Review Article

Risk factors assessment and risk prediction models in lung cancer screening candidates

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Abstract: From February 2015, low-dose computed tomography (LDCT) screening entered the armamentarium of diagnostic tools broadly available to individuals at high-risk of developing lung cancer. While a huge number of pulmonary nodules are identified, only a small fraction turns out to be early lung cancers. The majority of them constitute a variety of benign lesions. Although it entails a burden of the diagnostic work-up, the undisputable benefit emerges from: (I) lung cancer diagnosis at earlier stages (stage shift); (II) additional findings enabling the implementation of a preventive action beyond the realm of thoracic oncology. This review presents how to utilize the risk factors from distinct categories such as epidemiology, radiology and biomarkers to target the fraction of population, which may benefit most from the introduced screening modality.

Keywords: Lung cancer; risk factor; prediction model

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Introduction

Since February 2015 lung cancer screening by low-dose computed tomography (LDCT) in high-risk individuals is covered by the US health insurance. This considerable step ahead towards a reduction of lung cancer mortality in the future, has its roots in the National Lung Screening Trial (NLST) results (1). The implementation of the NLST protocol—three LDCT scans in the consecutive years post enrolment followed by four years of follow-up, has yielded cancer-related mortality reduction exceeding 20% (1). However, the 20% yield of mortality reduction has been used as an argument in the ongoing debate regarding LDCT screening efficiency and necessity (2-5). While a stimulating discussion must always be the component of the decision-making process leading to incorporation of novel modalities into large scale clinical practice, it is worth clarifying one issue. The interpretation of mortality reduction equated to saving one out of five lives of screenees is totally misleading. The NLST has never been aimed to measure the extent of lives saving during the continuous screening. Rather, it had been designed to show, as a proof of concept, with the sufficient statistical power and limited financial resources, that LDCT screening is capable of reducing lung cancer mortality (1,6,7). Therefore, there is nothing essentially inconsistent between the 20% reduction of mortality reported in NLST and the 88% survival rate in stage I lung cancer documented in the International Early Lung Cancer Action Project (I-ELCAP), in which screening has not been limited to the definite number of rounds (8-10). Using a mortality reduction modeling technique it has been shown the decrease of mortality in NY-ELCAP cohort may

have reached 45.6% (11). Moreover, a re-analysis of the dataset and statistical calculation demonstrated the mortality reduction in the NLST could have amounted to more than 20%, would the CT examination had been extended to four years of follow-up (12,13). Of note, lung cancer mortality in the New York State (NYS) cohort, comprising individuals from NY-ELCAP and ELCAP, compared to the unscreened cohorts of the American Cancer Society Cancer Prevention Study II (CPS II) and the Beta-Carotene and Retinol Efficacy Trial (CARET), showed a reduction in mortality by 36% and 64%, respectively (14). The study employed standardized mortality ratio among the cohorts of screened (NYS) or unscreened (CPS II, CARET) former and current smokers. Interestingly, a decrease in mortality after two LDCT rounds started in the fourth year of screening, reaching a maximum after six to eight years (14). This time-course revealing a beneficial outcome in the long-term perspective seems to be of utmost importance. However, attempts to draw ad hoc conclusions from the trials already implemented or terminated should be avoided.

Having put aside the general consideration regarding the ability of LDCT to save lives, the issue arises of its low efficacy to select individuals with lung cancer. In fact, the vast majority of pulmonary nodules detected are identified as benign (1,15-17). This, in turn, gives rise to a high number of false positive results, which, on the one hand, compromises specificity and positive predictive value (PPV) of LDCT screening, on the other, entails the burden of a costly diagnostic work-up (3,18). Keeping in mind that any screening, by definition, is offered to healthy, asymptomatic candidates, not surprisingly, any invasive diagnostic procedure carried out on them should be regarded as an utmost need. Therefore a lot of effort has recently been made to limit the number of false positive results either by risk factors assessment or risk prediction models implementation or advanced image analysis.

Low-dose computed tomography (LDCT) screening landscape based on the I-ELCAP, NLST and NELSON results

During the last two decades the learning curve of the LDCT screening intricacies has essentially been warranted by three trials. The I-ELCAP, which is a single-arm observational study, in 2000–2013 recruited 62,124 participants aged 40–90 years, with a high-risk of lung cancer being active smokers, second-hand smokers or having a history of occupational exposure (19). In 2006 based on the analysis of 31,567 individuals under screening, it was reported that 85% of diagnosed cancers were in clinical stage I and the estimated 10-year survival rate in this group was 88% (9). Unfortunately, as in all non-randomized trials, the biases associated with selection, lead time, length time and overdiagnosis could not be eliminated and mortality data were not in hand. This has prompted the need for randomized clinical trial designed to test the capability of LDCT as a regimen reducing lung cancer related mortality. Between 2002 and 2004 NLST enrolled 53,454 individuals, aged 55 to 74 years with at least 30 pack-years smoking history. They were randomized either to the low-dose CT or the chest X-ray group and followed-up until 2009. Lung cancer incidence was 13% higher in the LDCT group and relative mortality was reduced by 20% in comparison to the radiography group (1). The European randomized trial NELSON (acronym from Dutch: Dutch-Belgian Lung Cancer Screening Trial) accrued between 2004 and 2006 a total of 15,822 participants, aged 50–75 having smoking history of 15 pack-years or more. They were randomly assigned to the low-dose CT group or the control group (no screen). It was estimated that with this size of sample, a 25% mortality reduction could be demonstrated ten years after randomization (20,21). The results are due to be published in 2016. They are especially awaited in Europe, since the distinct LDCT intervention targets considerably dissimilar high-risk lung cancer population in terms of ethnicity, social habits, environmental exposures and genetic background in comparison to the United States population. Even though the LDCT screening landscape is shaped by three major trials, it is far from being uniform and unequivocal.

One of the trials, the non-randomized I-ELCAP presents a beneficial lung cancer stage shift resulting in a high curability and survival rate. The randomized NLST demonstrates a measurable decrease in mortality related to lung cancer, while the randomized NELSON trial remains an open question until its results are published. Additionally, one should be aware that each of the trials targets a diverse population characterized by unique demographic variables, uses distinct eligibility criteria with respect to age and smoking history, employs dissimilar definition of positive screening result (1,9,20-23). For instance a non-calcified pulmonary nodule is identified as a positive if measured diameter is larger than 5 mm, equal or larger than 4 mm or larger than 10 mm (volume exceeding 500 mm^3) in the I-ELCAP (9), NLST (1)

and NELSON (20) trial, respectively. Those interested in the details of the screening trials eligibility criteria, positive results definition and algorithms, are encouraged to peruse a vast number of recently published reviews (3,24-29).

Evidence-based screening work-up yields low false positivity rate

In the United States a program of low-dose CT screening covered by health insurance has been launched, while in the European Union, awaiting, hopefully conclusive, NELSON trial results, a set of recommendations has recently been published (30).

A positive result in LDCT screening is defined as a non-calcified solitary pulmonary nodule (SPN), with the specified diameter or volume. In fact, spheroidal lesions of augmented attenuation in lung parenchyma (i.e., SPN), measuring 2 mm or less, can be found in most of CT scans of adult persons (31). For baseline screening positive results were reported in 11–51 % of participants of the major trials, depending on the study protocol and algorithm. Among those detected nodules 1.1–2.0% were identified as early lung cancers, thereby categorizing the remaining 90–96% as the false positive results (1,9,17,32,33). One exception is the NELSON study, in which due to a unique classifying protocol (non-inclusion into positive results indeterminate nodules having a volume of 50–500 mm^3, requiring a repeat screen), a total of positive results is equal to 2%, yet false positive results amount to 59.4% (20,21). Inevitably, a high false positive rate (1-specificity) is the major disadvantage of any screening modality. False positive results lead to unnecessary diagnostic work-up with the use of invasive procedures, which have side-effects, may induce complications (e.g., chest tube insertion due to pneumothorax caused by CT-guided lung biopsy) and increase patients' anxiety (29). Ideally, a screening modality should operate in a digital 0-or-1 mode but this would entail one hundred percent specificity and sensitivity of a test. In reality test performance is much lower and can be enhanced either by an improvement of the particular method or by combining several methods/predictors to achieve a better final outcome. Risk prediction or stratification models are constructed to facilitate targeting a subpopulation which may benefit most from the screening procedure.

Recently, the following ways to diminish the rate of false positive results in the low-dose CT screening have been studied:

(I) Image analysis, i.e., assessing precisely a nodule dimension(s)/volume or extracting from a nodule CT image the set of features, which are likely to indicate malignancy;

(II) Risk factors assessment—a useful approach, facilitating the selection of individuals at-risk of lung cancer in whom screening is most beneficial, given that financial resources are limited and therefore a population screening ruled out;

(III) Lung cancer prediction models—a sophisticated, labor-consuming method, in which a pre-specified set of factors is included in the regression equation, constituting a cohesive tool for the formerly validated population to target beneficiaries in a cost-effective way.

Image analysis of a pulmonary nodule

It has extensively been documented the survival time of patients in whom lung cancer has been resected, dramatically decreases with the increasing dimensions of the lesion (29,34-36). Importantly, for tumors with a diameter <1.0 cm, 5-year survival rate has been reported to be 100% (30,35). Likewise, the NLST data demonstrated a 7-fold increase in the percentage of detected lung cancers between SPN range 7–10 mm and 11–20 mm (1.7% and 11.9%, respectively) (1,33). To combine a nodule diameter and morphology with its malignancy likelihood, a new tool of image analysis has been proposed by the American College of Radiology (ACR), namely the Lung CT Screening Reporting and Data System (Lung-RADS^{TM}) (37,38). It is based on I-ELCAP, NELSON and NLST data and represents a tentative compromise among experts. The system combines a nodule morphology (solid, part-solid, ground glass) with its average diameter (orthogonals, as opposed to the longest axial diameter in the NLST) and establishes nodule categories into negative and non-actionable (annual screening in 12 months), indeterminate (yet requiring LDCT within 6 months) and suspicious (three subcategories demanding CT in 3 months or PET, tissue sampling etc.). The diameter of a positive nodule (result) was elevated in comparison to I-ELCAP and NLST to equal or larger than 6 mm for solid and part-solid nodules and to equal or larger than 20 mm in case of ground glass nodules (37,38). These alterations have resulted in a considerably improved performance of LDCT screening. Lung-RADS used to analyze the NLST data, for the baseline screen, yielded false positive rate of 12.8% compared to 26.6% in accordance with the NLST criteria (39).

It was even more marked in the incidence screens, reaching a 4-fold decrease (5.3% *vs.* 21.8% for Lung-RADS and NLST criteria, respectively). Consequently, the PPV of Lung-RADS was 6.9%, whereas for NLST 3.8%, with still an observable improvement for the annual screens (39). The usefulness of ACR Lung-RADS has been demonstrated in another screened cohort, increasing the PPV by a factor of 2.5% to 17.3% (40). Not surprisingly, this standardized, comprehensive and clinical decision-oriented system has been proposed to be widely implemented in a semi-automated mode in order to properly handle a mounting number of CT examinations in the following years (41,42). Undoubtedly, the knowledge accumulated from the analysis of the I-ELCAP, NLST and NELSON data including patients' clinical outcome, enabled to refine a nodule size criterion. Both, I-ELCAP and NLST data have been re-analyzed to find out how would CT screening precision and workflow be changed, were the alternative nodule sizes be used. With regard to the I-ELCAP using a nodule threshold sizes of 6.0, 7.0, 8.0 and 9.0 mm, would yield positive results in 10.2%, 7.1%, 5.1% and 4.0%, respectively (43). This would substantially diminish the annual scans number. The unnecessary work-up could be reduced by 36%, 56%, 68% and 75%, respectively (43). Originally, in the NLST each non-calcified pulmonary nodule of 4 mm or larger was classified as a positive result, which totaled to 26.6% of positive baseline screens (1). Again, applying the alternative sizes of solid or part-solid nodules of 6.0, 7.0, 8.0 and 9.0 mm in the baseline screen, a corresponding reduction of positive results amounts to 10.5%, 7.2%, 5.3% and 4.1% , and proportional decrease of additional CT scans would have been 33.8%, 54.7%, 66.6% and 73.8%, respectively (44). However, one should be aware a maneuver of declining positive, i.e., demanding work-up, number of nodules, is inextricably linked to the delay of diagnosis and treatment in some patients. Recently reported analysis of the I-ELCAP data, detected in 57,496 baseline screenings followed by 64,677 annual repeat screens, 2,392 and 485 ground-glass nodules (GGN), respectively, of which altogether 84 were identified as adenocarcinomas (45). The median transition time from GGN to part-solid was 25 months and surgery was curative in 100% of cases. In conclusion, GGN may safely be followed in a 12-month screen, regardless of the size (45). The NELSON trial utilized more stringent inclusion criteria than in the NLST and displayed the lower rate of false positives. However, it was noted that the elongated gaps between sequential CT screens to 2 and 2.5 years, resulted in a higher percentage of stage III cancer in the third round and increased percentage of stage IV in the fourth round (3.9% *vs.* 13.3% in third and fourth round, respectively) (46). To compensate for this effect the recommended range for indeterminate nodules was narrowed from 100 to 300 mm^3, whereas the positive screen result was set up to the volume larger than 300 mm^3 (47).

Very recently an image analysis has been proposed to extract a data set of the attenuation coefficient patterns, residing within a pulmonary nodule CT scan. It is based on a precise mathematical algorithm analyzing the nodule heterogeneity and statistics (voxel intensities, texture features, spatio-frequency sub-band statistics) as well as nodule morphology (size, shape, surface features). Altogether more than five hundreds features is put into a single nodule characteristics. When these features of a nodule were combined with the patient's clinical data, including smoking history, pack years, nodule location etc., it was demonstrated to yield receiver operating characteristic under area curve (ROC AUC) of 0.87 and the false positive rate of 18%. The corresponding values for clinical data only yielded 0.80 and 44%, respectively (R. Bhagalia *et al.* Abstract 1019; The World Congress on Lung Cancer 2015).

In order to combine an effort aimed at standardization of the LDCT screening in terms of image acquisition, processing and analyzing with the use of an accessible technical and scientific resources, the Quantitative Imaging Biomarker Alliance (QIBA) has been launched, a multidisciplinary consortium, which is focused on the task of extracting a maximally reliable data from an image (48).

Risk factors (predictors) assessment

Lung cancer risk factors comprise a various classes of phenomena and features related to demographics, morbidity or environmental/occupational exposure, which are known to coincide, coexist or to increase the risk of lung cancer occurrence in an individual person.

A necessity of a risk factor usage is the consequence of economical constraints, which make the LDCT screening not affordable to the whole population (6,49-53), as opposed to breast, prostate and colorectal cancer.

Therefore the LDCT screening is directed to a fraction of population in high risk of lung cancer development.

Two modes of employing risk factors to increase true positive rate, i.e., sensitivity, may be distinguished: incorporating one or many of them into the process of

enrollment or utilizing a risk prediction model, in a form of the mathematical tool (a regression equation), allowing to target the most beneficiary portion of the population under investigation. Therefore candidates of the LDCT screening programs must fulfill two conditions to be eligible: they should be in age of 50 or more and should have had a history of smoking of at least 30 pack-years, unless other risk factors are identified (1,9,29).

Predictors (risk factors), which serve to assess the lung cancer risk or constitute the components to build the lung cancer risk prediction models, can be categorized into the following groups:

(I) Clinical/epidemiological (smoking history, age, family history, spirometry, COPD, emphysema);
(II) Radiological (SPN features: diameter/volume, spiculation, lobulation, location in a lung lobe, relation to pulmonary fissures, calcification pattern; parameters derived by mathematically advanced image analysis);
(III) Biochemical/genomic/epigenomic (protein and genomic validated clusters);
(IV) Others: sputum cytology (cell-CT analysis), exhaled breath analysis.

Cigarette smoke is an indisputable risk factor of lung cancer. It has been demonstrated in major prospective studies that there is a quantitative relationship between the lung cancer development and the extent of exposure to tobacco smoke (54-57). A cumulative exposure to smoke in pack-years (PY) can be misleading, since the lung cancer incidence increases by a factor of 4.5 in correlation with smoking duration, in comparison to a factor of 1.5 in correlation with daily consumption. Nevertheless, the exposure to cigarette smoke expressed in PY, as a major culprit of lung cancer, has been included to all, apart from Japanese, single-arm and randomized trials for LDCT screening (1,17,29). The exact number of pack-years ranges from 15 for NELSON to 30 in the NLST or guidelines issued in the past years by a various organizations like the American Association for Thoracic Surgery (AATS), the American College of Chest Physicians (ACCP) and The National Comprehensive Cancer Network (NCCN) (29). Importantly, the AATS and NCCN recommendations lower a cumulative PY exposure to 20, if additional risk factors such as chronic obstructive pulmonary disease (COPD) with forced expiratory volume in 1s of 70% or less than predicted, pulmonary fibrosis, environmental, occupational exposures (silica, heavy metals, beryllium, asbestos), any prior cancer or lung cancer family history, has been identified (29,58). Quite recently, it has been shown, analyzing a sub-cohort of 30+ pack-years former smokers in the Prostate, Lung, Colorectal and Ovarian trial, that the lung cancer risk decreases gradually in years since quitting (YSQ), as demonstrated in diminishing hazard ratio for the stratified groups (59). This can underpin establishing a YSQ cut-off point in the LDCT programs.

Another pivotal risk factor for screening eligibility criteria is a participant's age. In fact, this is the question at what age LDCT screening should be initiated and terminated to minimize harms and maximize benefits for a target cohort. Because only 5–10% of lung cancers in smokers occur below the age of 50 (57), the lower cut-off point, in the majority of trials, is set at the age of 50 (1,29). Yet, establishing the upper age cut-off level for screenees represents more complex issue. On the one hand, a life expectancy and comorbidities (respiratory and cardiovascular system) of an individual in the older age should be taken into account, on the other, 50% of all lung cancers occur in patients older than 65 (57). Although in the LDCT screening guidelines, the upper cut-off point has been fixed to 74 or 79 years of age, it is recommended to assess a participant's overall performance status to exclude those who are not candidates for an invasive diagnostic intervention or surgery, due to poor general health, inoperability status or documented refusal to undergo surgery. Generally, individuals who cannot achieve metabolic equivalent (MET) of 4 or 5, i.e., cannot rake leaves, wash a car or are not able to climb two flights of steps without stopping (60,61), should not be included into screening as having no prospective capacity for any intervention if found to have a positive result.

Low-dose CT is capable of detecting emphysema (62,63), which is a component of COPD. Even better characterization of individual COPD can be achieved by evaluating the extent of air-trapping and bronchial wall thickening (64). A combination of these components give rise to the distinct, clinically diagnosed, COPD phenotypes, with chronic bronchitis predominance ("blue bloater") or emphysema predominance ("pink puffer"). Both, lung cancer and COPD are tobacco-related diseases. COPD as a consequence of respiratory system exposure to cigarette smoke, constitutes the result of disturbed pulmonary ventilation (airflow obstruction) and perfusion. These disturbances, in turn, are elicited by a chronic inflammatory process in the airways evoked by the toxic fumes inhalation. Not surprisingly, emphysema and COPD are identified as the independent lung cancer risk factors and incorporated to the risk assessment calculators and lung cancer risk

prediction models (65-68). In the Danish Lung Cancer Screening Trial, lung cancer was associated with emphysema on baseline screen and later screens with the corresponding odds ratio equal to 1.8 and 2.6, respectively (69). Moreover, odds ratio was 5.1 linking lung cancer to interstitial abnormalities (69). Based on the review of 62,124 baseline LDCT scans of current, former and never-smokers, it was demonstrated the lung cancer prevalence for current smokers without emphysema was 1.1%, as compared to 2.3% for those with emphysema (odds ratio 1.8) (19). Thus, emphysema can be viewed as an independent predictor of the lung cancer prevalence.

The radiological features of pulmonary nodules, among them those, which are regarded to be the risk factors, were, to some extent, discussed in one of the previous paragraphs describing image analysis of a pulmonary nodule.

An urgent need to limit the number of false positive results in the LDCT screening stimulates an investigational effort in the field of biomarkers. They can be identified in a biological material, such as tissue, cells and biological fluids (blood, urine, exhaled breath condensate, sputum).

A majority of biomarkers is associated with (70-77):

(I) Genetic changes and gene expression alterations (gene or gene expression signature or profile in bronchial epithelium, sputum-derived cells or peripheral blood cells);
(II) Changes of level and/or composition of non-coding RNAs (microRNA) in sputum plasma or serum;
(III) Epigenetic changes, i.e., modified pattern of DNA methylation of particular genes in sputum, plasma or bronchial aspirates;
(IV) Detection of altered protein panel or proteomic profile in plasma, serum or bronchial biopsies;
(V) Detection of autoantibodies or tumor-associated antigens in serum;
(VI) Identification of volatile organic compounds profile in exhaled breath condensate.

The above-listed biomarkers belong to a class of diagnostic biomarkers. This means they are used to determine whether cancer is present in an individual with an asymptomatic, detectable disease such as pulmonary nodule on a CT scan, as opposed to prognostic biomarkers, which can assess the risk of developing lung cancer in individuals at risk but with no measurable signs of a disease (70,78). The underlying rationale of diagnostic biomarkers based on biological fluids, is that molecular alterations within cancer cells lead to the synthesis of distinct molecular compounds, which, if detected, may signify the presence of cancerous transformation in an individual under investigation. Ideally, checking one molecular biomarker in a participant of the LDCT screening, with identified suspicious nodule, should allow making diagnostic or therapeutic decision. However, since lung cancer development is a multi-factorial, complex process, with only partially unraveled mechanisms, it is unlikely to discover a single biomarker with genuine decision-making property. Yet, in the recent years, some attempts have been made to introduce a cluster of proteins or genes as the diagnostic marker. In a retrospective, multicenter trial, the classifier comprising five diagnostic and six normalization proteins, was applied to plasma samples of patients with 141 indeterminate pulmonary nodules (79). A negative predictive value (NPV) of the classifier for this set of indeterminate nodules, yielded 90%, which means it is useful in a malignancy exclusion (79). The set of eleven classifying proteins has been derived from mass spectrometry studies. Moreover, in a retrospective-prospective analysis of a study including 475 patients with nodules measuring 8–30 mm in diameter, it was shown that the use of the classifier would reduce the number of surgeries and invasive procedures by more than 30% (80).

Another example of a classifier allowing for a more conservative approach in patients with lung cancer suspicion, is genomic expression classifier (81). It requires bronchial epithelial cells and RNA extraction to assess expression of 17 genes, which were selected out of 232 genes associated with lung cancer development. The classifier comprises genes found to be related to three clinical covariates: gender, tobacco use and smoking history (81). The usefulness of gene expression classifier was proved and validated in the Airway Gene Expression in the Diagnosis of Lung Cancer (AEGIS 1 and AEGIS 2) trials (82). A total of 639 patients were enrolled to both trials. The determined gene expression profile from bronchial brushings, yielded a sensitivity of 88% and a NPV of 91% (82). The latter is very helpful for the decision making in case of a nondiagnostic bronchoscopy examination with nodules presented in the CT scan.

Risk prediction models

The vast majority of the discussed risk factors can be combined into a regression equation constituting a mathematical form of risk prediction model. In this case lung cancer mortality is the dependent variable (outcome, predicted variable), whereas the selected risk factors (predictors), are the independent variables. For a practical reason, only some demographic, clinical and radiological

predictors are included in the models. As opposed to hypothesis testing, in which a significant predictor is useful in excluding null hypothesis, in a risk prediction model, the predictor can be insignificant, still improving prediction and vice versa, a very significant predictor may not increase prediction value of the model (83,84). Each risk prediction model employs a distinct set of risk factors, has different design, covers particular geographical region, has requirements for patient contact, requires clinical data or biomarker information (83-86). During the last two decades many lung cancer models were published, out of which, merely a couple are in use (85), although the recommendations of the International Society for the Study of Lung Cancer are clear: only individuals with the highest risk of lung cancer, should be screened. This situation stems from the fact that every risk model is complicated mathematical tool, requiring pre-specified risk factors, then internal and/or external validation. All these steps are time-consuming and may turn out to be futile if, for example, one of the risk factors is inaccessible, since it demands contact with a patient or a biomarker reading (85,87,88).

Two pivotal components of a prediction model indicate its performance. Discrimination shows the ability to classify correctly, while calibration demonstrates if model-predicted probabilities, correspond to those observed in the real cohort, for which the model was created. The most often used measure of discrimination is the area under the receiver operator characteristic curve (AUC). The AUC equal to 0.5 is regarded as a random classification, whereas the area between 0.8 to 0.9 represents excellent discrimination (85).

The Bach model (3,85,89) used prospective follow-up data from population of smokers with or without asbestos exposure from the Beta-Carotene and Retinol Efficacy Trial (CARET). Predictors included age, sex, smoking intensity, duration, years since quitting smoking and asbestos exposure. The discrimination for this model measured by the AUC was equal to 0.72, which indicated a moderate discrimination. Hoggart and colleagues adapted the Bach model to evaluate the cohort of the European Prospective Investigation into Cancer and Nutrition (EPIC) trial (90). The five-year risk AUC for current, former and ever-smokers was close to 0.7 for all categories (90).

Raji and colleagues (91) validated Liverpool Lung Project (LLP) cohort, which predicts a 5-year risk of lung cancer and included predictors such as asbestos exposure, pneumonia, family history of cancer, prior malignancy and smoking duration. The validation was done on the three external cohorts: two European and one American. The resultant AUC ranged from 0.67 to 0.82 for the Liverpool cohort (91).

The entirely different approach in terms of number of risk factors included and the number of individuals in a cohort, was presented by Tammemagi and colleagues (83). In two models comprising 70,962 individuals (model 1: general population) and 38,254 individuals (model 2: ever-smokers subcohort) from the Prostate, Lung, Colorectal and Ovarian (PLCO) cancer screening trial the following, comprehensive set of risk factors were included: age, socioeconomic status, body mass index, family history of lung cancer, COPD, recent chest X-ray, smoking status (never, former, or current), pack-years smoked, and smoking duration (83). The model results were: the AUC for never- and ever-smokers was 0.84, while for the only smokers model of 0.74 (83). In 2013 a refined PLCO model (for smokers only) was published ($PLCO_{m2012}$), in which two predictors were added (personal history of cancer and ethnicity) and one predictor was excluded (previous CXR) (86). This model had an AUC of 0.797. When applied to the NLST data, $PLCO_{m2012}$ showed significantly higher sensitivity, better PPV with preserved specificity in comparison to the NLST eligibility criteria (86). Undoubtedly, the performance of this lung cancer risk prediction model is the best of proposed until recently.

Those interested in other risk prediction models incorporating a variety of risk factors including biomarker data, are encouraged to peruse the lately published reviews and research papers (65,86,92-103).

The presented efforts to include risk factors into the selection of screenees, building risk prediction models, aims at increasing a number of detected early cancer lesions in the LDCT screening process and at avoiding unnecessary diagnostic work-up, which is always costly and, occasionally, even harmful. However, keeping this in mind, one should be aware of a numerous benefits offered by the LDCT screen, which overreach the sole lung cancer fighting. In fact, the recent years have demonstrated how many various clinical fields are bridged by the LDCT screening, thus predisposing this modality to become a core of the preventive medicine.

Here we present the list of currently acknowledged applications/benefits of the LDCT screening, which span beyond the mortality reduction of lung cancer:

(I) Lung cancer stage shift improving the respectability, thus entailing a curability gain (9,29,33);

(II) Detection of a variety of chest and metabolic

diseases—coronary heart disease (104-107), interstitial lung diseases (69,108,109), COPD/Emphysema (62,64,69,109-115), osteoporosis (116,117), hypercholesterolemia (118);

(III) Increased rate of smoking cessation in the LDCT screening participants (119);

(IV) General health promotion by a habit of the regular medical examination, enhancement of self-surveillance and self-confidence embodied in the lifestyle modification aimed at the elimination of hazardous behavior;

(V) Shift from the interventional, reparative medicine to the preventive medical activity;

(VI) Let us hope that in the years to come, the LDCT screening will prolong survival and reduce mortality of individuals suffering from lung cancer. Perhaps it will improve general health as well.

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Footnote

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