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Systemic markers of oxidative status and colorectal adenomatous polyps

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Abstract

Purpose—Oxidative damage has been implicated in carcinogenesis. We hypothesized that elevated systemic oxidative status would be associated with later occurrence of colorectal adenomatous polyps, a precursor of colorectal cancer.

Methods—We examined the prospective association between four systemic markers of oxidative status and colorectal adenomatous polyps within a non-diabetic sub-cohort of the Insulin Resistance Atherosclerosis Study (IRAS) (n=425). Urine samples were collected from 1992–1994 and colorectal adenomas prevalence were assessed in 2002–2004. Oxidative status markers were assessed, which included four F_2-isoprostanes (F_2-IsoPs) from the classes III and IV: iPF2α-III, 2,3-dinor-iPF2α-III (a metabolite of iPF2α-III), iPF2α-VI, and 8,12-iso-iPF2α-VI. All biomarkers were quantified using liquid chromatography–tandem mass spectrometry. Prospective associations were assessed using multivariate logistic regression analysis.

Results—The adjusted ORs (95% CIs) for occurrence of colorectal adenomatous polyps and scaled to 1 SD of F_2-IsoP distribution were 1.16 (0.88–1.50), 0.88 (0.63–1.17), 1.04 (0.80–1.34), and 1.16 (0.90–1.48) for iPF2α-III, iPF2α-VI, 8,12-iso-iPF2α-VI, and 2,3-dinor-iPF2α-III, respectively.

Conclusion—The lack of association between F_2-IsoPs and adenomatous polyps does not support the hypothesis that elevated oxidative status is associated with colorectal adenomatous polyp occurrence during a 10-year period of follow-up.

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Author Contributions

Sharareh Siamakpour-Reihani, Peter Scarbrough, and Dora Il'yasova wrote the manuscript, Frances Wang and Ralph D'Agostino conducted the statistical analysis and participated in the discussions of the results, Ivan Spasojevic and Karel Base measured F_2-Isoprostanes, Rebecca Sedjo participated in the discussion of the results.

Keywords

oxidative stress; biomarkers; F2-isoprostanes; adenomatous polyps; adenoma; colorectal cancer; epidemiology

Introduction

External oxidative exposures (e.g. smoking, ionizing radiation, diet) are known to act as carcinogenic risk factors, damaging DNA, lipids, and proteins (1–5). These exposures are thought to interact with an individual's internal sources of reactive oxygen species, such as metabolism, and inflammation, to define one's oxidative status (6, 7). How this reductive-oxidative (redox) balance influences individual cancer predisposition is not well established. Several prospective studies of lung, breast, and prostate cancers have so far yielded inconsistent results (8–10). These studies assessed individual oxidative status at the systemic level (urinary excretion or plasma levels) of lipid peroxidation biomarkers, the F_2-isoprostanes (F_2-IsoPs) (11). Whether these inconsistent findings present spurious associations or reflect a complicated relationship between individual oxidative status and cancer risk remains an open question.

A common cancer outcome that may be related to redox balance is colorectal cancer (CRC), because CRC risk has been associated with oxidizing exposures, such as ionizing radiation and alcohol consumption (12–13). Adenomas or adenomatous polyps are common precursors to CRC (14–17). Oxidizing exposures, such as smoking and alcohol use have been associated with adenoma risk (18–20). Therefore, markers of redox balance may also be associated with adenoma risk. We hypothesized that individuals with elevated levels of systemic oxidative status markers would have a higher risk of colorectal adenomatous polyps, a precursor of colorectal cancer. We examined our hypothesis in a prospective study, using four urinary F_2-IsoPs to assess individual oxidative status.

F_2-IsoPs are formed during the non-enzymatic oxidation of arachidonic acid by different types of free radicals (21, 22). Depending on the position where the oxygen molecule is added to arachidonic acid, four regioisomers are formed, giving four F_2-IsoPs series. Furthermore, each series comprises 16 stereoisomers, which yields a final total of 64 possible isomers.

Arachidonic acid is ubiquitously integrated into the phospholipids comprising biological membranes and lipoproteins. Formed within these phospholipids, F_2-IsoPs are hydrolyzed from esterified lipids and metabolized via the beta-oxidation pathway. Both the original F_2-IsoPs and their metabolites are excreted in urine, with exertion of the metabolites being proportional to the formation of the original F_2-IsoPs (22). Urinary measurements of F_2-IsoPs have several advantages as compared to blood measurements, namely they present a time-integrated index of total body F_2-IsoP production, whereas the half-life of F_2-IsoPs in blood is measured in minutes and are not liable to autooxidation due to low lipid content of urine. Previous work has shown that F_2-IsoPs demonstrate sufficiently low (approximately 30%) intra-individual variation, making them potentially good biomarkers for assessing inter-individual variability in systemic redox status (23).

To examine our hypothesis, we measured multiple F_2-isoprostanes. Two F_2-IsoPs were selected from the III-series: iPF2α-III was selected because it is the first isomer proposed as an index of lipid peroxidation *in vivo* and, therefore, is the most frequently measured isomer (24). 2,3-dinor-iPF2α-III was selected as a beta-oxidation metabolite of iPF2α-III, addressing a theoretical concern that renal tissues may contribute disproportionally to the total production of iPF2α-III. In addition, we selected two F_2-IsoPs from the VI-series,

iPF2α-VI and 8,12-iso-iPF2α-VI, because they are most abundant in human urine (25). Due to their abundance, the VI-series F_2-IsoPs may be more sensitive biomarkers than the III-series. Furthermore, as shown by previous studies, associations may vary depending on the specific F_2-IsoP being measured (26, 27). By including multiple F_2-IsoP isomers, we increase sensitivity of the study to detect a possible association. Importantly, these four F_2-IsoP species have been validated as sensitive markers of oxidative stress in a clinical model (22).

Materials and Methods

Study Population

The Insulin Resistance Atherosclerosis Study (IRAS) was a multi-ethnic cohort. The subjects were recruited from four U.S. communities in 1992–1994 with the primary goal of assessing the relationship between insulin resistance, insulinemia, glycemia, other components of the insulin resistance syndrome, and prevalent cardiovascular disease. A total of 1626 individuals ages 40 to 69 years of age participated in the IRAS. (28). The colon study was nested in the IRAS cohort, where colonoscopies were conducted in the subcohort between 2002 and 2004; details are described elsewhere (29). Briefly, eligibility for colonoscopy was the following: surviving IRAS cohort participants who were ≥49 years of age, mentally eligible, and without serious concurrent illnesses (e.g. recent heart attack, oxygen dependent pulmonary disease, renal failure, prosthetic heart valve, or colon cancer). Participants who reported having adenomatous polyps at least five years prior to the study period of 2002–2004 were included, if their next colonoscopy exam was due within the study period.

A total of 600 IRAS participants had a colonoscopy, including those who had diabetes at baseline. This analysis excluded participants with diabetes at baseline, as increased oxidative status may be a consequence of this condition (24). Of the 600 IRAS participants, the analytical cohort for this study was comprised of 425 IRAS participants who were free of diabetes at baseline and had available baseline (1992–1994) urine sample for measurements of oxidative stress markers. All participants provided signed informed consent and the study was approved by the Institutional Review Boards of all collaborating organizations.

Colonoscopy

Experienced physicians performed the colonoscopies, reaching the cecum in 96% of participants. Size and location of all visible polyps were recorded and the polyps were removed. A standard histologic assessment was done by the local clinical laboratory. Within the analytical cohort, 331 participants (77.9%) had no adenomatous polyps or had hyperplastic polyps (further referred to as “no adenoma”). 94 participants (22.1%) had adenomatous polyps (referred to as “adenoma”). No carcinomas were diagnosed in this study population.

Urinary F_2-isoprostanes

At the baseline examination, morning spot urine samples were collected and stored at −70 °C. Four F_2-IsoPs (iPF2α-III, 2,3-dinor-iPF2α-III, iPF2α-VI, and 8,12-iso-iPF2α-VI) were quantified by liquid chromatography (LC) with tandem mass spectrometry (MS) detection (LC-MS/MS) on a Shimadzu 20A series LC and Applied Biosystems API 4000 QTrap MS/MS instruments, as previously described (24). Calibration of the instrument for sample collection was performed by adding pure F_2-IsoPs into pooled human urine and injected into the machine before and after the IRAS participants’ samples, covering the entire expected range of physiological F_2-IsoP concentrations. Lower limits of quantification (>80% accuracy) were 0.007, 0.34, 0.25, and 0.12 mg/mL for iPF2α-III; 2,3-dinor-iPF2α-III,

iPF2α-VI, and 8,12-iso-iPF2)-VI, respectively. Urinary levels of F_2-IsoPs were adjusted by creatinine to take into account differences in urine diluteness. Creatinine was assayed by a fast electrospray ionization–tandem MS method, as described previously (30).

Other Covariates

History of previous polyps was obtained through self-report at 2002–2004. The participants were asked whether they were ever told that they had colorectal polyps and about the date of diagnosis. Demographic data (age and gender), measurements of glucose tolerance, and data for other covariates were collected during baseline visits in 1992–1994. Race/ethnicity was self-reported. To insure valid measurements of glucose tolerance, all IRAS participants fasted for 12 hours and refrained from heavy exercise, smoking, and alcohol consumption for 24 hours before the visit. Glucose tolerance was measured precisely at each examination using an oral glucose tolerance test and the World Health Organization criteria. A 75-gram glucose load (Orange-dex; Custom Laboratories, Baltimore, MD) was administered over a period of <10 minutes. Blood was collected at 0 and 2 hours. Normal glucose tolerance (NGT) was defined as fasting glucose and 2-hour glucose < 140 mg/dl. Impaired glucose tolerance (IGT) was defined as fasting glucose < 140 mg/dl and 2-hour glucose 140 and <200 mg/dl.

Height was measured to the nearest 0.5 cm and weight was measured to the nearest 0.1 kg. These measurements have been conducted in duplicate following a standardized protocol, and averages were used in the analysis. Body mass index (BMI) was calculated as weight/height^2 (kg/m2). Smoking status was assessed by self-report. Alcohol consumption was assessed as part of the 114-item food frequency questionnaire (31, 32), which was modified for the IRAS to incorporate regional and ethnic food habits and supplements.

Statistical Analysis

Student's *t*-test and χ^2-test were used to assess differences in the distribution of demographic and baseline variables by adenoma versus no-adenoma status. Crude association between F_2-IsoPs and study characteristics were examined using Student's *t*-test, ANOVA, and Spearman corelation coefficient. Adjusted odds ratios (ORs) for the associations between each of the F_2-IsoPs and colorectal adenoma, along with their corresponding 95% confidence intervals (CIs), were calculated from logistic regression models. Model 1, the minimally adjusted model, included the demographic variables (age, gender, and race/ethnicity) and previous polyps as covariates. Model 2, the fully adjusted model, included additional adjustments for baseline glucose tolerance status (IGT or NGT), BMI, alcohol use and smoking history. All statistical analyses utilized two-sided tests with the threshold for statistical significance established as $p = 0.05$.

Results

Among the examined baseline characteristics, age and previous adenomatous polyps showed crude association with occurrence of adenoma in 2002–2004 (Table 1). Consistent with previous studies (8), females had higher levels of urinary F_2-IsoPs relative to male. As was shown previously in this cohort (29), race/ethnicity categories were associated with F_2-IsoP levels, with African Americans having the lowest levels of F_2-IsoPs (Table 2). Glucose tolerance was not associated with F_2-IsoP levels. Other characteristics, such as age, BMI, smoking history, and previous polyps were associated with some but not all F_2-IsoPs measured (Table 2).

The minimally and fully adjusted models (Model 1 and Model 2) showed similar results (Figure 1). In both models, the estimates of the associations between F_2-IsoPs and

adenomatous polyps varied around the null (Figure 1). The fully adjusted model yielded the following ORs (95% CIs) for occurrence of colorectal adenomatous polyps scaled to 1 SD of F_2-IsoP distribution: 1.16 (0.88–1.50), 0.88 (0.63–1.17), 1.04 (0.80–1.34), and 1.16 (0.90–1.48) for iPF2α-III, iPF2α-VI, 8,12-iso-iPF2α-VI, and 2,3-dinor-iPF2α-III, respectively. Similarly, we did not find an association between four F_2-IsoPs and advanced adenomatous polyps (n = 24); the ORs for the fully adjusted model with 95% CIs were 1.08 (0.79–1.44), 0.81 (0.55–1.13), 0.96 (0.70–1.28), and 1.12 (0.84–1.47) for iPF2α-III, 2,3-dinor-iPF2α-III, iPF2α-IV and 8,12-iso-iPF2α-VI, respectively.

We could not exclude the possibility that adenomas could be present at the time of urine collection; this was likely to be the case among the participants reporting previous polyps. To address this point, a sensitivity analysis was conducted. Namely, the individuals that reported previous polyps before 2002–2004 were excluded from the analysis. This exclusion did not influence the results; the ORs for the fully adjusted model, with 95% CIs, were 1.20 (0.89–1.59), 0.89 (0.62–1.23), 1.01 (0.74–1.34), and 1.11 (0.84–1.47) for iPF2α-III, 2,3-dinor-iPF2α-III, iPF2α-IV and 8,12-iso-iPF2α-VI, respectively.

Using the minimally adjusted model, we also examined associations with other risk factors for colorectal adenoma. Similar to previously published findings (33–35), occurrence of adenoma was associated with male gender, age, BMI, and smoking status (past, but not current). The associations with gender and smoking status were weak and not statistically significant (data not shown), as previously reported in other cohort studies (33–35).

Discussion

In this prospective study, we examined the potential association between the F_2-IsoPs and adenomatous polyps, a precursor to CRC. Our main finding is that urinary F_2-IsoPs are not associated with occurrence of adenomatous polyps during a 10 year period of follow-up. This suggests that higher oxidative status, as measured by lipid peroxidation, does not promote the development of adenomatous polyps. Furthermore, these findings imply that systemic oxidative status, assessed as oxidation damage to lipids, may not be a risk factor for CRC, although external oxidative exposures are established as risk factors for colorectal cancer. This controversy may be reconciled by considering the differential effects of extraneous exposures on local versus systemic oxidative status. It is possible that the external oxidative exposures promote local oxidative stress within colorectal mucosa and that such local redox shift is not reflected at the systemic level, because systemic oxidative status presents an integrative index of the redox balance of all tissues. It is also possible that oxidative status is more tightly regulated at the systemic level and less balanced at the tissue level. Our data from a previously published clinical model of oxidative stress supports this concept by demonstrating that the systemic oxidative stress induced by chemotherapy is balanced within 24 hours (30). However, tissue-specific side effects of chemotherapy are observed in the most metabolically active tissues (e.g. neurotoxicity and cardiotoxicity) (24). These data suggest that specific tissue-related markers of oxidative status might be more informative, compared to the systemic oxidative status measures, in determining whether internal oxidative stress is a risk factor for a specific cancer.

Previous studies have investigated the association of F_2-IsoPs with cancer, mainly focusing on iPF2α-III (also known as 15-F_{2t}-isoprostane). In men, the risk of lung cancer was increased at higher levels of urinary iPF2α-III, whereas no association was found among women (8). In a case-control study, nested within a multiethnic cohort, no association was found between serum iPF2α-III and the risk of prostate cancer or risk of advanced prostate cancer (9). For breast cancer, the results were even more puzzling; urinary iPF2α-III and 2,3-dinor-iPF2α-III were measured and these markers were associated with breast cancer

risk among women with BMI ≥29, whereas an inverse association was observed among women with low BMI (≤23) (10). Despite the differences in the results and the examined outcomes, the unifying theme in these findings is that none of the cancer types showed an overall association with different measures of systemic F_2-IsoP levels. Even the associations found within sub-groups showed different directions. The convincingly null associations between four urinary F_2-IsoPs (two of which were measured in previous studies) with colorectal adenomatous polyps add to the argument that there is no overall association between these oxidative status markers and certain cancer types. In addition, studies that showed positive associations (with lung and breast cancer) reported shorter follow-up periods (8, 10). For example, in the lung cancer study, the reported median time between specimen collection and diagnosis was one year (10). The studies with shorter follow-up periods could not rule out that clinically undetected malignancies may lead to an increase in urinary F_2-isoP levels. Therefore, it is possible that these putative positive associations could actually represent a consequence and not a cause of cancer.

The strengths of our study lies in the measurement of multiple F_2-IsoPs and in the fact that these F_2-IsoPs have been previously validated in a clinical model of oxidative stress (26). The study also appears to have good external validity, due to the fact that the positive associations with age, smoking status, BMI, and gender were similar to the values previously reported in the literature (33–35). The weakness of our study is lack of colonoscopy at the baseline, suggesting that some of the participants may have had adenoma polyps at the time of urine collection. Because colorectal polyps are often asymptomatic, a portion of the polyps discovered in 2002–2004 could have been present at baseline. The concern is that adenomatous polyps present at baseline could influence the baseline levels of F_2-IsoPs and therefore the results. However, this concern is applicable only to the findings of positive associations. Our null findings imply two possible scenarios if adenomatous polyps were present at the baseline: (1) F_2-IsoP levels remained unchanged during the development of adenomatous polyps or (2) developing these polyps decreased F_2-IsoP levels, which seems to be unlikely as there is no plausible biological hypothesis suggesting such change. To further address this issue, a sensitivity analysis was performed, where those who reported previous polyps were excluded from the analysis, a sub-group with the highest possibility of polyps present at baseline (n=46). This manipulation did not change the final results, suggesting that a potential source of weakness, applicable to this study, is unlikely to be a significant source of distortion in the final results.

In summary, our results do not support the hypothesis that internal systemic oxidative status increases the risk of precursors to CRC. We suggest that the next steps in this research should include specific tissue-related markers of oxidative status.

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Selected Abbreviations and Acronyms

BMI	Body mass index
CI	Confidence Interval
CRC	Colorectal cancer
F2-IsoP	F2-isoprostanes
IGT	Impaired glucose tolerance

IRAS	Insulin Resistance Atherosclerosis Study
LC	Liquid chromatography
MS	Mass spectrometry
NGT	Normal glucose tolerance
OR	Odds Ratio

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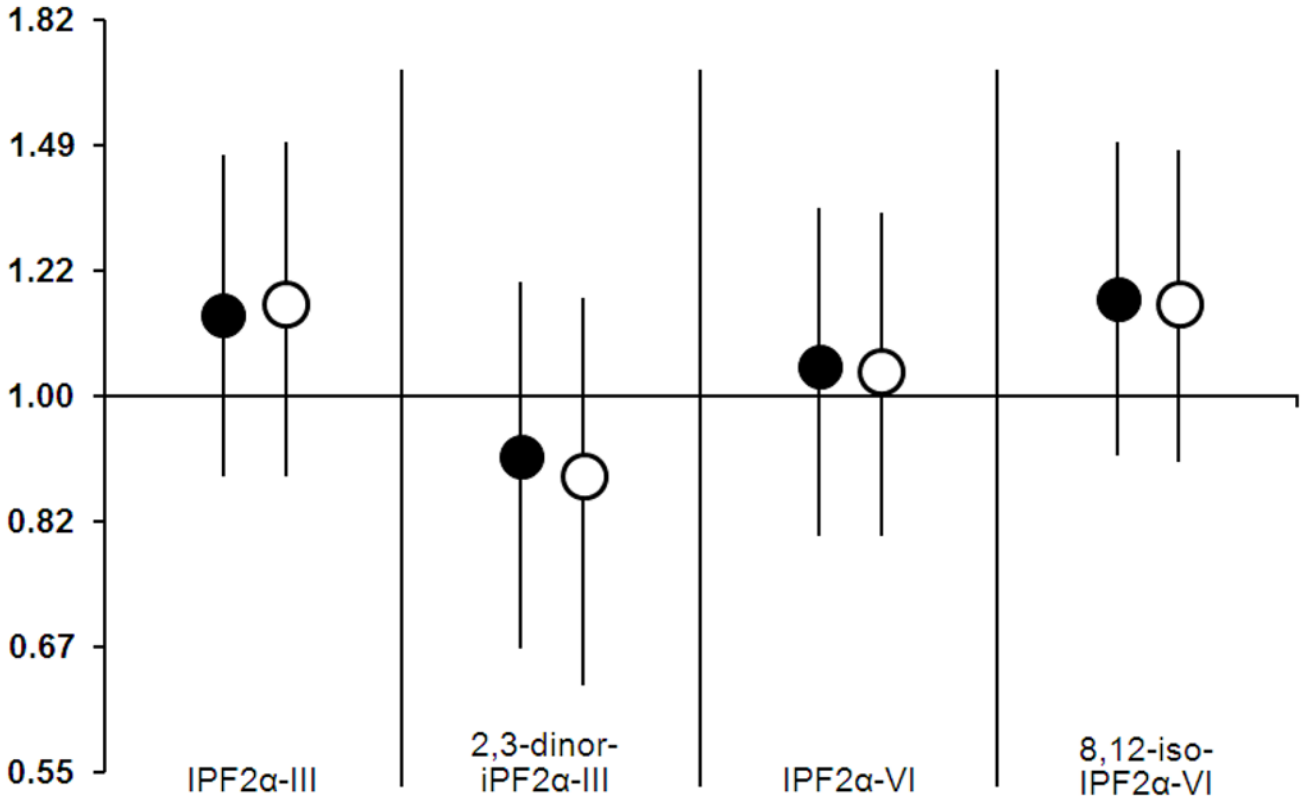

Figure 1.

Prospective association between urinary F_2-Isoprotsanes (ng/mg creatinine) and colorectal adenoma polyps. Model 1 (black circles) is a minimally adjusted model and includes age, gender, race/ethnicity and previous polyps as covariates. Model 2 (white circles) is a fully adjusted model with the additional covariates, IGT-status, BMI, alcohol use, and smoking. Both models showed similar results.

Table 1

Occurrence of colorectal adenoma by demographic characteristics and risk factors among 425 participants in the IRAS cohort study.

Characteristics		Adenomas	NO adenomas[a]
		N (%)	N (%)
Gender	Males	46 (48.9)	134 (40.5)
	Females	48 (51.1)	197 (59.5)
	p-value b	*0.14*	
Age[c]	40–49	21 (22.3)	136 (41.1)
	50–59	39 (41.5)	127 (38.4)
	60–69	34 (36.2)	68 (20.5)
	p-value	< 0.01	
Race/Ethnicity	Black	30 (31.9)	81 (24.5)
	Non-Hispanic White	34 (36.2)	136 (41.1)
	Hispanic	30 (31.9)	114 (34.4)
	p-value	0.34	
Glucose tolerance [c]	NGT	69 (73.40)	241 (72.8)
	IGT	25 (26.60)	90 (27.2)
	p-value	0.91	
BMI[c]	Normal (<25)	21 (22.3)	101 (30.6)
	Overweight (25–30)	46 (48.9)	145 (43.9)
	Obese (>30)	27 (28.7)	84 (25.5)
	p-value	0.30	
Smoking status [d]	Never	39 (41.5)	159 (48.0)
	Former	44 (46.8)	129 (39.0)
	Current	11 (11.7)	43 (13.0)
	p-value	0.39	
Previous polyps [c]	No	74 (78.7)	305 (92.2)
	Yes	20 (21.3)	26 (7.9)
	p-value	< 0.01	
Alcohol intake [c]	Never	36 (38.3)	135 (40.8)
	Ever	58 (61.7)	196 (59.2)
	p-value	0.66	

[a] No adenoma category include participants without polyps and with hyperplastic polyps;

[b] χ^2 test;

[c] Data collected from 1992–1994;

[d] Data collected in 2002–2004

Table 2

Baseline levels of urinary F_2-Isoprotsanes (ng/mg creatinine) in subgroups with different characteristics.

Characteristics		iPF2α-III	2,3-dinor-iPF2α-III	iPF2α-VI	8,12-iso-iPF2α-VI
A. Categorical demographic and baseline characteristics, Mean (SD)					
Case-control status	No-Adenoma, Controls (n=331) [a]	0.25 (0.17)	4.24 (2.68)	6.41 (3.38)	4.10 (2.60)
	Adenoma, Cases (n=94)	0.25 (0.19)	3.91 (2.10)	6.28 (3.95)	4.19 (3.09)
	p-value [b]	*0.7*	*0.3*	*0.8*	*0.8*
Gender	Females (n=245)	0.29 (0.19)	4.92 (2.72)	7.44 (3.95)	4.46 (2.90)
	Males (n=180)	0.18 (0.12)	3.13 (1.90)	4.94 (3.20)	3.66 (2.36)
	p-value [b]	*< 0.01*	*< 0.01*	*< 0.01*	*< 0.01*
Race/Ethnicity	African American (n=111)	0.19 (0.15)	3.47 (2.01)	5.30 (3.08)	3.34 (1.91)
	Non-Hispanic white (n=170)	0.24 (0.14)	3.97 (2.08)	6.20 (3.68)	4.09 (2.62)
	Hispanic (n=144)	0.30 (0.21)	4.93 (3.20)	7.43 (4.33)	4.77 (3.16)
	p-value [c]	*< 0.01*	*< 0.01*	*< 0.01*	*< 0.01*
Glucose Tolerance	NGT (n= 310)	0.25 (0.18)	4.04 (2.41)	6.32 (3.75)	4.15 (2.83)
	IGT (n= 115)	0.24 (0.15)	4.49 (2.93)	6.54 (4.07)	4.05 (2.36)
	p-value [b]	*0.47*	*0.11*	*0.60*	*0.74*
Smoking	Never (n= 198)	0.23 (0.17)	4.10 (2.60)	6.49 (3.96)	4.09 (2.78)
	Former (n= 173)	0.23 (0.15)	3.96 (2.12)	6.08 (3.85)	4.12 (2.76)
	Current (n= 54)	0.34 (0.21)	5.05 (3.45)	6.97 (3.46)	4.23 (2.30)
	p-value [c]	*< 0.01*	*0.02*	*0.30*	*0.95*
Previous polyps	No (n=379)	0.24 (0.17)	4.11 (2.63)	6.36 (3.90)	4.08 (2.63)
	Yes (n=46)	0.30 (0.20)	4.58 (1.94)	6.59 (3.53)	4.45 (3.29)
	p-value [b]	*0.04*	*0.25*	*0.70*	*0.39*
B. Continuous demographic and baseline characteristics					
Spearman Correlation Coefficients *(p-value)*					
Age		−0.02 *(0.66)*	−0.03 *(0.50)*	0.02 *(0.64)*	−0.19 *(< 0.01)*
BMI		0.02 *(0.68)*	0.21 *(< 0.01)*	0.04 *(0.46)*	0.15 *(0.002)*

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Characteristics	iPF2α-III	2,3-dinor-iPF2α-III	iPF2α-VI	8,12-iso-iPF2α-VI
Alcohol intake (g per day)	−0.14 (< 0.01)	−0.06 (0.19)	−0.13 (< 0.01)	−0.003 (0.95)

SD = Standard deviation

[a]No adenoma category include participants without polyps and with hyperplastic polyps;

[b]Student t-test;

[c]ANOVA F-test with *p*-value