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Urinary 1- and 3-methylhistidine, meat intake, and colorectal adenoma risk

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Abstract

Background—Self-reported red and processed meat intake has been positively associated with colorectal adenoma and cancer; however, measurement error in self-reported data can attenuate risk estimates, increasing the need for improved exposure assessment methods to better understand this association. A controlled feeding study revealed that urinary 1- and 3-methylhistidine were dose-dependently associated with meat intake; our aim was to examine these analytes in relation to colorectal adenoma.

Methods—Individuals undergoing routine cancer screening by sigmoidoscopy or colonoscopy were recruited for a colorectal adenoma case-control study; participants completed a food frequency questionnaire, meat questionnaire, and donated urine. Urinary 1- and 3-methylhistidine were measured in 131 case-control pairs (age, sex, and smoking matched); odds ratios (ORs) and 95% confidence intervals (CI) were calculated by logistic regression.

Results—Although the mean self-reported red meat intake was higher in cases (59g/day) than controls (48g/day), mean urinary 1- and 3-methylhistidine did not differ by case status (P values=0.72). Neither urinary 1-methylhistidine nor 3-methylhistidine were associated with colorectal adenoma ($OR_{\text{continuous}}=0.90$, 95% CI:0.53–1.54; $OR_{\text{continuous}}=0.90$, 95% CI:0.69–1.17, respectively). A variable combining self-reported red meat intake with urinary 1- and 3-methylhistidine levels was not associated with colorectal adenoma. Analyzing urine samples from multiple days from 17 individuals revealed intraclass correlations of 0.52 and 0.49 for 1- and 3-methylhistidine, respectively; this variability could result in attenuated risks.

Conclusion—Urinary 1- and 3-methylhistidine, measured in one sample, were not associated with colorectal adenoma.

Keywords

Urine; methylhistidine; meat; colorectal adenoma

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Introduction

The role of diet in cancer etiology has been investigated for many years; however, the evidence for specific beneficial or harmful dietary components has been largely inconclusive to date. Most epidemiologic studies rely on self-reported dietary data, which is subject to reporting bias and consequently results in misclassification. Biomarkers of dietary intake are not subject to the same errors associated with self-reported data and they may be able to better characterize true exposures by incorporating multiple factors, such as diet, lifestyle, the environment, and genetics; in addition, biomarkers may shed light on potential mechanisms underlying diet-cancer associations. Currently, however, very few biomarkers of dietary exposures have been identified and there are no established biomarkers of meat intake.

Despite the inherent difficulties with accurately assessing diet in epidemiologic studies, self-reported red and processed meat intake has been positively associated with colorectal adenoma and cancer, although the risks are modest, and the association between meat and other malignancies is less clear (WCRF/AICR, 2007). Since there are several potential mechanisms linking meat to carcinogenesis, including heterocyclic amines, polycyclic aromatic hydrocarbons, and *N*-nitroso compounds (Cross and Sinha, 2004), it is important to further investigate the role of meat in cancer etiology by using a more direct measure of exposure.

Both 1- and 3-methylhistidine are present in muscle and, therefore, they are both found in meat. It is known that the majority of urinary 1-methylhistidine is from dietary sources, particularly from meat (Sjolin *et al.*, 1987), whereas 3-methylhistidine is found in the diet and also occurs as a result of muscle catabolism (Lukaski and Mendez, 1980). A controlled feeding study investigated 1-methylhistidine and 3-methylhistidine as potential biomarkers of meat intake and found a dose-dependent association between meat intake and urinary excretion of 1- and 3-methylhistidine (Cross *et al.*, 2011). The aim of this study was to investigate urinary 1- and 3-methylhistidine in relation to colorectal adenoma.

Methods

Study Design

We selected individuals from a case-control study of colorectal adenoma conducted at the National Naval Medical Center (Bethesda, MD) (Sinha *et al.*, 1999). To be eligible for the original study conducted between 1994–1996, cases and controls had to be residents of the study area, aged between 18 and 74 years, and had never been diagnosed with Crohn's disease, ulcerative colitis, colorectal neoplasms, or cancer (except non-melanoma skin cancer), and scheduled to undergo routine colorectal cancer screening. The participation rates in the original study were 84% for cases and 74% for controls (Sinha *et al.*, 1999). All participants completed questionnaires on demographic factors and diet using a validated food frequency questionnaire (FFQ) that was a modified version of the 100-item Health Habits and History Questionnaire (Smucker *et al.*, 1989). In addition to the FFQ, participants completed a validated meat questionnaire that captured detailed information about usual meat intake (Cantwell *et al.*, 2004). Although the FFQ and meat questionnaire

were administered approximately three months after the screening exam, they asked the participants to record their usual diet during the previous 12 months. Cases were defined as patients who were diagnosed with colorectal adenoma at sigmoidoscopy or colonoscopy, and controls were deemed polyp-free in their distal colon and rectum by sigmoidoscopy.

To be eligible for the present study, participants must have completed an overnight urine collection and have sufficient sample remaining in storage. We identified 131 colorectal adenoma cases with no previous history of rectal bleeding and complete questionnaire data, and we matched these to an equal number of controls by age category (5-year groups), sex, and smoking status (ever or never).

Urine Sample Collection and Analysis

The overnight urine collections were non-fasting and they were collected approximately 60–90 days after the colorectal cancer screening exam. Furthermore, we had urine samples from multiple days from 17 individuals, 10 of whom had an overnight urine sample from three different days (there was a median of 5.3 days between the first and third urine collection), and 7 of whom had an overnight urine sample from two different days (a median of 2.0 days apart); these samples were used to assess the variability of 1-methylhistidine and 3-methylhistidine. Urinary 1- and 3-methylhistidine were measured at SAIC (Frederick, MD) using gas chromatography-mass spectrometry and a solid phase extraction method. Cases were placed in batches next to their matched controls, with 36 samples per batch.

Statistical Analysis

Means and frequencies for characteristics of the cases and controls were compared and *P* values were calculated by t-test for continuous variables and by a Chi squared test for categorical variables. We calculated Pearson correlation coefficients for self-reported meat intake variables and urinary 1- and 3-methylhistidine among the controls only.

Odds ratios (OR) and 95% confidence intervals (CI) were calculated by unconditional logistic regression. Models were adjusted for the following covariates: age, sex, education, race, body mass index (BMI), family history of cancer, smoking status, total hours spent in moderate and vigorous physical activity, and fiber intake (g/day). We investigated continuous variables for red meat and white meat (per 10 g/1000kcal) and for processed meat (per 5 g/1000kcal), as well as the log-transformed urine measures of 1- and 3-methylhistidine. We also analyzed both the self-reported dietary data and the urinary markers categorically, using quartile cutpoints determined from the distribution among the controls. Finally, we formed a meat-exposure index that combined the self-reported dietary data and the urinary markers. We identified a group of individuals who were in the highest quartile of self-reported red meat intake and also in the highest quartile of urinary 1-methylhistidine or 3-methylhistidine. In a dichotomous analysis, we determined whether those in this high exposure group were more likely to have had an adenoma than those who did not fall in the highest quartile for both the self-reported meat consumption data and the urine data. We also examined the combined meat intake-urinary data as a categorical variable in logistic regression models using those who were in both the lowest quartile of the self-reported data and the lowest quartile of the urine data as the referent group, those in the

highest quartile of both as the high exposure group, and the remaining people as the middle category.

Results

Cases and controls were approximately 57 years old, 77% were male, 48% were never smokers, and 7–8% were current smokers (Table 1). Both cases and controls were predominantly non-Hispanic white (~86%), with no family history of cancer (~86%), and a mean BMI of 27kg/m² (Table 1). The only observed difference was that cases consumed more red and processed meats than controls (P value=0.02, P value=0.01, respectively).

Urinary excretion of 1-methylhistidine and 3-methylhistidine did not differ between the cases and controls (P values = 0.72; Table 2). While 1-methylhistidine and 3-methylhistidine were correlated with each other ($r=0.60$), their correlations with the self-reported meat variables were weaker (Table 3); 1-methylhistidine was weakly correlated with red meat, white meat, and processed meat ($r=0.21$, $r=0.18$, $r=0.21$, respectively), but 3-methylhistidine was only correlated with white meat ($r=0.25$).

Using self-reported meat intake, there was a suggestive positive association for red meat intake and colorectal adenoma (OR=1.11, 95% CI: 0.97–1.28 per 10g/1000kcal), and a suggestive inverse association for white meat and colorectal adenoma (OR=0.89, 95% CI: 0.78–1.02 per 10g/1000kcal); but no association for processed meat (OR= 0.99, 95% CI: 0.90–1.10 per 5g/1000kcal, Table 4). Neither urinary 1-methylhistidine nor 3-methylhistidine were associated with colorectal adenoma (OR=0.90, 95% CI: 0.53–1.54; OR=0.90, 95% CI: 0.69–1.17, respectively, Table 5). The addition of red and white meat intake as covariates in the models for urinary 1- and 3-methylhistidine and colorectal adenoma did not affect the results (1-methylhistidine: OR_{continuous}=0.90, 95% CI: 0.53–1.53; 3-methylhistidine: OR_{continuous}=0.94, 95% CI: 0.72–1.22 (data not shown).

Using the self-reported dietary data and the urine data, we created a combined exposure variable. Comparing individuals in the highest quartile of both self-reported red meat intake and urinary 1-methylhistidine (or 3-methylhistidine) to all others did not reveal any associations with colorectal adenoma; we also examined a three-level categorical combined exposure variable and the risk remained null (Table 6).

Finally, we examined the variability of 1-methylhistidine and 3-methylhistidine by measuring repeat urine samples from 17 individuals with multiple sample days. The intraclass correlations for 1-methylhistidine and 3-methylhistidine were 0.52 and 0.49, respectively (Figure 1 and Figure 2).

Discussion

In our study using a single urine sample, neither urinary 1-methylhistidine nor 3-methylhistidine was associated with colorectal adenoma. Combining self-reported meat intake data with the urinary data also failed to reveal any associations with colorectal adenoma. However, a small sub-study within 17 individuals identified that these urinary

analytes had a level of intra-individual variation that could result in attenuated risk estimates if only one urine sample is analyzed.

This study was designed to follow-up the dose-dependent association observed between urinary 1- and 3-methylhistidine and meat intake in a controlled feeding study (Cross *et al.*, 2011), a study suggesting that these urinary analytes could be potential biomarkers of meat intake. Although 3-methylhistidine excretion is also related to muscle mass and catabolism (Lukaski and Mendez, 1980), several other studies have reported increased urinary excretion of 3-methylhistidine after meat intake (Block *et al.*, 1965; Elia *et al.*, 1980; Huszar *et al.*, 1983; Lukaski and Mendez, 1980). In contrast, the majority of 1-methylhistidine excreted in the urine is from dietary sources (Sjolin *et al.*, 1987), and measuring this analyte predicted vegetarian status in a study of 126 individuals (Myint *et al.*, 2000).

Although we did not observe a significant association between 1- or 3-methylhistidine and colorectal adenoma, the urinary levels of these analytes in this study were in the same range as those previously reported (Cross *et al.*, 2011), suggesting that the lack of association was not due to low exposure. If a biomarker can capture different data to that obtained from self-reported data, it could be used to complement self-reported data rather than replace it. We did investigate combining the urinary data with the self-reported dietary data but we were not able to detect any associations in this study.

One possible explanation for our null results could relate to the short half-life (~12 hours) of 1- and 3- methylhistidine (Sjolin *et al.*, 1987) and the frequency of meat intake (e.g., daily versus occasionally); therefore, 1- and 3- methylhistidine may be good short-term biomarkers of intake, but insufficient measures of long-term meat intake. Nevertheless, a previous study in free-living individuals did find a positive correlation ($r = 0.77$) between 3-methylhistidine and meat intake reported by dietary recall one year previously (McKeown-Eyssen *et al.*, 1986). A small subset analysis we conducted within our study on 17 individuals with multiple urine samples revealed that 1- and 3-methylhistidine varied within individuals between sample days, suggesting that one urine sample may not be sufficient to represent usual exposure perhaps due to the variability in the frequency of meat intake. The level of variability we observed in 1- and 3-methylhistidine could attenuate risk estimates by a factor of two. Unfortunately, we were unable to determine how many urine samples would be required to adequately assess meat intake from our dataset. Finally, if urinary levels of 1- and 3-methylhistidine are reflecting total meat intake, then our null findings may be the result of the contrasting effects of red compared with white meat on colorectal carcinogenesis; both red meat and processed meats have been positively associated with colorectal adenoma and cancer but white meat has not (WCRF/AICR, 2007). Urinary 1- and 3-methylhistidine levels will also not address potential mechanisms relating meat to cancer, such as exposure to heterocyclic amines and polycyclic aromatic hydrocarbons, compounds formed when meat is cooked well-done by high-temperature cooking methods.

Limitations of our study included the case-control design, although the use of a precursor lesion lessens some of the associated caveats of this study design, and the small sample size, which limits our ability to detect associations with variable data. There is also a possibility that there was misclassification of controls who underwent a sigmoidoscopy rather than a

colonoscopy; although approximately two-thirds of adenomas and cancers arise in the distal colon and rectum within reach of the sigmoidoscope (Parkin *et al.*, 2002). Furthermore, the urine samples were collected after the screening procedure and, therefore, individuals may have subsequently changed their diet; however, a previous analysis in the same study population did observe a positive association between urinary mutagenicity, proposed to be linked to meat intake, and colorectal adenoma (Peters *et al.*, 1994). We must also consider that long-term storage of urine samples may affect the measurement of 1- and 3-methylhistidine. In addition to the inherent instability of urinary markers and the small number of samples, it is well-known that FFQ data is associated with some degree of measurement error, which may have biased the results towards the null. One additional specific caveat was the lack of information on menopausal status in this study; however, 73% of the women were over the age of 51 years and thus likely post-menopausal.

Despite the limitations, this study had several strengths, including the ability to capture two types of exposure data, both self-reported data and the use of biospecimens. The study also had complete case-ascertainment since all participants were screened, meaning the controls were confirmed free from polyps; finally, since the endpoint studied was a precursor lesion, the chances of behavioral and metabolic changes induced by the presence of cancer were minimized.

In conclusion, neither urinary 1-methylhistidine nor 3-methylhistidine was associated with colorectal adenoma; however, a small sub-study revealed considerable intra-individual variability in these urinary analytes. Analyzing these potential urinary markers of meat intake in a single urine sample did not reveal any additional information on the meat and colorectal cancer hypothesis. Our data suggests that future studies of dietary biomarkers in urine should consider collecting multiple urine samples to better characterize exposures.

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Abbreviations

BMI	body mass index
CI	confidence interval
FFQ	food frequency questionnaire
OR	odds ratio

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Figure 1.
Urinary 1-methylhistidine ($\mu\text{mol/day}$) within individuals for multiple sample days

Figure 2.
Urinary 3-methylhistidine ($\mu\text{mol/day}$) within individuals for multiple sample days

Table 1

Distribution and means (SD) for characteristics in 131 cases and 131 controls in the Navy study*

	Cases	Controls	<i>P</i> value [†]
Men, n (%)	101 (77)	101 (77)	1.00
Women, n (%)	30 (23)	30 (23)	
Age (years)	57.6 (9.0)	57.3 (9.0)	0.84
Race, n (%)			
Non-Hispanic Whites	111 (85)	114 (87)	
Other	20 (15)	17 (13)	0.59
Education, n (%)			
< College	47 (36)	37 (28)	
College/Graduate	84 (64)	94 (72)	0.19
Smoking status, n (%)			
Current	10 (8)	9 (7)	
Former	58 (44)	59 (45)	
Never	63 (48)	63 (48)	0.81
Pack years	19.0 (28.8)	14.0 (26.4)	0.15
Family history of cancer, n (%)			
Yes	20 (15)	17 (13)	
No	111 (85)	114 (87)	0.59
BMI (kg/m ²)	26.9 (4.1)	26.6 (5.0)	0.67
Physical activity (moderate + vigorous hrs/wk)	8.3 (9.3)	8.0 (6.0)	0.78
Diabetes, n (%)			
Yes	7 (5)	12 (9)	
No	124 (95)	119 (91)	0.23
Frequency of alcohol/day	1.43 (2.05)	1.64 (2.13)	0.43
Caloric intake (kcal/day)	1698 (661)	1662 (617)	0.64
Total meat (g/day)	103.1 (54.3)	94.9 (45.5)	0.19
Red meat (g/day)	59.0 (42.6)	47.6 (33.0)	0.02
White meat (g/day)	44.0 (26.3)	47.3 (30.0)	0.35
Processed meat (g/day)	22.7 (23.0)	16.0 (14.8)	0.01

* number of individuals (with percentages) for categorical variables and means (with standard deviations) for continuous variables

[†] *P* values were calculated by independent t-tests for continuous variables and by Chi squared test for categorical variables

Table 2

Urinary 1- and 3-methylhistidine levels in men and women from the Navy study

	Cases	Controls	<i>P</i> value*
1-methylhistidine (μmol/day)	n=130	n=129	
Mean (standard deviation)	171.2 (93.4)	175.7 (110.1)	0.72
Median	150.9	149.6	
25 th –75 th percentile	96.7–216.1	97.6–226.4	
3-methylhistidine (μmol/day)	n=126	n=125	
Mean (standard deviation)	508.4 (571.4)	533.9 (576.4)	0.72
Median	286.0	352.3	
25 th –75 th percentile	145.3–657.8	159.3–714.3	

* *P* values were calculated by independent t-tests

Table 3

Pearsons correlations (and *P* values) for urinary analytes and self-reported dietary data among controls only

	Urinary 1- methylhistidine		Urinary 3- methylhistidine		Red meat		White meat		Processed meat	
		<i>r</i> (95% CI)	<i>P</i> value	<i>r</i> (95% CI)	<i>P</i> value	<i>r</i> (95% CI)	<i>P</i> value	<i>r</i> (95% CI)	<i>P</i> value	
Urinary 1-methylhistidine	1									
Urinary 3-methylhistidine		0.60 (0.47–0.70)	<0.0001			0.21 (0.03–0.37)	0.019	0.18 (0.01–0.34)	0.038	
Red meat		1				–0.06 (–0.22–0.12)	0.54	0.25 (0.08–0.41)	0.004	
White meat					1			0.04 (–0.13–0.21)	0.646	
Processed meat						1		0.11 (–0.06–0.28)	0.208	
								1		

Table 4

OR and 95% confidence intervals for colorectal adenoma by self-reported meat intake

Quartile	OR (95% CI) *			
	Q1	Q2	Q3	Q4
Red meat				
Quartile cutpoints ^	0 – 15.9	>15.9 – 24.6	>24.6 – 40.9	>40.9 – 89.3
OR (95% CI)	1.0	0.74 (0.36–1.52)	1.37 (0.67–2.82)	1.40 (0.66–2.96)
White meat				
Quartile cutpoints ^	0 – 16.5	>16.5 – 27.0	>27.0 – 40.7	>40.7 – 128.4
OR (95% CI)	1.0	0.83 (0.40–1.69)	0.96 (0.47–1.98)	0.64 (0.30–1.36)
Processed meat				
Quartile cutpoints ^	0 – 3.1	>3.1 – 7.6	>7.6 – 12.9	>12.9 – 45.5
OR (95% CI)	1.0	0.76 (0.36–1.62)	0.93 (0.43–2.01)	0.98 (0.43–2.23)
				0.99 (0.90–1.10) ‡

* Adjusted for age, sex, education, race, BMI, family history of cancer, smoking status, total hours spent in moderate + vigorous physical activity, and fiber intake (g/day)

^ g/1000kcal

‡ per 10 g increase per 1000kcal

‡ per 5 g increase per 1000kcal

Table 5

OR and 95% confidence intervals for colorectal adenoma by urinary 1- and 3-methylhistidine levels

		OR (95% CI) *			
		Q1	Q2	Q3	Q4 Continuous
Log 1-methylhistidine					
Quartile cutpoints	3.44 – 4.58		>4.58 – 5.01	>5.01 – 5.42	>5.42 – 6.61
OR (95% CI)	1.0		0.81 (0.40–1.66)	0.97 (0.46–2.05)	0.78 (0.35–1.74) 0.90 (0.53–1.54)
Log 3-methylhistidine					
Quartile cutpoints	3.78 – 5.07		>5.07 – 5.86	>5.86 – 6.57	>6.57 – 8.20
OR (95% CI)	1.0		0.89 (0.43–1.85)	0.90 (0.44–1.85)	0.70 (0.34–1.46) 0.90 (0.69–1.17)

* Adjusted for age, sex, education, race, BMI, family history of cancer, smoking status, total hours spent in moderate + vigorous physical activity, and intake of fiber (g/day)

Table 6

OR and 95% confidence intervals for colorectal adenoma by combined self-reported meat intake data and urinary 1- and 3-methylhistidine

	OR (95% CI)*			Dichotomous**
	Category 1†	Category 2‡	Category 3^	
Red meat/1-methylhistidine	1.0	1.37 (0.49–3.83)	2.88 (0.63–13.21)	2.03 (0.73–5.72)
Red meat/3-methylhistidine	1.0	0.61 (0.20–1.91)	0.40 (0.08–1.98)	0.67 (0.23–1.93)

* Adjusted for age, sex, education, race, BMI, family history of cancer, smoking status, total hours spent in moderate + vigorous physical activity, and intake of fiber (g/day)

† lowest quartile in both red meat and methylhistidine

‡ those not in category 1 or category 3

^ highest quartile in both red meat and methylhistidine

** Those in the highest quartile of red meat and in the highest quartile of urinary 1-methylhistidine (17 cases and 8 controls) or 3-methylhistidine (9 cases and 9 controls) compared to all others