Received: 23 February 2023 | Revised: 10 April 2023 | Accepted: 2 May 2023

DOI: 10.1002/cncr.34925

ORIGINAL ARTICLE

Assessing the impact of increasing lung screening eligibility by relaxing the maximum years-since-quit threshold. A simulation modeling study

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Funding information
National Cancer Institute, Grant/Award Number: U01CA253858

Abstract

Background: In 2021, the US Preventive Services Task Force expanded its lung screening recommendation to include persons aged 50–80 years who had ever smoked and had at least 20 pack-years of exposure and less than 15 years since quitting (YSQ). However, studies have suggested that screening persons who formerly smoked with longer YSQ could be beneficial.

Methods: The authors used two validated lung cancer models to assess the benefits and harms of screening using various YSQ thresholds (10, 15, 20, 25, 30, and no YSQ) and the age at which screening was stopped. The impact of enforcing the YSQ criterion only at entry, but not at exit, also was evaluated. Outcomes included the number of screens, the percentage ever screened, screening benefits (lung cancer deaths averted, life-years gained), and harms (false-positive tests, overdiagnosed cases, radiation-induced lung cancer deaths). Sensitivity analyses were conducted to evaluate the effect of restricting screening to those who had at least 5 years of life expectancy.

Results: As the YSQ criterion was relaxed, the number of screens and the benefits and harms of screening increased. Raising the age at which to stop screening age resulted in additional benefits but with more overdiagnosis, as expected, because screening among those older than 80 years increased. Limiting screening to those who had at least 5 years of life expectancy would maintain most of the benefits while considerably reducing the harms.

Conclusions: Expanding screening to persons who formerly smoked and have greater than 15 YSQ would result in considerable increases in deaths averted and life-years gained. Although additional harms would occur, these could be moderated by ensuring that screening is restricted to only those with reasonable life expectancy.

KEYWORDS
early detection of cancer, lung neoplasms, screening, smoking

INTRODUCTION

The US Preventive Services Task Force (USPSTF) expanded its lung screening recommendation to include individuals aged 50–80 years who had ever smoked and had at least 20 pack-years of exposure and no more than 15 years since quit (YSQ) smoking.[1] Compared with the 2013 USPSTF recommendations, the new screening eligibility criteria lowered the minimum age for screening from 55 to 50 years and lowered the minimum pack-years threshold from 30 to 20 pack-years. However, the USPSTF did not change the YSQ criterion for those who used to smoke.

Several studies have suggested that determining screening eligibility according to individual risk, calculated using a multivariate model (or risk-based), instead of current eligibility criteria, which are based on smoking history and age (risk factor–based), would result in increased health gains.[2–8] This is largely because risk-based screening shifts the age range when screening occurs to older ages, when lung cancer risk is highest, even among people who already quit smoking.[2,3] In contrast, current criteria concentrate screening at younger ages because people exit screening as they quit smoking and surpass the 15 YSQ threshold.[2,3]

Recent observational and modeling studies have suggested that the YSQ criterion excludes from screening a considerable number of individuals aged 50–80 years who are at high risk for lung cancer, reducing its potential effectiveness.[9–15] In particular, a recent US modeling study found that, among a set of strategies using a 20-pack-years minimum threshold, screening those with longer YSQ criterion (20 or 25 YSQ) were the most cost-effective.[9]

In 2021, the American Cancer Society invited us to contribute analyses to the update of their lung cancer screening guideline. The society expressed an interest in exploring outcomes based on relaxed YSQ criteria because of their concern about evidence suggesting that the current restrictive YSQ criterion was eliminating a significant fraction of adults who would still qualify for screening if eligibility were based on the absolute risk associated with age and pack-year history alone. Here, we use two Cancer Intervention and Surveillance Modeling Network (CISNET) lung cancer natural history models to estimate the benefits and harms of lung screening strategies that relax the YSQ and age at stop criteria and compare their performance with the current USPSTF 2021 recommendation.

MATERIALS AND METHODS

We used two CISNET lung cancer natural history models, which were among the four used in the decision analysis supporting the USPSTF 2021 guidelines[2]: the Microsimulation Screening Analysis-Lung Model from Erasmus University Medical Center (*Erasmus MISCAN*) and the University of Michigan model (*Michigan*). Only two of the four models participated in these analyses because of competing obligations.

Both models can simulate the natural history of lung cancer given an individual's sex, birth year, and smoking history. Individual smoking histories for the US population are generated using the CISNET Smoking History Generator (SHG), a microsimulation model that simulates smoking histories for US birth cohorts.[2,16–19] The models use similar smoking dose-response modules[2,16] and lung cancer sojourn time distributions[20,21]; however, they use different lung cancer survival models and make different assumptions about screening false-positive rates.[2,3] In particular, the Erasmus MISCAN model produces outcomes consistent with the National Lung Screening Trial protocols, whereas the Michigan model has been updated to reflect screening sensitivities and specificities based on the Lung Imaging Reporting and Data System (Lung–RADS) protocol.[2] Moreover, the Erasmus MISCAN model simulates the lung cancer natural history from birth to death (forward model), whereas the Michigan model simulates lung cancer incidence first and then retrospectively generates the lung cancer natural history. The use of two independent models allows for exploration of the impact of differing model structures and assumptions. More details about each model are provided in the Supporting Materials (see the section on model descriptions and Table S1) and are available in the literature.[2,3,9,20–22]

We used the natural history models to evaluate the impact of annual low-dose computed tomography (LDCT) lung cancer screening according to the current USPSTF screening eligibility criteria versus alternative screening eligibility strategies that modify the YSQ threshold and the way that the YSQ criterion is implemented.

Consistent with previous work,[2,3,9,22–24] we used the CISNET SHG to simulate individual smoking and life histories of 1 million men and 1 million women from the US 1960 birth cohorts from ages 45 to 100 years or death, whichever occurs first. The simulated individual histories include age-specific smoking status and intensity (cigarettes per day) and the age at death from causes other than lung cancer. These were used as input by the two CISNET lung cancer natural history models. The models then simulated the lung cancer screening outcomes for each simulated individual under the different screening scenarios described below.

Modeled outcomes include the percentage of individuals eligible for screening; measures of benefit, such as lung cancer deaths averted; lung cancer mortality reduction and life-years gained (LYG) versus a no-screening scenario; and measures of harm, such as the number of LDCT screens and false-positive screens per person screened, the number of overdiagnosed cases, and the number of radiation-induced lung cancer deaths (Michigan model). We also estimated the number of participants needed to screen (NNS) to prevent one lung cancer death, measured over a lifetime of screening. The results are presented per 100,000 individuals in the general population alive at age 45 years, so they are comparable across scenarios.

Scenarios

All scenarios assumed a screening starting age of 50 years and a minimum criterion of 20 pack-years. For the first set of scenarios, we set the stop-screening age at 80 years, but later relaxed this restriction. We assumed perfect screening uptake and adherence among those eligible for screening to focus exclusively on the impact of varying the screening eligibility criteria. Smoking cessation and the risk of competing causes of death were assumed to be unaffected by screening.

We first assessed the impact of using different YSQ thresholds. We considered thresholds of 10, 15, 20, 25, and 30 YSQ. In these scenarios, the YSQ criterion was checked and enforced at age 50 years and at each subsequent individual annual screen. We labeled these scenarios as *withYSQ*.

We then assessed the impact of enforcing the YSQ criterion only at the time of entry into the screening program. That is, in these scenarios, if an individual ever meets the eligibility criteria, including the YSQ, they will enter the program. However, once into the program, these individuals can continue to be screened until the stopping age even if they eventually exceed the maximum YSQ threshold. We call these scenarios *NoYSQExit*. This scenario mirrors the experience of participants in the National Lung Screening Trial, although current USPSTF recommendations specify that, once YSQ exceeds 15 years, adults are no longer eligible for screening.

We then evaluated the impact of removing the YSQ criterion; i.e., a scenario (*NoYSQ*) in which the eligibility criteria consist only of age at start, age at stop, and minimum pack-years. Finally, we evaluated the impact of relaxing the maximum stop-screening age to 85, 90, 95 or 100 years in the NoYSQ scenario.

Sensitivity analysis

We ran all scenarios under a 5-year life expectancy criterion with perfect assessment. That is, we assumed that screening would only occur among those who have 5 years or more of life left in the simulation, based on the SHG-simulated age at death from other causes.[2,3,9]

RESULTS

As the YSQ criterion is relaxed, the number of LDCT screens and both the benefits of screening, measured as the number of lung cancer deaths averted and LYG, and the potential harms, measured as false positives, overdiagnosis, and the number of radiation-induced lung cancer deaths, increase. Figure 1 illustrates the number of LDCT screens per 100,000 population and the number of lung cancer deaths averted per 100,000 versus the no-screening scenario for all evaluated scenarios according to both natural history models (Erasmus MISCAN and Michigan). Figure 2 illustrates the number of LDCT screens per 100,000 population and the LYG versus no-screening scenario for all evaluated scenarios according to each natural history model. Table 1 shows the benefits of screening under each of the scenarios evaluated according to the Michigan model and Table 2 lists the corresponding harms. Results from the Erasmus MISCAN model are presented in the Supporting Materials (see Tables S2–S3).

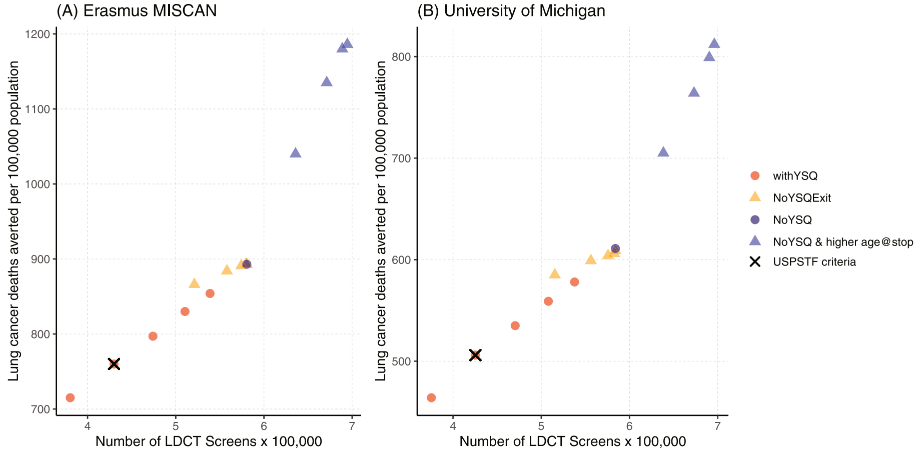

FIGURE 1 (A,B) The number of LDCT screens versus the number of lung cancer deaths averted according to each of the CISNET models. Three different YSQ scenarios were considered: (1) varying the maximum YSQ criterion in the current 2021 USPSTF guidelines (withYSQ; YSQ threshold of 10,15, 20, 25 and 30 years), (2) enforce the maximum YSQ criteria only at entry to the screening program (NoYSQExit; YSQ threshold of 10, 15, 20, 25, and 30 years), and (3) screening eligibility criteria based on only age and pack-years of smoking (NoYSQ). NoYSQ strategies also varied the age at which screening stops (ages 80, 85, 90, and 95 years). The current USPSTF 2021 scenario is highlighted with an X. CISNET indicates Cancer Intervention and Surveillance Modeling Network; LDCT, low-dose computed tomography; MISCAN, Microsimulation Screening Analysis-Lung Model from Erasmus University Medical Center; USPSTF, US Preventive Services Task Force; YSQ, years since quitting.

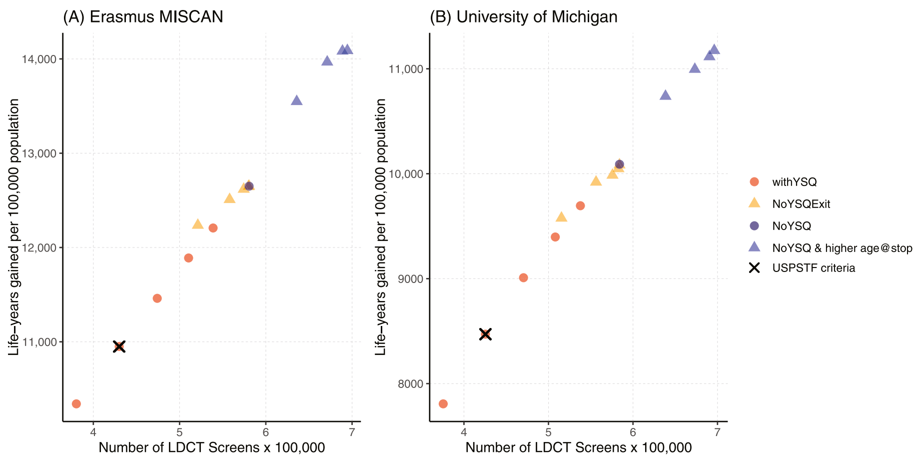

FIGURE 2 (A,B) The number of LDCT screens versus the life-years gained according to each of the CISNET models. Three different YSQ scenarios were considered: (1) varying the maximum YSQ criterion in the current 2021 USPSTF guidelines (withYSQ; maximum YSQ threshold of 10, 15, 20, 25 and 30 years), (2) enforce the maximum YSQ criteria only at entry to the screening program (NoYSQExit; YSQ threshold of 10, 15, 20, 25, and 30 years), and (3) screening eligibility criteria based on only age and pack-years of smoking (NoYSQ). NoYSQ strategies also varied the age at which screening stops (ages 80, 85, 90, and 95 years). The current USPSTF 2021 scenario is highlighted by an X. CISNET indicates Cancer Intervention and Surveillance Modeling Network; LDCT, low-dose computed tomography; MISCAN, Microsimulation Screening Analysis-Lung Model from Erasmus University Medical Center; USPSTF, US Preventive Services Task Force; YSQ, years since quitting.

Although results from the Erasmus MISCAN and Michigan models differ in absolute numbers, particularly for false-positive rates, the general patterns and the relative performance of alternative screening strategies are consistent between the two models. We choose to emphasize the Michigan model because it reflects screening sensitivities and specificities based on the Lung–RADS protocol[2] and because it also models radiation-induced lung cancer deaths.

Varying the maximum YSQ criterion in current USPSTF criteria

According to the Michigan model, 23% of the 1960 US birth cohort would be eligible for screening at some point during their lifetime according to the current USPSTF criteria (withYSQ-50-80-20-15 [the withYSQ scenario in which screening starts at age 50 years, stops age 80 years, the individual has a minimum of 20 pack-years of smoking, and they have a maximum of 15 YSQ]). This would result in 425,373 screening examinations, 506 lung cancer deaths averted, and 8471 LYG per 100,000 population (Figures 1 and 2, Table 1). The NNS to prevent one lung cancer death would be 45. In terms of harms, screening according to USPSTF criteria would result in 1.06 false-positive screens per person screened, 72 overdiagnosed lung cancer cases, and 12.8 radiation-induced lung cancer deaths per 100,000 population (Table 2).

If the maximum YSQ threshold were increased to 25 years (withYSQ-50-80-20-25), 24% of the 1960 US birth cohort would be screen-eligible, resulting in 508,064 screens (19.4% increase vs. USPSTF criteria), 559 lung cancer deaths averted (10.5% increase), and 9397 LYG (10.9% increase) per 100,000 population (Figures 1 and 2, Table 1). The NNS would be 43 (4.4% decrease). In terms of harms (Table 2), under this scenario, the false-positive screens per person screened would be 1.21 (14.2% increase vs. USPSTF criteria), the number of overdiagnosed cases would be 79 (9.7% increase), and the number of radiation-induced lung cancer deaths would be 15.1 (18% increase).

Enforce the maximum YSQ criterion only at entry to the screening program: NoYSQExit

Enforcing the YSQ criterion only at the time of entry into the screening program (NoYSQExit) results in increased benefits but also increased harms because more screening occurs at older ages. For example, screening under the scenario with criteria similar to those of the USPSTF recommendations, but in which individuals who formerly smoked and are already enrolled in screening do not exit the program when exceeding the maximum YSQ threshold (NoYSQExit-50-80-20-15), results in 556,275 screens (30.8% increase vs. USPSTF criteria), 599 lung cancer deaths averted (18.4% increase), and 9920 LYG (17.1% increase) per 100,000 population (Figures 1 and 2, Table 1). The NNS would be 38 (15.6% decrease). In terms of harms (Table 2), under this scenario, the false-positive screens per person screened would be 1.35 (27.4% increase vs. USPSTF criteria), the number of overdiagnosed cases would be 98 (36.1% increase), and the number of radiation-induced lung cancer deaths would be 16 (25% increase).

If the maximum YSQ threshold at entry were increased to 25 years, but individuals who formerly smoked and are already enrolled do not exit screening even if they eventually exceed the maximum YSQ (NoYSQExit-50-80-20-25), then 582,799 screens (37.0% increase vs. USPSTF criteria), 606 lung cancer deaths averted (19.8%

TABLE 1 Benefits of 15 selected screening programs by varying the maximum years-since-quit criterion or the age at which screening stops when the maximum years-since-quit criterion is excluded for the 1960 US birth cohort, based on the Michigan model.

Scenario[a]	Eligible, %	No. of LDCT screens	Screen-detected lung cancer cases	Lung cancer mortality reduction, %	Lung cancer deaths averted	Life-years gained	Life-years gained per lung cancer deaths averted	LDCT screens per lung cancer deaths averted	LDCT screens per life-years gained	NNS
withYSQ-50-80-20-10	21.5	375,454	1595	9.9	464	7807	16.8	810	48	46
withYSQ-50-80-20-15[b]	23.0	425,373	1727	10.8	506	8471	16.7	840	50	45
withYSQ-50-80-20-20	23.7	470,459	1836	11.4	535	9009	16.8	880	52	44
withYSQ-50-80-20-25	24.0	508,064	1920	11.9	559	9397	16.8	909	54	43
withYSQ-50-80-20-30	24.0	537,764	1984	12.3	578	9695	16.8	931	55	42
NoYSQExit-50-80-20-10	21.5	515,366	2018	12.5	585	9577	16.4	881	54	37
NoYSQExit-50-80-20-15	23.0	556,275	2070	12.8	599	9920	16.6	928	56	38
NoYSQExit-50-80-20-20	23.7	575,751	2089	12.9	604	9986	16.5	954	58	39
NoYSQExit-50-80-20-25	24.0	582,799	2097	13.0	606	10,048	16.6	961	58	40
NoYSQExit-50-80-20-30	24.0	584,013	2099	13.0	609	10,084	16.6	959	58	39
NoYSQ-50-80-20	24.0	584,062	2097	13.0	611	10,090	16.5	957	58	39
NoYSQ-50-85-20	24.0	638,458	2538	15.1	705	10,738	15.2	906	59	34
NoYSQ-50-90-20	24.0	673,162	2832	16.3	764	10,995	14.4	881	61	31
NoYSQ-50-95-20	24.0	690,494	2982	17.1	799	11,115	13.9	864	62	30
NoYSQ-50-100-20	24.0	696,138	3012	17.4	812	11,174	13.8	857	62	30

Note: Numbers are per a 100,000 individuals in the general population alive at age 45.

Abbreviations: LDCT, low-dose computed tomography; NNS, number needed to screen; YSQ, years since quit.

[a]The screening strategies correspond to the YSQ scenario, age at the start of screenings, age at which screenings stop, the minimum pack-years of smoking, and the maximum YSQ (e.g., *withYSQ-50-80-20-10* indicates the *withYSQ* scenario, start screening at age 50 years, stop screening at age 80 years, a minimum of 20 pack-years of smoking, and a maximum of 10 years since quitting). Three different YSQ scenarios were considered: (1) varying the maximum YSQ criterion in the current US Preventive Services Task Force 2021 recommendation (withYSQ), (2) enforce the maximum YSQ criteria only at entry to the screening program (NoYSQExit), and (3) screening eligibility criteria based on only age and pack-years of smoking (NoYSQ).

[b]US Preventive Services Task Force 2021 recommendation.

TABLE 2 Harms of 15 selected screening programs by varying the maximum years-since-quit criterion or the age at which screening stops when the maximum years-since-quit criterion is excluded for the 1960 US birth cohort, based on the Michigan model.

Scenario[a]	LDCT screens	Mean LDCT screens per person screened	Mean false-positive results per person screened	Overdiagnosed cases	Overdiagnosis: Percentage of all lung cancer cases	Overdiagnosis: Percentage of screen-detected lung cancer cases	Radiation-related lung cancer deaths
withYSQ-50-80-20-10	375,454	17.5	1.01	66	1.2	4.2	11.4
withYSQ-50-80-20-15[b]	425,373	18.5	1.06	72	1.2	4.1	12.8
withYSQ-50-80-20-20	470,459	19.9	1.13	77	1.3	4.2	14.1
withYSQ-50-80-20-25	508,064	21.2	1.21	79	1.4	4.1	15.1
withYSQ-50-80-20-30	537,764	22.4	1.27	83	1.4	4.2	15.9
NoYSQExit-50-80-20-10	515,366	24.0	1.34	96	1.7	4.8	14.9
NoYSQExit-50-80-20-15	556,275	24.2	1.35	98	1.7	4.7	16.0
NoYSQExit-50-80-20-20	575,751	24.3	1.35	98	1.7	4.7	16.5
NoYSQExit-50-80-20-25	582,799	24.3	1.36	99	1.7	4.7	16.6
NoYSQExit-50-80-20-30	584,013	24.3	1.36	100	1.7	4.7	16.7
NoYSQ-50-80-20	584,062	24.3	1.35	100	1.7	4.8	16.7
NoYSQ-50-85-20	638,458	26.6	1.47	156	2.7	6.1	18.2
NoYSQ-50-90-20	673,162	28.0	1.55	205	3.5	7.2	19.0
NoYSQ-50-95-20	690,494	28.8	1.58	238	4.0	8.0	19.3
NoYSQ-50-100-20	696,138	29.0	1.59	244	4.1	8.1	19.3

Note: Numbers are per a 100,000 individuals in the general population alive at age 45.

Abbreviations: LDCT, low-dose computed tomography; NNS, number needed to screen; YSQ, years since quit.

[a]The screening strategies correspond to the YSQ scenario, age at the start of screenings, age at which screenings stop, minimum pack-years of smoking, and maximum YSQ. Three different YSQ scenarios were considered: (1) varying the maximum YSQ criterion in the current US Preventive Services Task Force 2021 recommendation (withYSQ), (2) enforce the maximum USQ criteria only at entry to the screening program (NoYSQExit), and (3) screening eligibility criteria based on only age and pack-years of smoking (NoYSQ).

[b]US Preventive Services Task Force 2021 recommendation.

increase) and 10,048 LYG (18.6% increase) per 100,000 population would occur (Figures 1 and 2, Table 1). The NNS would be 40 (11.1% decrease). In terms of harms (Table 2), under this scenario, the false-positive screens per person screened would be 1.36 (28.3% increase vs. USPSTF criteria), the number of overdiagnosed cases would be 99 (37.5% increase), and the number of radiation-induced lung cancer deaths would be 16.6 (29.7% increase).

Screening eligibility criteria based on only age and pack-years: NoYSQ

Completely removing the YSQ criterion (NoYSQ-50-80-20) would not meaningfully increase the percentage of the population eligible for screening but would result in 584,062 screening examinations (37.3% increase vs. USPSTF criteria), 611 lung cancer deaths averted (20.8% increase), and 10,090 LYG (19.1% increase) per 100,000 population (Figures 1 and 2, Table 1). The NNS would be 39 (13.3% decrease). In terms of harms (Table 2), under this scenario, the false-positive screens per person screened would be 1.35 (27.4% increase vs. USPSTF criteria), the number of overdiagnosed cases would be 100 (38.9% increase), and the number of radiation-induced lung cancer deaths would be 16.7 (30.5% increase).

Increase age at stop in the NoYSQ scenario

Increasing the age at the stop of screening results in considerable increases in both the benefits and harms from screening, particularly the lung cancer deaths prevented and the overdiagnosed cases. For example, under the NoYSQ scenario, increasing the age at which screening stops to 90 years would result in 673,162 screens (58.3% increase vs. USPSTF criteria), 764 lung cancer deaths averted (51.0% increase), and 10,995 LYG (29.8% increase) per 100,000 population (Figures 1 and 2, and Table 1). The NNS would be 31 (31.1% decrease). In terms of harms (Table 2), under this scenario, the false-positive screens per person screened would be 1.55 (46.2% increase vs. USPSTF criteria), the number of overdiagnosed cases would be 205 (184.7% increase), and the number of radiation-induced lung cancers would be 19 (48.4% increase).

Excluding those with limited life expectancy

Restricting screening to those with at least 5 years of life expectancy considerably reduces the number of overdiagnosed cases (Tables 4 and S5) while preserving a large proportion of the benefits from screening (Tables 3 and S4). For example, according to the Michigan model, focusing on the scenario with NoYSQ and stopping screening at age 80 years, restricting screening to those with at least 5 years of life expectancy reduces the lung cancer deaths averted by 5.6% (577 vs. 611 per 100,000 population) and reduces the LYG by 0.7% (10,019 vs. 10,090 per 100,000 population). In contrast, the number of screens decreases by 6.8% (544,580 vs.584,062 per 100,000), and the number of overdiagnosed cases by decreases 55.0% (45 vs.100). The number of radiation-induced lung cancers would remain similar since these are caused by the radiation received earlier in life and thus not affected by screening at older ages.

DISCUSSION

We evaluated the impact of relaxing the maximum YSQ criterion and the age at which screening is stopped on the benefits and harms of annual LDCT lung cancer screening for people who ever smoked and have at least 20 pack-years of smoking history. Our findings suggest that increasing or removing the YSQ threshold or enforcing it only as an entry (but not an exit) criterion would result in considerable increases in the number of lung cancer deaths averted and LYG from screening. The modeling results suggest that comparable increases in the number of LDCT screens and in the number of overdiagnosed cases would also occur. Increasing the age at which to stop screening would also result in increased benefits, but with increases in estimated overdiagnosed cases. Nonetheless, sensitivity analyses suggest that, if screening were limited to those with a reasonable life expectancy (at least 5 years), most of the benefits of expanding screening would remain while limiting the harms.

Our results agree with the findings of a recent cost-effectiveness analysis of lung cancer screening by the CISNET lung group. The analysis indicated that, among strategies with 20 pack-years as eligibility criterion, those strategies with longer YSQ than the current USPSTF recommendation criterion of 15 YSQ would be more cost-effective.[9] This comparative modeling study was based on four lung cancer natural history models, including the two models used in our current analysis. Our findings are also consistent with observational studies showing that the YSQ criterion excludes individuals at high risk of lung cancer from LDCT screening.[10–15]

The apparent net benefits of including persons who formerly smoked with longer YSQ in LDCT screening can be explained by changes in the age at which screening occurs at the individual and population levels. First, although smoking cessation reduces the risk of lung cancer relative to that of a person who continues to smoke, the lung cancer risk in people who formerly smoked continues to increase in absolute terms as they age. Indeed, some people who used to smoke and currently are not eligible for screening have higher lung cancer risk than younger individuals who are screen-eligible. For example, using the PLCOm2012 lung cancer risk-prediction model,[25] a White man aged 75 years with some college education who formerly smoked, has a 30-pack-year smoking history and 20 YSQ (and thus is not eligible for screening), and has no other risk factors would have a lung cancer 6-year incidence probability of 2%. In contrast, a White man aged 60 years with a 30-pack-year smoking history (30 years of smoking one pack per day) who currently smokes (and thus is screen-eligible), has some college education, and has no other risk factors would have a lung cancer 6-year incidence probability of 1.5%. At the population level, relaxing

TABLE 3 Benefits of 15 selected screening programs by varying the maximum years-since-quit criterion or the age at which screening stops when the maximum years-since-quit criterion is excluded for the 1960 US birth cohort, based on the Michigan model[a].

Scenario[b]	Eligible, %	LDCT screens	Screen-detected lung cancer cases	Lung cancer mortality reduction, %	Lung cancer deaths averted	Life-years gained	Life-years gained per lung cancer deaths averted	LDCT screens per lung cancer deaths averted	LDCT screens per life-years gained	NNS
withYSQ-50-80-20-10	20.9	350,195	1473	9.5	443	7783	17.6	790	45	47
withYSQ-50-80-20-15[c]	22.4	396,974	1598	10.2	479	8415	17.6	830	47	47
withYSQ-50-80-20-20	23.1	439,346	1699	10.8	507	8889	17.5	866	49	45
withYSQ-50-80-20-25	23.3	474,636	1779	11.4	534	9362	17.5	889	51	44
withYSQ-50-80-20-30	23.4	502,340	1838	11.7	547	9555	17.5	918	53	43
NoYSQExit-50-80-20-10	20.9	479,264	1858	11.9	556	9573	17.2	863	50	38
NoYSQExit-50-80-20-15	22.4	518,157	1905	12.1	565	9806	17.4	917	53	40
NoYSQExit-50-80-20-20	23.1	536,685	1923	12.2	572	9933	17.4	939	54	40
NoYSQExit-50-80-20-25	23.3	543,392	1930	12.3	577	10,015	17.4	942	54	40
NoYSQExit-50-80-20-30	23.4	544,541	1928	12.3	575	10,027	17.4	947	54	41
NoYSQ-50-80-20	23.4	544,580	1934	12.3	577	10,019	17.4	943	54	40
NoYSQ-50-85-20	23.4	584,815	2261	14.0	656	10,658	16.2	891	55	36
NoYSQ-50-90-20	23.4	606,182	2456	15.1	706	10,940	15.5	858	55	33
NoYSQ-50-95-20[d]	23.4	614,502	2545	15.6	730	10,999	15.1	842	56	32

Note: Numbers are per a 100,000 individuals in the general population alive at age 45.

Abbreviations: LDCT, low-dose computed tomography; NNS, number needed to screen; YSQ, years since quit.

[a]We screened only individuals with at least 5 years of life expectancy.

[b]The screening strategies correspond to the YSQ scenario, age at the start of screenings, age at which screenings stopped, minimum pack-years of smoking, and maximum YSQ. Three different YSQ scenarios were considered: (1) varying the maximum YSQ criterion in the current US Preventive Services Task Force 2021 recommendation (withYSQ), (2) enforce the maximum YSQ criteria only at entry to the screening program (NoYSQExit), and (3) screening eligibility criteria based on only age and pack-years of smoking (NoYSQ).

[c]US Preventive Services Task Force 2021 recommendation.

[d]Scenario NoYSQ-50-100-20 is identical to NoYSQ-50-95-20 under the *5 years of life expectancy* restriction.

TABLE 4 Harms of 15 selected screening programs by varying the maximum years-since-quit criterion or the age at which screening stops when the maximum years-since-quit criterion is excluded for the 1960 US birth cohort, based on the Michigan model[a].

Scenario[b]	LDCT screens	Mean LDCT screens per person screened	Mean false-positive results per person screened	Overdiagnosed cases	Overdiagnosis: Percentage of all lung cancer cases	Overdiagnosis: Percentage of screen-detected lung cancer cases	Radiation-related lung cancer deaths
withYSQ-50-80-20-10	350,195	16.8	1.0	34	0.6	2.3	11.4
withYSQ-50-80-20-15[c]	396,974	17.7	1.0	37	0.6	2.3	12.8
withYSQ-50-80-20-20	439,346	19.0	1.1	41	0.7	2.4	14.1
withYSQ-50-80-20-25	474,636	20.4	1.1	42	0.7	2.4	15.1
withYSQ-50-80-20-30	502,340	21.5	1.2	43	0.8	2.3	15.8
NoYSQExit-50-80-20-10	479,264	22.9	1.3	44	0.8	2.4	14.9
NoYSQExit-50-80-20-15	518,157	23.1	1.3	45	0.8	2.4	16.0
NoYSQExit-50-80-20-20	536,685	23.2	1.3	45	0.8	2.3	16.5
NoYSQExit-50-80-20-25	543,392	23.3	1.3	46	0.8	2.4	16.6
NoYSQExit-50-80-20-30	544,541	23.3	1.3	45	0.8	2.3	16.7
NoYSQ-50-80-20	544,580	23.3	1.3	45	0.8	2.3	16.7
NoYSQ-50-85-20	584,815	25.0	1.4	63	1.1	2.8	18.2
NoYSQ-50-90-20	606,182	25.9	1.4	77	1.3	3.1	19.0
NoYSQ-50-95-20[d]	614,502	26.3	1.5	87	1.5	3.4	19.3

Note: Numbers are per a 100,000 individuals in the general population alive at age 45.

Abbreviations: LDCT, low-dose computed tomography; NNS, number needed to screen; YSQ, years since quitting.

[a]We screened only individuals with at least 5 years of life expectancy.

[b]The screening strategies correspond to the YSQ scenario, age at the start of screenings, age at which screenings stop, minimum pack-years of smoking, and maximum YSQ. Three different YSQ scenarios were considered: (1) varying the maximum YSQ criterion in the current US Preventive Services Task Force 2021 recommendation (withYSQ), (2) enforce the maximum YSQ criteria only at entry to the screening program (NoYSQExit), and (3) screening eligibility criteria based on only age and pack-years of smoking (NoYSQ).

[c]US Preventive Services Task Force 2021 recommendation.

[d]Scenario NoYSQ-50-100-20 is identical to NoYSQ-50-95-20 under the *5 years of life expectancy* restriction.

the YSQ criterion would result in a *proportional* shift of screening from younger to older ages, when lung cancer risk is highest, while still increasing the numbers of younger at-risk adults who currently are disqualified when they reach 15 YSQ (see Figures S1–S3). Therefore, increasing or removing the maximum YSQ threshold moves screening into the ages when it is more likely to find cancers and to prevent deaths from lung cancer. At the same time, this results in increases in overdiagnosis, because competing causes of death are also more prevalent at older ages, and thus the probability of finding and treating cancers that would not have been detected clinically in the absence of screening increases. The tradeoffs of shifting screening to older ages are also observed in the scenarios that evaluated increasing the age at which to stop screening, which indicated greater benefits versus other strategies that use a younger age at which to stop, particularly for lung cancer deaths prevented, but also indicated considerable increases in overdiagnosis rates, particularly when screening continues after age 90 years. These patterns are also seen when comparing screening strategies using individual risk assessment (risk-based) for eligibility versus strategies based on age, pack-years, and YSQ. The better performance of risk-based screening, particularly in terms of lung cancer deaths prevented but less so in terms of LYG, is in part because it shifts screening to older ages relative to pack-year and YSQ strategies.[2,3,8] The scenarios related to progressively older stopping ages demonstrate the increasing harms associated with screening when screening continues without consideration of life-limiting comorbidity but also the significant reduction in harms when screening is only offered to older adults in good health with considerable estimated remaining years of life.

The CISNET lung cancer natural history models have been validated and widely used to inform lung cancer screening strategies in the United States and elsewhere.[2,3,8,9,16,18,22,24,26–28] Although the predictions of the two models differ in absolute numbers, the relative performance of alternative strategies and the general conclusions are consistent between the two models. Our study, however, has some limitations. Our simulations were based on an idealized assumption of 100% screening uptake and adherence. This allows us to focus on the relative performance of screening under various eligibility criteria. Heterogeneity in uptake or adherence could affect the relative performance of the strategies evaluated but was beyond the scope of this analysis. Second, although, smoking still accounts for the majority of lung cancer risk in the United States,[29] another limitation is that the lung cancer natural history models used in this analysis only consider age, sex, and individual smoking history but do not include other relevant lung cancer risk factors. Third, the simulations were restricted to the US 1960 birth cohort. This allows our findings to be directly comparable to the decision analyses that were done in support of the current USPSTF recommendations.[2] Fourth, the analysis of the impact of restricting screening to only those with at least 5 years of life expectancy was based on an idealized assumption of perfect life-expectancy assessment. Whereas perfect assessment of longevity is unrealistic, the potential for averting preventable deaths in older adults with significant remaining longevity, and in contrast, the considerable harms when we fail to assess longevity, provide important insights into the critical need to ensure that screening is both offered and restricted only to those in good health to benefit from it, because it would maintain most of the health gains while considerably limiting the potential harms. If implemented under these conditions based on clinicians' medical judgment and existing clinical tools, expanding screening selectively to more individuals at high risk of lung cancer, either for some additional years of screening or for a qualifying adult who has never been screened or has initiated screening late in life, would result in net health gains. Finally, the estimates of radiation-induced lung cancer deaths are conservative because they were based on the linear, no-threshold dose-risk estimates from the seventh report of the National Academy of Sciences Biological Effects of Ionizing Radiation VII (BEIR VII),[30] which extrapolates risks from the exposures experienced by atomic bomb survivors to those undergoing much lower dose medical imaging.[31,32] Moreover, we did not consider other potential radiation-induced cancer sites, such as breast cancer.[33]

In summary, we used two validated lung cancer natural history models to assess the impact of expanding current screening eligibility by relaxing the YSQ criterion. The analysis suggests that expanding screening to individuals who formerly smoked with more longer than 15 YSQ would result in considerable increases in lung cancer deaths prevented and LYG; and, although additional harms would occur, these could be moderated by ensuring that screening is restricted to only those with reasonable life expectancy.

AUTHOR CONTRIBUTIONS

Rafael Meza: Conceptualization, formal analysis, funding acquisition, and writing–original draft. **Pianpian Ca**o: Model simulations, analysis, and writing–review and editing. **Koen de Nijs:** Model simulations, analysis, and writing–review and editing. **Jihyoun Jeon:** Formal analysis and writing–review and editing. **Robert A. Smith:** Conceptualization, formal analysis, and writing–review and editing. **Kevin ten Haaf:** Conceptualization, formal analysis, and writing–review and editing. **Harry de Koning:** Conceptualization, formal analysis, funding acquisition, and writing–review and editing.

ACKNOWLEDGMENTS

We acknowledge and thank the following members of the American Cancer Society Guideline Development Group: Andrew M. Wolf, MD; Timothy R. Church, PhD; Ya-Chen Tina Shih, PhD; and American Cancer Society staff (Deana Baptiste, PhD) for their thoughtful comments and feedback during the analysis. We also acknowledge Ella Kazerooni, MD, MS, for guidance regarding the patterns of follow-up testing of positive screens in the United States. This work was supported by the National Institutes of Health/National Cancer Institute (grant U01CA253858).

CONFLICT OF INTEREST STATEMENT

Robert A. Smith is employed by the American Cancer Society, which receives grants from private and corporate foundations, including foundations associated with companies in the health sector, for research outside the submitted work. His salary is solely funded through American Cancer Society funds. Kevin ten Haaf reports grants/contracts from Cancer Australia, Cancer Research UK, the Department of Health and Ageing (Australian Government), the Horizon 2020 Framework Programme, the University of Zurich (Switzerland), the US National Cancer Institute, and ZonMw all outside the submitted work. The remaining authors made no disclosures.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Meza R, Cao P, de Nijs K, et al. Assessing the impact of increasing lung screening eligibility by relaxing the maximum years-since-quit threshold. A simulation modeling study. *Cancer*. 2023;1-12. doi:10.1002/cncr.34925