



July 17, 2024

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Dear Dr. Nicholson:

We are writing to you and your colleagues on the USPSTF to request that the 2021 lung cancer screening (LCS) recommendation statement be reconsidered immediately based on evidence related to the years-since-quit-smoking criterion in the recent update of the American Cancer Society (ACS) LCS guideline. Specifically, we ask that the USPSTF reconsider the criterion of 15 years since quit (YSQ), and preferably eliminate altogether the YSQ criterion for LCS eligibility as it applies to people who formerly smoked. The USPSTF recommendations are critically important in providing clinicians with the most up-to-date practice guidance on preventive services, and for “A” and “B” recommended services, to ensure health insurance plans are covering these services at no cost to patients as required by the Affordable Care Act, and that CMS can provide coverage of these services to its beneficiaries.

Over the years, screening recommendations, with a few exceptions, have been more similar than different. Where differences exist, they can be judged to be due to differences in methodology, approaches to evidence, judgments about the balance of benefits and harms, and the available evidence when the guideline was updated. The most recent examples of the latter are the decisions the ACS made in 2018 and the USPSTF made in 2021 to lower the age to begin colorectal cancer (CRC) screening from age 50 to 45. Strong evidence of the birth cohort effect on rising CRC incidence had not yet been published when the USPSTF updated their CRC screening recommendation in 2016.¹

We are facing a similar situation today with the difference in the 2021 USPSTF LCS recommendation and the 2023 ACS LCS guideline. Most recommendations for LCS today recommend that adults ages 50-80 who currently or formerly smoked (if former, quit within 15 years) and have a 20-year or greater pack year history of smoking, undergo annual LCS. Although both the NLST and the NELSON trials excluded persons who formerly smoked after

different durations since cessation, neither study described the logic for the years-since-quit (YSQ) criterion, nor has the evidence supporting a YSQ cutoff on absolute risk of developing lung cancer been cited or discussed in the previous two USPSTF evidence syntheses reports or recommendation statements. The CISNET modelers did examine longer durations of YSQ in their simulations, which were efficient, but the USPSTF retained 15 YSQ. The assumption may have been that since YSQ was included in the eligibility criteria for LCS in the trials, the YSQ criterion should be carried over into defining the target population for LCS. In fact, this was the reason that the ACS' 2013 guideline also recommended that adults who formerly smoked should not undergo screening after 15 YSQ (YSQ15). Also underpinning the recommendation very likely has been the unexamined belief that quitting smoking will lead to a yearly cumulative effect on reducing the risk of lung cancer; thus, after 15 or more years since quit, risk of lung cancer will be so low that LCS is not justified. Unfortunately, this assumption about lung cancer risk in people who formerly smoked, which was built into the trial designs and carried forward into LCS recommendations, is mistaken.

In 1993, Halpern, et al. published a study on patterns of absolute risk of lung cancer mortality in people who formerly smoked, noting that it was well established that the relative risk (RR) of lung cancer declines after cessation compared with continuing smoking, but that patterns of *absolute risk* following smoking cessation, including the effect of age at cessation, were largely unexplored.² Halpern, et al. used ACS Cancer Prevention Study II data to model absolute lung cancer risk in persons who never smoked, formerly smoked, and currently smoked, and observed similar patterns of absolute risk of lung cancer death by age for all ages of smoking cessation up to the mid-60s. Lower risk of lung cancer death was observed for those quitting earlier in life, and the risk for all persons who formerly smoked was significantly lower than that for persons who currently smoked. However, for those who quit before age 50, risk of lung cancer death rose gradually with age at a rate greater than that for persons who never smoked, and the risk of lung cancer death for those who quit between ages 50 and 64 leveled off near the risk attained at the time of quitting smoking, and then rose sharply near age 75. Although the RR in persons who formerly smoked was lower compared with persons who continued to smoke, age at quitting had a strong effect on continuing risk. Based on this publication, and more recent studies showing elevated lung cancer risk in individuals who formerly smoked, the ACS guideline update focused on the evidence for continuing absolute risk of lung cancer after smoking cessation and observed not only that lung cancer risk did not continuously decline after cessation, but, after a short duration since quitting, increased with rising age. The concordance between data from the trials, observational studies, and modeling led to the elimination of the YSQ criterion in the updated ACS LCS guideline.

Four separate studies in addition to the USPSTF 2021 evidence synthesis supported the ACS guideline update. A reference for the 2023 ACS guideline is included here as well.

1. Kondo KK, Rahman B, Ayers CK, Relevo R, Griffin JC, Halpern MT. Lung cancer diagnosis and mortality beyond 15 years since quit in individuals with a 20+ pack-year history: A systematic review. *CA Cancer J Clin.* 2024;74: 84-114.
2. Landy R, Cheung LC, Young CD, Chaturvedi AK, Katki HA. Absolute lung cancer risk increases among individuals with >15 quit-years: Analyses to inform the update of the American Cancer Society lung cancer screening guidelines. *Cancer.* 2024;130: 201-215.
3. Meza R, Cao P, de Nijs K, Jeon J, Smith RA, Ten Haaf K, de Koning H. Assessing the impact of increasing lung screening eligibility by relaxing the maximum years-since-quit threshold: A simulation modeling study. *Cancer.* 2024;130: 244-255.
4. Hendrick RE, Smith RA. Benefit-to-radiation-risk of low-dose computed tomography lung cancer screening. *Cancer.* 2024;130: 216-223.
5. Wolf AMD, Oeffinger KC, Shih TY, Walter LC, Church TR, Fontham ETH, Elkin EB, Etzioni RD, Guerra CE, Perkins RB, Kondo KK, Kratzer TB, Manassaram-Baptiste D, Dahut WL, Smith RA. Screening for lung cancer: 2023 guideline update from the American Cancer Society. *CA Cancer J Clin.* 2024;74: 50-81.

Starting with the observation that data on continuing risk after smoking cessation had not been examined, the ACS commissioned a systematic review of the literature.³ The search identified articles through February 14, 2023, and yielded 22 studies from 26 publications. The reviewers concluded that although the risk of lung cancer declined gradually after cessation compared to continuing to smoke, there were no clinically significant differences when comparing individuals in the quit-year categories just before and beyond YSQ15. Similarly, compared to individuals who never smoked, lung cancer incidence for those beyond YSQ15 can remain up to 10 times greater through 30 YSQ.

Landy, et al. utilized PLCO (adults with ≥ 20 pack-years), NLST (adults with ≥ 30 pack-years), and National Health Interview Survey (NHIS) 2015–2018 data in an analysis for the 2023 ACS guideline update of persons who ever smoked to estimate absolute lung cancer risk over time in adults who quit smoking.⁴ Their analysis also examined the impact of relaxing USPSTF recommendations to 20, 25, and 30 YSQ, and eliminating YSQ entirely. Similar to Halpern, et al., Landy, et al. observed a flattening or decline in risk for a short period after cessation, after which the influence of aging overcomes the effect of smoking cessation and absolute lung cancer risk increases at an average of approximately 4% per year. In the PLCO data, beyond YSQ15 in persons with a 20+ pack year history of smoking, the percentage change in absolute risk increased approximately 9% per year and was already rising in the period before YSQ15. Landy, et al. also estimated significant gains in deaths averted and life years gained from eliminating the YSQ criterion.

ACS commissioned two CISNET modeling groups (Erasmus and Michigan) to use their models to evaluate similar scenarios of age to start and stop screening, pack-year history, three scenarios of YSQ for individuals who formerly smoked, and ages beyond age 80 to stop screening to measure outcomes. Compared with scenarios that included \leq YSQ15 criterion for individuals who formerly smoked, removing YSQ resulted in a 37.3% increase in screening examinations, a 20.8% increase in lung cancer deaths averted, and a 19.1% increase in life years gained (LYG) per 100,000 population.⁵ The models also observed a drop in the number needed to screen (NNS) to save one life from 45 (with YSQ) to 39 (without YSQ), indicating that the increase in the number of examinations did not result in an overall lower-risk target population recommended to attend screening. Each scenario of easing and eliminating YSQ resulted in increased eligibility for LCS, increased the estimated numbers of deaths averted and LYG, and estimated increased harms (false positives, biopsies, overdiagnosis and radiation-induced lung cancer deaths). However, even with an increased number of eligible adults, added scans, and increases in harms, it has been shown that easing the YSQ criterion up to 25 years was more efficient and cost-effective compared with enforcing YSQ15 to start and continue screening.⁶ Further, with respect to harms, Meza et al. noted that harms would be significantly reduced by ensuring that LCS was restricted to individuals with reasonable life expectancy (> 5 years).⁵

Most of the additional examinations estimated in the modeling are taking place in an older age group among those ages 50-80 who, under the current USPSTF recommendation would be no longer eligible for no-cost lung cancer screening once they reached YSQ15. This is an important observation. Most adults who have acquired a 20+ pack year history probably are eligible to begin screening at age 50, and only an estimated 1% have a 20+ pack year history and have quit smoking more than 15 years previously. This means that the increase in the size of the target population for LCS (estimated by Landy, et al. to be about 4.9 million individuals⁷) mostly are those who would *not* lose eligibility to continue screening due to having reached YSQ15. For most of these individuals, their absolute risk of lung cancer is as high, or higher, at 15 YSQ compared with those who remain eligible under the 2021 recommendation criteria.

In an editorial in Cancer accompanying two of the supporting articles for the 2023 ACS guideline update, Dr. Martin Tammemagi outlined a number of compelling reasons for removing YSQ from LCS eligibility criteria, including:⁸

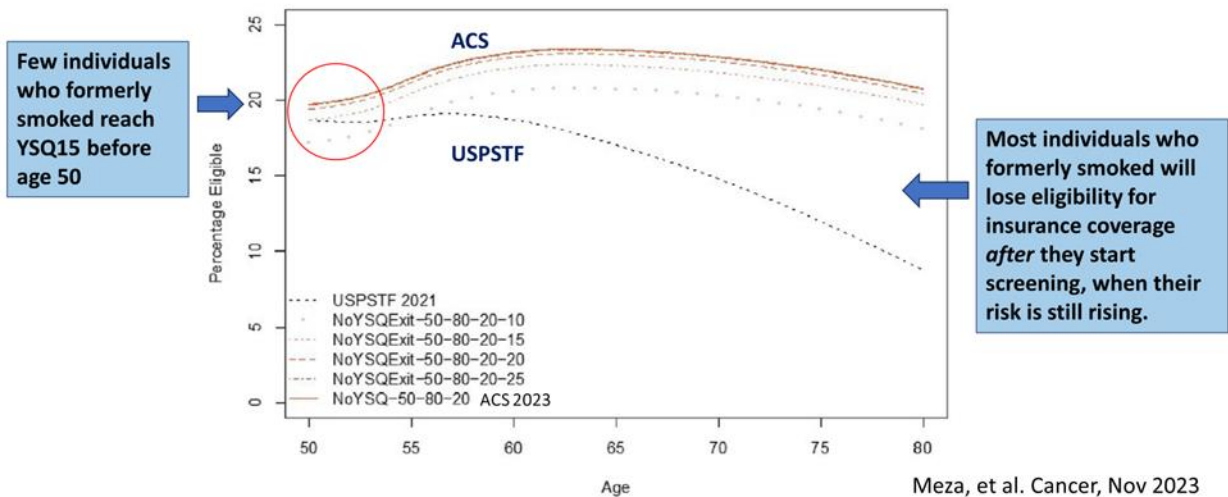
- The ACS guideline update did not just rely on modeling to drop YSQ. Tammemagi points out that real-person, prospective cohort data from the NCI's PLCO trial support the conclusions drawn in the modeling studies, the ACS evidence synthesis, and the ACS guideline.
- All risk-factor based guidelines fail to deliver equal treatment for equal risk, but the inclusion of YSQ has a substantial impact on defining high-risk individuals as low-risk. He

gives an example: An individual aged 70 years who is a high school graduate with a body mass index of 26 kg/m², COPD, a personal history of cancer, a family history of lung cancer, who smoked an average of 30 cigarettes a day for 40 years and quit smoking 16 years ago has a PLCOm2012 6-year lung cancer risk of 12%, which greatly exceeds existing thresholds ranging from 1-2%. Yet, this individual does not qualify for LCS due to YSQ.

- Persons who formerly smoked, adjusted for other factors, tend to live longer than persons who currently smoked, resulting in a greater contribution to life-years-gained when a lung cancer death is averted.
- The absolute numbers of lung cancer deaths in the U.S. in former smoking individuals exceeds those of current smoking individuals, a pattern expected to continue past 2065.

In our judgment, a rapid review by the USPSTF of the evidence and logic for removing YSQ as a criterion in LCS eligibility is justified due to the size of the affected population (approximately 4.9 million adults), the fact that most individuals who formerly smoked will initially qualify for screening (see figure below) and then will lose their eligibility when their absolute risk is rising, and the stark reality that lung cancer is the leading cause of cancer death, and a disease of high lethality when diagnosed late.

Percentage of the US 1960 birth cohort eligible for low-dose computed tomography screening at each age for the scenarios with the maximum years-since-quitting (YSQ) criterion enforced only at entry into the program (YSQ = 10, 15, 20, 25, 30) to illustrate the *small* effect of the YSQ criterion on eligibility to initiate screening and the larger effect of ≤15 YSQ on eligibility to continue screening



Based on the new evidence showing that absolute lung cancer risk increases over time rather than declines, and that this increase is especially high in individuals who have a 20+ pack year

history, we are recommending the 2021 USPSTF lung cancer screening recommendation statement for an immediate update, and respectfully request that the USPSTF reconsider their 2021 lung cancer screening recommendation now rather than later in order to examine this new information on lung cancer risk after smoking cessation in persons with a history of 20+ years of smoking.

Thank you for considering our request. If you have any questions, please contact Dr. Robert A. Smith, Senior Vice President, Cancer Screening, and Director, Center for Early Cancer Detection Science, American Cancer Society at Robert.Smith@cancer.org.

Respectfully,

American Cancer Society Cancer Action Network

American Lung Association

End Lung Cancer Now

Free ME from Lung Cancer

LiveLung

Lung Cancer Research Foundation

LUNgevity Foundation

National LGBTQI+ Cancer Network

Prevent Cancer Foundation

Upstage Lung Cancer.org

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3. Kondo KK, Rahman B, Ayers C, Revelo R, Halpern M. Lung Cancer Risk and Mortality beyond 15 Years since Quitting in 20+ Pack Year Persons who Formerly Smoked: A Systematic Review. *CA Cancer J Clin (in press)*. 2023.
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American Cancer Society lung cancer screening guidelines. *Cancer*. Jan 2024;130(2):201-215. doi:10.1002/cncr.34758.

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7. Landy R, Cheung LC, Young CD, Chaturvedi AK, Katki HA. Absolute lung cancer risk increases among individuals with >15 quit-years: Analyses to inform the update of the American Cancer Society lung cancer screening guidelines. *Cancer*. Nov 1 2023;doi:10.1002/cncr.34758.
8. Tammemagi MC. Time to quit using quit time as a lung cancer screening eligibility criterion. *Cancer*. Jan 2024;130(2):182-185. doi:10.1002/cncr.34999.