Thieme

Lung Cancer Screening by Low-Dose Computed Tomography – Part 1: Expected Benefits, Possible Harms, and Criteria for Eligibility and Population Targeting

Lungenkrebs-Screening mittels Niedrigdosis-Computertomografie – Teil 1: Erwarteter Nutzen, mögliche Schäden und Kriterien für die Eignung und das Targeting der Bevölkerung

Authors
Rudolf Kaaks[1, 2], Stefan Delorme[3]

Affiliations
1 Division of Cancer Epidemiology, German Cancer Research Centre, Heidelberg, Germany
2 Translational Lung Research Center (TLRC) Heidelberg, Member of the German Center for Lung Research (DZL), Germany
3 Division of Radiology, German Cancer Research Centre, Heidelberg, Germany

Correspondence
Prof. Rudolf Kaaks
Division of Cancer Epidemiology
German Cancer Research Center (DKFZ),
Im Neuenheimer Feld 581, 69120 Heidelberg, Germany
Tel.: +49/62 21/42 22 00
r.kaaks@dkfz.de

Prof. Dr. Stefan Delorme
Division of Radiology
German Cancer Research Center (DKFZ),
Im Neuenheimer Feld 280, 69120 Heidelberg, Germany
Tel.: +49/62 21/42 24 61
s.delorme@dkfz.de

ZUSAMMENFASSUNG

Hintergrund Zahlreiche Studien in den USA und Europa haben zeigen können, dass durch Screening mit Niedrigdosis-Computertomografie (Low-Dose-CT, LDCT) der Lunge die Sterblichkeit an Lungenkrebs gesenkt werden kann, haben aber auch damit verbundene Risiken aufgezeigt, die sich durch ionisierende Strahlung, emotionalen Stress, Eingriffe infolge falsch positiver Befunde oder Überdiagnose ergeben. Um zu gewährleisten, dass die Risiken durch den möglichen Nutzen (abgewendeter Tod durch Lungenkrebs, Gewinn an Lebensjahren) aufgewogen werden, sollte Lungenkrebs-Screening auf Personen zielen, deren Lungenkrebsrisiko erhöht ist und deren verbleibende Lebenserwartung ausreichend hoch ist.

Methoden und Schlussfolgerungen Im Ganzen beträgt die Senkung der Lungenkrebssterblichkeit durch LDCT-Screening ca. 20 %. In Anbetracht der mit dem Alter abnehmenden Lebenserwartung, insbesondere bei langjährigen aktiven Rauchern, nimmt das Risiko der Überdiagnose jenseits des 75. Lebensjahres deutlich zu. Vor dem 50. Lebensjahr ist die Lungenkrebsinzidenz hingegen zu gering, als dass Risiken und auch Kosten ein angemessener Nutzen gegenübersteht. Konzise Kriterien, wie in den NLST- und NELSON-Studien angewendet, stellen einen grundlegenden Anhalt für geeignete Einschlusskriterien dar. Ihnen stehen Modelle zur Risikoprädiktion gegenüber, die neben dem Geschlecht das Alter und die Rauchanamnese als kontinuierliche Variablen verwenden. Verglichen mit konzisen Kriterien konnten mithilfe dieser Modelle 10–20 % mehr Patienten mit Lungenkrebs bei gleicher Gesamtzahl gescreenter Personen identifiziert werden. Zugleich können sie zu einer größeren Sicherheit beitragen, dass die Screening-Teilnehmer ein ausreichend hohes Lungenkrebsrisiko haben, sodass die Risiken aufgrund von Strahlung und den Folgen falsch positiver Screening-Ergebnisse aufgewogen werden.

Kernaussagen:
▪ Durch LDCT-Screening kann die Lungenkrebssterblichkeit signifikant gesenkt werden.

- Um Überdiagnose zu beschränken, sollte nach dem 75. Lebensjahr kein LDCT-Screening mehr erfolgen.
- Durch den Einsatz von Risikomodellen kann der Nettonutzen des Lungenkrebs-Screenings verbessert werden.

ABSTRACT

Background Trials in the USA and Europe have convincingly demonstrated the efficacy of screening by low-dose computed tomography (LDCT) as a means to lower lung cancer mortality, but also document potential harms related to radiation, psychosocial stress, and invasive examinations triggered by false-positive screening tests and overdiagnosis. To ensure that benefits (lung cancer deaths averted; life years gained) outweigh the risk of harm, lung cancer screening should be targeted exclusively to individuals who have an elevated risk of lung cancer, plus sufficient residual life expectancy.

Methods and Conclusions Overall, randomized screening trials show an approximate 20 % reduction in lung cancer mortality by LDCT screening. In view of declining residual life expectancy, especially among continuing long-term smokers, risk of being over-diagnosed is likely to increase rapidly above the age of 75. In contrast, before age 50, the incidence of LC may be generally too low for screening to provide a positive balance of benefits to harms and financial costs. Concise criteria as used in the NLST or NELSON trials may provide a basic guideline for screening eligibility. An alternative would be the use of risk prediction models based on smoking history, sex, and age as a continuous risk factor. Compared to concise criteria, such models have been found to identify a 10 % to 20 % larger number of LC patients for an equivalent number of individuals to be screened, and additionally may help provide security that screening participants will all have a high-enough LC risk to balance out harm potentially caused by radiation or false-positive screening tests.

Key Points:
- LDCT screening can significantly reduce lung cancer mortality
- Screening until the age of 80 was shown to be efficient in terms of cancer deaths averted; in terms of LYG relative to overdiagnosis, stopping at a younger age (e. g. 75) may have greater efficiency
- Risk models may improve the overall net benefit of lung cancer screening

Citation Format
- Kaaks R, Delorme S. Lung Cancer Screening by Low-Dose Computed Tomography – Part 1: Expected Benefits, Possible Harms, and Criteria for Eligibility and Population Targeting. Fortschr Röntgenstr 2021; 193: 527–536

Background

In Germany, lung cancer (LC) is the leading cause of cancer death among men and the second leading cause among women just after breast cancer [1]. Most LC patients in Germany have advanced (stage III, IV) tumors at the time of diagnosis. However, if identified in an early stage, surgical resection allows a favorable prognosis, especially for non-small cell lung cancer subtypes (NSCLC), with a 5-year survival of 77 % and higher for small, localized (stage-IA) tumors compared to a 1-year survival rate of less than 20 % for patients with advanced and metastasized (stage IV) cancer [2]. The large difference in survival between early- and late-stage LC patients indicates early LC detection as a possible means for lung cancer mortality reduction.

Effects on lung cancer mortality – current state of evidence

The efficacy of screening by low-dose computed tomography (LDCT) on LC mortality has been evaluated in randomized trials, including the US National Lung Cancer Screening Trial (NLST) (N = 53,454 participants [3, 4], the Dutch-Belgian NELSON trial (N = 15,882) [5], and a series of smaller trials (N = 2,450 to 4,104) in Italy, Denmark, Germany, and the United Kingdom [6–11]. In the NLST, CT screening was compared to standard chest X-ray (CXR) in the control arm, whereas all other trials had a control arm without screening intervention. The NELSON trial included a total of four screens at intervals of 1, 2, and 2.5 years, respectively, while the NLST used three and all five smaller European trials used four or more rounds of annual screening. The Italian MILD study also had an additional biennial screening arm (N = 1,186). The European trials differed only moderately in the choice of screening eligibility criteria based on age and smoking history but varied more substantially in radiologic criteria used for nodule management and LC detection in the baseline and incidence screening (▶ **Table 1**).

In the NLST, CT screening for men and women combined resulted in a 20 % overall reduction of mortality from LC compared to standard chest X-ray screening (hazard ratio [HR] = 0.80 [95 % CI 0.73–0.93]). Follow-up analyses of the NLST data [12] suggested that the reduction in LC mortality by LDCT was stronger among women (mortality hazard ratio = 0.73, 95 % CI 0.6–0.9) than among men (HR = 0.93 [95 % CI 0.8–1.08]) ($p_{heterogeneity}$ = 0.08), possibly because female LC patients more often than male patients had non-small cell tumors, particularly adenocarcinomas [10, 12], which have longer tumor sojourn times [13, 14] and may be more often detected in earlier and still curable stages, particularly if they are surrounded by ventilated lung tissue. NELSON, the second largest trial worldwide, 10 years after randomization showed a significant reduction in LC mortality among men (HR = 0.76 [95 % CI: 0.61–0.91]) and a statistically non-significant mortality reduction in a parallel and smaller cohort of women (HR = 0.67 [95 % CI: 0.38–1.14]). In Germany, the LUSI study showed an overall hazard ratio for LC mortality of HR = 0.74 [95 % CI: 0.46–1.19] for men and women combined, which was not sta-

▶ **Table 1** Selected key characteristics of randomized trials of LC screening by LDCT screening vs. a control arm of X-ray (NLST) or no screening (all other trials).

▶ **Tab. 1** Ausgewählte Schlüsselmerkmale randomisierter Studien zum LC-Screening durch LDCT-Screening versus einem Kontrollarm für Röntgen (NLST) oder ohne Screening (alle anderen Studien).

trial, country, starting date	N (men/women)	eligibility			nodule management	
		age (inclusion)	smoking		prevalence screen	incidence screen
NLST, USA 2002 –	53,454 (31,532/21,922)	55–74	≥30 pack yrs Quit ≤ 15 yrs	+ –	**D** ≥ 4 mm D < 4 mm	**D** ≥ 4 mm D < 4 mm
DANTE, Italy 2001 –	2,450 (2,450/0)	60–74	> 20 pack yrs Quit < 10 yrs	+ –	**D** > 5 mm **D** ≤ 5 mm	new **D** > 5 mm or any growth no new; no growth; NCN ≤ 5 mm
ITALUNG, Italy 2004 –	3,206 (2,074/1,132)	55–69	> 20 pack yrs Quit < 10 yrs	+ –	**D** ≥ 5 mm < 5 mm	new > 3mm; any growth no new; no growth
DLCST, Denmark 2004 –	4,104 (2,267/1,837)	50–70	> 20 pack yrs Quit < 10 yrs	+ +/– –	**D** > 15 mm **D** = 5–15 mm **D** < 5 mm	any new; **VDT** < 400 d **VDT** 400–600 d no new; **VDT** > 600 d
MILD, Italy 2005 –	4,099 (2,716/1,383)	50 +	> 20 pack yrs Quit < 10 yrs	+ +/– –	**V** > 250 mm³ **V** = 60–250 mm³ **V** < 60 mm³	new > 250 mm³ new 0–250 mm³ no new
NELSON, Belgium & Netherlands 2003 –	15,422 (13,195/2,594)	50–74	≥ 15 c/d × ≥ 25 yrs, ≥ 10 c/d × ≥ 30 yrs Quit < 10 yrs	+ +/– –	**V** > 500 m³; **VDT** < 400 d **V** = 50–500 mm3; **VDT** 400–600 d **V** < 50 mm³; **VDT** > 600 d	new > 500 mm³; **VDT** < 400 d new 50–500 mm³; **VDT** 400–600 d none, new < 50 mm³; **VDT** > 600 d
LUSI, Germany 2007 –	4,052	50–69	≥ 15 c/d × ≥ 25 yrs, ≥ 10 c/d × ≥ 30 yrs Quit < 10 yrs	+ +/– –	**D** > 10 mm or **VDT** < 400 d **D** = 5–19 mm or **VDT** = 400–600 d **D** < 5 mm or **VDT** > 600 d	new > 10mm; **VDT** < 400 d **VDT** 400–600 d no new; no growth; **VDT** > 600 d

tistically significant. However, secondary analyses suggested a significant reduction in LC mortality among women (HR = 0.31 [95 %CI: 0.10–0.96], p = 0.04), but no reduction among men (HR = 0.94 [95 %CI: 0.54–1.61], p = 0.81). The other European trials reported on LC mortality only for both sexes combined. In ITALUNG (Tuscany, Italy), after a median follow-up time of 8.5 years, LDCT screening led to a non-significant 30 % reduction in LC mortality (RR = 0.70; 95 % CI 0.47 to 1.03), whereas the Italian DANTE trial (HR = 0.99 [95 % CI: 0.69–1.43]) [7] and the Danish DLCST study (HR = 1.03 [CI 0.66–1.06]) [11] showed no mortality reduction at all. The Italian MILD trial [8] had an excess of long-term and heavy smokers in the CT arm compared to the controls due to improper randomization of participants, but after multi-variable adjustments for confounding by age, gender, and lifetime pack years of smoking showed a significant 39 % risk reduction for LC mortality at 10 years post-randomization (HR 0.61 [95 % CI: 0.39–0.95]) [9]. Overall, a meta-analysis of European trials shows a significant reduction of LC mortality by approximately 20 % in CT compared to control arms (▶ **Fig. 1**), in line with findings from NLST. Whereas the NLST also showed a statistically significant reduction in all-cause mortality (HR = 0.94 [CI 0.88–1.00]), NELSON (HR = 1.01 [CI 0.92–1.11]), or any of the smaller Europe-

an trials (HR ranging from 0.84 [CI 0.69–1.03] in ITALUNG to 1.01 [CI 0.82–1.25] in DLCST) showed no clear evidence for overall mortality reduction.

Potential of harms of screening

The benefits of screening (reduction in LC mortality) must be reconciled with several potential harms, related to radiation, the sequelae of false-positive screening tests, and overdiagnosis.

Radiation risks

LDCT screening exposes individuals to excess radiation for regular screening as well as follow-up examinations of indeterminate findings, which may increase long-term risk of cancer. Based on models developed by the Biological Effects of Ionizing Radiation committee (BEIR) [15], using a linear no-threshold (LNT) model to extrapolate from cancer risks with high radiation exposures (atomic bomb survivors; medical imaging), several investigators estimated the lifetime contribution of LDCT screening to radiation-induced mortality due to LC as well as other major cancers (in particular, breast cancer). Estimates vary depending on specific model assumptions for physical radiation doses received, phys-
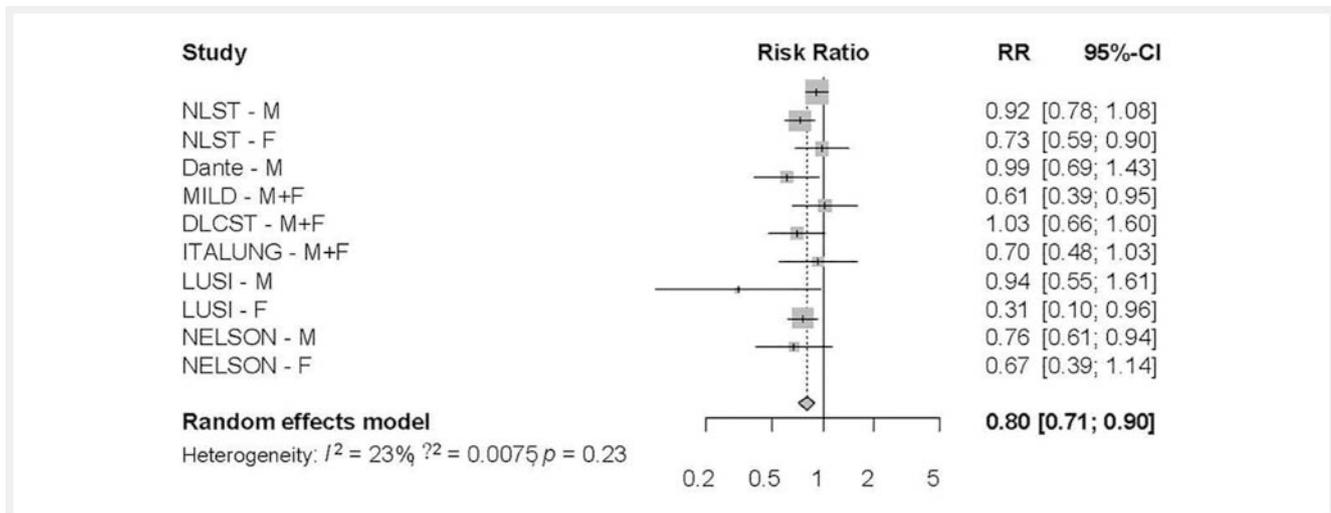
▶ **Fig. 1** Mortality risk reduction (hazard ratio) for lung cancer in screening trials comparing CT screening with standard chest X-ray (NLST study) or with no screening (all other studies): forest plot and random effects meta-analysis.

▶ **Abb. 1** Verringerung des Mortalitätsrisikos (Hazard Ratio) für Lungenkrebs in Screening-Studien zum Vergleich des CT-Screenings mit Standard-Röntgenaufnahmen des Brustkorbs (NLST-Studie) oder ohne Screening (alle anderen Studien): Forest Plot und Metaanalyse der zufälligen Effekte.

ical vs. biologically effective radiation doses at various organ sites, weightings for excess risk estimates on an additive vs. multiplicative scale, and interactions between smoking and radiation exposures [16–19]. In general, radiation-induced cancer risks are higher for women than for men, and in the case of exposures at a younger compared to an older age. For NLST participants, assuming an average, cumulative effective radiation dose of 8 mSV, the average lifetime risk of radiation-induced LC death was estimated at 4 per 10,000 men and women combined [18]. A more recent study conducted in the Italian COSMOS trial [19] – a non-randomized study of men and women aged 50 and older with ≥20 pack years of smoking with up to 10 annual screening rounds – obtained detailed radiation dosimetry records for annual LDCT screening as well as for additional (PET/CT) examinations for individuals with suspicious pulmonary nodules. At the 10th year of annual screening, a median cumulative effective dose of 9.3 mSv for men, and 13.0 mSv for women had been reached. Based on organ-specific effective radiation doses, individuals' estimated lifetime risks (incidence) of any major radiation-induced cancer (thoracic and abdominal organs & bone marrow) were systematically below 5 per 10,000 for men and below 10 per 10,000 for women, with an average of 2.4 per 10,000 for both sexes combined [19]. Under prudent assumptions of $CTDI_{vol} = 1.5$ mGy per CT screening, a dose and dose-rate effectiveness factor (DDREF) of 1.0 for all organ-tumor entities, and conservative weightings of absolute (additive) vs. relative (multiplicative) risk increases, the German Federal Office for Radiation Protection (*Bundesamt für Strahlenschutz*, BfS) estimated that, in the German population, annual screening between the ages of 50 and 54, with an effective radiation dose of 1.5 mSv per CT scan, may cause a lifelong risk of death from radiation-induced cancer (lung, breast, and other major cancers) of 0.07 % among women and about 0.03 % among men [20]. With improving technology, however, the effective LDCT dose per

CT scan is likely to decrease to 1.0 mSv or even lower in the near future [21, 22].

False-positive test results and invasive follow-up diagnostics

In NLST, pulmonary nodules with a largest diameter of ≥4 mm were considered suspicious and classified as test-positive, and about 39 % of participants had at least one positive test result of which 96.4 % turned out to be false-positive [4]. Since the NLST trial, radiologic criteria for detecting potentially malignant nodules have been sharpened, using higher minimal nodule size cut-offs combined with longitudinal nodule growth (volume doubling times, VDT) as additional criteria for positive screening detection [23], improving test specificity with a minimal loss of sensitivity [24]. In NELSON, a volumetric nodule measurement protocol was used, and only large nodules (> 500 mm³) or nodules between 50 and 500 mm³ with VDT < 400 days (or newly appearing since previous screening) were regarded as screen-positive. With this strategy, 458 (6 %) of the 7582 screened participants had a positive screening test result, with 200 (2.6 % of all participants) being diagnosed with lung cancer. A positive screening result had a predictive value of 40.6 % and only 1.2 % of all scan results were false-positive [25].

False-positive screening tests cause serious harm, especially when they trigger invasive medical follow-up investigations for benign lesions. Invasive diagnostic workup is generally performed only after further intermediate imaging by CT or PET, or antibiotics treatment for exclusion of infectious lesions. Nonetheless, in NLST, cumulated over three screening rounds, 1.2 % of screening participants underwent needle biopsy or bronchoscopy, and 0.7 % had endoscopic thoracic surgery or thoracotomy but turned out not to have lung cancer [4]. Equivalent numbers in NELSON were 1.2 % and 0.6 %, respectively [26]. A more recent analysis of NLST

data by Pinsky et al. [27] showed that the cumulative proportion of participants receiving a false-positive screening test (reanalyzed according to Lung-RADS criteria [28]) increased from 12.9 % for individuals in the lowest, to 25.9 % for those in highest decile of lung cancer risk estimated by a risk model (PLCO$_{M2012}$) developed in the prospective Prostate, Lung, Ovary, Colorectum and Ovary (PLCO) trial in the USA [29]. The cumulative proportion undergoing thoracic surgery, thoracotomy, or biopsy after a false-positive screening test also increased with lung cancer risk from 0.7 % to 2.0 %. In parallel, the cumulative probability of receiving a true-positive LC diagnosis varied also from 0.95 % in the lowest risk decile to 10.5 % in the highest, corresponding to ratios of true-positive diagnoses over invasive procedures after false-positive diagnoses of 1.35 to 5.25, respectively [27].

Even when false-positive screening tests do not lead to invasive diagnostic investigations, they are a source of considerable psychosocial stress, affecting quality of life. Studies in various screening trials have documented distress, a state of anxiety, and diminished health-related quality of life among participants who received an indeterminate screening result [30–32], although these effects appear to be often transient and were found to diminish after a follow-up period of 6 months or longer. It therefore is important that screening participants should be duly informed about possible negative psychosocial consequences and how to interpret their own screening results.

Overdiagnosis

Overdiagnosis refers to tumors that without screening would not have become manifest in a person's lifetime and reflects an individual's probability of dying from competing causes within the lead time window of early tumor detection [33]. It causes serious harm, as it leads to aggressive treatments with major loss of quality of life. The extent of overdiagnosis in CT screening has been estimated by assessing the excess cumulative incidence between screened and unscreened (control arm) participants in randomized trials, over a prolonged observation period after the last screening visit. Expressed as a proportion of screening-detected lung cancer cases, and after an average follow-up period of about 4.5 to 5 years since the last screening visit, this excess ranged from none in the ITALUNG trial [6], to 18.5 % (95 % CI: 5.4 %–30.6 %) in the NLST [34], 19.7 % (95 %CI: –5.2 %-41.6 %) in NELSON [5] and 67.2 % (95 % CI: 37.1 %-95.4 %) in the Danish Lung Cancer Screening Trial (DLCST) [35]. Excess incidence in "stop-screen" trials, however, will provide an overestimate of overdiagnosis if the follow-up times after last screening participation do not exceed even the longest tumor lead times for most study participants, which likely was the case in each of the above analyses. In a more recent analysis of NLST data, after extended follow-up of about 9 years since last screening, the excess incidence in the LDCT arm shrunk to zero, compared to the CXR control arm [36].

Parallel to excess incidence estimates, statistical modeling approaches have been used to estimate mean preclinical sojourn times of lung tumors combined with the sensitivity of LDCT detection, and from these, to predict the extent of overdiagnosis for a broad spectrum of theoretical (simulated) screening scenarios [37–39]. Modeling of data from the NLST [13, 34] and

LUSI trials [14] yielded estimates for mean preclinical sojourn times [MPST] of lung tumors ranging from about 4 to 6 years depending on major histologic tumor sub-type, with longer sojourn times especially for adenocarcinomas, and extremely long MPST up to about 9 [14] or even 30 years [34] for a smaller subset of bronchioloalveolar carcinomas. In the LUSI study, it was further estimated that, for all histologic types combined, close to half of screening-detected tumors had a lead time ≥4 years, and about one third had a lead time ≥6 years [14]. Individuals whose remaining life expectancies are below these lead times will be at risk for overdiagnosis, and this may be of particular concern in long-term (and still recent) smokers age 75 or above.

To whom should screening be targeted?

Screening should be targeted to individuals who are expected to have a sufficiently high prevalence or short-term incidence of clinically manifest LC within an upcoming time window for screening (e. g. next 5 years), while being in sufficiently good health to expect a meaningful gain in life years in case of early cancer detection. Age and smoking history are major determinants of both lung cancer risk and residual life expectancy [40]. With regard to smoking history, epidemiologic modeling studies have shown that lung cancer risk increases approximately linearly with total lifetime smoking duration (years), whereas in a non-linear fashion it also depends on smoking intensity (cigarettes per day), with relative risk increases gradually tailing off with increasing intensities [41, 42]. Simplified models often use cumulative pack-years – i. e., the product of duration time intensity – as a summary measure for lifetime exposure, even though this may somewhat diminish the accuracy of lung cancer risk estimates [43]. Compared to continuing smokers, the relative risk of lung cancer among ex-smokers declines steadily with increasing years after cessation, although an excess risk generally remains compared to never smokers, even after prolonged time periods since quitting [41, 42, 44].

Recommended criteria for LC screening eligibility so far have been defined mostly in terms of lower and upper age limits, minimal lifetime cumulative smoking exposure, and maximum time since smoking cessation, extending from criteria used in trials, in particular the NLST [37, 45–48].

Based on quantitative simulation models (see below), judging by the good overall balance between the projected reduction in lung cancer mortality and the gain in life years (LYG) versus expected biopsies or surgeries for benign lesions and cases of overdiagnosis, the US Preventive Services Task Force (USPSTF) recommends annual screening for men and women age 55 to 80 (stopping age) with a minimum of 30 pack years of cumulative lifetime smoking exposure and who have not quit smoking for more than 15 years (coded: A-55-80-30-15) – a scenario similar to that of the NLST trial (A-55-75-30-15) but with a stopping age of 80 instead of 75 years [37, 45]. Other US organizations as well as expert organizations in Canada and Europe followed the original NLST criteria, i. e., with a stopping age of 75 [49–51].

In Germany, analyses of survey data show that about 3.0 million men and women would be eligible according to NLST criteria,

and 3.2 million according to the extended USPSTF criteria. Based on risk prediction models (see below), it can be further estimated that about 40 % or 45 % of yearly incident lung cancer cases would occur in these two risk sets [52]. Using the criteria of the NELSON trial, which require a more moderate smoking history of ≥ 10 cigarettes a day for 30 years or ≥ 15 cigarettes a day for 25 years but more stringent criteria for maximum time since smoking cessation (< 10 years) and cover an overall younger age range of 50 to 75 years, 5.5 million German ever smokers would be eligible, among whom about 47 % of incident lung cancer cases occur [52].

Simulation modeling of expected benefits and harms

For the USA [37, 53, 54] and other countries [39, 55, 56], detailed quantitative modeling studies have been performed to predict the benefits and harms of screening over a broad range of possible inclusion criteria – i. e., based on combinations of screening starting ages, stopping ages, cumulative smoking history, maximum time since smoking cessation, and screening intervals. While models differed in structure, they were calibrated mostly to incidence and mortality data (stratified by age, sex, histology, and tumor stage) from the NLST and PLCO trials, as well as to data from national cancer incidence and mortality registries. In all simulations, broadening the eligible age range or using less stringent criteria for lifetime smoking exposure and/or time since quitting increased the population numbers eligible for screening, and led to larger proportions of LC deaths avoided (up to a maximum of about 20 % – the percent reduction observed in the NLST). However, when considering screening scenarios lying on an overall efficiency border (i. e., providing greatest benefit at a given total number of screenings to be performed), an increase in benefits that resulted from the use of broadened eligibility criteria would systematically come at the cost of larger numbers that need to be screened (NNS), higher numbers of biopsies or surgeries for benign lesions, and higher financial costs per LC death averted or LYG.

Initial modeling analyses for the USA [37] showed that scenarios stopping screening at age 80 or above will avert more cancer deaths for a number of screenings performed than scenarios stopping at age 75 or earlier, due to the high proportion of lung cancers occurring in the oldest age groups. This finding led the USPSTF to define its guidelines for LC screening, extending NLST criteria to screening up to age 80 [37, 45]. However, the oldest also have the highest risk of being overdiagnosed, while their average number of LYG per LC death averted is relatively small, and more recent simulations showed that, with screening benefit defined as LYG relative as either a ratio or a difference to overdiagnosed cases, screening will be more efficient when stopped at 75 years compared to 80 or older [53].
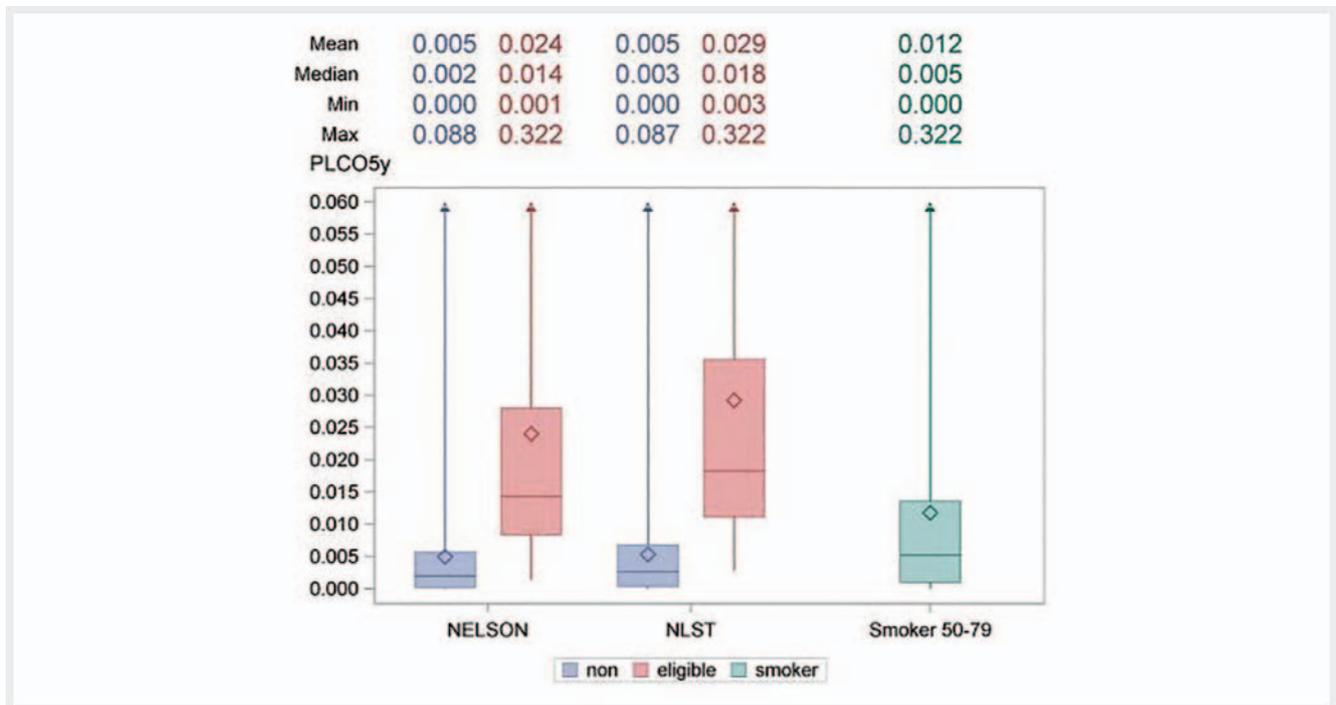
For radiation risks, first modeling studies indicated that, over a wide range of screening scenarios and averaged across all screening-eligible individuals, LC deaths averted through screening will largely outweigh the longer-term (lifetime) risk of radiation-induced lung cancer mortality, by an average factor of about 20 [37, 39, 57], where the radiation-induced LC risk was mostly extrapolated from the estimates by Bach et al. [18]. The estimates from the COSMOS trial suggest one radiation-induced major cancer would be expected for every 108 lung cancers detected through screening [19], confirming relatively low overall radiation harm even when all major cancers are considered. Nonetheless, in younger age groups, for whom long-term radiation risks are higher, but whose immediate lung cancer incidence will be lower, radiation risks may be an issue. To minimally offset the lifetime risk of radiation-induced cancer of about 0.03–0.07 %, as estimated for 50–54 year old men and women in Germany [20], screening participants should have a 5-year lung cancer risk of about 0.5 % or higher if one assumes at least 80 % sensitivity of lung cancer detection and 20 % mortality risk reduction by LDCT screening. Theoretical calculations [58] and analyses of population survey data [52, 59] show that NELSON, NLST, or USPSTF criteria may include a proportion of individuals (e. g. younger ages, who quit smoking more than 10 years ago) for whom the ratio of lung cancer deaths to radiation-induced risks and harms related to biopsy or surgery of benign lesions will be less favorable, and who should not be included in screening (see also ▶ **Fig. 2**).

Regarding false-positive results, recent analyses by Pinsky et al. [27] show that, even within the limits of NLST eligibility criteria, the ratio of true-positive lung cancer diagnoses to invasive diagnostic workup (bronchoscopic or surgical biopsies) triggered by a false-positive screening test varied from about 1.35 for individuals in the lowest decile of 5-year lung cancer risk ($PLCO_{M2012}$, 5-year risk < 1.0 %) to about 5.25 in the highest decile (5-year risk ≥ 6.5 %) [27]. Thus, the ratio of screening benefit (LC mortality reduction, for true positives) versus the risk of undergoing invasive investigations following a false-positive screening test may strongly depend on an individual's actual lung cancer risk, and improves as risk increases.

Screening eligibility based on model estimates of absolute lung cancer risk

An alternative to concise inclusion criteria based on age limits, minimal cumulative smoking history, and maximum years since cessation, e. g. as defined by USPSTF, NLST, or NELSON, is the use of more refined statistical models for the prediction of an individual's absolute LC risk, based on age, sex, detailed smoking history, presence of pulmonary disease (e. g., chronic COPD, emphysema), family or personal history of cancer, and further predictor variables. Compared to concise eligibility criteria, using risk models to identify individuals at the highest predicted lung cancer risks were found to generally identify about 10 % to 20 % more future lung cancer cases for an equal number of individuals to be screened [29, 60–62]. In various populations this corresponded to a 5-year risk threshold of about 1.5–1.7 %; see [52] for review. The latter approach also provides a better guarantee that each eligible subject will have a minimal individual lung cancer risk required to optimally offset the harms that may result from radiation of invasive investigations triggered by false-positive screening tests. On the other hand, risk-based selection tends to elect individuals in higher age groups [29, 52, 60–62] who have a higher risk of overdiagnosis. Comparative modeling shows [54] that, for equal numbers of individuals screened, risk-based strategies may avert more lung cancer deaths than current USPSTF recommendations, but

	Mean	0.005	0.024	0.005	0.029	0.012
	Median	0.002	0.014	0.003	0.018	0.005
	Min	0.000	0.001	0.000	0.003	0.000
	Max	0.088	0.322	0.087	0.322	0.322

▶ **Fig. 2** Box plots of absolute 5-year risk of LC as estimated by the PLCOM2012 model, for German ever-smoking adults (men and women) eligible by NELSON or NLST criteria (data from the German "Gesundheit Deutschland aktuell" [GEDA] study, 2008–2013).

▶ **Abb. 2** Box-Plots des absoluten 5-Jahres-LC-Risikos nach dem PLCOM2012-Modell für deutsche, rauchende Erwachsene (Männer und Frauen), die nach NELSON- oder NLST-Kriterien zugelassen sind (Daten der deutschen "Gesundheit Deutschland aktuell" GEDA) -Studie, 2008–2013).

with only modestly higher LYG and with considerably more over-diagnosis. However, excluding individuals with life expectancies < 5 years from screening retains the life-years gained by risk-based screening, while reducing overdiagnosis by about two thirds [54].

Summary: weighting expected benefits vs. harms, eligibility criteria, and shared decision-making

LC screening should be targeted to individuals who for an upcoming time frame (e. g. next 5 years) have a sufficiently high LC risk as to have a larger anticipated benefit than harm, at acceptable financial costs to the society. Defining exact minimal risk thresholds, however, is complex as these will depend on the relative weights given to specific units of benefit (e. g. LYG) and harm (e. g. quality-adjusted life years [QALYs] lost due to overdiagnosis, radiation-induced cancers or complications from invasive investigations after false-positive screening tests). Nonetheless, risk analyses and modeling studies provide a number of indications for optimizing eligibility criteria for LC screening in Germany:

- The risk of overdiagnosis can be high among individuals with limited residual life expectancies (e. g. less than about 6 years), and may be a concern, especially among continuing smokers 75 years and older. Future work may focus on differentiated assessments of individual residual life expectancy, using questionnaire data and clinical fitness indicators.

- Screening should not be considered before age 50, as the incidence of LC will often be too low, even among longer-time smokers, for screening to be economically cost-effective.
- Concise criteria such as those used in the NLST or NELSON trials may provide good basic guidelines for screening eligibility. Compared to the NLST criteria (about 3.0 million eligible subjects in Germany), the NELSON criteria (younger age at start, less stringent cumulative smoking history, but more stringent regarding maximum time since cessation; about 5.5 million eligible subjects) may capture about 20 % more incident LC cases, but at the cost of about 50 % more individuals screened per cancer case detected. A limitation of concise criteria, however, is that they provide a reasonable guarantee only for the average risk of the population screened, but not for the minimally required risk for each screening participant.
- Compared to NLST or NELSON criteria, using risk models such as PLCOM2012 will generally increase the number of life years gained through screening for an equal number of individuals screened. Additionally, at the level of each single screening participant, this approach provides a stronger guarantee for a positive balance of screening benefits (lung cancer deaths averted, LYG) vs. harm caused by radiation or false-positive screening tests.

Conclusion

While LDCT screening has the clear potential to reduce LC mortality, it should, to ensure net clinical benefit, be targeted exclusively to individuals with a sufficiently elevated LC risk, while still being in sufficiently good health to gain a meaningful extension of life expectancy in the case of cancer detection. Concise criteria as used previously in NLST or NELSON can provide minimal guidance for screening eligibility but may include individuals whose risks are potentially too low to offset the risks of harm that may be caused by false-positive screening or radiation. Eligibility based on a minimal risk threshold, estimated by a basic model using age, sex, and smoking history, may provide better guarantee that individual screening participants will all have a minimal lung cancer risk required to offset the risks of potential harms, while increasing screening efficiency in terms of mortality reduction at a given number of people screened.

Proper implementation of LDCT screening should be based on shared decision-making between potential screening participants and trained clinicians, during a medical visit prior to the screening event. During this visit, the responsible clinician should accurately convey both the potential benefits and risks of lung cancer screening, and explain reasons for either recommending screening, or denying access to it.

Conflict of Interest

The authors declare that they have no conflict of interest.

References

[1] Barnes B, Kraywinkel K, Nowossadeck E et al. Bericht zum Krebsgeschehen in Deutschland 2016. In: Robert Koch-Institut Gesundheitsberichterstattung-Hefte 2016 doi:10.17886/rkipubl-2016-014

[2] Goldstraw P, Chansky K, Crowley J et al. The IASLC Lung Cancer Staging Project: Proposals for Revision of the TNM Stage Groupings in the Forthcoming (Eighth) Edition of the TNM Classification for Lung Cancer. Journal of Thoracic Oncology: official publication of the International Association for the Study of Lung Cancer 2016; 11: 39–51. doi:10.1016/j.jtho.2015.09.009

[3] Aberle DR, Berg CD, Black WC et al. The National Lung Screening Trial: overview and study design. Radiology 2011; 258: 243–253. doi:10.1148/radiol.10091808

[4] Aberle DR, Adams AM, Berg CD et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. The New England Journal of Medicine 2011; 365: 395–409. doi:10.1056/NEJMoa1102873

[5] de Koning HJ, van der Aalst CM, de Jong PA et al. Reduced Lung-Cancer Mortality with Volume CT Screening in a Randomized Trial. The New England Journal of Medicine 2020; 382: 503–513. doi:10.1056/NEJMoa1911793

[6] Paci E, Puliti D, Lopes Pegna A et al. Mortality, survival and incidence rates in the ITALUNG randomised lung cancer screening trial. Thorax 2017; 72: 825–831. doi:10.1136/thoraxjnl-2016-209825

[7] Infante M, Cavuto S, Lutman FR et al. Long-Term Follow-up Results of the DANTE Trial, a Randomized Study of Lung Cancer Screening with Spiral Computed Tomography. American Journal of Respiratory and Critical Care Medicine 2015; 191: 1166–1175. doi:10.1164/rccm.201408-1475OC

[8] Pastorino U, Rossi M, Rosato V et al. Annual or biennial CT screening versus observation in heavy smokers: 5-year results of the MILD trial. European Journal of Cancer Prevention: the official Journal of the European Cancer Prevention Organisation 2012; 21: 308–315. doi:10.1097/CEJ.0b013e328351e1b6

[9] Pastorino U, Silva M, Sestini S et al. Prolonged lung cancer screening reduced 10-year mortality in the MILD trial: new confirmation of lung cancer screening efficacy. Annals of Oncology: Official Journal of the European Society for Medical Oncology/ESMO 2019; 30: 1672. doi:10.1093/annonc/mdz169

[10] Becker N, Motsch E, Trotter A et al. Lung cancer mortality reduction by LDCT screening – results from the randomised German LUSI trial. International Journal of Cancer Journal International du Cancer 2019. doi:10.1002/ijc.32486

[11] Wille MM, Dirksen A, Ashraf H et al. Results of the Randomized Danish Lung Cancer Screening Trial with Focus on High-Risk Profiling. American Journal of Respiratory and Critical Care Medicine 2016; 193: 542–551. doi:10.1164/rccm.201505-1040OC

[12] Pinsky PF, Church TR, Izmirlian G et al. The National Lung Screening Trial: results stratified by demographics, smoking history, and lung cancer histology. Cancer 2013; 119: 3976–3983. doi:10.1002/cncr.28326

[13] Ten Haaf K, van Rosmalen J, de Koning HJ. Lung cancer detectability by test, histology, stage, and gender: estimates from the NLST and the PLCO trials. Cancer Epidemiology, Biomarkers & Prevention: a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 2015; 24: 154–161. doi:10.1158/1055-9965.Epi-14-0745

[14] Gonzalez Maldonado S, Motsch E, Trotter A et al. Overdiagnosis in lung cancer screening – estimates from the German Lung Cancer Screening Intervention Trial. International Journal of Cancer Journal International du Cancer 2020 [in press]

[15] National Research Council. Health Risks from Exposure to Low Levels of Ionizing Radiation: BEIR VII Phase 2. Washington, DC: The National Academies Press. 2006. doi:10.17226/11340

[16] Brenner DJ. Radiation risks potentially associated with low-dose CT screening of adult smokers for lung cancer. Radiology 2004; 231: 440–445. doi:10.1148/radiol.2312030880

[17] Berrington de Gonzalez A, Kim KP, Berg CD. Low-dose lung computed tomography screening before age 55: estimates of the mortality reduction required to outweigh the radiation-induced cancer risk. Journal of Medical Screening 2008; 15: 153–158. doi:10.1258/jms.2008.008052

[18] Bach PB, Mirkin JN, Oliver TK et al. Benefits and harms of CT screening for lung cancer: a systematic review. JAMA: The Journal of the American Medical Association 2012; 307: 2418–2429. doi:10.1001/jama.2012.5521

[19] Rampinelli C, De Marco P, Origgi D et al. Exposure to low dose computed tomography for lung cancer screening and risk of cancer: secondary analysis of trial data and risk-benefit analysis. BMJ 2017; 356: j347. doi:10.1136/bmj.j347

[20] Personal communication Dr Elke Nekolla, Bundesamt für Strahlenschutz. In 2020

[21] Huber A, Landau J, Ebner L et al. Performance of ultralow-dose CT with iterative reconstruction in lung cancer screening: limiting radiation exposure to the equivalent of conventional chest X-ray imaging. European Radiology 2016; 26: 3643–3652. doi:10.1007/s00330-015-4192-3

[22] Hassani C, Ronco A, Prosper AE et al. Forward-Projected Model-Based Iterative Reconstruction in Screening Low-Dose Chest CT: Comparison With Adaptive Iterative Dose Reduction 3D. Am J Roentgenol American Journal of Roentgenology 2018; 211: 548–556. doi:10.2214/ajr.17.19245

[23] Lung RADs. Lung CT Screening Reporting & Data System. In: American College of Radiology 2019

[24] Pinsky PF, Gierada DS, Black W et al. Performance of Lung-RADS in the National Lung Screening Trial: a retrospective assessment. Annals of Internal Medicine 2015; 162: 485–491. doi:10.7326/m14-2086

[25] Horeweg N, van der Aalst CM, Vliegenthart R et al. Volumetric computed tomography screening for lung cancer: three rounds of the NELSON trial. The European Respiratory Journal 2013; 42: 1659–1667. doi:10.1183/09031936.00197712

[26] van Klaveren RJ, Oudkerk M, Prokop M et al. Management of lung nodules detected by volume CT scanning. The New England Journal of Medicine 2009; 361: 2221–2229. doi:10.1056/NEJMoa0906085

[27] Pinsky PF, Bellinger CR, Miller DP Jr. False-positive screens and lung cancer risk in the National Lung Screening Trial: Implications for shared decision-making. Journal of Medical Screening 2018; 25: 110–112. doi:10.1177/0969141317727771

[28] Lung RADS. Lung CT Screening Reporting & Data System (Lung-RADS). In American College of Radiology Committee on Lung-RADS®. Lung-RADS Assessment Categories version 1.1. Available at HYPERLINK "https://www.acr.org/-/media/ACR/Files/RADS/Lung-RADS/LungRADSAssessmentCategoriesv1-1.pdf" https://www.acr.org/-/media/ACR/Files/RADS/Lung-RADS/LungRADSAssessmentCategoriesv1-1.pdf. Accessed on January 1, 2020

[29] Tammemagi MC, Katki HA, Hocking WG et al. Selection criteria for lung-cancer screening. The New England Journal of Medicine 2013; 368: 728–736. doi:10.1056/NEJMoa1211776

[30] Byrne MM, Weissfeld J, Roberts MS. Anxiety, fear of cancer, and perceived risk of cancer following lung cancer screening. Medical decision making: An international Journal of the Society for Medical Decision Making 2008; 28: 917–925. doi:10.1177/0272989x08322013

[31] Brain K, Lifford KJ, Carter B et al. Long-term psychosocial outcomes of low-dose CT screening: results of the UK Lung Cancer Screening randomised controlled trial. Thorax 2016; 71: 996–1005. doi:10.1136/thoraxjnl-2016-208283

[32] Rasmussen JF, Siersma V, Malmqvist J et al. Psychosocial consequences of false positives in the Danish Lung Cancer CT Screening Trial: a nested matched cohort study. BMJ open 2020; 10: e034682. doi:10.1136/bmjopen-2019-034682

[33] Davies L, Petitti DB, Martin L et al. Defining, Estimating, and Communicating Overdiagnosis in Cancer Screening. Annals of Internal Medicine 2018; 169: 36–43. doi:10.7326/m18-0694

[34] Patz EF Jr, Pinsky P, Gatsonis C et al. Overdiagnosis in low-dose computed tomography screening for lung cancer. JAMA Internal Medicine 2014; 174: 269–274. doi:10.1001/jamainternmed.2013.12738

[35] Heleno B, Siersma V, Brodersen J. Estimation of Overdiagnosis of Lung Cancer in Low-Dose Computed Tomography Screening: A Secondary Analysis of the Danish Lung Cancer Screening Trial. JAMA Internal Medicine 2018; 178: 1420–1422. doi:10.1001/jamainternmed.2018.3056

[36] [Anonym]. Lung Cancer Incidence and Mortality with Extended Follow-up in the National Lung Screening Trial. Journal of thoracic oncology: official publication of the International Association for the Study of Lung Cancer 2019; 14: 1732–1742. doi:10.1016/j.jtho.2019.05.044

[37] de Koning HJ, Meza R, Plevritis SK et al. Benefits and harms of computed tomography lung cancer screening strategies: a comparative modeling study for the U.S. Preventive Services Task Force. Annals of Internal Medicine 2014; 160: 311–320. doi:10.7326/m13-2316

[38] Ten Haaf K, de Koning HJ. Overdiagnosis in lung cancer screening: why modelling is essential. Journal of Epidemiology and Community Health 2015; 69: 1035–1039. doi:10.1136/jech-2014-204079

[39] Treskova M, Aumann I, Golpon H et al. Trade-off between benefits, harms and economic efficiency of low-dose CT lung cancer screening: a microsimulation analysis of nodule management strategies in a population-based setting. BMC Medicine 2017; 15: 162. doi:10.1186/s12916-017-0924-3

[40] Knoke JD, Shanks TG, Vaughn JW et al. Lung cancer mortality is related to age in addition to duration and intensity of cigarette smoking: an analysis of CPS-I data. Cancer epidemiology, biomarkers & prevention: A ;publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 2004; 13: 949–957

[41] Lubin JH, Caporaso N, Wichmann HE et al. Cigarette smoking and lung cancer: modeling effect modification of total exposure and intensity. Epidemiology 2007; 18: 639–648. doi:10.1097/EDE.0b013e31812717fe

[42] Vlaanderen J, Portengen L, Schüz J et al. Effect modification of the association of cumulative exposure and cancer risk by intensity of exposure and time since exposure cessation: a flexible method applied to cigarette smoking and lung cancer in the SYNERGY Study. American Journal of Epidemiology 2014; 179: 290–298. doi:10.1093/aje/kwt273

[43] Thomas DC. Invited commentary: is it time to retire the "pack-years" variable? Maybe not! American Journal of Epidemiology 2014; 179: 299–302. doi:10.1093/aje/kwt274

[44] Peto R, Darby S, Deo H et al. Smoking, smoking cessation, and lung cancer in the UK since 1950: combination of national statistics with two case-control studies. BMJ 2000; 321: 323–329. doi:10.1136/bmj.321.7257.323

[45] Moyer VA. Force USPST. Screening for lung cancer: U.S. Preventive Services Task Force recommendation statement. Annals of Internal Medicine 2014; 160: 330–338. doi:10.7326/m13-2771

[46] Field JK, Aberle DR, Altorki N et al. The International Association Study Lung Cancer (IASLC) Strategic Screening Advisory Committee (SSAC) response to the USPSTF recommendations. Journal of Thoracic Oncology: Official publication of the International Association for the Study of Lung Cancer 2014; 9: 141–143. doi:10.1097/jto.0000000000000060

[47] Kauczor HU, Bonomo L, Gaga M et al. ESR/ERS white paper on lung cancer screening. European Radiology 2015; 25: 2519–2531. doi:10.1007/s00330-015-3697-0

[48] Wood DE, Kazerooni EA, Baum SL et al. Lung Cancer Screening, Version 3.2018, NCCN Clinical Practice Guidelines in Oncology. Journal of the National Comprehensive Cancer Network: JNCCN 2018; 16: 412–441. doi:10.6004/jnccn.2018.0020

[49] Canadian Task Force on Preventive Health Care. Recommendations on screening for lung cancer. CMAJ: Canadian Medical Association Journal = Journal de l'Association Medicale Canadienne 2016; 188: 425–432. doi:10.1503/cmaj.151421

[50] Kauczor HU, Baird AM, Blum TG et al. ESR/ERS statement paper on lung cancer screening. European Radiology 2020. doi:10.1007/s00330-020-06727-7

[51] AWMF. S3-Leitlinie Prävention, Diagnostik, Therapie und Nachsorge des Lungenkarzinoms. In, AWMF-Registernummer: 020/007OL 2018

[52] Hüsing A, Kaaks R. Risk prediction models versus simplified selection criteria to determine eligibility for lung cancer screening – an analysis of German federal-wide survey and incidence data. Europen Journal of Epidemiology 2020 [in press]

[53] Han SS, Ten Haaf K, Hazelton WD et al. The impact of overdiagnosis on the selection of efficient lung cancer screening strategies. International Journal of Cancer Journal international du cancer 2017; 140: 2436–2443. doi:10.1002/ijc.30602

[54] Ten Haaf K, Bastani M, Cao P et al. A comparative modeling analysis of risk-based lung cancer screening strategies. Journal of the National Cancer Institute 2019. doi:10.1093/jnci/djz164

[55] Ten Haaf K, Tammemagi MC, Bondy SJ et al. Performance and Cost-Effectiveness of Computed Tomography Lung Cancer Screening Scenarios in a Population-Based Setting: A Microsimulation Modeling Analysis in Ontario, Canada. PLoS Medicine 2017; 14: e1002225. doi:10.1371/journal.pmed.1002225

[56] Tomonaga Y, Ten Haaf K, Frauenfelder T et al. Cost-effectiveness of low-dose CT screening for lung cancer in a European country with high prevalence of smoking-A modelling study. Lung Cancer (Amsterdam, Netherlands) 2018; 121: 61–69. doi:10.1016/j.lungcan.2018.05.008

[57] Mascalchi M, Sali L. Lung cancer screening with low dose CT and radiation harm-from prediction models to cancer incidence data. Annals of Translational Medicine 2017; 5: 360. doi:10.21037/atm.2017.06.41

[58] Bach PB, Gould MK. When the average applies to no one: personalized decision making about potential benefits of lung cancer screening. Annals of Internal Medicine 2012; 157: 571–573. doi:10.7326/0003-4819-157-8-201210160-00524

[59] Katki HA, Kovalchik SA, Berg CD et al. Development and Validation of Risk Models to Select Ever-Smokers for CT Lung Cancer Screening. JAMA: The Journal of the American Medical Association 2016; 315: 2300–2311. doi:10.1001/jama.2016.6255

[60] Katki HA, Kovalchik SA, Petito LC et al. Implications of Nine Risk Prediction Models for Selecting Ever-Smokers for Computed Tomography Lung Cancer Screening. Annals of Internal Medicine 2018; 169: 10–19. doi:10.7326/m17-2701

[61] Ten Haaf K, Jeon J, Tammemagi MC et al. Risk prediction models for selection of lung cancer screening candidates: A retrospective validation study. PLoS Medicine 2017; 14: e1002277. doi:10.1371/journal.pmed.1002277

[62] Li K, Husing A, Sookthai D et al. Selecting High-Risk Individuals for Lung Cancer Screening: A Prospective Evaluation of Existing Risk Models and Eligibility Criteria in the German EPIC Cohort. Cancer Prev Res (Phila) 2015; 8: 777–785. doi:10.1158/1940-6207.capr-14-0424