

Achieving Greater Benefit of Lung Cancer Screening to Reduce Mortality with Inclusion of More African American/Black Individuals - A Secondary Analysis of National Lung Screening Trial Data

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Key Points

Question: Could lung cancer mortality benefits achievable with lung screening be greater than those estimated by the National Lung Screening Trial (NLST) if screening reaches higher proportions of African American/Black (AA/Black) individuals than in the original NLST cohort?

Findings: In this secondary analysis of a randomized controlled study, increasing the prevalence of AA/Black individuals in our hypothesized populations resulted in greater relative reductions of lung cancer and all-cause mortality than observed in the NLST.

Meaning: The potential to achieve greater reductions in lung cancer mortality than originally estimated by the NLST with inclusion of more AA/Black participants stresses the critical importance of improving lung screening access for AA/Black current and former smokers.

Tweet

As we work to improve #lungcancerscreening #equity and #inclusion, how might our expectations for #lungcancer mortality reduction differ from original NLST estimates? Transportability provides a clue.

Abstract

Importance

The potential to achieve greater reductions in lung cancer mortality than originally estimated by the NLST with the inclusion of more AA/Black participants stresses the importance of working to improve access to lung cancer screening for AA/Black current and former smokers, a population presently with the highest lung cancer morbidity and mortality.

Objective

We aimed to estimate lung cancer and all-cause mortality reductions achievable with lung cancer screening via low dose computed tomography (LDCT) of the chest in populations with greater proportions of African American/Black screening participants than seen in the original NLST cohort.

Design

Cox proportional hazard models were employed to estimate the hazard ratio (HR) and 95% confidence interval (CI) of lung cancer mortality and all-cause mortality according to low dose CT (LDCT) screening compared with chest radiograph screening. Using a transportability formula, we predicted the effect of LDCT screening among hypothetical populations by varying the distributions of AA/Black individuals, females, and current smokers.

Setting

This study was conducted as a transportability of existing randomized clinical trial data (NLST).

Participants

This study included 53,452 participants from the NLST. NLST participants were current or smokers, ages 55-74, with at least 30 pack year smoking history and less than 15 years since quit.

Intervention

Lung screening with low dose CT of the chest, as compared to chest radiography.

Main Outcomes and Measures

Lung cancer mortality and all-cause mortality

Results

Of 2376 AA/Black individuals and 51076 non-AA/Black individuals enrolled in the NLST, 21922 (41.0%) were female and the mean (SD) age was 61.4 (5.0) years. Over a median follow-up of 6.7 years, we found greater relative reduction of lung cancer mortality with LDCT screening among the synthesized population with a higher proportion of AA/Black individuals (e.g., HR [95% CI]= 0.82 [0.72-0.92] among the population with 13.4 % AA/Black individuals as compared to HR [95% CI] = 0.84, 95% CI: 0.76–0.96 in the entire NLST). We also found a further reduction in lung cancer mortality by LCDT screening among the hypothetical population with a higher proportion of male or current smokers, along with a higher proportion of AA/Black individuals (e.g., HR 0.68 (CI: 0.48-0.97) among the population with 60% AA/Black and 20-40% female). Similar trends were observed for all-cause mortality but with a smaller magnitude and wider CI.

Conclusions and Relevance

The potential to achieve greater reductions in lung cancer mortality than originally estimated by the NLST with the inclusion of more AA/Black participants stresses the critical importance of working to improve access to lung cancer screening for AA/Black current and former smokers.

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NON-AUTHOR CONTRIBUTIONS

Not applicable

ACCESS TO DATA AND DATA ANALYSIS

Dr. Prosper and Dr. Inoue, as well as Dr. Hsu, Dr. Bui and Dr. Aberle, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Introduction

Lung cancer is the third most common cancer in the United States, and the leading cause of cancer-related death [1]. In the United States, AA/Blacks are disproportionately affected by cancer, experiencing the highest rate of death and lowest rates of survival for most cancers. This statistic is particularly true of lung cancer, with AA/Black men experiencing higher rates of lung cancer death than any other racial or ethnic group [2].

The landmark National Lung Screening Trial (NLST), a large randomized clinical trial (RCT) involving 53,452 participants that enrolled participants between 2002 and 2004, demonstrated a 20% reduction in lung cancer mortality with annual lung cancer screening using low dose computed tomography (LDCT) of the chest when compared with chest x-ray [3]. In light of the results of the NLST and a comparative modeling study [4], the United States Preventive Services Task Force (USPSTF) issued a Grade B recommendation that current and former smokers between ages 55-80 years, with ≥ 30 pack-year smoking history and ≤ 15 years since quitting receive annual lung cancer screening with LDCT. The Center for Medicare and Medicaid Services followed with a National Coverage Decision, providing lung cancer screening as a covered benefit. Notably, since the reporting of NLST results in 2011, additional RCTs have supported the NLST's findings including the Netherlands–Leuven Longkanker Screenings Onderzoek (NELSON) [5] and Multicentric Italian Lung Detection (MILD) [6] trials, demonstrating 24% and 39% reduction in lung cancer mortality with LDCT screening versus no screening, respectively. Most recently, the USPSTF has expanded lung screening eligibility to include current and former smokers between ages 50-80 years with ≥ 20 pack-year smoking history and ≤ 15 years since quitting [7].

The benefits of lung screening with LDCT are now well-accepted. However, to date, much of what is referenced in support of the importance of lung screening in AA/Black current and former smokers is based on analysis of clinical screening programs [8-10]. These descriptive analyses provide important insight into the effects of screening in eligible Black participants, yet RCTs remain the gold standard in the assessment of the efficacy of clinical interventions.

Early on, recognizing the importance of proportionate inclusion of eligible participants from varied demographic categories, the NLST made specific efforts to recruit AA/Black participants. Seven NLST-American College of Radiology Imaging Network (ACRIN) sites were identified with a strong performance in overall recruitment, successful enrollment of underserved participants, and locations centered in culturally diverse communities. These recruitment sites developed strategic plans for the enrollment of racial and ethnic minorities, evaluating potential barriers to recruitment and collaborating on solutions. As a result, institutions with specific minority recruitment plans enrolled higher numbers of AA/Black participants – 9.5% as compared to 2.0% in institutions without specific recruitment plans [11]. In total, among the 53,452 participants in the NLST, 4.4% self-identified as AA/Black [3].

Still, the relatively low overall participation of AA/Black individuals in the NLST has been identified as a potential barrier for extrapolating these encouraging results to populations with higher proportions of AA/Black individuals [12]. Sub-analysis of the NLST by race revealed that these participants reported a higher prevalence of poor prognostic indicators associated with worse lung cancer outcomes including current smoker status (though they reported lower overall cigarette consumption), being unmarried, lacking completion of a college degree, and higher numbers of comorbidities than White participants. Despite an increased prevalence of these poor prognostic indicators among AA/Black participants, those who received lung cancer screening with LDCT experienced the greatest reduction in lung cancer mortality of any racial/ethnic group. AA/Black participants experienced a lung cancer mortality hazards ratio (HR) of 0.61 vs. 0.86 in White participants, and 0.72 in other/non-reported individuals. AA/Black participants also experienced an all-cause mortality HR of 0.81 vs. 0.95 in White participants[13]. However, subgroup analyses of RCTs by race limit interpretation of an intervention's effect to specific racial/ethnic groups (e.g., all AA/Blacks, all Whites, etc). Transportability allows for evaluation of an intervention across a population with different proportions of individuals from various racial groups. Using transportability we can further evaluate the potential benefit of LDCT screening among populations with higher prevalences of

AA/Black individuals (than 4.4%), mirroring populations of interest such as adults in the United States.

Therefore, utilizing a transportability formula, we predicted the effect of LDCT screening on lung cancer and all-cause mortality reduction across populations with demographics that significantly differ from the original NLST population. This statistical approach improves our ability to identify the potential benefits of lung screening implementation in health systems serving populations with higher proportions of AA/Black individuals.

Materials and Methods

Data Sources and Study Population

The NLST was a multicenter randomized clinical trial to assess the clinical effectiveness of lung screening with LDCT of the chest. The NLST included participants aged 55-74 years at the time of randomization with a history of cigarette smoking of at least 30 pack-years, and current smoker status or a quit date within the previous 15 years. A total of 53,452 participants were enrolled at 33 screening centers across the United States between August 2002 to April 2004 and randomly assigned to three rounds of annual screening with LDCT screening or chest x-ray (CXR) screening at a 1:1 ratio. More details in the NLST protocol can be found in prior literature [14]. As all source data used in this secondary analysis was anonymized and had been previously published, IRB review was not required. Study data was analyzed from September 1 through February 28, 2021. Our study followed the reporting requirements of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement (Online Supplementary Material).

Measurements

Demographic characteristics including age (years, continuous), sex (male or female), race and ethnic group (White, AA/Black, or others), education status (less than college, college or higher, others), marital status (single, married, widowed or divorced), smoking status (current or former smokers), and pack-years of smoking (continuous) were self-reported at baseline.

Mortality data were obtained through the annual questionnaires and searches on the National Death Index (NDI). Participants were followed from the time of entry into the study until death, loss to follow-up, or through the end of the study on December 31, 2009 (the original NLST publication set the final status of lung cancer mortality at January 15th, 2009).

Statistical Analyses

Cox proportional hazard models were employed to estimate the hazard ratio of lung cancer mortality and all-cause mortality according to LDCT (vs CXR) screening. To assess changes in the estimated effect of lung cancer mortality and all-cause mortality derived from the NLST population to the hypothesized target populations, we applied a transportability formula. Transportability is a statistical approach that allows for the extrapolation of results from a randomized clinical trial to a target population in which an intervention is being considered, using a combination of results from the original RCT participants and data on the background characteristics of the target population [15].

In this formula (the inverse-odds weighting approach), we emulated the target population from the original NLST participants using the weights created by the odds of being in the NLST as opposed to the target population. Additional details on the application of transportability can be found elsewhere [15, 16].

Aiming to demonstrate the effects of race, sex, and smoking status on mortality reduction with LDCT screening across a synthetic population, we applied a transportability formula to NLST data in three settings. First, we transported the estimated effect from the NLST population to the hypothesized target populations by varying the distribution of AA/Black individuals. Second, we transported the estimated effect to the hypothesized target populations by varying the distributions of AA/Black individuals and sex simultaneously. Lastly, we transported the estimated effect to the hypothesized target populations by varying the distributions of AA/Black individuals and smoking status simultaneously. The 95% confidence intervals (CIs)

were calculated by repeating the analyses on 200 bootstrapped samples. All statistical analyses were performed with R version 4.0.2 [17].

Results

Of 53452 participants enrolled in the NLST, 21922 (41.0%) were female and the mean (SD) age was 61.4 (5.0) years. At the trial enrollment, AA/Black participants were more likely to be female, less educated, single or widowed/divorced, and former smokers, and have a smaller number of pack-years of smoking compared with non-AA/Black participants (Table 1).

Increasing the prevalence of AA/Black individuals in our hypothesized external populations resulted in an increased relative reduction of lung cancer mortality with LDCT screening (Figure 1A) when compared to the 16% reduction in lung cancer mortality seen in the NLST (using the extended analysis period of December 31, 2009). For example, in a population comprised of 13.4% AA/Black individuals (mirroring US Census data [18]), the relative reduction in lung cancer mortality across the population was 18% (95% CI: 8-28), increased from 16% (95% CI: 4-24) in the NLST which included 4.4% AA/Black individuals. Among a population comprised of 46.3% AA/Black individuals (mirroring Washington city, District of Columbia [18]), we found a large further reduction in lung cancer mortality by LDCT screening (29% [95% CI: 2-46]).

Increasing the proportion of AA/Black individuals within our synthetic population to 40% resulted in an increased relative reduction in lung cancer mortality to 26% (95% CI: 3-42) across the population. Similarly, though more subtly, increasing the prevalence of AA/Black individuals in our hypothesized external populations to 13.4% and 40% resulted in an increased relative reduction of all-cause mortality with LDCT screening to 8% (95% CI: 1-15) and 13% (95% CI: 2-24), respectively (Figure 1B).

Varying the distribution of race and sex simultaneously, we also saw increased reductions in lung cancer mortality with greater proportions of AA/Black individuals and lower proportions of female participants (Figure 2A). For instance, the greatest statistically significant lung cancer mortality benefit across the population, with an HR 0.68 (CI: 0.48-0.97), was seen with a

population that was 60% AA/Black and 20-40% female. Notably, reduction in all-cause mortality increased with higher proportions of AA/Black individuals, regardless of the proportion of female participants (Figure 2B).

By varying the distribution of race and smoking status simultaneously, we observed the greatest reduction in lung cancer mortality by increasing the number of AA/Blacks and current smokers, with up to a 45% reduction in lung cancer mortality (adjusted HR: 0.55, CI: 0.31-0.96) in a population with 100% AA/Black current smokers (Figure 3A). Among all of our synthetic populations, the greatest reduction in all-cause mortality was seen with a population comprised of 100% AA/Black participants and current smokers, but the 95% CI included the null (adjusted HR: 0.79, CI: 0.50-1.13; Figure 3B).

Discussion

Extrapolation of NLST results to synthetic populations with higher proportions of AA/Black individuals using a transportability formula suggests that the lung cancer mortality reduction achievable with LDCT screening is potentially greater than that originally reported. Creating a synthetic population that mirrors the proportion of AA/Black individuals in the United States (without changing the distribution of other variables from the original NLST population), we would expect a lung cancer mortality reduction of 18% [18].

It is important to note that the mortality reduction we have modeled via transportability is limited by the original RCT data to which it is applied. A review of the transported effect of LDCT screening with varied proportions of AA/Black participants (Figure 1) highlights these limitations. Given that only 4.4% of the original NLST population was comprised of AA/Black participants, the confidence interval in our predicted estimates crosses 1.0, and data becomes insufficient for further extrapolation at a proportion of 60% AA/Black participants. Equally important to understand is the fact that the maximal lung cancer and all-cause mortality reduction that can be theoretically achieved with our synthetic populations (at a proportion of

100% AA/Black) is almost the same as the mortality reduction achieved in the 2,376 AA/Black NLST participants, or 39%.

Transportability analysis is a powerful tool that helps us to posit clinical trial results in synthetic populations that better mirror real-world patient populations. In these examples, transportability allowed us to estimate the effect of LDCT screening on lung cancer and all-cause mortality reduction across several hypothetical populations with varied proportions (i.e., 0-100%) of AA/Blacks, women, and current smokers. In contrast, subgroup analysis, the most common approach utilized when focusing on a specific population, would have only allowed us to estimate the effect among the population with 0% or 100% proportion of a specific variable (i.e., among AA/Blacks, women, current smokers, etc), indicating that transportability approach may be able to provide more detailed and flexible information than attainable through subgroup analysis. Moreover, while the present study only varies the prevalence of one variable (i.e., sex or smoking status) in addition to that of Black individuals for simple illustration, the transportability approach allows us to include as many measured variables as necessary, and to quantify the intervention effect across any target populations of interest under the required causal assumptions [15, 16]. The transportability approach can also be applied in other important topics such as cost-effectiveness of LDCT screening. Given the heterogeneous incremental cost-effectiveness ratios of LDCT screening across individuals' demographic characteristics [19, 20], future studies are needed to extend the findings of its cost-effectiveness analysis to the target population of interest using transportability analysis.

Limitations

Notwithstanding such advantages of transportability, it must be understood that this statistical method is not a replacement for equitable and inclusive recruitment of diverse groups of clinical trial participants. Had the NLST research team not made a concerted effort to increase enrollment of AA/Black participants through a partnership with seven NLST-ACRIN sites, our ability to apply transportability to original NLST data would likely have been much more statistically limited. Thus, the transportability analysis does not completely negate the need for

future clinical trials, but this statistical tool would provide us valuable information on i) what kind of populations would get the benefit from the intervention and ii) to what extent the expected intervention effects are, for such future trials.

We additionally recognize that accurately reflecting the racial demographics of our population with RCT recruitment is only one of the limitations in extrapolating clinical trial results to real-world settings. Clinical trial participants receive careful surveillance and as a result, have higher levels of adherence than that seen in clinical practice. NLST participants achieved a greater than 90% adherence rate to screening [3], much higher than those reported in clinical programs [21, 22]. Despite evidence of mortality benefit with lung screening and the fact that screening is a covered benefit in eligible individuals by both private insurers and Medicare, the utilization of, and adherence to, lung cancer screening remains suboptimal, and far below the adherence seen in the NLST. A review of the American College of Radiology Lung Cancer Screening Registry in 2016 revealed a woefully low 1.9% utilization rate among 7.6 million eligible smokers [23]. Moreover, while lung screening is currently underutilized by eligible participants as a whole, AA/Black current and former smokers are disproportionately challenged in entry and adherence to lung cancer screening, are less likely to receive lung cancer screening, and experience longer times to follow-up than White patients [12, 24]. Cited barriers to cancer screening for eligible individuals include limited access, fear, fatalism, mistrust of the medical system, and experiences with racism [8, 25, 26]. In addition, evidence revealed the original USPSTF lung screening eligibility criteria to be insufficiently inclusive of AA/Black current and former smokers, who develop lung cancer at younger ages with a lower cumulative pack-year smoking history than current eligibility cutoffs [10]. The newly revised LDCT screening eligibility by the USPSTF mitigate the exclusion of AA/Black smokers from potential screening benefits by reducing the eligibility age to 50 years and smoking intensity to 20 or more pack-years [7]. As we continued to improve risk-based criteria for screening, this approach increases the number of AA/Black individuals at highest risk of lung cancer.

Conclusions

Even with the myriad barriers to enrollment in and ultimately adherence to lung screening with LDCT, extrapolation of NLST results to diverse populations with increased proportions of AA/Black screening participants is nonetheless encouraging. The potential to achieve greater reductions in lung cancer mortality than originally estimated by the NLST with the inclusion of more AA/Black participants stresses the critical importance of working to improve access to lung cancer screening for AA/Black current and former smokers.

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Table 1. Demographic characteristics of the study population in the National Lung Screening Trial (NLST). Note, AA/Black participants were more likely to have completed less than college education, be unmarried and former smokers, with lower overall pack year smoking history.

Characteristics	AA/Black participants (N=2,376), No (%)	Non-AA/Black participants (N=51,076) , No (%)
Age, mean (SD), y	60.5 ± 4.8	61.5 ± 5.0
Sex		
Male	1300 (54.7)	30230 (59.2)
Female	1076 (45.3)	20846 (40.8)
Ethnic group		
Hispanic	15 (0.6)	920 (1.8)
Non-Hispanic	2341 (98.5)	49777 (97.5)
<i>Others or missing</i>	20 (0.9)	379 (0.7)
Education status		
Less than college	1250 (52.6)	22145 (43.4)
College or higher	1070 (45.0)	27753 (54.3)
<i>Others or missing</i>	56 (2.4)	1178 (2.3)
Marital Status		
Single	265 (11.2)	2193 (4.3)
Married	910 (38.3)	34679 (67.9)
Widowed/Divorced	1181 (49.7)	13885 (27.2)
<i>Missing</i>	20 (0.8)	319 (0.6)
Smoking status		
Current	798 (33.6)	26894 (52.7)
Former	1578 (66.4)	24182 (47.3)
Pack-years of smoking, mean (SD), y	48.9 ± 19.0	56.3 ± 24.1

NLST, National Lung Screening Trial; LSS, Lung Screening Study; ACRIN, American College of Radiology Imaging Network; BMI, body mass index.

Figure 1. Transported effect of lung screening by low-dose CT on lung cancer-related mortality from the National Lung Screening Trial (NLST) to hypothetical populations by varying the distribution of the AA/Black population. Solid line represents the mean hazard ratio; dashed lines represent 95% confidence intervals.

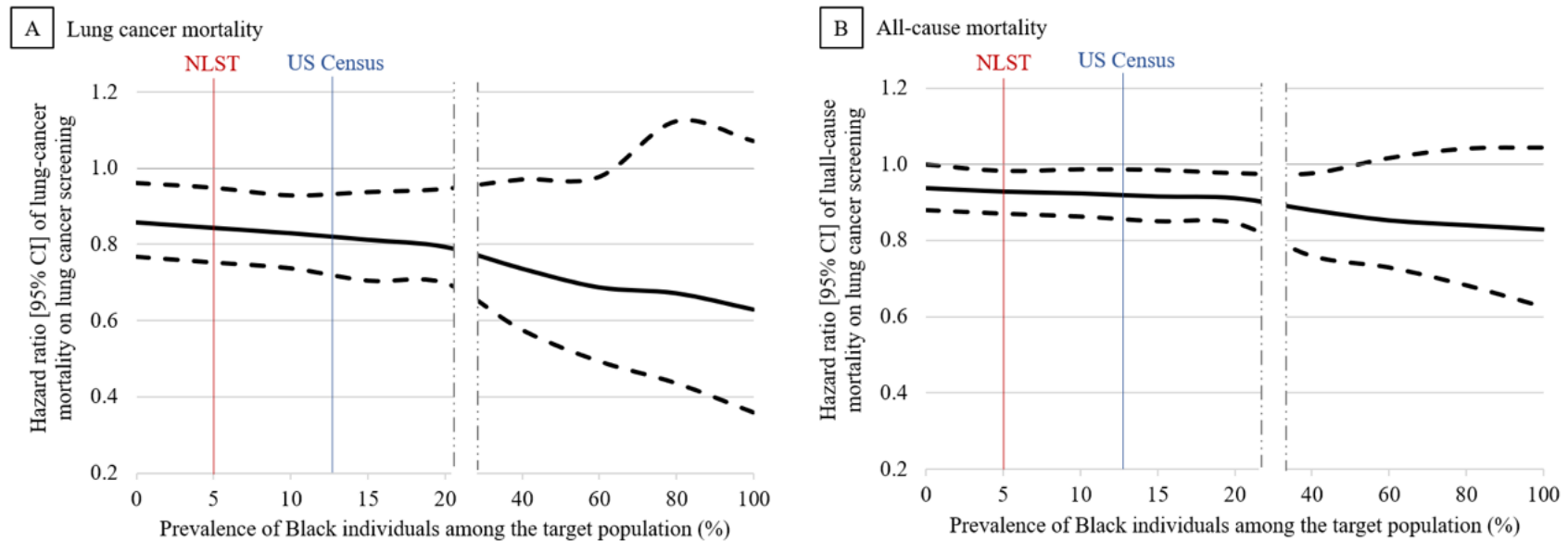
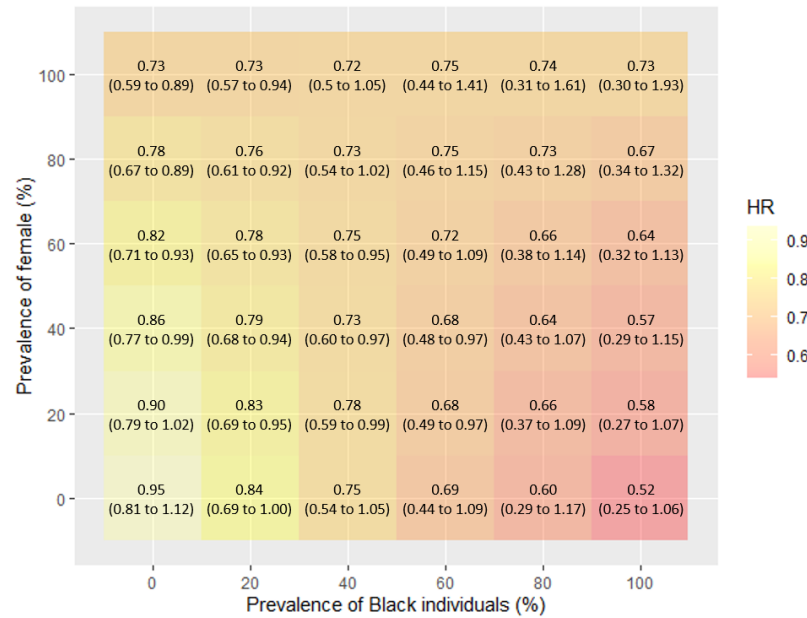


Figure 2. Transported effect of lung screening by low-dose CT on lung cancer-related mortality from the National Lung Screening Trial (NLST) to hypothetical populations by varying the distribution of the AA/Black population and sex. As female sex decreases, and the prevalence of AA/Black individuals increases, the hazard ratio for both lung cancer mortality and all-cause mortality decrease.

A Lung cancer mortality



B All-cause mortality

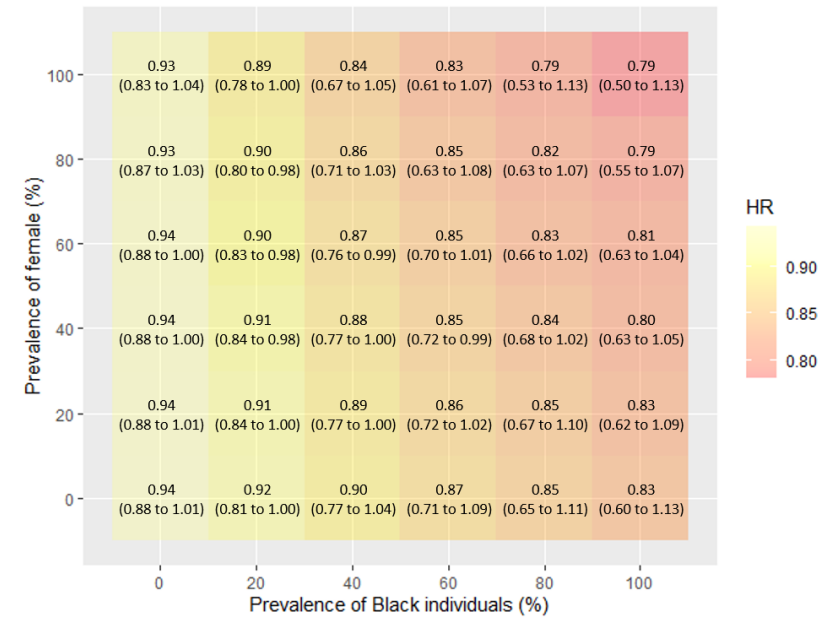
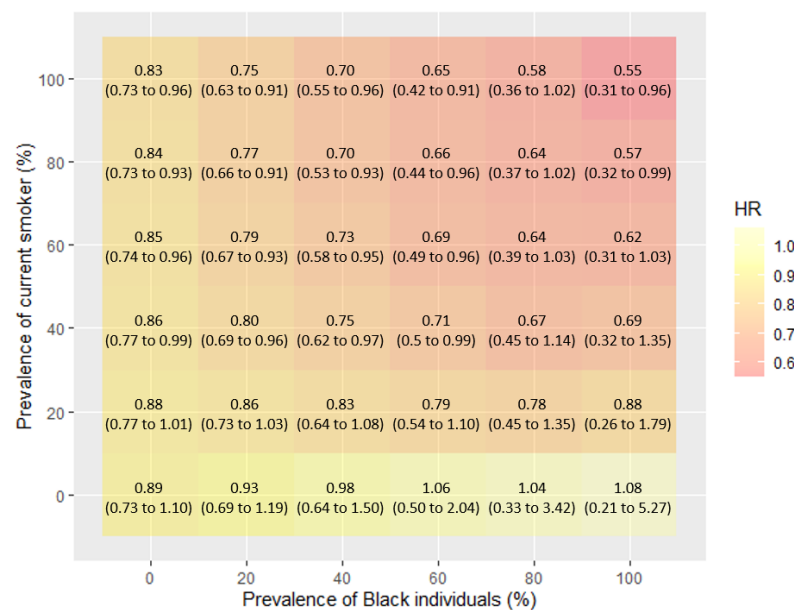


Figure 3. Transported effect of lung screening by low-dose CT on lung cancer-related mortality from the National Lung Screening Trial (NLST) to hypothetical populations with varying the distribution of the AA/Black population and smoking status. With current smokers and AA/Black individuals increase, the hazard ratio (HR) for lung cancer mortality and all-cause mortality both drop.

A Lung cancer mortality



B All-cause mortality

