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Cardiovascular disease risk factors and oxidative stress among premenopausal women

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ABSTRACT

Oxidative stress is one hypothesized mechanism linking anthropometric, behavioral, and medical risk factors with cardiovascular disease (CVD). We evaluated cross-sectional associations between CVD risk factors and biomarkers of oxidative stress, and investigated these biomarkers as predictors of incident diabetes and hypertension among premenopausal women. F_2-isoprostane (F_2-IsoP) and metabolite (15-F_{2t}-IsoP-M), reliable biomarkers of oxidative stress, were measured in urine samples collected at enrollment from 897 premenopausal women (ages 35–54) enrolled in the Sister Study cohort without a CVD history. Blood pressure, waist circumference, and body mass index (BMI) were measured at enrollment by trained study personnel. Diabetes and cigarette smoking were self-reported via enrollment questionnaires. Over a maximum follow-up of 11.5 years, participants self-reported incident diabetes and hypertension diagnoses on mailed questionnaires. In cross-sectional analyses, both F_2-IsoP and 15-F_{2t}-IsoP-M were positively associated with BMI, waist circumference, diastolic blood pressure, and current smoking. F_2-IsoP was elevated among those with diabetes, and 15-F_{2t}-IsoP-M increased with higher systolic blood pressure. Prospective analyses suggested an increased hypertension risk among those with elevated 15-F_{2t}-IsoP-M (highest vs. lowest quartile: hazard ratio = 2.34; 95% CI: 1.20–4.56). Our results suggest that urinary F_2-IsoP and 15-F_{2t}-IsoP-M are positively associated with adiposity measures, blood pressure, and cigarette smoking. Further investigation is warranted to evaluate 15-F_{2t}-IsoP-M as a predictor of hypertension.

1. Introduction

An overabundance of reactive oxygen species (ROS) relative to antioxidant defense, termed oxidative stress, may play a critical role in the pathogenesis of several chronic diseases, including cardiovascular diseases (CVD). ROS are hypothesized to drive the development and progression of atherosclerosis through the peroxidation of polyunsaturated fatty acids (PUFAs) in lipoproteins, producing a chronic inflammatory state that leads to plaque formation and rupture [1]. Thus markers of lipid peroxidation may be useful indicators of vascular disease risk.

Classical risk factors for atherosclerosis and subsequent occlusive events, such as obesity and cigarette smoking, have been associated with increased lipid peroxidation, a potential pathway through which these factors may influence vascular disease development [1]. F_2-isoprostanes (F_2-IsoPs), stable products of the peroxidation of arachidonic acid, are widely considered the current 'gold standard' measure of oxidative stress in vivo [2], and elevations in both urinary and plasma concentrations of these biomarkers have been observed among current smokers and individuals with diabetes, hypertension, and obesity [3–5]. However, most previous investigations of relationships between F_2-IsoPs and these key CVD risk factors have been conducted in small, clinical cohorts, often comprised of patients with advanced disease. Furthermore, the few studies to date in healthy populations have relied exclusively on the measurement of plasma F_2-IsoPs or unmetabolized F_2-IsoPs in urine [3–5]. F_2-IsoPs measured in plasma may be subject to autoxidation during sample collection and storage [6], while unmetabolized F_2-IsoPs in urine may reflect local F_2-IsoP production in the kidneys, rather than systemic oxidative stress [7]. Thus the predominant urinary F_2-isoprostane metabolite, 2,3-dinor-5,6-dihydro-15-F_{2t}-isoprostane (15-F_{2t}-IsoP-M), which is independent of local renal

Abbreviations: CVD, cardiovascular disease; F_2-IsoP, F_2-isoprostane; 15-F_{2t}-IsoP-M, F_2-isoprostane metabolite; BMI, body mass index; Cr, creatinine

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production, may be a better marker of systemic oxidative stress in vivo. To our knowledge, associations between 15-F_{2t}-IsoP-M and major CVD risk factors have not been comprehensively evaluated in a young, CVD-free population.

The objective of this study was to examine cross-sectional associations between risk factors for CVD and oxidative stress, as measured by urinary F_2-IsoP and 15-F_{2t}-IsoP-M, in a cohort of premenopausal women without a history of cardiovascular conditions. Additionally, we evaluated whether urinary F_2-IsoP and 15-F_{2t}-IsoP-M concentrations were associated with incident diabetes and hypertension over a maximum follow-up of 11.5 years.

2. Materials and methods

2.1. Study population

Participants in these analyses were controls in a case-control study of oxidative stress and breast cancer risk nested within the prospective Sister Study cohort [8]. Between 2003 and 2009, over 50,000 women from the U.S. and Puerto Rico were recruited into the Sister Study through a national multi-media campaign and a network of breast cancer professionals and volunteers. Women were eligible to participate in the Sister Study if they were ages 35–74 years and free of breast cancer themselves at enrollment, but had a sister with a breast cancer diagnosis. All participants provided written informed consent. The study was approved by the Institutional Review Board of the National Institute of Environmental Health Sciences, the National Institutes of Health, and the Copernicus Group.

Sister Study participants eligible for inclusion in the control sample were ages 35–54 years, premenopausal, had at least one intact ovary, and had a urine sample collected at enrollment. Women were considered premenopausal if they self-reported at least one menstrual cycle within the 12 months prior to enrollment, or were aged 54 years and younger and their only reason for not experiencing menses was hysterectomy (without bilateral oophorectomy). A total of 922 women remained breast cancer free as of December 31, 2012 and were selected as control participants. For these analyses, we excluded women who reported a history of heart attack, angina, stroke, transient ischemic attack, or congestive heart failure (N = 23) on enrollment questionnaires. We also excluded those classified as having type 1 diabetes, defined as a self-reported diabetes diagnosis before age 30, due to their small number (N = 2). Thus final analyses include 897 women.

2.2. CVD risk factor assessment

During a home visit at Sister Study enrollment, trained study personnel used standardized protocols to measure blood pressure, height, weight, and waist circumference. Three sitting measurements, approximately 1–2 min apart, were taken for systolic and diastolic pressure. If both arms could be used, measurements were taken from alternating arms, starting with the left arm (Left→Right→Left). Otherwise, three readings were taken from the available arm. The average of the three readings was used in all analyses. Height and weight were measured without shoes, and waist circumference was measured using a cloth tape measure over skin or lightweight clothing. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared (kg/m^2).

Sociodemographic information and current cigarette smoking, physical activity, and use of medications for high blood pressure were assessed via questionnaire at Sister Study enrollment. Participants also self-reported any previous diagnosis of diabetes, age at diabetes diagnosis, and use of diabetes medication on enrollment questionnaires. We classified women as having type 2 diabetes if they reported a diabetes diagnosis at age 30 years or older and/or were currently taking diabetes medication (self-reported diagnosis only: N = 11; diabetes medication only: N = 5; self-reported diagnosis and diabetes medication: N = 15). According to the methods described by D'Agostino et al. [9,10], we also calculated an absolute measure of 10-year general CVD risk. This risk score was developed in the Framingham Heart Study and incorporates information on non-laboratory-based risk factors, including gender, age, systolic blood pressure, hypertension treatment, smoking, diabetes, and BMI.

Incident diabetes and hypertension events were ascertained via detailed follow-up questionnaires, completed by participants every 2–3 years, and brief health update questionnaires completed annually. Women were asked to report a diagnosis of diabetes or hypertension, as well as the date of diagnosis.

2.3. Oxidative stress measurement

Sister Study participants provided first morning urine samples during the enrollment home visit. Urine samples were shipped frozen to the Eicosanoid Core Laboratory at Vanderbilt University Medical Center, where gas chromatography/negative ion chemical ionization mass spectrometry (GC/NICI MS) was used to measure F_2-IsoP and 15-F_{2t}-IsoP-M. Detailed protocols for these methods have been published [11–13]. To account for urine diluteness, all values of F_2-IsoP and 15-F_{2t}-IsoP-M were adjusted for creatinine concentrations and are reported as ng/mg of creatinine (ng/mg Cr).

2.4. Statistical analysis

Values of F_2-IsoP and 15-F_{2t}-IsoP-M were log-transformed to approximate a normal distribution. Unadjusted and multivariable linear regression models, with log-transformed F_2-IsoP and 15-F_{2t}-IsoP-M as the dependent variable, were used to evaluate cross-sectional associations with continuous (age, systolic blood pressure, diastolic blood pressure, BMI, waist circumference, 10-year CVD risk score) and dichotomous (current smoking, prevalent diabetes,) variables. Due to evidence of collinearity between BMI and waist circumference, and between systolic and diastolic blood pressure, these variables were not entered together in the same linear regression models. We further considered adjustment for education level (less than Bachelor's degree, Bachelor's degree, higher than Bachelor's degree), race (white, non-white), and physical activity (total MET [metabolic equivalent] hours/week). Estimates were largely unchanged; therefore, we present results without adjustment for these additional variables. For associations between F_2-IsoP and 15-F_{2t}-IsoP-M and systolic and diastolic blood pressure measures, we performed sensitivity analyses excluding those who reported taking high blood pressure medication at enrollment (N = 114).

Using general linear models, we calculated multivariable-adjusted geometric means of F_2-IsoP and 15-F_{2t}-IsoP-M within categories of all risk factor variables. BMI and waist circumference were categorized according to established guidelines [14,15], and systolic blood pressure, diastolic blood pressure, and 10-year CVD risk score were categorized using study-specific quartiles.

Cox proportional hazards regression models were used to estimate associations between F_2-IsoP and 15-F_{2t}-IsoP-M and incident diabetes and hypertension. Person-time at risk was defined independently for each outcome, as the time between Sister Study enrollment and date of self-reported diagnosis or date of last contact, whichever came first. Participants who reported a diagnosis prior to Sister Study enrollment were excluded from analyses specific to that outcome (diabetes: N = 46; hypertension: N = 144). For incident hypertension analyses, we further excluded any others who reported high blood pressure medication use at enrollment (N = 3), or had a systolic blood pressure ≥140 or a diastolic blood pressure ≥90, as measured at the enrollment home visit (N = 2). F_2-IsoP and 15-F_{2t}-IsoP-M were categorized into quartiles for analyses of hypertension. Multivariable models for hypertension were adjusted for age, education, race, physical activity, BMI, and current smoking at enrollment. Tests for linear trend were conducted by