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Research Article

Validation of Self-Reported Smoker and Second Hand Smoke Exposure by Urinary Cotinine within The Malaysian Cohort Project

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Abstract

Background: Validation of self-reported questionnaire is very crucial in ensuring the quality and reliability of data collection.

Objective: The aim of this study were i) to validate the questionnaire on tobacco smoke intake and second hand smoke exposure among The Malaysian Cohort (TMC) subjects through the determination of urinary cotinine levels, ii) to determine the optimal cut-off point of urine cotinine that discriminates smokers from non-smokers and iii) to estimate misclassification rate between self-reported smoking and urinary cotinine level..

Methods: Urine samples from a total of 775 The Malaysian Cohort subjects (104 smokers, 102 former smokers and 569 non-smokers) were obtained and urinary cotinine levels were determined by high-performance liquid chromatography (HPLC). Correlation between self-reported questionnaires and urinary cotinine were compared using Spearman's correlation tests. The Receiver Operating Characteristic (ROC) curved was performed to define the optimal cut-off point and the diagnostic ability of urinary cotinine.

Results: Urinary cotinine concentration significantly ($p<0.001$) correlated with smoking status ($r=0.46$), the average number of cigarettes smoked per day ($r=0.53$), duration of smoking ($r=0.33$) and number of cigarettes packed per year ($r=0.47$). Smokers and second hand smokers have significantly higher median cotinine levels (978.40 and 21.31 respectively) compared to non-smokers (15.52) and non-exposed (13.60) subjects. Cotinine level at cut-off value of 1.51 ng/mg creatinine is able to distinguish smokers and non-smokers with a sensitivity of 45.8%, specificity of 96.7%, 84.6% positive predictive value and 81.7%. negative predictive value. The false positive rate and false negative rate were low with 15.4% and 18.3%, respectively.

Conclusion: Cotinine level of 1.51 ng/mg creatinine indicated the optimal cut-off value to distinguish smokers and non-smokers. Self-reported smoking questionnaire showed significant correlation with urinary cotinine and indicated only small misclassification rate. Thus, the self-reported smoking questionnaire can be used to assess smoking exposure with careful interpretation.

Keywords: Urine Cotinine, Self-reported Tobacco intake, second hand smoke.
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INTRODUCTION

Tobacco smoking is the main cause of premature and preventable deaths worldwide. It is estimated that smoking kills 20,000 Malaysians annually and will increase to 30,000 by the year 2020 if the pattern of smoking remains the same[1] . The prevalence of current smoker in Malaysia was 22.8% reported by The National Health Morbidity Survey 2015 (95%CI: 21.9, 23.8) with

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nearly five million Malaysians aged 15 years and above estimated as smokers[1]. The smoking prevalence was comparable with India (24.3%) but lower than other neighboring countries such as Thailand (45.6%), Vietnam (50%), Philippines (53.8%) and China (66.9%) [2,3]. In addition, the prevalence of exposure to second hand smoke (smokers and non-smokers) in Malaysia was 37.1% (95%CI: 35.6, 38.6). Smoking accounted for 16.49 % of the National Health Expenditure in Malaysia or 0.74 % of the GDP. The burden of smoking related diseases; chronic obstructive pulmonary diseases, ischemic heart disease, and lung cancer were 67.53% of the total health care cost with an estimate of RM 1,974,950,532.78 (US$ 533,770,414)[4].

Conventionally, smoking is often assessed by questionnaire due to feasibility and cost effectiveness, however this method is prone to bias and may lead to underestimation of the true prevalence[5,6]. Recall bias and denial due to social stigma are the main source of self-reporting bias especially when the subjects are under pressure because of social or medical disapproval, misunderstanding, intentional deception, embarrassment and shame[7-10]. A number of studies have made an effort to validate self-reported smoking, for example by using exhaled carbon monoxide[11-13], serum, plasma or urine levels of nicotine[14] and also urinary cotinine[15-17]. Nicotine is the primary metabolite that plays important role in tobacco addiction[9]. Thus cotinine, the major metabolite of nicotine, is currently regarded as the best biomarker to detect primary and second hand smokers [18]. To date, biochemical verification on urine cotinine is globally accepted as the gold standard in determining smoking status due to its longer half-life (>20 hours), specificity to nicotine intake, five times higher level in the urine compared to other biological matrixes [19,20,21] and ability to distinguish smokers from non-smokers [18,22,23].

The questionnaire which were used for assessment of tobacco smoke intake and second hand smoke exposure was a modified version of the Global Adult Tobacco Survey (GATS) from the Global Tobacco Surveillance. This tool was design to monitor adult tobacco used and generate comparable data within and across countries systematically. In addition, it is also feasible, cost effective and can be used in population setting. The results from the survey eventually help public health authority to enhance capacity to design, implement and evaluate tobacco control interventions[24-25].

It is crucial to validate the TMC tobacco smoke intake questionnaire since the outcome can be used for documenting the extent of the tobacco epidemic, estimating population risk and smoking-attributable disease burden, and evaluating the progress of tobacco control programs[26].

The aims of this study were; i) to assess the validity of self-reported TMC questionnaire on tobacco smoke intake and secondhand smoke exposure using urinary cotinine concentration, ii) to determine the optimal cut-off point of urine cotinine that discriminates smokers from non-smokers and iii) to estimate misclassification rate between self-reported smoking and urinary cotinine level.

MATERIALS AND METHODS

Data sources and study samples

The study sample was selected from the Malaysian Cohort Project (TMC), a prospective population-based cohort including 106,527 volunteers aged between 35 and 70 years old[27]. Subjects were recruited between April 2006 and September 2012 from regions across Malaysia. For this cross-sectional study, a total of 775 subjects which comprised of 104 smokers, 102 former smokers and 569 non-smokers were randomly selected. Those who underwent nicotine replacement therapy during the recruitment were excluded from this study. All subjects gave written informed consent to participate in the study.

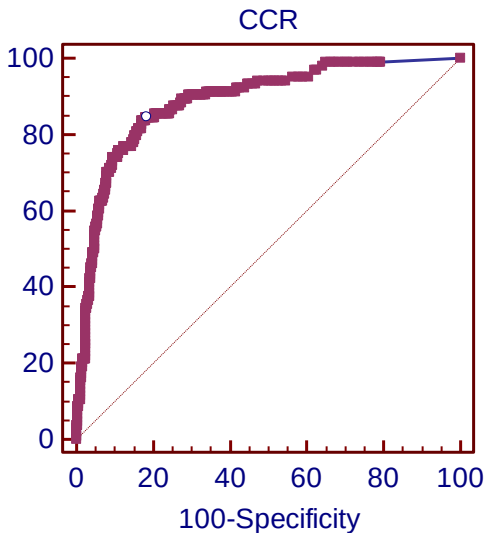

Figure 1: Receiver Operating Curve Characteristics (ROC) of the normalised cotinine level measured as cotinine in ng per creatinine in mg. Smokers were well differentiated from non-smokers; AUC: 0.89.

Self-reported smoking and related status

Current smokers were defined as those who responded affirmatively to questions on: i) ever use of tobacco products, ii) smoked at least 100 sticks cigarettes in entire life, and iii) still smoking. Ex-smokers were those responded positively to the question (i) and (ii) and negative for (iii) **(Supplementary data**). Conversely, the non-smokers were defined as those who responded negatively to all three questions. Non-smokers were further divided into (i) passive smokers, who were exposed to second hand smoke either from family and workplace and (ii) non-smokers who have no exposure to second hand smoke. Others information related to smoking were also recorded such as quantity of cigarettes, duration of smoking, age started to smoke and type of tobacco used .

Urinary cotinine determination

Urine samples were collected prior to 8 hours fasting. Urinary cotinine were extracted and measured by using the high performance liquid chromatography (HPLC)

system (Agilent 1200 Series) according to the method described previously with slight modifications[28]. Briefly, urine samples were hydrolysed with 10 M sodium hydroxide, followed by liquid-liquid extraction with dichloromethane. The extracts were dried under nitrogen stream and reconstituted with 200 µl mobile phase comprised of 0.07M citric acid: 0.1 M sodium acetate: acetonitrile: methanol (10:5:3:2), pH 4.4 adjusted by acetic acid. Cotinine was eluted isocratically on a LC-8-DB Supelcosil column (250 mm X 5 µm ID) and detected by photodiode array detector at 260 nm. The detection limit of this method is 5 ng/ml. The cotinine levels were subsequently normalized with urinary creatinine (Cr) and the data were reported as cotinine/creatinine ratio (CCR), (ng/mg Cr). The urinary creatinine levels were measured by using Urinary Creatinine Detection Kit (Arbor Assays; Luminos USA) with absorbance values read by using microplate reader (Biotek, US) at λ= 490nm. Urinary cotinine levels were analysed as both adjusted and unadjusted values by creatinine level.

Table 1: Demographic data of the study (n=775)

Characteristic		N (%)
Age (years)	<40	75 (9.6)
	41-50	303 (39.1)
	51-60	315 (40.7)
	>61	82 (10.6)
Gender	Male	375 (48.4)
	Female	400 (51.6)
Ethnic groups	Malays	193 (24.9)
	Chinese	441 (56.9)
	Indian	134 (17.3)
	Others	7 (0.9)
Education level	No formal education	37 (4.8)
	Primary	106 (13.7)
	Secondary	378 (48.8)
	Tertiary	254 (32.8)
Marital status	Single	61 (7.9)
	Married	652 (84.1)
	Widowed	38 (4.9)
	Divorced	24 (3.1)
Working status	Working	291 (37.5)
	Not working	484 (62.5)
Type of tobacco use	Filtered kretek	201 (25.9)
	White cigarette	197 (25.4)
	Filtered white cigarette	196 (25.3)
	Kreteks	30 (3.9)
	Paper cigarette (rokok daun)	14 (1.8)
	C*igar*	5 (0.6)
	Pipe	5 (0.6)
	C*heroot*	4 (0.5)
	Bidis	3 (0.4)
	Chewed tobacco	3 (0.4)

Statistical Analyses

Non-parametric test was done due to the fact that the distribution of the data was not normal even though data transformation has been applied. Differences between groups were compared using Kruskal Wallis and Mann-Whitney tests. Correlation between urine cotinine concentration with smoking characteristics were analysed using Spearman's rank correlation.

The Receiver Operating Characteristic (ROC) curve was performed to obtain the optimal cut off to discriminate smokers from non-smokers as well as passive smokers and non-smokers. The optimal cut-off point commonly used Youden index (J) method[29]. This method defines the optimal cut-point as the point maximizing the Youden function which was the difference between true positive rate and false positive rate over all possible cut-point values. An optimal cut-point was referred when the point classifies most of the individuals correctly. ROC curve mapped the sensitivity versus 100 − specificity for all possible values of the cut-point between smokers and non-smokers.

A cut-off point of cotinine level in the urine with AUC = 100 discriminates individuals perfectly as smokers, while, an AUC = 50 means that there was no substantial difference between the level of urinary cotinine values of the two groups (smokers and non-smokers)[29].

A significance threshold was set at $p<0.05$. All statistical analyses were conducted using IBM SPSS (Version 19).

RESULTS

Based on the self-reported tobacco smoking questionnaire, a total of 104 (13.4%) smokers, 101 (13.0%) ex-smokers and 570 (73.6%) non-smokers were classified based on different ethnic groups: Chinese (56.9%), Malay (24.9%), Indian (17.3%) and others (0.9%) (**Table 1 and Table 2**). In general, majority of the

Table 3: Correlation between urinary cotinine concentration with self reported tobacco intake questionnaire

Item	Correlation coefficient (r)	p value
Smoking status	0.46	0.001*
Average cigarettes smoked per day	0.53	0.001*
Age started to smoke	-0.08	0.443
Smoking duration (years)	0.33	0.001*
Smoking history (packed/years)	0.47	0.001*

subjects were female, married (84.1%), aged between 51 to 60 years old (40.7%), had secondary education (48.8%), unemployed (62.5%) and smoking using white cigarette/ filtered white cigarette (50.7%) (**Table 1**).

Most of the subjects have reported previous history of smoking more than 20 packs of cigarettes per year (36.54%). However, the median of urinary cotinine and CCR were highest in subjects with history of smoking 11

Table 2: Urinary cotinine and cotinine/creatinine ratio (CCR) levels by smoking characteristics.

			Cotinine concentration (ng/ml)	**CCR (ng/mg Creatinine)**
Smoking characteristics	**n**	**%**	**Median±(IQR)**	**Median±(IQR)**
Smoking status				
Smoker	104	13.42	978.4(1612.75)	9.72±(20.12)
Ex-Smoker	101	13.03	17.85(54.16)[a]	0.22±(0.82)[a]
Non-smoker	570	73.55	15.50(34.25)[a]	0.29±(0.84)[a]
Smokers				
Averaged number of cigarette smoked per day				
<10	52	50.01	454.62 (1021.98)	4.80 (15.35)
11 to 20	42	40.38	1328.26 (1398.66)[b]	17.46 (30.04)[b]
>20	10	9.61	1196.65 (1349.28)[b]	15.06 (42.06)[b]
Age started smoking				
< 17	27	25.96	876.17 (1094.87)	10.31 (19.19)
18 - 25	61	58.65	1160.28 (1793.56)	14.15 (32.73)
> 25	16	15.38	609.87 (1110.35)	6.19 (10.42)
Tobacco smoking history (pack-years)				
<10	34	32.69	278.62 (685.81)	2.69 (7.18)
11 to 20	29	27.88	1160.28 (1730.60)[c]	17.35 (37.81)[c]
>20	38	36.54	1350.41 (1317.56)[c]	15.37 (30.98)[c]
Non-smokers				
No second hand smoke exposure at home and workplace	264	46.4	13.60(30.36)	0.28(0.79)
Second hand smoke exposure at home	96	16.87	21.31(62.47)[d]	0.44(1.41)
Second hand smoke exposure at workplace	143	25.13	15.19(47.76)[d]	0.28(1.02)

[a] $p<0.05$ as compared to smokers
[b] $p<0.05$ as compared to number of cigarette smoked per day <10
[c] $p<0.05$ as compared to tobacco smoking history (pack-years) <10

Smokers showed significantly higher median of urine cotinine and CCR (urine cotinine: 978.4 ng/ml; CCR: 9.72 ng/mg Cr) as compared to ex-smokers (urine cotinine: 17.85 ng/ml; CCR: 0.22 ng/mg Cr) and non-smokers (urine cotinine: 15.50 ng/ml; CCR: 0.29 ng/mg Cr). The levels of urine cotinine and CCR were significantly increased in smokers who reported intake of 11-20 cigarettes per day in comparison to less than 10 cigarettes per day, 1328.26 ng/ml vs. 454.62 ng/ml and 17.46 ng/mg Cr vs. 4.81 ng/mg Cr), respectively (**Table 2**). Similar increment was observed in smokers with more than 20 cigarettes per day as compared to those with less than 10 cigarettes per day (urine cotinine: 1196.65 ng/ml vs. 454.62 ng/ml and CCR: 15.06 ng/mg Cr vs. 4.80 ng/mg Cr). More than half of the subjects had started smoking at the age of 18-25 years old (58.65%) and this data is in agreement with the levels of urine cotinine and CCR measured in which the highest median was shown by this age group (**Table 2**).

to 20 packs per year. Second hand smoke exposure at home and at workplace showed significant difference in urinary cotinine level compared to no exposure with the highest level of cotinine found in subjects who had reported exposure at home, followed by exposure at workplace.

In addition, we found that the creatinine-adjusted urinary cotinine levels were positively correlated with smoking status ($r=0.46$, $p=0.001$), averaged number of cigarettes smoked per day ($r=0.53$, $p=0.001$), smoking duration ($r=0.33$, $p=0.001$) and smoking history (number of pack per year) ($r=0.47$, $p=0.001$) as per self-reported questionnaires (**Table 3**).

The cut-off point for cotinine at 1.51 ng/mg Cr gave a good discrimination between smokers and non-smoker as showed by the Receiver Operating Characteristic (ROC) curve with area under the curve, AUC = 0.89 (**Figure 2**). Majority of the smokers had urinary cotinine level more than 1.51 ng/mg Cr (84.6%), while 81.7% non-smokers and 84.3% ex-smokers had urinary cotinine

Table 4: Contingency table of Cotinine concentration at cut off value of 1.51 ng/mg creatinine

	Number of subjects, n (%)		
Smoking status	**Cotinine concentration >1.51 ng/mg creatinine**	**Cotinine concentration ≤1.51 ng/mg creatinine**	**Total**
Smokers	88 (84.6)	16 (15.4)	104
Ex-smokers	16 (15.7)	86 (84.3)	102
Non-smokers	104 (18.3)	465 (81.7)	569
Total	208 (26.84)	567 (73.16)	775

Table 5: Diagnostic parameters of cotinine concentration.

		Cotinine concentration		
Self-reported smoking	**Smoking status**	**Smokers**	**Non-smokers**	
	Smokers	88 (TP)	16 (FP)	**PPV**: 0.85
	Non-smokers	104 (FN)	465 (TN)	**NPV**: 0.82
		Sensitivity: 0.46	**Specificity**: 0.97	

TP: True Positive, FP: False Positive, FN: False Negative, TN: True Negative, PPV: Positive Predictive Value, NPV: Negative Predictive Value

level less than 1.51 ng/mg Cr (**Table 4**). The cut-off value also gave a good diagnostic accuracy results with sensitivity of 42.3%, 96.7% specificity, 84.6% positive predictive value and 81.7% negative predictive value. The false positive rate and false negative rate were low with 15.4% and 18.3%, respectively (**Table 5**). The prevalence of smoking was lower based on self- reported questionnaire (13.42%) as compared to prevalence using cotinine levels above 1.51 ng/mg Cr (26.84%).

DISCUSSION

Based on the self-reported data, the prevalence of smoking from this study was 13.42% which was lower than the recent prevalence data from the Malaysia National Health and Morbidity Survey (22.8%)[1]. However, based on the laboratory results obtained in this current study, prevalence value was slightly higher (26.84%) and closed to the value reported by the Malaysia National Health and Morbidity Survey. The discrepancy of the prevalence might be due to the under-reporting of the result. This is consistent with previous study that also found underestimation of self-reported smoking while cotinine was considered as more accurate biomarker of smoke exposure[30]. In this study, we found smokers have significantly higher levels of urinary cotinine as compared to ex-smokers and non-smokers. There was a relationship between urinary cotinine and smoking among the smokers with the higher number of cigarettes smoked per day correlated with higher levels of the measured urinary cotinine. In addition, the questionnaire items which were smoking status, averaged number of cigarettes smoked per day, smoking duration and number of cigarettes packed per year indicated significantly moderate correlation (0.33-0.47) with urine cotinine. These results were consistent with other findings conducted in a similar population[14]. The results showed that, although self-reporting questionnaires typically underestimate the smoking rate, such outcomes are still highly consistent with those determined through a urinary test. Thus, self-reporting questionnaires can serve as an effective tool for assessing smoking behaviour. Taken together, these results indicated that our questionnaires are consistent in capturing smoking and secondhand smoker status.

To date, there is no standardised urinary cotinine cut-off value for differentiating smokers from non-smoker. It remains arbitrary due to the overlap between non-smokers who are highly exposed to second hand smoke and occasional smokers or those who inhale very little smoke. Our study indicate that the cotinine cut-off value of 1.51 ng/mg Cr was an optimal value to distinguish the smoking status with an acceptable sensitivity and specificity in the Malaysian population. However, our proposed cut-off value was higher than the value reported from a population study among young Malaysian adults in 2009[14]. It is important to note that our data used adjusted creatinine-corrected cotinine level for differences in urinary excretion volume whereas the latter was without creatinine normalization. Moreover, the difference in population age may contribute to the discrepancy, as younger adult smokers are likely in the process of becoming established smokers.

Nonetheless, the disparity of the cut-off value is very much dependent on the concentration of the urinary

cotinine. The concentration of urinary cotinine are reliant on individual variability such as the duration and the intensity of exposure or smoking, the pattern of smoking and nicotine uptake, metabolism and elimination rate [31-33]. Furthermore, the cut-off points of urinary cotinine may also be influenced by ethnic specificity due to racial differences in nicotine pharmacokinetics and genetic polymorphisms[10-34].

The range of misclassification between self-reported non-smokers and ex-smokers obtained in this study using the optimal urinary cotinine cut-off value of 1.51 ng/mg Cr was in accordance with another study conducted in the Aboriginal population[35].However, some studies reported a wider range, between 6.4% to 57.1% in Aboriginal and Indian populations[36,37]. In spite of this, the comparison of smoking misclassification across studies needs to be interpreted cautiously as each study is different in terms of design and methodology such as the cut off points to distinguish smokers from non-smokers, the use of creatinine normalization, study settings (clinical settings compared with community based studies), denominators used for misclassification rates (smokers compared with non-smokers), analytical techniques (gas chromatography compared with radioimmunoassay), racial differences in nicotine metabolism, education level, past smoking history and smoking habits (smoking behaviours that may affect nicotine intake)[9,10,34]. In this study, measurement of cotinine level was performed by using HPLC tool, which provides superior sensitivity and specificity as compared to other biochemical techniques used in cotinine quantitation such as enzyme-linked immunosorbent assay[38] and colorimetric-based autoanalyser assay[39], but more cost effective as compared to higher end mass spectrometry[40] and radioimmunoassay[41]. The positive correlation between the measured creatinine-adjusted urinary cotinine and smoking status demonstrates the reliability of this practical yet economical approach for evaluating exposure to smoking, especially in laboratories not equipped with high-end mass spectrometry system.

The grey zone still exists between occasional smokers and non-smokers exposed to second hand smoke, where differentiation is deemed challenging. This is further supported by the fact that the serum cotinine level in these occasional smokers decreased rapidly in a short period of time as compared to their 'heavier' counterparts[10]. Nevertheless, the use of a biological marker such as cotinine as applied in this study to validate self-reported data on smoking is relevant as recall bias and social stigma have been implicating the accuracy of the self-reported data in the form of questionnaire where under-reporting of the true smoking event was consistently observed[10]. Apart from its applicability for validating self-reported smoking data, this urinary cotinine assessment can be incorporated as additional assessment on high-risk population who is exposed to second-hand smoke towards smoking-related diseases. Nonetheless, more studies are needed to link those diseases to cotinine levels with careful interpretation particularly in relation to the cut-off points prior to its clinical application.

CONCLUSION

Cotinine level of 1.51 ng/mg creatinine indicated the optimal cut-off value to distinguish smokers and non-smokers. Self-reported smoking questionnaire showed significant correlation with urinary cotinine and indicated only small misclassification rate. Thus, the self-reported smoking questionnaire can be used to assess smoking exposure with careful interpretation.

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