Original Article

Assessing how lung cancer screening guidelines contribute to racial disparities in screening access

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Background: Lung cancer (LC) is the leading cause of cancer-related deaths in the United States (U.S.), with non-White people who smoke often bearing the burden of the highest rate of LC mortality. This is often due to later stage diagnoses, leading to poor prognosis and outcomes. We assess here how the eligibility criteria for LC screening set by the U.S. Preventive Services Task Force (USPSTF) and the Centers for Medicare and Medicaid Services (CMS) could contribute to racial disparities in screening access.

Methods: This paper analyzes data from the National Health and Nutrition Examination Survey (NHANES), an annual survey conducted by the Centers for Disease Control and Prevention (CDC) that gathers health and nutrition data from a representative sample of the U.S. population. After excluding those who were ineligible for LC screening, the final cohort of participants was 5,001, which consisted of 2,669 people who formerly smoked and 2,332 people who currently smoke.

Results: Out of 608 participants who were eligible for LC screening, 77.5% were non-Hispanic White (NHW) and 8.7% were non-Hispanic Black (NHB) participants versus 69.4% and 10.8% among 4,393 ineligible participants. Age, pack-years, and age along with pack-years were the most frequent reasons for ineligibility. LC screening ineligible NHW participants were statistically significantly older and had higher mean pack-years than the other racial and ethnic groups. NHB participants among the ineligible group had higher urinary cotinine levels compared to NHW participants.

Conclusions: This paper underscores the need for more individualized risk estimates when determining eligibility for LC screening, which could include biomarkers of smoking exposure. The analysis shows that current screening criteria, which rely solely on factors such as age and pack years, contribute to LC racial disparities.

Keywords: Lung cancer screening; cotinine; biomarkers; race; low-dose computed tomography (LDCT)

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Introduction

Lung cancer (LC) is currently the third most common cancer in the United States (U.S.) and the leading cause of cancer related deaths (1). In 2022, an estimated 236,740 people will be newly diagnosed with LC and 130,180 will die from this disease (2). Of those with LC in the U.S., only 19% are diagnosed at the localized stage while 55% are diagnosed at a later stage, when the cancer has already metastasized. The prognosis for such late diagnosed LC is poor, with a 5-year relative survival of only 7% (1).

However, emphasis on screening and early detection in the past decade has resulted in a stage shift for LC diagnoses, with an increasing percentage of people being diagnosed with localized-stage LC—which has a 61.2% 5-year relative survival (1,2). Since LC outcomes are highly dependent on the stage of diagnosis, LC screening has been considered a powerful tool in decreasing LC mortality in the U.S. (2).

In 2021, The U.S. Preventive Services Task Force (USPSTF) released updated guidelines for annual LC screening. Currently, screening with low-dose computed tomography (LDCT) is recommended for adults between the ages 50 and 80 years old with at least a 20 pack-year smoking history who currently smoke or who have quit smoking in the past 15 years (3). These guidelines were modified from the original guidelines that the USPSTF released in 2013, which recommended screening for those between the ages 55 and 80 years old with at least a 30 pack-year smoking history who either currently smoke or who have quit smoking in the past 15 years (4).

The current USPSTF guidelines for LC screening were primarily informed by the results of three studies: The Early Lung Cancer Action Project (ELCAP), The National Lung Screening Trial (NLST), and Nederlands-Leuvens Longkanker Screenings Onderzoek (NELSON) (3). ELCAP was the first study conducted in the U.S. which demonstrated that LDCT screening for LC increases the likelihood of earlier stage LC detection through increased detection of small non-calcified nodules (5). The results of ELCAP were echoed in NLST and NELSON, which were the only RCTs adequately powered to detect the impact of screening on LC mortality (3). In NLST, a 20% relative risk reduction for LC mortality was observed in those who were screened with LDCT compared to those screened with chest radiographs (6). Similarly, the incidence rate ratio for LC mortality in the NELSON trial was 0.75 in those screened using LDCT compared to no screening (7). Given these positive findings, the USPSTF recommended age and cigarette smoking exposure cutoffs for LC screening that were similar to the eligibility criteria in ELCAP, NLST, and NELSON (3).

It is important to note that the studies which informed the USPSTF LC screening guidelines include a homogeneous population in terms of the race and ethnicity of the participants. Of the 1,000 participants in the original ELCAP study, 91% of them were White, 5% were Black, 2% were Hispanic, and 2% were of other ethnic origin (5). Similar racial distributions were observed in NLST: of the 53,454 participants, 90.9% were White in the LDCT group and 90.8% were White in the chest radiography group, while only 4.5% were Black in the LDCT group and 4.4% were Black in the chest radiography group (6). The NELSON trial, conducted in the Netherlands and Belgium, did not report racial distributions (7). The lack of a conspicuous number of racial and ethnic minority participants in these studies begs the question whether the USPSTF guidelines for LC screening are truly generalizable to all racial groups.

Racial disparities in LC screening have become increasingly evident. For example, though Black men have the highest rates of LC incidence and mortality and though Black individuals are disproportionately diagnosed at later stages of LC, they are underrepresented in LC screening, primarily due to not meeting screening criteria (2). The USPSTF 2021 guidelines for LC screening acknowledge that the smoking exposure cutoff for screening was lowered from 30 pack-years in the 2013 guidelines to 20 pack-years in the current guidelines, in part to improve racial disparities in LC screening (8). We analyze here the National Health and Nutrition Examination Survey (NHANES) dataset to assess if racial disparities in screening eligibility still persist despite the changes in guidelines.

Highlight box

Key findings

- Non-White people who smoke have been systematically left out of lung cancer screening efforts, though they stand to benefit most and are at the highest risk for poor lung cancer outcomes.

What is known and what is new?

- Black people who smoke have a higher risk of developing late-stage lung cancer and a higher risk of lung cancer mortality than White people who smoke, though they smoke fewer cigarettes.
- Despite having lower average smoking exposure, most of non-White people who smoke have higher average levels of urinary cotinine, indicating a higher level of exposure to carcinogens found in tobacco.

What is the implication, and what should change now?

- Current lung cancer screening criteria should be re-examined, since it does not adequately capture the risk of non-White people who smoke. Biomarkers such as cotinine should be considered in the development of new risk-based models for screening eligibility.

Methods

NHANES is a cross-sectional survey administered by the Centers for Disease Control and Prevention (CDC) that is intended to assess the health of civilians in the

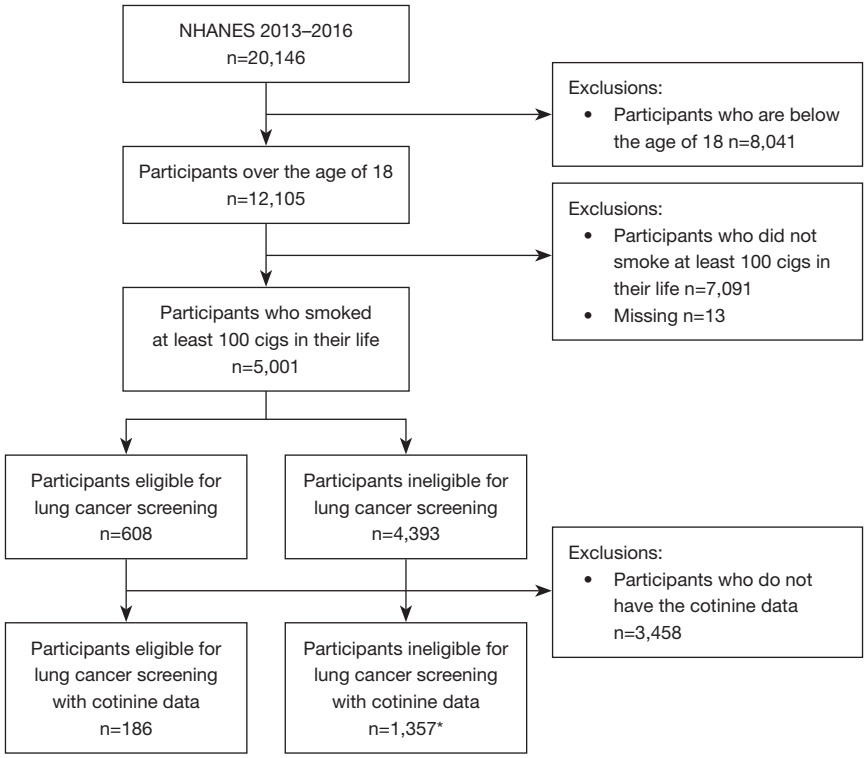

Figure 1 Selection of participants. NHANES, National Health and Nutrition Examination Survey. *, 21 have cotinine below detection limits.

U.S. Non-institutionalized adults and children residing in the U.S. are included in the NHANES, which uses a complex, multi-stage probability sampling design to create a nationally representative sample of the U.S. population. Several thousand people residing in counties all over the U.S. are selected to participate in each 2-year data cycle of NHANES. NHANES consists of a health interview, physical examination, and laboratory testing. Data from NHANES are de-identified and publicly available.

Data for this study were derived from the NHANES 2013–2014 and NHANES 2015–2016 cycles, when 20,146 participants were interviewed, 12,105 of which were 18 years or older. This age cutoff was chosen since most of the variables regarding smoking status in NHANES are recorded only in participants ages 18 and older. The standard cutoff of at least 100 cigarettes smoked in a lifetime was used to designate which participants have ever smoked. Participants who did not know if they had smoked 100 cigarettes in their lifetimes, refused to answer this question, or who had never smoked (had smoked fewer than 100 cigarettes in their lifetimes) were excluded from the present analysis ($n_{excluded}$=7,104). The final cohort consisted of 5,001 participants, of which 2,669 were people who formerly smoked and 2,332 were people who currently smoke (*Figure 1*). Pack-years were estimated using age, lifetime duration of smoking cigarettes, and smoking intensity, defined as number of cigarettes smoked per day.

Eligibility for LC screening was defined as people who met the criteria set by the USPSTF and the Centers for Medicare and Medicaid Services: individuals aged 50 to 80 years old, who have at least a 20 pack-year smoking history, and either currently smoke or formerly smoked and quit within the past 15 years. Of the 5,001 participants who had ever smoked that were included in the cohort, 608 were eligible for LC screening and 4,393 were ineligible for LC screening. In this analysis, we used the age range of 50 to 79 years old for eligibility because the NHANES dataset codes participants ages 80+ as 80 years old.

Secondary analyses were conducted to assess racial differences in urinary cotinine levels within participants who had ever smoked. Cotinine is one of the primary metabolites of nicotine and can be used as a biomarker for tobacco and carcinogen exposure (9). Total urinary cotinine was measured in NHANES using isotope dilution high-

performance liquid chromatography and tandem mass spectrometric methods. The lower limit of detection for urinary cotinine is 0.03 ng/mL. For those who had cotinine below the lower limit of detection, an imputed value was used, equal to the lower limit of detection divided by the square root of 2 (0.021 ng/mL). From the 5,001 participants who had ever smoked and who were aged 18 years and older in the NHANES 2013–2014 and NHANES 2015–2016 datasets, 1,543 participants had urinary cotinine data ($n_{excluded}$=3,458). The study was conducted in accordance with the ethical standards of the Declaration of Helsinki (as revised in 2013).

Statistical analysis

All statistical analyses were performed on Stata software, version 14.2. Since NHANES uses a multi-stage probability sampling design, weighted analyses were conducted using survey procedures to obtain national estimates. The data were declared as survey data using *svyset*. Summary statistics were obtained using *svy linearized*. Figures were generated using Stata 14.2.

All the continuous variables were compared using analysis of variance (ANOVA)/Kruskal-Wallis test, while all the categorical variables were compared using the Chi-square test of association.

Results

There were 608 participants who would have been eligible for screening according to national guidelines, 394 males and 214 females; of those 4,393 ineligible participants, 2,573 were males and 1,820 females. The mean age of the participants among the eligible group was significantly higher than in the ineligible group {59.8 years [standard error (SE): 0.4] versus 48.1 years (SE: 0.5); P≤0.001} and so was the mean pack-years [38.8 (SE: 1.0) versus 13.4 (SE: 0.6); P≤0.001]. The mean time since quitting smoking in years of the participants eligible for LC screening was 6.4 years (SE: 0.7), while in those who are ineligible it was 17.9 years (SE: 0.4) (P≤0.001).

Among screening eligible participants, there were no statistically significant differences in demographics or smoking variables across races. Most of the participants eligible for screening were people who currently smoked across all races (*Table 1*).

Among screening ineligible participants, non-Hispanic White (NHW) participants were statistically significantly older and had a higher mean pack-years than the other racial and ethnic groups; the proportion of females was higher among NHW and non-Hispanic Black (NHB) participants than the other racial and ethnic groups.

The mean age was similar across races. Mean pack-years and years since quitting smoking were higher in NHW participants than in any other racial group. Two thirds of the ineligible NHB participants were people who currently smoked versus roughly a little more than one third of the other major racial groups.

The ratios of the population proportion eligible for screening over the ineligible (*Figure 2*) shows that only for NHW and other including multi-racial participants is the number of eligible participants higher than the number of ineligible; for all other racial and ethnic groups, the eligibility ratio is below 1.

Reasons for ineligibility

Looking into the reasons of ineligibility for LC screening, we observed that age alone, pack-years alone and age along with pack-years were the most frequent reasons for ineligibility. Roughly half of the ineligible were excluded due to both age and pack-years, with significant differences across racial and ethnic groups; 51.4% of other Hispanic participants were ineligible because of age and pack-years, versus only 37% of NHW participants (*Figure 3*).

Within the subgroup of ineligible participants due to pack-years only, the mean pack-years in NHW participants [8.3 (SE: 0.3)] was significantly higher than in any other racial group (P≤0.001) (*Table 2*).

Distribution of cotinine

The mean urinary cotinine from ineligible participants was very similar across racial groups, with the exception of Mexican American and other Hispanic participants, which both had significantly lower cotinine levels (*Figure 4A*).

When the analysis was restricted to participants who were ineligible due to pack-years (*Figure 4B*), NHW, NHB and non-Hispanic Asian (NHA) participants had very similar mean values of urinary cotinine.

Discussion

Our analyses demonstrated that a larger percentage of racial and ethnic minority participants than White participants are still ineligible for LC screening, based on the 2021 USPSTF LC screening guidelines. It is evident that current,

Table 1 Characteristics of the sample-NHANES 2013–2016 (n=5,001)*

Screening eligibility	Mexican American (n=637)	Other Hispanic (n=511)	Non-Hispanic White (n=2,267)	Non-Hispanic Black (n=1,045)	Non-Hispanic Asian (n=336)	Other, multi-racial (n=205)	Total (n=5,001)	P value
Eligible, n (%)	61 (5.9)	56 (7.5)	314 (13.2)	126 (9.9)	19 (5.7)	32 (16.9)	608	
Age, years, mean (SE)	60.9 (0.9)	58.8 (0.9)	59.5 (0.4)	60.5 (0.6)	65.1 (2.5)	61.1 (1.3)	59.8 (0.4)	0.2
Sex, n (%)								0.1
Male	43 (69.6)	36 (66.6)	189 (57.3)	93 (69.9)	16 (87.5)	17 (47.5)	394	
Female	18 (30.4)	20 (33.4)	125 (42.7)	33 (30.1)	3 (12.5)	15 (52.5)	214	
Pack-years, mean (SE)	32.8 (1.7)	39.7 (3.0)	39.7 (1.3)	32.8 (1.8)	35.7 (3.8)	36.8 (2.6)	38.8 (1.0)	0.2
Years since quitting smoking, mean (SE)	4.2 (1.5)	0.9 (0.5)	6.9 (0.7)	5.1 (1.3)	6.2 (1.4)	8.2 (4.6)	6.4 (0.7)	0.3
Smoking status, n (%)								0.1
Former	19 (34.3)	15 (29.3)	54 (19.6)	25 (20.0)	8 (39.2)	8 (21.7)	129	
Current	42 (65.7)	41 (70.7)	260 (80.4)	101 (80.0)	11 (60.8)	24 (78.3)	479	
Ineligible, n (%)	576 (94.1)	455 (92.5)	1,953 (86.8)	919 (90.0)	317 (94.3)	173 (83.1)	4,393	
Age, years, mean (SE)	43.0 (1.0)	43.5 (1.0)	49.6 (0.7)	46.8 (0.7)	46.4 (1.5)	42.6 (2.0)	48.1 (0.5)	<0.001
Sex, n (%)								<0.001
Male	395 (71.7)	270 (62.7)	1,050 (52.4)	510 (51.2)	252 (76.6)	96 (57.5)	2,573	
Female	181 (28.2)	185 (37.3)	903 (47.6)	409 (48.8)	65 (23.4)	77 (42.5)	1,820	
Pack-years, mean (SE)	7.7 (0.5)	8.5 (0.7)	15.5 (0.7)	8.7 (0.4)	8.6 (0.8)	10.1 (1.6)	13.4 (0.6)	<0.001
Years since quitting smoking, mean (SE)	13.2 (0.5)	13.6 (1.0)	19.2 (0.6)	16.5 (0.7)	15.0 (1.1)	12.7 (2.0)	17.9 (0.4)	<0.001
Smoking status, n (%)								<0.001
Former	362 (57.9)	305 (61.3)	1,193 (64.7)	410 (39.0)	197 (60.6)	73 (45.4)	2,540	
Current	214 (42.1)	150 (38.7)	760 (35.3)	509 (61.0)	120 (39.4)	100 (54.6)	1,853	

*, all percentages and means are calculated using sampling weights. NHANES, National Health and Nutrition Examination Survey; SE, standard error.

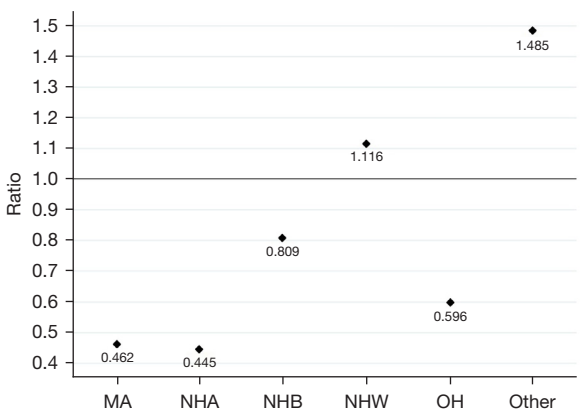

Figure 2 Ratio of eligible over ineligible participants according to race. MA, Mexican American; NHA, non-Hispanic Asian; NHB, non-Hispanic Black; NHW, non-Hispanic White; OH, other Hispanic; Other, other including multi-racial.

updated, LC screening guidelines systematically under-screen non-White people who smoke. However, this is the first attempt, to our knowledge, at using NHANES data to quantify the phenomenon and analyze the reasons for it, following the 2021 change in USPSTF LC screening guidelines. The observation of racial disparities in screening is not unique to LC. The development of new screening tests has historically increased racial disparities for cancer outcomes, at least initially (10). Though racial disparities in screening narrow as new screening tests become more widely implemented, they still persist, for example, for prostate, colorectal, and breast cancer, which are the cancers with the highest incidence and mortality aside from LC (2,11-15). People belonging to racial and ethnic minority groups are less likely to be screened for these cancers though they often have higher incidence and mortality rates than White people.

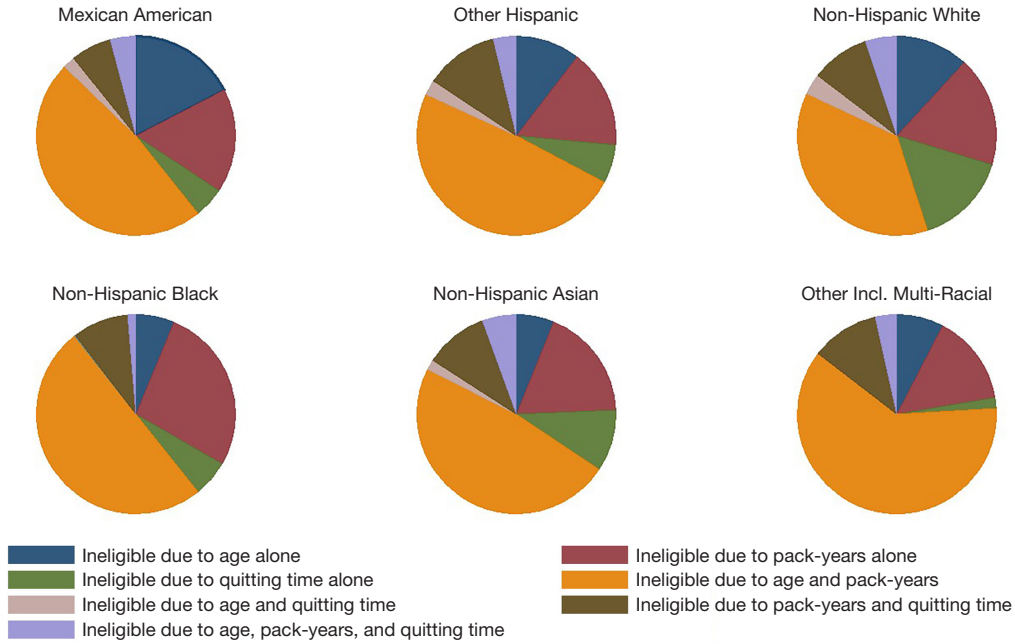

Figure 3 Distribution of reasons for ineligibility of LDCT lung cancer screening according to race. LDCT, low-dose computed tomography.

For LC in particular, stage at diagnosis is the strongest predictor for survival (16). LC has a relative 5-year survival rate of 22.9%, making it one of the most deadly cancers, more deadly than breast, colorectal, and prostate cancers (17). Racial and ethnic minorities are known to be diagnosed at a later stage (3,18,19). Since screening is one of the key tools for the early detection of cancer, it is important to understand why non-White populations, in particular, Black adults, are left out of screening efforts. In addition to classic barriers to screening for those who are eligible, Black people who smoke were found to be less likely to meet the 2013 USPSTF LC screening eligibility criteria in a previous study, primarily because they smoke fewer pack-years on average than White people who smoke (19). Furthermore, Black people who smoke are more likely to be diagnosed with LC at an earlier age than White people who smoke, suggesting that the screening age minimum cutoff of 50 years might not be equally appropriate for all races (16). We show here that non-White people who smoke who are ineligible for LC screening based on the 2021 USPSTF guidelines were still predominantly ineligible either due to not meeting both the minimum age and smoking exposure requirements or due to solely not meeting the minimum smoking exposure requirement. It is important to acknowledge that a smaller proportion of White than non-White people who smoke were ineligible due to these criteria.

From the data presented in this analysis, it is evident that the USPSTF LC screening guidelines fail to capture a significant portion of the at-risk population. By failing to base LC screening guidelines on information from more diverse study populations, non-White populations have been systematically left out of LC screening eligibility—even though results of previous studies have indicated, for example, that Black people may have the most to gain from LDCT screening in terms of reducing mortality rates (10).

In order to improve the risk profile estimate and expand screening to those who need it most, it is important to acknowledge that pack-years might not be the most appropriate measure of tobacco exposure, and that the addition of metabolic biomarkers could improve the individual assessment of LC risk. Cotinine is one of the main metabolites of nicotine, which can be used as an accurate measure of recent nicotine exposure, and consequently, tobacco exposure (20). It is easily measurable in saliva, serum, and urine and has a half-life of 16–18 hours (20,21). Previous studies have demonstrated a dose-dependent association between cotinine and LC risk (22,23). From the present analysis, we observed that though ineligible NHB participants had lower mean pack-years

Table 2 Distributions of age, time since quitting smoking, and pack-years by race according to the reasons for ineligibility

Reason for ineligibility*	Mexican American	Other Hispanic	Non-Hispanic White	Non-Hispanic Black	Non-Hispanic Asian	Other, multi-racial	P value (median)
Ineligible due to age alone							
% within race	13.9	10.7	12.0	6.9	7.9	13.7	
Age, years	36	39	40	36	36	34	0.02
Ineligible due to pack-years alone							
% within race	15.6	15.0	17.8	27.6	18.0	19.3	
Pack-years	4.6	4.4	8.3	6.9	5.4	7.2	<0.001
Ineligible due to time since quitting smoking alone							
% within race	6.2	6.8	15.1	5.7	8.1	6.8	
Quit time, years	30	28.5	30	30	30	27.5	0.14
Ineligible due to age and pack-years							
% within race	49.3	51.4	37.0	46.8	48.9	51.8	
Age, years	35	33	34	33	35	32	0.07
Pack-years	1.95	2	4	3.3	2.1	3	<0.001
Ineligible due to age and time since quitting smoking							
% within race	1.8	2.2	3.5	0.8	2.1	1.9	
Age, years	48.5	44.5	80	80	49	80	<0.001
Quit time, years	22	20	40	35	28	33	0.001
Ineligible due to pack-years and time since quitting smoking							
% within race	8.4	10.2	9.4	10.0	10.4	4.8	
Pack-years	4.6	6.2	7.5	8.2	9.5	12.1	0.002
Quit time, years	25	30	30	25	26	34	0.0118
Ineligible due to age, pack-years, and time since quitting smoking							
% within race	4.7	3.7	5.2	2.4	4.7	1.7	
Age, years	45	48	80	80	48	41	<0.001
Pack-years	7.4	5	6.8	6.1	5.3	2.6	0.4164
Quit time, years	20	22	27	30	20.5	22.5	0.003

*, all percentages are calculated using sampling weights.

than ineligible NHW participants, they still had similar or higher mean urinary cotinine levels.

There are several reasons why non-White racial groups may have higher levels of exposure to carcinogens from tobacco at lower levels of cigarette smoking. Smoking behaviors differ across racial and ethnic groups. Black people who smoke are more likely to smoke menthol cigarettes than White people who smoke, which have been shown to promote deeper smoke inhalation through soothing respiratory irritation commonly associated with smoking (24-26). Some mentholated brands also have higher concentrations of tar and nicotine per cigarette (27). The

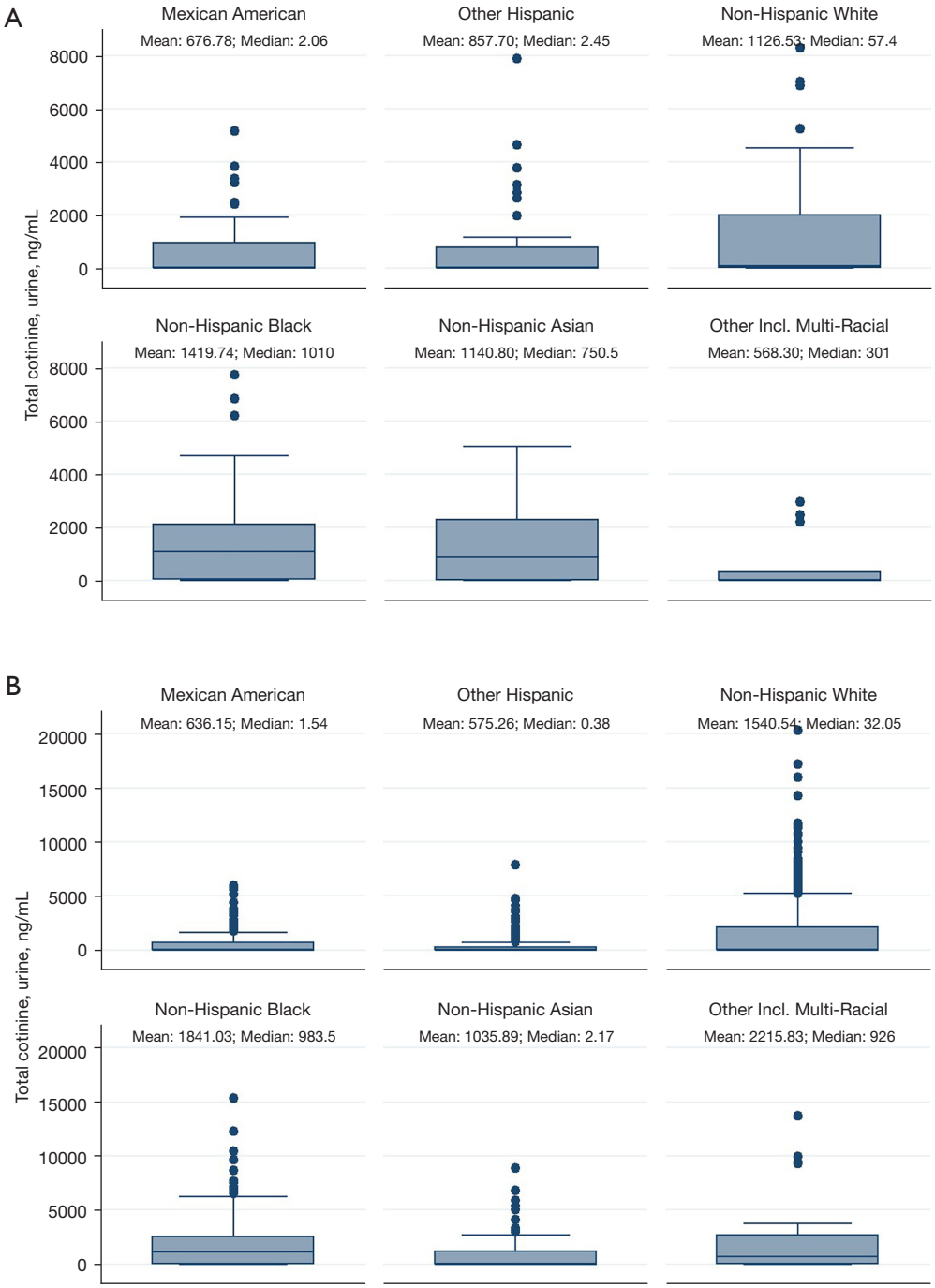

Figure 4 Distribution of urinary cotinine according to race in (A) ineligible, and (B) ineligible due to pack-years only participants.

chance of environmental tobacco exposure is not equally distributed across races. For example, Black children and adults have the highest risk of environmental tobacco smoke exposure, when compared to all other races (28). It has been reported that nicotine metabolism and clearance vary with race and ethnicity, even after adjusting for environmental exposures (27), although recent data have downplayed cotinine's ability to adequately measure such racial differences

in metabolism (29). Higher levels of cotinine are associated with increased risk of LC, thus screening guidelines that are primarily based on the amount of cigarettes smoked inadequately capture individual LC risk (30).

Risk prediction models have been recommended as an alternative method of identifying high-risk individuals who should be eligible for LC screening. One risk-based prediction model that has been validated by researchers in several countries is the PLCOm2012 model (31), which utilizes variables such as age, race or ethnicity, education, body mass index, personal history of cancer, family history of LC, smoking status, intensity, duration, and quitting time to assess an individual's 6-year risk of developing LC (32). Though the PLCOm2012 model has been shown to decrease screening disparities between White and Black people who smoke when compared to the USPSTF 2021 LC screening guidelines, racial disparities in screening still persisted (32). Therefore, individual biomarkers might serve as a powerful tool to improve prediction models and inform screening guidelines.

The results of this study should be interpreted by taking into account several limitations. We were unable to utilize the most recent data cycles from NHANES because they were lacking certain smoking questionnaire variables necessary to calculate pack-years.

Our selection included participants aged from 50 to 79 because NHANES codes participants ages 80 and older as 80 years old. Hence we lost the potentially eligible participants who were exactly 80 years old.

Smoking history is derived from a questionnaire, and, as such, is subject to self-reporting bias. Additionally, cotinine is not the measure of life-long exposure, given its relatively short half-life.

However, this review has several strengths. NHANES provides us a nationally representative dataset, hence the conclusions can be generalized for the whole U.S. population. Furthermore, to our knowledge, this the first study to use urinary cotinine data from NHANES in relation to screening eligibility and report its distribution across racial and ethnic groups.

Conclusions

Current LC screening guidelines do not adequately capture at-risk individuals who are non-White. Future analyses should focus on determining appropriate individualized guidelines and consider including biomarkers. This is essential to ensure insurance coverage for LDCT screening in high-risk populations that are currently underscreened (10). Urinary cotinine is an example of a good, rapid, non-invasive measure to determine recent exposure to nicotine and, by proxy, exposure to tobacco carcinogens. Risk-based models that include several indicators of tobacco exposure, not just pack-years, should be utilized to improve LC outcomes in non-White populations and to decrease the racial disparity in LC mortality.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-816/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the ethical standards of the Declaration of Helsinki (as revised in 2013).

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