Supplementary Materials

The Association of Computed Tomography Screening With Lung Cancer Stage Shifts and Mortality in the United States

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Supplementary methods

Joinpoint Regression

Trends in the proportion of patients diagnosed with stage I NSCLC, lung cancer incidence, incidence-based mortality, and mortality from 2010-2018 were evaluated using the National Cancer Institute's Joinpoint Regression Program. The National Cancer Institute's Joinpoint Regression Program is a statistical software package (Joinpoint Regression Program, Version 4.8.0.1 - April 2020; Statistical Methodology and Applications Branch, Surveillance Research Program, National Cancer Institute) that fits joinpoint models to trend data (e.g., the year-to-year percentages of patients diagnosed with stage I non-small-cell lung cancer, cancer incidence, cancer mortality). Specific details regarding the Joinpoint model have been described previously by Kim and colleagues (Kim HJ, *Statistics in Medicine* 2000; 19:335-351: (correction: 2001;20:655)). Briefly, the Joinpoint Regression Program tests two joinpoint models: the null model (the model with the lower number of joinpoints) and the alternative model (the model with a greater number of joinpoints). To infer the location of joinpoints, the Joinpoint Regression Program uses a grid search method (Lerman PM, *Journal of the Royal Statistical Society: Series C (Applied Statistics)* 1980;29:77-84). Of note, instead of the researchers selecting the joinpoints *a priori*, the location of the joinpoints are estimated by the grid search method. Confidence intervals for the joinpoints estimated by the model are calculated using the approach previously described by Lerman (Lerman PM, *Journal of the Royal Statistical Society: Series C (Applied Statistics)* 1980;29:77-84).

Then, to evaluate whether the alternative model fits the data better than the null model, the Joinpoint Regression Program calculates a ratio—denoted as T—of the sum of squared errors from the null model divided by the sum of squared errors from the alternative model. A large ratio indicates that the alternative model fits the data better than the null model while a ratio close to one indicates that the alternative and null models fit the data similarly. To determine whether the alternative model fits the data significantly better than the null model, the Joinpoint Regression Program uses the permutation method. The residuals obtained from the null model are randomly permuted. A permutation dataset, including the

permuted residuals and modeled values from the null model, is then created. Using the permutation dataset and alternative model, the ratio T is computed. In the present study, this process was repeated 4,500 times to create a distribution of T values. The *p*-value is the proportion of T values in this distribution that are greater than or equal to the T value calculated using the original dataset. If the p-value <0.05, the null model is rejected and the alternative model (the model with the greater number of joinpoints) is selected.

For each joinpoint segment, the average annual percentage rate change (APC) is calculated. Confidence intervals and p-values for the APC are calculated based on a t distribution.

Sensitivity Analyses Conducted using Joinpoint Regression

Sensitivity analyses were conducted allowing for up to two joinpoints. We chose to conduct these sensitivity analyses to determine whether the Joinpoint Software would select more than one joinpoint, as this would indicate that there were two statistically significant changes in the rate of stage I disease identified during the study period. If two joinpoints were identified, this would require further investigation to understand other possible contributing factors that may change the rate of stage I disease identified. Importantly, however, these sensitivity analyses did not change our results.

Definitions of Patient Subgroups

Patient subgroups were determined according to patient race and area of residence (high income vs. low income, well-educated vs. less-educated). The National Cancer Data Base records median household income and the percent of adults age 25 and over who did not graduate from high school for each patient's area of residence. The income groups evaluated in the present study were defined according to median household income quartiles based on income ranges among all United States zip codes. The

education groups evaluated in the present study were defined according to quartiles of the percent of adults age 25 and over who did not graduate from high school based on 2016 American Community Survey Data.

Definition of the "Lung Cancer Screening Rate"

The lung cancer screening rates used in Supplemental Table 4 are estimates obtained from the American Lung Association (https://www.lung.org/research/state-of-lung-cancer/methodology-and-sources https://www.lung.org/research/state-of-lung-cancer/methodology-and-sources) The number of people in the United States eligible for lung cancer screening and the number of people in the United States receiving lung cancer screening were estimated using the 2019 Behavioral Risk Factor Surveillance System from the Centers for Disease Control and the National Health Institute Survey. A logistic regression model was used to identify variables that were most strongly associated with having either a greater than 30 pack-year smoking history (for current smokers) and fewer than 15 years since quitting smoking (for former smokers). The number of eligible individuals and the number of eligible individuals who were screened were then calculated. To compute the lung cancer screening rate, the number of eligible individuals who were screened were then divided by the total number of eligible individuals.

Methodology used to Estimate the Number of Deaths Averted

To estimate the number of deaths averted due to a shift towards earlier stages of disease diagnosed after the introduction of lung cancer screening in the U.S., we did the following. First, we evaluated changes in the hazard of death before and after the introduction of lung cancer screening using a Cox proportional hazard model, adjusting for important patient, hospital, and regional characteristics. The covariates included in this model were patient sex, age, race/ethnicity, median census tract income,

percentage of individuals without a high school education living in that patients' zip code, insurance status, distance from hospital, comorbidity score, histologic subtype, facility type (e.g., community, academic), metropolitan/urban/rural status, region of residence (e.g., northeast, east north central, pacific), clinical stage group, receipt of immunotherapy, receipt of chemotherapy, receipt of radiation, and receipt of surgery. Second, using the results of the Cox proportional hazards model, we predicted the probability of death for each year of diagnosis and clinical stage group (e.g., stage I, II, III, and IV). Probabilities of death were imputed for the year 2018 because mortality data in the NCDB is not available for 2018. Third, we calculated the predicted number of deaths by multiplying the probabilities of death—previously calculated for each year of diagnosis and clinical stage group—by the actual number of lung cancers diagnosed—stratified by clinical stage group—each year. We then summed the predicted number of deaths to calculate the total number of deaths that occurred from 2014-2018. The sum of the predicted deaths in this step represents the number of deaths that actually occurred from 2014-2018 in the **presence** of the stage shift. Fourth, we repeated step three. However, for this step, we assumed that *no* stage shift occurred from 2014-2018. The sum of the predicted number of deaths in this step represents the number of deaths that would have occurred in the **absence** of a stage shift. Fifth, we subtracted the actual number of deaths (number of deaths in the **presence** of a stage shift) from the estimated number of deaths (number of deaths in the **absence** of a stage shift). We then multiplied this estimate by (1/0.65) because the NCDB includes approximately 65% of all lung cancers diagnosed annual in the United States.[3]

Figure A. Consort Diagram

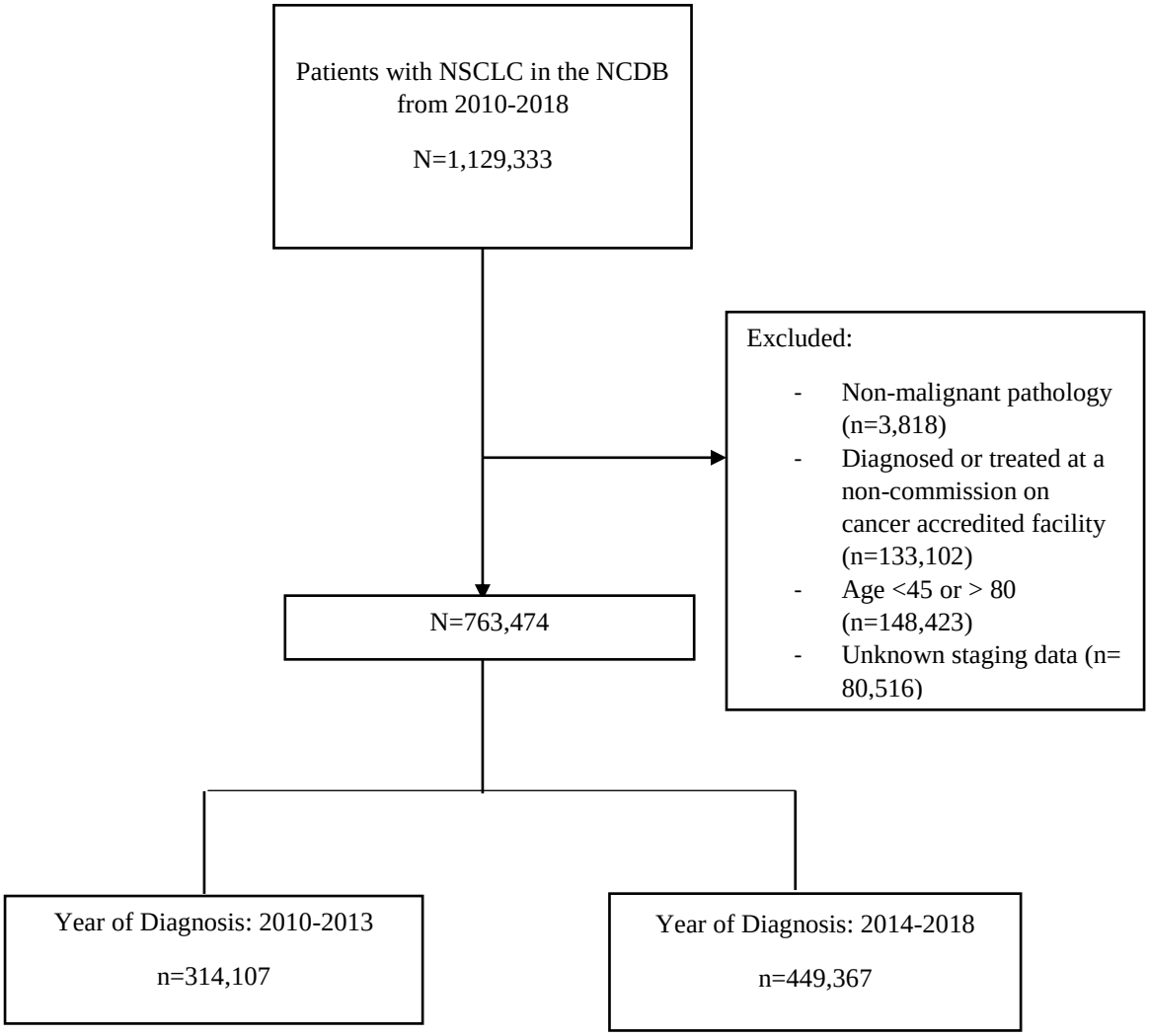

Figure B. Sensitivity Analyses of the Likelihood of Being Diagnosed with a Lower Stage of NSCLC Varying the Time of Introduction of the Intervention. The x-axis is the year when the intervention was introduced. The y-axis is the odds ratio. The odds ratio reported in this figure represents the increase in the odds per year of being diagnosed with one stage lower from the time of introduction of the intervention to 2018 divided by the increase in the odds per year of being diagnosed with one stage lower from 2010 to the time of introduction of the intervention.

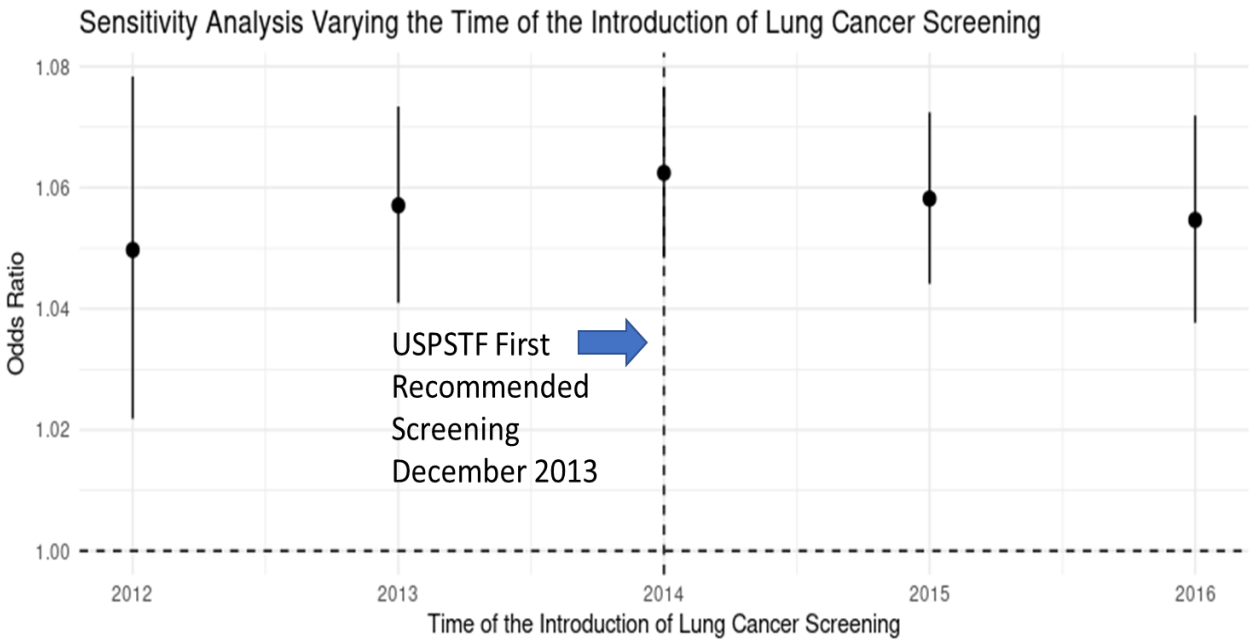

Figure C. Sensitivity Analysis of the Year-to-year Percentages of Stage I Disease Diagnosed from 2010-2018 Only Among Patients Diagnosed with Non-indolent Histologic Subtypes (excluding typical carcinoid tumors and tumors formerly classified as Bronchioloalveolar Carcinoma) of NSCLC. The x-axis is the year of diagnosis. The y-axis is the percentage of patients diagnosed with stage I NSCLC. Each consecutive annual interval is represented as a point value. The vertical dotted line represents the date of the first lung cancer screening recommendation issued by the United States Preventive Services Task Force.

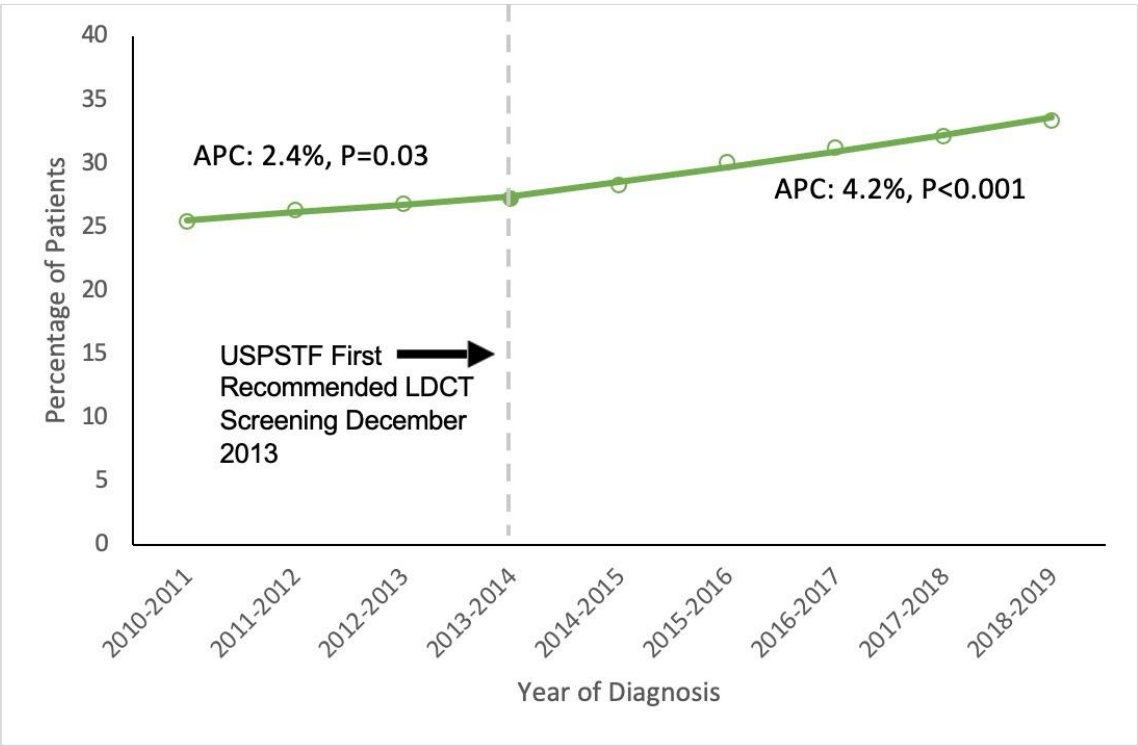

Figure D. Trends in the Percentage of Patients Diagnosed with NSCLC by Stage, Including Unknown Stage, from 2010-2018. The x-axis is the year of diagnosis. The y-axis is the percentage of NSCLC cases diagnosed by clinical stage group.

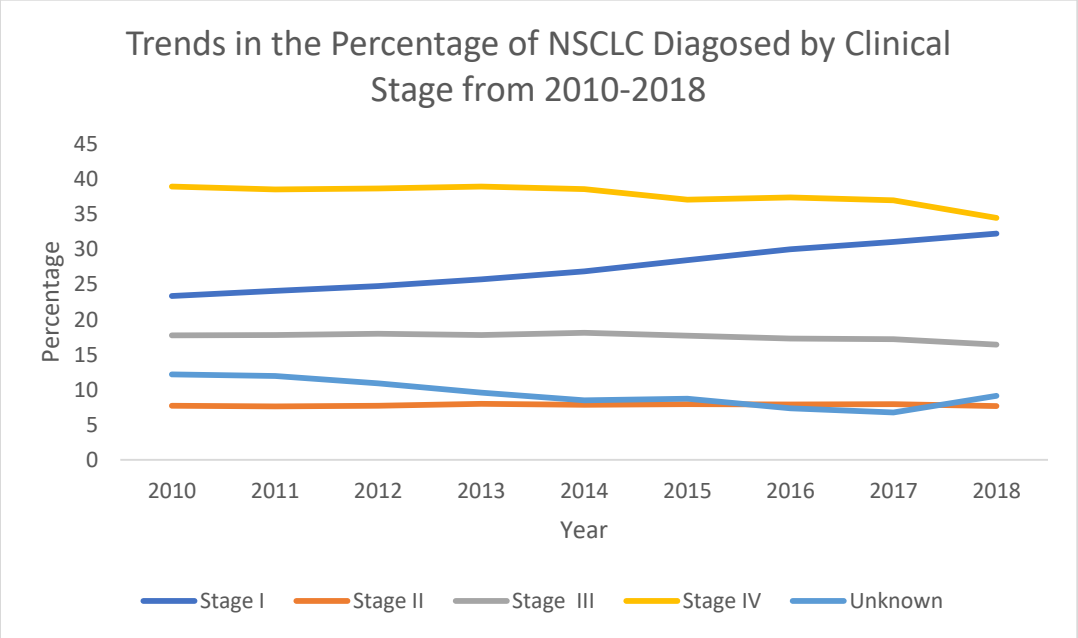

Figure E. Sensitivity Analysis of the Year-to-year Percentages of Stage I Disease Diagnosed from 2010-2018, Considering Patients—who we Previously Excluded Because they had Unknown Staging Information—as Having More Advanced Stages of Disease. The x-axis is the year of diagnosis. The y-axis is the percentage of patients diagnosed with stage I NSCLC. Each consecutive annual interval is represented as a point value. The vertical dotted line represents the date of the first lung cancer screening recommendation issued by the United States Preventive Services Task Force.

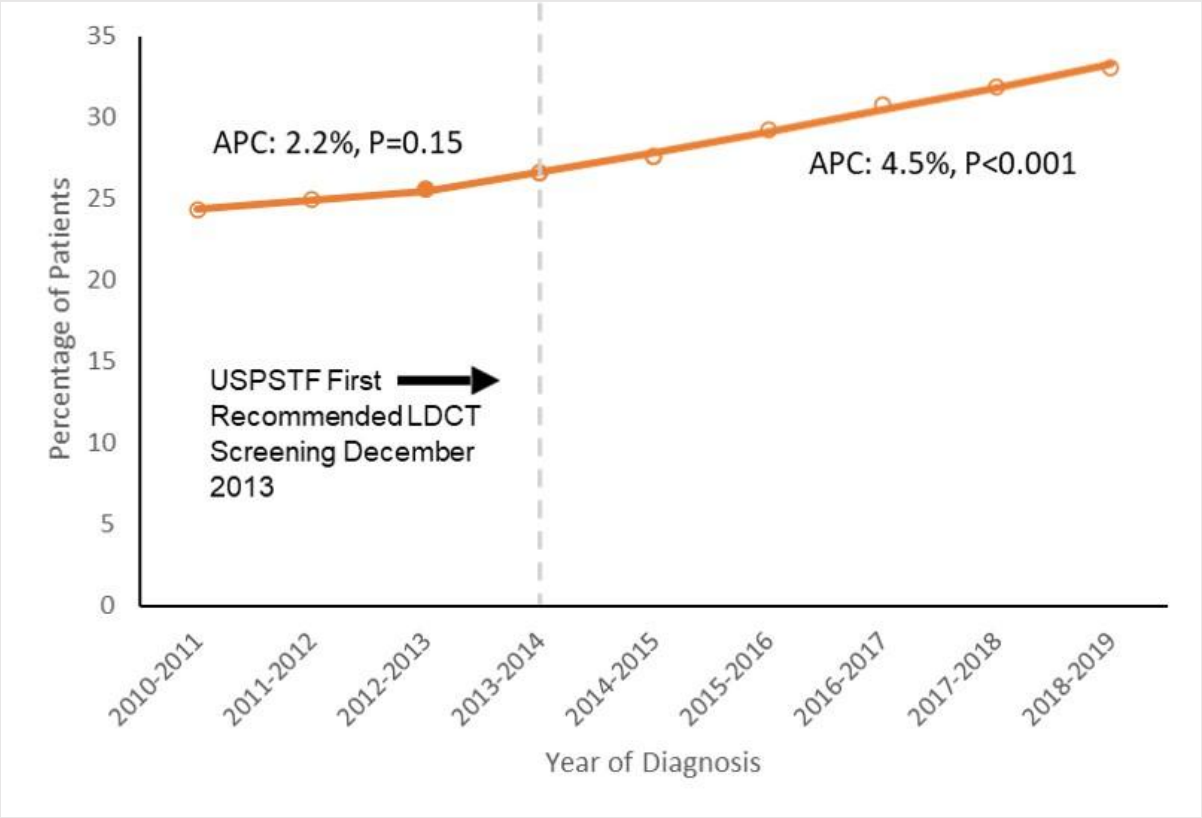

Figure F. The total number of NSCLC deaths averted from 2014-2018 due to increases in the earlier-detection of non-small-cell lung cancer. The orange line represents the multivariable-adjusted number of deaths that occurred from 2010-2018. This line represents the **true** number of deaths that occurred. The blue line represents the multivariable-adjusted number of deaths that occurred **if the shift towards earlier stages of disease identified from 2014-2018 did not occur.** The difference between the two lines represents the number of deaths averted due to a shift towards earlier stages of disease identified from 2014-2018. To obtain an estimate of the total number of deaths averted due to earlier-detection of disease from 2014-2018 in the United States, this difference was multiplied by (1/0.65) because the National Cancer Database includes approximately 65% of lung cancers diagnosed in the United States. See the methods in the Supplementary Appendix for more details on how the number of deaths averted due to a shift towards earlier stages of disease diagnosed was estimated.

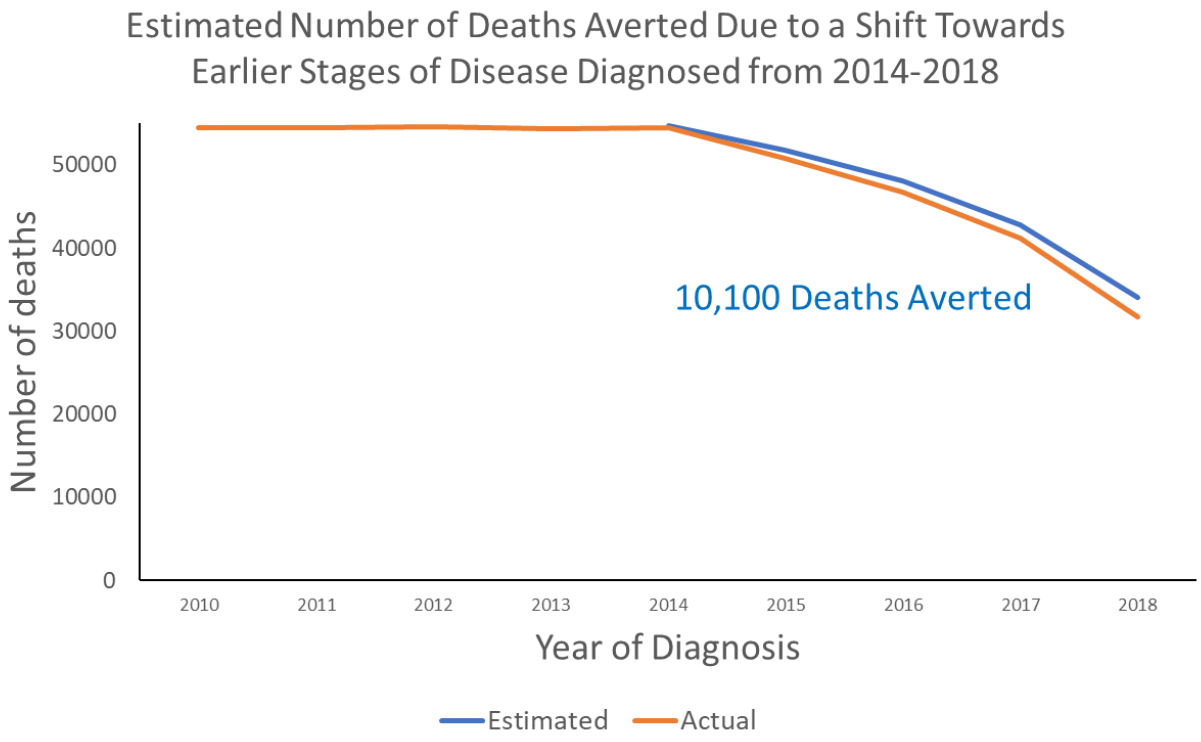

Table A. ICD-0-3 Codes[1]

	SEER Histology ICD-0-3 Codes
Adenocarcinoma	8140/3, 8550/3, 8551/3, 8260/3, 8230/3, 8253/3, 8254/3, 8480/3, 8144/3
Squamous Cell Carcinoma	8070/3, 8071/3, 8072/3, 8073/3, 8074/3, 8075/3, 8076/3, 8078/3, 8083/3
Large Cell Carcinoma	8012/3, 8013/3, 8014/3
Adenosquamous Cell Carcinoma	8560/3
Typical Carcinoid	8240/3, 8241/3, 8242/3, 8243/3, 8244/3, 8245/3, 8246/3
NSCLC Formerly Classified as Bronchiolo-alveolar Adenocarcinoma	8250/3, 8251/3, 8252/3, 8255/3, 8256/3, 8257/3

Table B. Lung Cancer Screening Rates by U.S. State According to the State of Lung Report[2]

SEER Registry*	**Lung Cancer Screening Rate in 2018**	**Above or Below the National Lung Cancer Screening Rate in 2018**
Connecticut	7.6%	Above
Michigan	8.9%	Above
Hawaii	3.7%	Below
Iowa	10.4%	Above
New Mexico	1.5%	Below
Washington	6.1%	Above
Utah	3.3%	Below
Alaska	6.4%	Above
California	1.5%	Below
Kentucky	11.7%	Above
Louisiana	2.8%	Below
New Jersey	3.2%	Below
Georgia	5.6%	Below

Table C. The Percentage of Patients Diagnosed with Stage I NSCLC by Histologic Subtype from 2010-2018 in the National Cancer Database

Histology	Annual Percent Change	95% CI	P-Value
Adenocarcinoma			
2010-2012[1]	3.5%	1.0% to 6.0%	0.02
2013-2018	1.3%	0.9% to 1.8%	0.001
Squamous Cell Carcinoma			
2010-2018[2]	-1.2%	-1.4% to -1.0%	<0.001
Large Cell Carcinoma			
2010-2012[1]	-14.9%	-29.5% to 2.6%	0.08

2013-2018	-5.3%	-8.2% to -2.2%	0.009
Adenosquamous Cell Carcinoma			
2010-2018[2]	-4.5%	-5.8% to -3.1%	<0.001
Typical Carcinoid Tumor			
2010-2018[2]	0.3%	-1.2% to 1.8%	0.63
Tumors Formerly Classified as Bronchioloalveolar Carcinoma			
2010-2014[3]	-11.4%	-15.3% to -7.2%	0.002
2015-2018	-2.3%	-6.6% to 2.2%	0.23

[1]Joinpoint was identified in 2012

[2]No joinpoint was identified from 2010-2018

[3]Joinpoint was identified in 2014

References

1. Travis, W. D.; Brambilla, E.; Nicholson, A. G.; Yatabe, Y.; Austin, J. H. M.; Beasley, M. B.; Chirieac, L. R.; Dacic, S.; Duhig, E.; Flieder, D. B.; Geisinger, K.; Hirsch, F. R.; Ishikawa, Y.; Kerr, K. M.; Noguchi, M.; Pelosi, G.; Powell, C. A.; Tsao, M. S.; Wistuba, I.; Panel, W., The 2015 World Health Organization Classification of Lung Tumors: Impact of Genetic, Clinical and Radiologic Advances Since the 2004 Classification. *J Thorac Oncol* 2015, *10* (9), 1243-1260.
2. "Key Findings: State of Lung Cancer." Key Findings | American Lung Association, www.lung.org/research/state-of-lung-cancer/key-findings.
3. Mallin K, Browner A, Palis B, et al. Incident Cases Captured in the National Cancer Database Compared with Those in U.S. Population Based Central Cancer Registries in 2012-2014. Ann Surg Oncol 2019;26:1604-12.