Distinctive Metabolomics Profiles associated with African American Current Smokers Who Have High Aggressive Prostate Cancer

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BACKGROUND

Smoking has not been an established risk factor for prostate cancer (PCa), and has not been emphasized in PCa prevention. However, recent studies have shown increasing evidence that there is a higher risk of biochemical recurrence, PCa mortality, and metastasis among current smokers, presenting an urgent need in re-evaluating the association between smoking and aggressive PCa. This study aimed to determine whether smoking increase the likelihood of developing a more aggressive prostate cancer.

METHODS

Participants. Equal numbers of African Americans (AAs) and European Americans (EAs) by smoking status (never/former/current) matched with PCa aggressiveness, BMI, 5-year age group, and year of baseline recruitment, totaling 480 participants, were included in the metabolomics study. PCa cases were classified according to Gleason score (sum of 2 Gleason grades from 2 areas that make up most of the cancer), histologic stage, and prostate-specific antigen (PSA) at diagnosis as follows:

- High aggressiveness = Gleason score ≥ 8 OR PSA > 20 ng/mL OR Gleason score = 7 and stage T3–T4;
- Low aggressiveness = Gleason score < 7 and stage T1–T2 and PSA <10 ng/mL.

Targeted metabolomics. Nicotine metabolites in plasma were assessed using TSQ Quantiva™ triple quadrupole mass spectrometer (Thermo Fisher Scientific) interfaced to a Waters ACQUITY UPLC.

Untargeted metabolomics. Untargeted metabolomics profiling were performed by Metabolon (Durham, NC).

Data analysis. Univariate analysis and machine learning algorithms including principal component analysis (PCA), partial least squares-discriminant analysis (PLS-DA) were used to identify metabolites of interests.

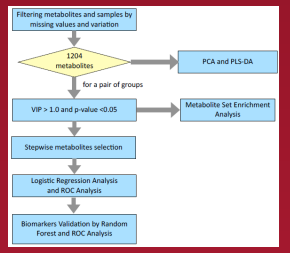

Figure 1. Analysis workflow.

RESULTS

AA participants were significantly younger (mean=61.4, SD=7.7) compared with EAs (mean=63.5, SD=7.5). Global metabolic profiles detected a total of 1,487 metabolites. After excluding metabolites with missing values in more than 50% of the samples (n=280) and with small standard variation (<0.15, n=3), we observed a distinct cluster of participants from AA aggressive PCa patients and current smokers that were separated from EAs and never smokers. With BH-adjusted p-value < 0.05 and fold change > 2, we identified 10 significantly dysregulated metabolites between AA and EA among high aggressive PCa and current smokers. Further, 36 metabolites between current and never smokers among AA high aggressive PCa were significantly dysregulated, but none of them are annotated as tobacco metabolites.

Table 1. Demographic characteristics of study participants.

	High PCa aggressiveness (n=240)	Low PCa aggressiveness (n=239)	*p
	N (%)		
Age	63.0±7.8	61.9±7.6	0.14
Race			NA
African American	120	119	
European American	120	120	
BMI	29.6±6.0	28.5±5.4	0.04
Underweight (<18.5)	1	4	0.08
Normal weight (18.5-24.9)	48	53	
Overweight (25-29.9)	91	108	
Obese (>30)	94	72	
Missing	6	2	
Smoking Status			0.90
Never	80	79	
Former	95	99	
Current	65	61	
Education			0.03
≤ High school	118	113	
Some college degree	110	98	
Grad/Prof degree	12	28	
Study Site			0.06
North Carolina	14	25	
Louisiana	226	214	

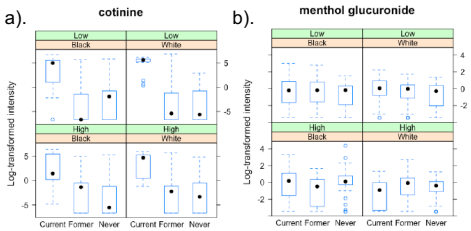

Figure 2. Box plots on levels of cotinine and menthol glucuronide among 479 PCa patients stratified by PCa aggressiveness, race, and smoking status.

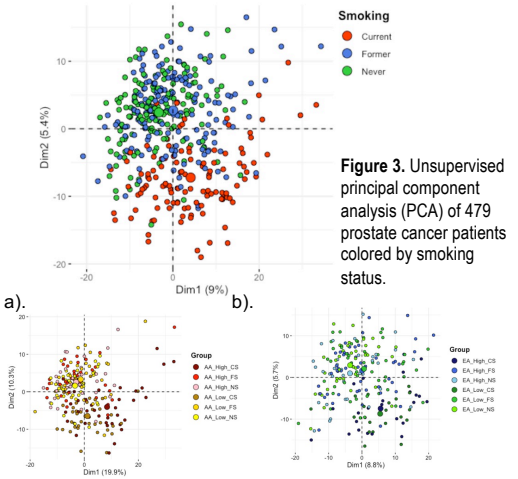

Figure 3. Unsupervised principal component analysis (PCA) of 479 prostate cancer patients colored by smoking status.

Figure 4. PCA of metabolites with p-value < 0.00001 depicting a.) AA from 409 metabolites; b.) EA from 285 metabolites.

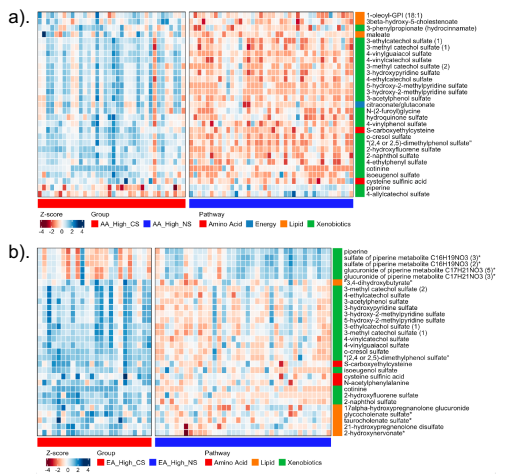

Figure 5. Significant metabolites from smoking (PLS-DA VIP > 2.0, p < 0.05) among high aggressive PCa patients of a) AA; and b) EA.

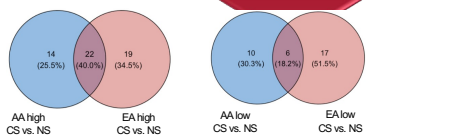

Figure 6. Venn diagram of significant metabolites (VIP > 2, p < 0.05) by high and low PCa aggressiveness.

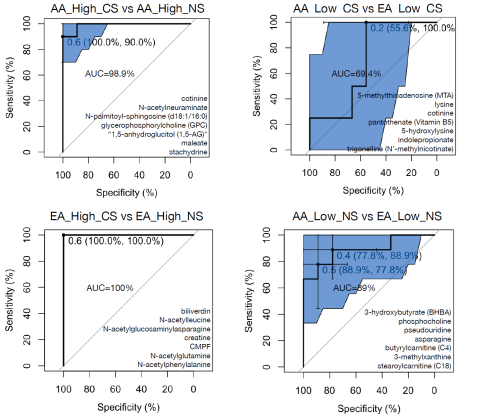

Figure 7. Multi-marker analysis representing metabolite panels distinguishing different groups.

CONCLUSIONS

- Our study presented distinctive metabolomics profiles specific to AA current smokers who had high aggressive PCa.
- Multi-markers were identified, with the potential to understand the relationships between smoking and aggressive PCa.

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