or 3 years by physicians board certified in either internal medicine or environmental/occupational medicine. Diagnoses for each FCC participant, including those of diabetes and major cancers (i.e., breast, prostate, lung, colon, skin and urinary system cancers, leukemia and lymphoma), were based on ICD-9 codes assigned by a medical record coder during the yearly review of each medical chart.

Among members of the FCC who had extremely minimal amounts of uranium exposure (< 2% over lifetime background level), we conducted a prospective nested case-control study of prostate cancer. All cases and controls were Caucasian, as 99.5% of the FCC members were Caucasian. In this study, 24 eligible incident prostate cancers were randomly selected from eligible incident prostate cancer cases (n = 86) diagnosed between 1990 and 2006. All selected prostate cancers were confirmed via medical records. The average duration from baseline sample to the diagnosis of prostate cancer was 11 years (range: 6–14 years). Using risk set sampling, controls who never had prostate cancer during the whole study period of the FCC were selected from the remaining eligible male FCC cohort members, and were matched individually with cases (1:1) on age (± 3 years at case diagnosis). All participants

provided written consent to participate in the FCC and to have their data and samples used for research studies.

Blood and urine collection and storage

All participants in our study had at least 8 hours of food fasting (except water) before blood draw. Blood samples were collected in tubes that contain liquid sodium heparin. All collected blood samples were processed within 8 hours and stored in freezers (−70°C) before measurement. Urine samples were also collected in clean tubes and stored in −70 °C freezer before assay.

Laboratory assay

All markers in matched case and control set were measured within same run.

Measurement of plasma glucose—Level of plasma glucose was measured with the Beckman Synchron CX3 Clinical Chemistry Analyzer (Beckman Instruments Inc., Brea, CA). The overall precision of the assay expressed as percentage of coefficient of variation (CV) for the measurement was < 3.5%.

Measurement of urine F2-isoprostanes—Urine F2-isoprostanes was measured by gas chromatography (GC)/negative ion chemical ionization mass spectrometry. The method has been reported previously.[25] Briefly, GC used a 15m, 0.25 mm diameter, 0.25 m film thickness, DB 1701 fused silica capillary column (Fisons, Folsom, California). The column temperature was programmed from 190 to 300 C at 15 °C per minute. The metabolite was chemically synthesized and converted to an 18 O_2-labled derivative which was used as an internal standard. Precision of the assay is 4% and accuracy is 97%.[25]

Measurement of plasma FlOPs—Measurement of FlOPs was performed with previously described procedures.[26] Briefly, we extracted plasma with ethanol/ether (3:1, v/v). The extracted samples were subsequently centrifuged at 3,000 rpm for 10 min at 4°C to collect supernatant. Fluorescence was determined with a fluorescent spectrophotometer. The excitation/emission wavelengths were 360/420 nm for FlOP_360, 320/420 nm for FlOP_320 and 400/475 nm for FlOP_400. We expressed the level of fluorescence as relative fluorescent intensity units per milliliter of plasma. FlOP_360 represents oxidation products that are generated from oxidized phospholipids or from lipid oxidation products reacting with proteins, DNA and carbohydrates in presence of phospholipids. FlOP_320 is formed when oxidation products such as lipid hydroperoxides, aldehydes, and ketones react with DNA in the presence of metals. Finally, FlOP_400 reflects the interaction between MDA, proteins and phospholipids.[27] The within-run average CVs for FlOP measurements were < 13%.

Measurement of plasma CML—Plasma CML was measured using previously described method.[28, 29] The within run average CVs were less than 10%. A competitive ELISA assay was conducted using monoclonal anti-CML antibody (6D12) and a secondary antibody, alkaline phosphate labeled anti-mouse lgG1.

Statistical analysis

We compared the baseline characteristics, plasma glucose, urine F2-isoprostanes, plasma FlOPs, CML between cases and controls. Pearson correlations between urine F2-isoprostanes, plasma FlOPs, CML and glucose were assessed in controls.

The associations of urine F2-isoprostanes, plasma FlOPs and CML with prostate cancer were analyzed with conditional logistic regression model. In the model, levels of F2-isoprostanes and CML were normal distributed, and were transformed into one standard deviation increase. As levels of plasma FlOPs were not normal distributed, we transformed the variables into logarithmic scale and recoded them into approximately one standard deviation increase before they were used in the logistic regression model. Because our study had a small sample size and all baseline characteristics were not significantly different between cases and controls, we analyzed the associations of urine F2-isoprostanes, plasma FlOPs and CML with prostate cancer without adjustment for covariates. *P* value in two sides < 0.05 was considered to be statistical significant. All analyses were conducted with the Statistical Analysis System (Version 9.3, SAS Institute Inc., Cary, NC).

Results

Baseline characteristics and plasma glucose of the men in cases and controls

At baseline, the average age of cases and controls was 60 years (range: 48–76 years). Prostate cancer cases had no significantly different age, BMI, proportion of family history of prostate cancer, history of BPH, history of hypertension, history of diabetes, smokers and plasma glucose levels as compared to controls (Table 1).

Correlations between urine F2-isoprostanes, plasma FlOPs, CML and glucose in controls

In controls, levels of FlOP_360 were positively correlated with FlOP_400 ($r = 0.51$, $P = 0.012$). Higher levels of CML were associated with increased levels of plasma glucose ($r = 0.64$, $P < 0.001$). All the other variables were not correlated (all $P > 0.100$).

Association of urine F2-isoprostanes, and plasma FlOPs and CML with prostate cancer incidence

At baseline, levels of plasma CML were significantly higher in prostate cancer cases than in controls (Table 2). Levels of urine F2-isoprostanes and plasma FlOPs were not significantly different between prostate cancer cases and controls.

In the conditional logistic regression model, higher levels of CML were associated with increased risk of incident prostate cancer (Relative risk of per one standard deviation increase of CML = 1.79, 95% confidence interval = 1.00–3.21). In the model, CML accounted for ~8% variance of prostate cancer liability. Urine F2-isoprostanes and plasma FlOPs were not associated with prostate cancer incidence (Table 3).

Discussion

To our knowledge, this is the first prospective study demonstrating that higher levels of plasma CML were associated with increased risk of prostate cancer. However, associations of urine F2-isoprostanes and plasma FlOPs with prostate cancer were not observed. Thus, AGE appeared to be more important than global and lipid oxidation markers for the development of prostate cancer.

In this study, we have measured markers of global oxidation (FlOPs), lipid oxidation (F2-isoprostanes), and glycation (AGE). We did not observe an elevation of global oxidation or lipid oxidation, but only an increased glycation in prostate cancer cases as compared to controls. Two possible reasons can explain this: First, one of the major end-stage AGE is CML which was measured in this study. The formation of CML is a complicated process requiring multiple pathways, in which certain pathways for CML production do not necessarily require an environment with oxidative stress. Indeed, CML positively correlated with glucose, but not with FlOPs and urine F2-isoprostanes in our study. Although oxidative stress may promote CML formation at certain reaction step, CML largely reflect long-term hyperglycemia and glycation status rather than ongoing oxidative stress as quantified by plasma FlOPs and urine F2-isoprotanes. Thus, the levels of CML were not always parallel with the levels of global and lipid oxidation between cases and controls. Second, hyperglycemia is a powerful factor to stimulate glucose oxidation and uptake; hyperglycemia inhibits fatty acid uptake and oxidation in type 2 diabetes and insulin resistance patients.[30–32] In this study, both cases and controls had 20% of diabetes. For the rest, most of them were overweight, and more or less had insulin resistance and hyperglycemia. Therefore, it is possible that under hyperglycemia, glycation scenario, lipid oxidation is inhibited and global oxidation (FlOPs) may not be elevated. This statement is partially supported by another epidemiologic study, in which measurement of urine F2-isoprostanes is inversely associated with the risk of type 2 diabetes.[33]

The null association between biomarkers of oxidative stress and prostate cancer incidence is consistent with several prospective studies and a randomized control trial, in which antioxidant intake, and serum antioxidants and F2-isoprostanes were not associated with incident prostate cancer.[8, 9, 11] However, inconsistent with above studies, several cross-sectional studies collected blood samples after prostate cancers were diagnosed, and found that participants with prostate cancer had higher levels of F2-Isoprostane, malondialdehyde by thiobarbituric acid assay, and lower activities of superoxide dismutase and glutathione peroxidase than those without prostate cancer.[10, 12, 34, 35] Therefore, elevated oxidative stress in patients with prostate cancer in the above cross-sectional studies is likely to be the outcome of the prostate cancer or its comorbidities. High level of oxidative stress is unlikely considered to be an etiologic factor for prostate cancer incidence.

The relationship between AGE and prostate cancer has biological basis. The RAGE is present in many organs in human including prostate.[36] Generally, higher expression of RAGE is related to the progression of many cancers, and blockade of RAGE suppresses the tumor growth and metastases.[37–39] Further, prostate cancer tissue had been suggested to have higher mRNA expression of RAGE than normal prostate tissue.[22] This has raised the

possibility that interaction of AGE and RAGE plays an important role in the development of prostate cancer. Lastly, the participants of our study were in overweight range. Hypoxia is more likely observed in overweight and obese individuals than in normal-weight people.[28] AGE can aggravate the cell damage under hypoxia condition and promote the hypoxia-induced injury such as endoplasmic reticulum in kidney and prostate, which is important for tumor development.[29] Other mechanisms of AGE on prostate cancer merit further studies.

There are several advantages of this study. Because this is an age-matched case-control study, the major confounding by age can be well controlled. Further, the prospective study design allowed us to exclude the potential reverse causation between biomarkers and prostate cancer, and a suggestive causation relationship between CML and prostate cancer can be made. Finally, we have measured many biomarkers of oxidative stress from different pathways, which allowed us to have a comprehensive understanding of the impact of oxidative stress on prostate cancer incidence.

One of the major limitations of this study is small sample size. Thus, we may have insufficient power to discover the relationship between biomarkers of oxidative stress and prostate cancer. In addition, we did not assess the relationship between the levels of plasma CML with prostate cancer severity due to limited data. As the cohort mostly consists of diabetic and hyperglycemic patients, the findings may not be extrapolated to the general population. Lastly, due to small sample size, we did not have the power to adjust covariates in the model. However, this is unlikely a big issue, as all major baseline characteristics between cases and controls were either matched or not significantly different.

Conclusion

Higher levels of plasma CML were associated with increased risk of prostate cancer. However, global and lipid oxidation markers were not associated with risk of prostate cancer. Since this is the first prospective study in human suggesting a positive relationship between plasma CML and prostate cancer, further prospective studies with large sample size are warranted to confirm our results.

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Abbreviations

AGE	advanced glycation end products
CML	carboxymethyllysine
CVs	coefficient of variations
FCC	Fernald Community Cohort
PCa	prostate cancer

FlOPs	fluorescent oxidation products
FMMP	Fernald Medical Monitoring Program
GC	gas chromatography
RAGE	receptor of advanced glycation end products
ROS	reactive oxygen species

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Clinical Practice Points

- Novel biomarkers that are able to accurately predict risk prostate cancer, and can be used as a treatment target for PCa are lacking.
- Biomarkers of oxidative stress and AGEhave been linked to the development of prostate cancer, but evidence from human studies is either scarce or controversial.
- Higher levels of plasma CML (a major end-stage AGE), but not biomarkers of oxidative stress (urine F2-isoprostanes and plasma FlOPs), were associated with increased risk of prostate cancer.
- The positive relationship between CML and prostate cancer suggests a potential new pathway for PCa prediction and treatment.
- Further prospective studies with large sample size are warranted to confirm our results.

Table 1

Baseline characteristics and plasma glucose of the men in cases and controls in the Fernald Medical Monitoring Program, 1990–1993 (n = 48)

Variables	Cases (n = 24)	Controls (n = 24)	*P* value
Age (year)[a]	58.9 (11.0)	61.0 (7.6)	0.447
Body mass index (kg/m^2)[a]	27.5 (3.2)	29.5 (4.3)	0.084
Family history of prostate cancer (%)	8.3	12.5	0.637
History of benign prostatic hyperplasia (%)	33.3	33.3	1.000
History of hypertension (%)	37.5	50.0	0.383
History of diabetes (%)	20.8	16.7	0.712
Smoking (%)			0.763
Past and current smoker (%)	62.5	66.7	
Never smoked (%)	37.5	33.3	
Glucose (mg/dL)	112 (36)	102 (24)	0.287

[a]Values are means (standard deviation).

Table 2

The levels of urine F2-isoprostanes, plasma fluorescent oxidation products and carboxymethyllysine at baseline among cases and controls in the Fernald Medical Monitoring Program, 1990–1993 (n = 48)

Variables	Cases (n = 24)	Controls (n = 24)	*P* value
F2 isoprostanes (ng/ml)[a]	1.94 (0.94)	2.17 (1.29)	0.488
FLOP_360 (fluorescent intensity/ml)	227 (206, 260)	222 (187, 311)	1.000
FLOP_320 (fluorescent intensity/ml)	358 (322, 500)	480 (345, 608)	0.087
FLOP_400 (fluorescent intensity/ml)	56.8 (45.6, 89.3)	63.0 (48.7, 90.9)	0.568
Carboxymethyllysine (μg/ml)[a]	182 (57)	152 (44)	**0.047**

[a]Values are shown in means (standard deviation), otherwise the values are displayed in medians (inter-quartile range) if the distribution of the variable is skewed. FLOP: fluorescent oxidation products.

Table 3

Associations of urine F2-isoprostanes, plasma fluorescent oxidation products and carboxymethyllysine with prostate cancer in the Fernald Medical Monitoring Program, 1990–2006: conditional logistic regression model in continuous scale (n = 48)

Variables	Unit[a]	Relative risk (95% confidence interval)
F2 isoprostanes (ng/ml)	1.3	0.56 (0.21, 1.49)
FLOP_360 (fluorescent intensity/ml) in logarithmic scale	0.3	1.05 (0.67, 1.63)
FLOP_320 (fluorescent intensity/ml) in logarithmic scale	0.7	0.64 (0.28, 1.45)
FLOP_400 (fluorescent intensity/ml) in logarithmic scale	0.7	0.85 (0.42, 1.70)
Carboxymethyllysine (μg/ml)	40	**1.79 (1.00, 3.21)**

[a]Values are approximately 1 standard deviation in controls.