Published OnlineFirst November 4, 2019; DOI: 10.1158/1055-9965.EPI-19-0653

Urinary Cotinine Is as Good a Biomarker as Serum Cotinine for Cigarette Smoking Exposure and Lung Cancer Risk Prediction

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ABSTRACT

Background: Cotinine is a metabolite of nicotine. Serum and urinary cotinine are validated biomarkers for cigarette exposure. Their performance for lung cancer risk prediction has not been simultaneously examined in epidemiologic studies.

Methods: A nested case–control study, including 452 incident lung cancer cases and 452 smoking-matched controls in the Shanghai cohort study, was conducted. Mass spectrometry–based methods were used to quantify cotinine in serum and urine samples collected from current smokers at baseline, on average 10 years before cancer diagnosis of cases. Logistic regression was used to estimate ORs, 95% confidence intervals (CI), and AUC ROC for lung cancer associated with higher levels of cotinine.

Results: Serum and urinary cotinine levels were significantly higher in lung cancer cases than controls. Compared with the lowest quartile serum cotinine (≤0.40 nmol/mL), the OR of lung cancer for smokers in the highest quartiles (>1.39 nmol/mL) was 5.46 (95% CI, 3.38–8.81). Similarly, the OR was 5.49 (95% CI, 3.39–8.87) for highest (>16.38 nmol/mg creatinine) relative to the lowest quartile of urinary total cotinine (≤4.11 nmol/mg creatinine). A risk prediction model yielded an AUC of 0.72 (95% CI, 0.69–0.75) for serum cotinine and 0.72 (95% CI, 0.69–0.75) for urinary total cotinine combined with smoking history.

Conclusions: Urinary and serum cotinine have the same performance in prediction of lung cancer risk for current smokers.

Impact: Urinary cotinine is a noninvasive biomarker that can replace serum cotinine in risk prediction of future lung cancer risk for current smokers.

Introduction

Lung cancer is the leading cause of cancer-related mortality in the United States and worldwide (1, 2). Cigarette smoking accounts for up to 90% of lung cancer–related deaths (3). Patients diagnosed with localized lung cancer have a 5-year survival of 56% compared with less than 5% for those diagnosed with metastatic lung cancer (4). However, only 16% of lung cancers are localized and 57% are metastatic at initial diagnosis (4). The National Lung Screening Trial showed that yearly low-dose CT resulted in increased detection of early stage lung cancer and significantly decreased lung cancer–related mortality by 20% in current and former smokers based on their self-reported smoking history (5). An objective biomarker for smoking exposure may increase the precision in identifying high-risk smokers for lung cancer screening and early detection.

Cotinine is a major metabolite of nicotine, the primary addictive agent in cigarette smoke (6). While nicotine itself is not a carcinogen, the quantity of nicotine intake and the metabolism of nicotine can influence or provide an indication of smoking behaviors such as smoking intensity, frequency, and the depth of inhalation by smokers, which contribute to their risk variation of lung cancer (7). In large epidemiologic studies, serum cotinine has been shown to be associated with risk of lung cancer incidence (8, 9). We have shown previously that among multiple cigarette smoke biomarkers including urinary tobacco-specific nitrosamine *N*-Nitrosonornicotine (NNN), 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL), and phenanthrene tetraol (PheT), urinary total cotinine was the strongest independent predictor of lung cancer risk (7, 10, 11). However, the performance of urinary cotinine in lung cancer risk prediction has not been directly compared with that of serum cotinine in prospective studies. Utilizing the resources of the Shanghai cohort study, the objective of this analysis is to simultaneously examine the associations of serum and urinary cotinine with risk of lung cancer, as well as their performance in lung cancer risk prediction.

Materials and Methods

Subjects

This analysis was based on two previous investigations for urinary and serum biomarkers and risk of lung cancer (9, 10). The original source of study subjects was the Shanghai cohort study, a prospective cohort of 18,244 male residents in the city of Shanghai, China when they were 45–64 years old at enrollment during 1986 through 1989 (12, 13). In addition to in-person interviews for information on use of tobacco and alcohol, we collected a 10-mL random nonfasting blood sample and a single-void urine specimen from each of

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Cancer Epidemiol Biomarkers Prev 2020;29:127–32

doi: 10.1158/1055-9965.EPI-19-0653

Published OnlineFirst November 4, 2019; DOI: 10.1158/1055-9965.EPI-19-0653

participants at baseline. We collected both blood and urine samples from study participants at the same time, mostly between 5 pm and 9 pm. The Shanghai cohort study has been approved by the Institutional Review Boards at the Shanghai Cancer Institute (Shanghai, China) and the University of Pittsburgh (Pittsburgh, PA).

Nested case–control study

The detail of the nested case–control study of lung cancer within the Shanghai cohort study was reported previously (10). Briefly, identification of incident lung cancer cases and deaths was accomplished through annual in-person repeat interviews of all surviving cohort members or next-of-kin of deceased participants, supplemented with routine review of reports from the population-based Shanghai Cancer Registry (for cancer) and from the Shanghai Municipal Vital Statistics Office (for death). As of December 31, 2006, 706 cohort participants developed lung cancer.

Among them, 574 were current smokers at the time of biospecimen collection who were eligible for the urinary tobacco smoke biomarkers and lung cancer study (10). For each case, one control subject was randomly chosen from all eligible ones within the cohort who were current smokers at biospecimen collection, free of cancer, and alive at the time of cancer diagnosis of the index case. Controls were matched to the index case by age at enrollment (±2 years), date of biospecimen collection (±1 month), and neighborhood of residence at recruitment.

Laboratory measurements

All serum and urine samples of selected cases and controls were retrieved from the biospecimen bank. To reduce the number of freeze/thaw cycles per sample, multiple aliquots of serum and urine samples were made for each subject, respectively. One aliquot of urine and one aliquot of serum samples were chosen for laboratory assays of biomarkers included in this study. The serum or urine aliquots of each case–control pair were placed next to each other, respectively, so that the laboratory tests for cotinine in serum or urine from the index case and his matched control were conducted in the same batch. The laboratory personnel were blind to the case/control status of the test samples.

Total cotinine in urine, after treated with β-glucuronidase, was quantified using a validated gas chromatography–mass spectrometry method at University of Minnesota (Minneapolis, MN; ref.14). Free cotinine in serum was quantified using the LC/MS-MS at BEVITAL Laboratory (www.bevital.no; ref. 15), as part of the Lung Cancer Cohort Consortium (LC3; refs. 9, 16). The detection limit of total cotinine in urine and free cotinine in serum was 9 pmol/mL and 1 pmol/mL, respectively. The intraday coefficients of variation (CV) of both assays was <3% and interday CVs < 6% (9, 10). Urinary creatinine was assayed by Fairview-University Medical Center Diagnostic Laboratories with a Kodak Ektachem 500 chemistry analyzer.

There were 574 matched case–control pairs of smokers with available urinary total cotinine measurement (10). Among them, 454 pairs were selected for the LC3 study based on availability of serum samples, and two pairs were excluded due to failed assays. This analysis included 452 case–control pairs with available data on both serum and urinary cotinine.

Statistical analysis

Serum cotinine was expressed in nmol/mL and urinary cotinine in nmol/mg creatinine to adjust for differences in water contents in spot urine samples of individual subjects. Because of the skewness of their distributions toward higher values, the median and interquartile values [i.e., the 25th percentile (P_{25}) – the 75th percentile (P_{75})] of serum and urinary cotinine are presented. The Spearman correlation coefficients (r) were calculated for correlation between serum and urinary cotinine. The χ^2 test and Wilcoxon non-parametric testing were used to compare distributions of categorical variables between lung cancer cases and controls. For statistical analysis for continuous values, the logarithmically transformed values of serum and urinary cotinine were used, and their geometric means and 95% confidence intervals (CI) are presented. ANOVA method was used to examine the differences in geometric means of both serum and urinary cotinine across varying number of cigarettes per day.

Conditional logistic regression models were used to calculate ORs and their corresponding 95% CIs and P values. For both urinary and serum cotinine, participants were grouped into quartiles based on the distribution of each cotinine measurement among all controls. Multivariable models for the associations for serum and urinary cotinine with lung cancer risk were adjusted for body mass index (BMI), number of cigarettes per day, and number of years of smoking. The linear trend test for the associations was based on ordinal values (0, 1, 2, and 3) of cotinine quartile categories.

To evaluate the performance of serum and urinary cotinine in prediction of lung cancer risk, various nested multivariate conditional logistic regression models were developed and their log-likelihood ratio (LLR) test statistics were compared. In addition, we calculated the AUC ROC for both serum and urinary cotinine with and without number of cigarettes per day and years of smoking to classify participant's lung case/control status.

Statistical analyses were implemented with SAS Software (version 9.3; SAS Institute). All P values reported are two-sided, and those that were less than 0.05 were considered to be statistically significant.

Results

The median (P_{25} – P_{75}) age of patients at lung cancer diagnosis was 67.6 (63.3–72.3) years and the corresponding figures for controls at the time of cancer diagnosis of index cases was 67.4 (63.5–71.9) years. The median (P_{25} – P_{75}) time interval from baseline biospecimen collection to lung cancer diagnosis was 10.2 (5.8–14.8) years.

The distributions of education level and number of alcoholic drinks per week were comparable between lung cancer cases and controls (**Table 1**). Controls had slightly higher median BMI (kg/m^2) than cases ($P = 0.011$). Lung cancer cases reported greater number of cigarettes smoked per day and greater number of years of smoking, and had significantly higher concentrations of serum and urinary cotinine than controls at baseline.

Both serum and urinary cotinine increased with increasing number of cigarettes per day in both cases and controls. Among controls, the geometric means (95% CIs) of serum free cotinine for <10, 10–<20, and 20+ cigarettes per day were 0.27 (0.20–0.35), 0.58 (0.49–0.69), and 0.95 (0.85–1.06) nmol/mL, respectively ($P < 0$ 0.001). The corresponding geometric means (95% CIs) of urinary total cotinine were 2.6 (1.8–3.6), 6.7 (5.6–7.9), and 10.5 (9.4–11.9) nmol/mg creatinine ($P < 0.001$). No significant association was observed between geometric mean of either serum or urinary cotinine and number of years of cigarette smoking (both P's ≤ 0.15). Urinary total cotinine concentrations were highly correlated with serum free cotinine ($r = 0.85$; $P < 0.001$; **Fig. 1**). High BMI was moderately associated with lower concentrations of serum cotinine ($r = -0.22$; $P < 0.001$) or urinary cotinine ($r = -0.21$; $P < 0.001$) after adjustment for number of cigarettes per day.

Cotinine levels in either serum or urine was associated with significantly increased risk of lung cancer (**Table 2**). Compared with the lowest quartile, the ORs (95% CIs) for lung cancer in the highest

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Table 1. Demographic and lifestyle characteristics of lung cancer cases and controls among current smokers, the Shanghai cohort study.

	Cases	Controls	P^a
Total number of subjects	452	452	
Level of education, *n* (%)			
No formal education	45 (10.0)	39 (8.6)	0.192
Primary school	161 (35.6)	140 (31.0)	
Secondary school	246 (54.4)	273 (60.4)	
Median (25th–75th percentiles)			
Age (year)	57.7 (54.3–61.3)	57.5 (54.2–61.1)	0.456
BMI (kg/m^2)	21.0 (19.3–23.1)	21.6 (19.7–23.9)	0.011
No. of cigarettes per day	20 (15–20)	15 (10–20)	<0.001
No. of years of smoking	37 (31–41)	33 (25–40)	<0.001
No. of alcoholic drinks/ week	3.61 (0–23.33)	3.85 (0–15.76)	0.374
Urinary cotinine (nmol/mg creatinine)	15.1 (9.7–21.5)	9.1 (4.1–16.4)	<0.001
Serum cotinine (nmol/mL)	1.32 (0.92–1.79)	0.84 (0.40–1.39)	<0.001

Abbreviation: No., number.
[a]Derived from Wilcoxon non-parametric test (for medians) or χ^2 (for frequencies) statistics.

Table 2. Association between cotinine concentrations in quartile and risk of lung cancer among current smokers, the Shanghai cohort study.

Biomarker in quartile	No. of cases	No. of controls	OR (95% CI)[a]	OR (95% CI)[b]
Serum cotinine in quartile (nmol/mL)				
1st (≤0.40)	31	113	1.00 (reference)	1.00 (reference)
2nd (0.40–0.84)	62	113	1.83 (1.09–3.07)	1.44 (0.83–2.50)
3rd (0.84–1.39)	154	113	4.32 (2.66–7.02)	2.96 (1.74–5.04)
4th (>1.39)	205	113	5.46 (3.38–8.81)	3.36 (2.00–5.64)
P_{trend}			<0.001	<0.001
Urinary total cotinine in quartile (nmol/mg creatinine)				
1st (≤4.11)	29	113	1.00 (reference)	1.00 (reference)
2nd (4.11–9.15)	66	113	2.08 (1.23–3.53)	1.75 (1.00–3.07)
3rd (9.15–16.38)	159	113	4.52 (2.79–7.31)	3.49 (2.07–5.88)
4th (>16.38)	198	113	5.49 (3.39–8.87)	3.66 (2.18–6.14)
P_{trend}			<0.001	<0.001

Abbreviation: No., number.
[a]ORs were derived from conditional logistic regression models that retained case–control pairs, of which controls were matched to the index cases on current smoking status, age, neighborhood of residence, and year and month of sample collection. Models were adjusted for BMI.
[b]Further adjusted for number of cigarettes per day and number of years of smoking.

quartile of serum and urinary cotinine were 5.46 (3.38–8.81) and 5.49 (3.39–8.87), respectively, before adjustment for number of cigarettes per day and years of smoking, and 3.36 (2.00–5.64) and 3.66 (2.18–6.14) after adjustment for smoking history variables (all $P_{trend} < 0.001$). Further adjustment for other tobacco biomarkers including NNAL, PheT, and the nicotine metabolizer status did not materially change the association between serum or urinary cotinine levels and lung cancer risk (data not shown).

Table 3 shows the LLR test statistics for various nested conditional logistic regression models that included BMI, number of cigarettes, and years of smoking only (M0), plus serum cotinine alone (M1), or urinary cotinine alone (M2) or both (M3). Compared with base model (M0), addition of serum cotinine (M1) or urinary cotinine (M2) significantly improved the goodness-of-fit (both *P*'s < 0.001). When comparing M3 with either M1 or M2, the improvement of goodness-of-fit measured by the net difference in LLRs was statistically significant for urinary cotinine but not for serum cotinine (**Table 3**). The same conclusion was drawn for modelling on continuous values of serum and/or urinary cotinine for lung cancer risk (data not shown). The lung cancer risk predication model yielded the same AUC for serum cotinine (0.67; 95% CI, 0.64–0.70) as urinary cotinine (0.67; 95% CI, 0.63–0.70). With addition of number of cigarettes per day and years of smoking, these risk prediction models also produced the identical AUCs for serum and urinary cotinine (AUC = 0.72; 95% CI, 0.69–0.75). Addition of either serum or urinary cotinine to the model with number of cigarettes per day and years of smoking (AUC = 0.68; 95% CI, 0.64–0.71) significantly increased AUC by 0.04 (95% CI, 0.02–0.06; $P = 0.001$; **Fig. 2A** and **B**).

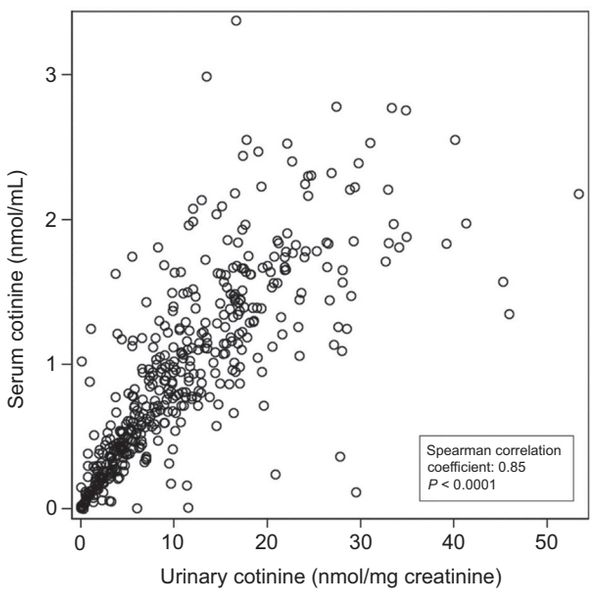

Figure 1.
Scatter plot for serum cotinine concentration (nmol/mL) by urinary cotinine concentration (nmol/mg creatinine) among all smoking controls in the Shanghai cohort study.

Discussion

Our study demonstrates that cotinine concentrations in serum and urine samples collected from free living smokers significantly improved over a model on risk of lung cancer on the basis of self-reported number of cigarettes per day and years of smoking. The association between cotinine measurements in either urine or serum after adjustment for cigarettes per day and years smoking show that the cotinine biomarker measurement remained statistically significant, suggesting that cotinine may provide additional information on self-reported smoking history for determination of individual smoker's lung cancer risk. Additional adjustment for nicotine metabolizer status determined by *CYP2A6* genotype (17) and other cigarette smoke constituent metabolites including NNAL and PheT (10) did not materially change the association between serum or urinary cotinine and lung cancer risk. The prediction of future lung cancer risk by either

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Table 3. LLR test for various conditional logistic regression models in prediction of lung cancer risk with serum and/or urinary cotinine, the Shanghai cohort study.

Model	Additional variables to the base model	Global test			Compared to base model			Net effect of serum or urinary cotinine (M3 vs. M1 or M2)		
		LLR	df	*P*	LLR	df	*P*	LLR	df	*P*
M0	Base model[a]	105.97	3	<0.001	Ref	—	—	—	—	—
M1	Serum cotinine in quartile	139.84	6	<0.001	33.87	3	<0.001	4.99	3	0.173
M2	Urinary total cotinine in quartile	143.42	6	<0.001	37.45	3	<0.001	8.57	3	0.036
M3	Serum and urinary cotinine in quartile	148.41	9	<0.001	42.45	6	<0.001	—	—	—

[a]Including BMI (kg/m^2), number of cigarettes per day, and number of years of smoking.

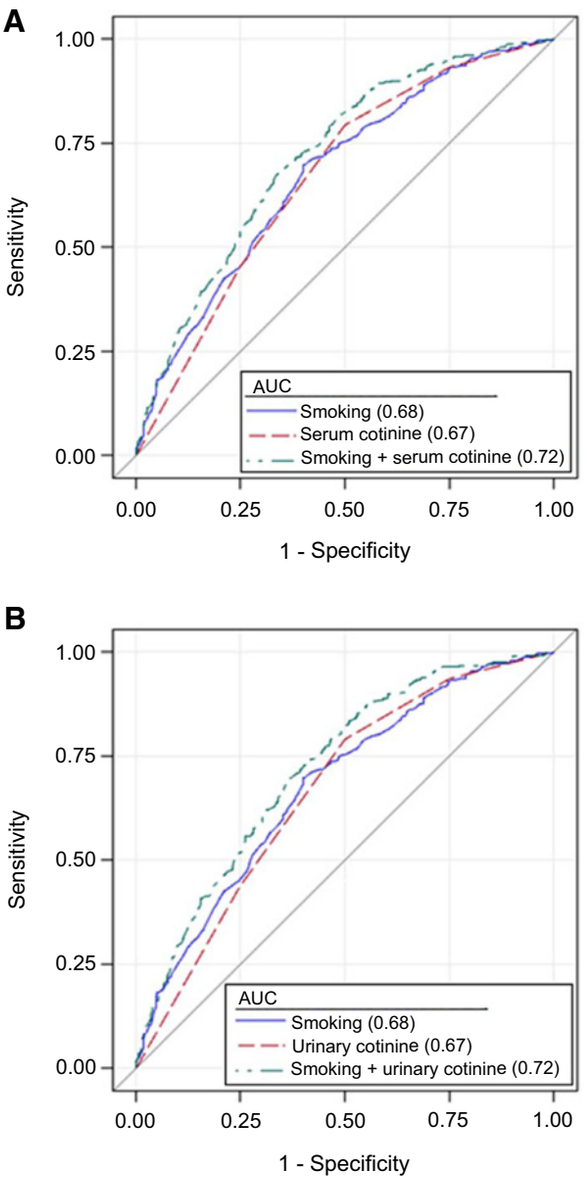

Figure 2.
AUCs for classification of lung cancer status by different risk prediction models. Serum cotinine with and without smoking history variables (cigarettes per day and years smoked; **A**), and urinary total cotinine with and without smoking history variables (**B**).

serum or urinary cotinine or both for current smokers can be on average 10 years before clinical diagnosis. In addition, the performance of risk prediction for lung cancer by urinary cotinine was identical to that by serum cotinine. Ours is the first study to provide direct evidence in support of urinary cotinine to be as good a predictor as serum cotinine for prediction of lung cancer risk. Our results suggest that noninvasive urine-based cotinine can replace blood-based cotinine for prediction of disease risk, and may be beneficial to future studies and clinical care because it is much easier for the collection of urine samples than blood samples, resulting in a higher level of patient compliance.

The associations between blood/circulating or urinary cotinine and lung cancer risk have been examined in previous epidemiologic studies. In a nested case–control study of lung cancer involving 1,741 lung cancer cases and 1,741 matched controls in a Norwegian population, increasing levels of serum cotinine, which was measured using a qualitative immunoassay, was associated with significantly increased risk of lung cancer (8). That study included never, former, and current cigarette smokers, as well as users of other tobacco products, but smoking status was not matched between cases and controls. The OR for lung cancer for the highest level of serum cotinine ($\geq$378 ng/mL or $\geq$2.33 nmol/mL) was 55.1 (95% CI, 35.5–85.0) compared with the lowest level ($\leq$5.0 ng/mL or 0.03 nmol/mL), most of which were nonsmokers. In a recent report based on the international LC3 involving 5,364 lung cancer cases and 5,364 smoking-matched controls from 20 prospective cohorts worldwide including our study, increasing level of circulating cotinine measured by LC/MS-MS was significantly associated with increasing lung cancer risk. Among all self-reported current smokers (2,519 case–control pairs), OR for lung cancer in the highest level of circulating cotinine ($\geq$2.500 nmol/mL) was 4.15 (95% CI, 2.59–6.66) compared with the lowest cotinine ($\leq$0.115 nmol/mL; ref. 9). We previously reported that compared with the lowest tertile (<5.85 nmol/mg creatinine), the highest tertile of urinary total cotinine ($\geq$13.65 nmol/mg creatinine) was associated with a more than 6-fold increase in lung cancer risk (OR = 6.40; 95% CI, 4.36–9.43; ref. 10). However, no large epidemiologic studies have examined simultaneously the associations for serum and urinary cotinine with lung cancer risk.

Studies for the development of methodology for cotinine measurement have shown that the correlation coefficient between circulating and urinary cotinine was higher ($r > 0.90$) in more restricted settings for blood and urine sample collection (18) than in less controlled setting ($r = 0.70$–0.82; refs. 19–21). Our study, in which serum and urine samples were randomly collected from current smokers, produced a correlation coefficient of 0.85, similar to those of previous studies with less controlled setting for biospecimen collection.

Our study has several strengths. The prospective study design established a temporal relationship between serum and urinary cotinine and risk of lung cancer. A relatively large sample size

produced robust estimates of relative risk and risk prediction for lung cancer. Biospecimens for cotinine measurement were collected an average 10 years prior to lung cancer diagnosis, minimizing the potential change of smoking behavior and nicotine metabolism due to the progression and/or subclinical symptom of lung cancer. Both serum and urine samples were collected at the same baseline visit, allowing us to directly compare their performance on lung cancer risk prediction. In addition, the collection of biospecimens usually took place between 5 pm and 9 pm for most participants. This consistency in the timing of the day for the collection of biospecimens, although not fasting, may capture very well the total nicotine intake from tobacco use during the past 12–16 waking hours given a half-life for cotinine of 16–19 hours (22), so that the intraindividual variability in cotinine concentration would be minimized. This study also has several limitations. Biospecimens were only collected once at baseline, which might not represent the long-term nicotine intake from cigarette smoking. Such misclassification usually resulted in an association toward null, thus the magnitude of the association between serum or urinary cotinine and lung cancer risk observed may be underestimated. Another limitation is that the study included only men, so our results may not be directly applicable to women, given that circulating cotinine produced a lower integrated AUC in women than in men in the recent report from LC3 (9). A separate study is needed for serum versus urinary cotinine in prediction of lung cancer risk for women. In addition in the LC3 study, $P_{\text{heterogeneity}}$ in the cotinine–lung cancer risk association among different regions was significant ($P = 0.02$; ref. 9), suggesting that our results from this Chinese population may not be generalizable to U.S. or European populations. Given a large ethnic variation in the genetic polymorphisms of *CYP2A6* (23), the main gene that metabolizes nicotine, additional studies in different populations are warranted to replicate our findings before they could be clinically used for screening and identification of smokers at high risk of lung cancer.

In summary, our study demonstrates that urinary cotinine was highly correlated with serum cotinine in randomly collected biospecimens from free living smokers. Both serum and urinary cotinine had the same performance in risk assessment and risk prediction of future lung cancer risk for current smokers. As a noninvasive biomarker, urinary cotinine may replace serum cotinine to stratify smokers at high or low risk of lung cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

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Acknowledgments

The authors thank Ms. Xue-Li Wang of the Shanghai Cancer Institute for supervising the field work of the Shanghai Cohort Study. We also thank the Shanghai Cancer Registry for assistance with identification of cancer outcomes in the Shanghai Cohort Study. The Shanghai Cohort Study was supported by the NCI grant no. R01CA1144034 and UM1CA182876, and the Lung Cancer Cohort Consortium (LC3) by NCI grant no. 1U01CA155340. Research reported in this article was supported by the NCI of the NIH under award number T32CA186873.

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Received June 7, 2019; revised August 1, 2019; accepted October 29, 2019; published first November 4, 2019.

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Published OnlineFirst November 4, 2019; DOI: 10.1158/1055-9965.EPI-19-0653

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Cancer Epidemiol Biomarkers Prev 2020;29:127-132. Published OnlineFirst November 4, 2019.