REVIEW ARTICLE

Prevention and Early Detection for NSCLC: Advances in Thoracic Oncology 2018

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ABSTRACT

Lung cancer remains the leading cause of cancer-related mortality worldwide. Tobacco consumption remains the most important risk factor. Although the prevalence of smoking has decreased overall, it continues to be a significant burden for global health. It is estimated that there are still nearly 1 billion cigarette smokers worldwide. Prevention strategies have largely focused on tobacco control and prevention. However, we have witnessed a dramatic increase in the use of e-cigarettes and other vaping products. Primary chemoprevention has historically not been a successful strategy for lung cancer; however, focused approaches in specific groups of patients at high risk for development of lung cancer are underway. The majority of cases with NSCLC are diagnosed with locally advanced or metastatic disease, where the overall prognosis remains very poor. Early-stage NSCLC on the other hand has a much better prognosis and can usually be treated radically with either surgical resection or radical radiotherapy, with relatively favorable long-term outcomes. In addition to image-based screening, other methods such as breath-based and biofluid-based approaches are now being investigated for early detection of NSCLC. This review will focus on recent advancements in the field of prevention, screening, and early detection of NSCLC.

Keywords: Prevention; Screening; Early detection

Introduction

Lung cancer remains the leading cause of cancer related mortality responsible for one in five cancer-related deaths worldwide. Although smoking rates have decreased across the world, the incidence of lung cancer has plateaued with an estimated 1.8 million new cases expected to be diagnosed globally in 2019.[1] In the United States alone, 228,150 new cases are expected over the next year.[2] There is a major unmet need for the development of effective prevention, screening, and

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early detection methods. Tobacco is the leading carcinogen. With nearly 90% of lung cancer attributable to cigarette smoking, tobacco control remains essential to reducing lung cancer morbidity and mortality.[3] Despite decades of progress in reducing overall cigarette consumption, tobacco remains a real challenge due to the emergence of other combustible tobacco products including cigars, hookah, and noncombustible tobacco products such as electronic cigarettes (also known as e-cigarettes, e-cigs, electronic nicotine delivery system [ENDS], or vapes). In recent years, discussion of new tobacco products other than cigarettes has focused largely on e-cigarettes, an ENDS that has emerged as a potential alternative to combustible cigarettes and a potential aid to smoking cessation. The long-term effects of e-cigarettes on smoking cessation and general health remain unknown. Smoking cessation is the most effective intervention for lung cancer prevention and programs are now in place to offer counseling, support, and treatment of tobacco addiction. Chemoprevention, defined as the use of natural or synthetic agents to prevent, delay, or reverse carcinogenic progression to invasive cancer has been successfully implemented in various other malignancies, but trials have not been successful in primary or secondary prevention of lung cancer.

Based on the results of the National Lung Cancer Screening Trial (NLST), in 2013, the United States Preventative Services Task Force (USPSTF) changed its long-standing stance that there was insufficient evidence to recommend low-dose computed tomography (LDCT) screening for lung cancer and current guidelines in the United States now recommend annual screening for lung cancer with LDCT in adults aged 55 to 80 years who have a 30 pack-year smoking history and currently smoke or have quit within the past 15 years.[4] Based on data from this large trial and subsequent guidelines, several U.S. centers incorporated programs to implement LDCT screening and pulmonary nodule clinics. This was a landmark development, as for the first time there was direct evidence that we could actively use screening to prevent lung cancer–related morbidity and mortality. This past year we also witnessed results from the population-based Dutch-Belgian NELSON trial which showed that LDCT screening reduced lung cancer mortality by 26% in men and 39% in women at 10 years.[5] This, combined with the pre-existing evidence from NLST, provides robust evidence that LDCT screening for lung cancer in high-risk populations reduces disease-specific mortality. One aspect of computed tomography (CT) screening needing to be minimized is the potential for false-positive findings. Noninvasive biomarkers, including those found in breath, are currently under development in an attempt to aid screening programs in reducing false-positive results. In addition, there have been recent reports of using blood-based biomarkers to identify patients at highest risk for development of lung cancer.[6,7]

In this review, we provide the latest information from recent publications and abstracts presented at major academic meetings such as the World Conference on Lung Cancer (WCLC), the American Association for Cancer Research, the American Society of Clinical Oncology, and the European Society of Medical Oncology. The focus will be on the latest updates in prevention, screening, and early detection of lung cancer including smoking cessation, chemoprevention, screening, and early diagnostic approaches (Fig. 1).

Lung Cancer Prevention

Smoking Cessation

With nearly 90% of the world's lung cancers attributable to cigarette smoking, tobacco control remains essential to reducing lung cancer morbidity and mortality.[3] Despite decades of progress in reducing cigarette consumption, it is estimated that there are still nearly 1 billion cigarette smokers worldwide with 80% of current smokers living in low- or middle-income countries.[8] As an example, in the United States there are an estimated 34 million smokers, representing 14% of the entire adult

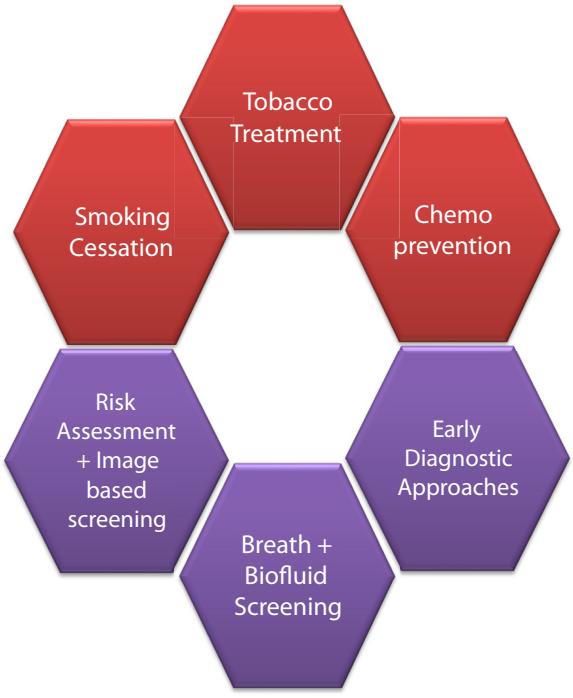

Figure 1. Strategy of prevention (*red*) using smoking cessation, tobacco treatment, and chemoprevention. Early detection approaches (*purple*) involving risk assessment and images- based screening, breath-based and biofluid screening, and early diagnostic approaches.

population.[9] Smoking remains higher among particular populations including males; those with lower socioeconomic status; those with significant physical disability or mental illness; lesbian, gay, bisexual, and transgender persons; and certain racial and ethnic groups.[9] Even in low and medium Human Development Index countries, cigarette consumption is associated with lower socioeconomic status. These disparities in adult smoking prevalence result in unequal tobacco-related disease burden and represent formidable challenges for tobacco control.[10] Although cigarette smoking remains the most common form of tobacco use, dual and poly-tobacco use has become more prevalent with the recent emergence of other tobacco products (OTPs) beyond cigarettes such as cigars, hookah, and noncombustible tobacco products such as snus, e-cigarettes, and heat-not-burns. More than 20% of cigarette smokers older than the age of 15 years surveyed internationally report concurrent use of combustible cigarettes and at least one OTP.[11] Although the effect of poly-tobacco use on lung cancer remains unclear, there is an assumption that tobacco control efforts to reduce or eliminate use of combustible cigarettes will result in a decline in lung cancer morbidity and mortality.

In recent years, discussion of OTPs has focused largely on e-cigarettes, an ENDS that has emerged as an alternative to combustible cigarettes and a potential aid to smoking cessation. The long-term effects of e-cigarette use remain unclear, especially among younger and pregnant users.[12] Most, although not all, public health experts are of the opinion that switching completely from cigarette smoking to using e-cigarettes would be expected to reduce smoking-related health risks including that of lung cancer.[13-15] Adult smokers commonly report using e-cigarettes in an attempt to stop smoking, but evidence is limited regarding their actual effectiveness in achieving smoking abstinence.[16] Results from a recently completed randomized controlled trial (RCT) conducted in the United Kingdom found that e-cigarettes were more effective for smoking cessation than nicotine-replacement therapy when both products were accompanied by behavioral support.[17] Although these findings are extremely encouraging, more research is needed on the potential benefits and harms of e-cigarettes to inform and influence smoking cessation guidelines and tobacco control policy. In particular, the dramatic surge in sales and use of e-cigarettes among youths is concerning because of the known adverse effects of nicotine on the developing brain and the unknown impact of youth e-cigarette use on adulthood smoking and health.[18,19]

Worldwide implementation of comprehensive tobacco control remains essential for achieving success in reducing the overall tobacco-related disease burden. Leveraging the well-established public health advances in vaccination, King and Graffunder[20] summarized best practices in global tobacco control by incorporating four evidence-based population health components including (1) tobacco price increases, (2) smoke-free policies, (3) hard-hitting media campaigns, and (4) access to cessation treatment. There continues to be robust evidence that strong tobacco control policies reduce smoking prevalence and disease burden. Improving access to evidence-based tobacco addiction treatment including cessation medications and behavioral counseling is essential. Along these lines, the Global Bridges Healthcare Alliance for Tobacco Dependence Treatment has provided funding to address the global tobacco treatment delivery barriers faced by low- and middle-income communities including the need for tobacco treatment training for health care providers and, as a result, to date, approximately 9000 health care providers in low- and middle-income communities worldwide have been trained in tobacco dependence treatment.[21]

Lung Cancer Treatment and Smoking Cessation

Historically acknowledged as central to primary prevention of lung and other tobacco-related cancers, there is now compelling data for tertiary prevention with evidence that continued tobacco use has multiple adverse effects on cancer treatment outcomes including reduced survival, greater probability of recurrence, second primary malignancies, greater symptom burden, and poorer quality of life.[3,22] Additionally, a recent report has shown a potential $3.4 billion incremental cost of treating cancer failures associated with continued smoking among patients with cancer in the United States each year.[23] As such, most leading cancer organizations, including the International Association for the Study of Lung Cancer (IASLC), strongly endorse advising patients to quit smoking and establishing evidence-based tobacco treatment delivery as an indicator of high-quality cancer care.[24-26] Although a recent lung cancer provider survey conducted by IASLC showed strong endorsement for the importance of smoking cessation for cancer patients, it has not yet been adopted widely as a standard of care.[27] There are several new U.S. initiatives underway focused on supporting effective implementation of smoking cessation in routine cancer care.[28] In partnership, the American Association for Cancer Research and the National Cancer Institute convened a task force that has recommended standard tobacco use definitions and an assessment tool (the Cancer Tobacco Use Questionnaire) that can be used in cancer research and clinical settings.[29] In 2017, the National Cancer Institute launched the Cancer Center Cessation Initiative (C3I) with the long-term goal of helping cancer centers build and

implement sustainable tobacco cessation treatment programs to routinely address smoking cessation with cancer patients.[30] Through C3I, multidisciplinary implementation teams will conduct quality improvement studies focusing on overcoming patient, clinician, clinic, and health system barriers, refining electronic medical records and clinical workflows to ensure the systematic identification and documentation of smokers and the routine delivery of evidence-based tobacco cessation treatment services. These and other studies underway will provide a much-needed blueprint for feasible, acceptable, and sustainable tobacco treatment delivery in lung cancer care.

Chemoprevention

Chemoprevention, defined as the use of natural or synthetic agents to prevent, delay, or reverse carcinogenic progression to invasive cancer has been successfully implemented in various malignancies. Based on the success of selective estrogen receptor modulators in preventing and reducing the risk of breast cancer and the use of aspirin to reduce the incidence of colon cancer, there has been an interest to develop similar strategies to prevent the development of lung cancer. Our understanding of the molecular and biological basis of lung cancer has increased considerably over the past 2 decades, which has greatly improved our ability to develop interventions aimed at reducing incidence of cancer. Building on pre-clinical evidence that the prostaglandin pathway is altered in a subset of subjects with squamous cell lung cancer, a clinical trial of iloprost was designed for lung cancer chemoprevention. The primary objective of this trial was to compare the reversal of premalignant histologic changes in the bronchial epithelium of patients at high risk for lung cancer (defined as $>$20 pack years of smoking with sputum atypia or endobronchial dysplasia) treated with iloprost versus placebo. Using a combination of the average score of all bronchial biopsy results, the worst biopsy score, and the dysplasia index, an improvement was seen in former smokers but not in current smokers.[31] Other chemoprevention trials using agents such as sulforaphane (NCT03232138), Lovaza (made with fish oils) plus curcumin C3 complex (NCT03598309) and are ongoing as well as work evaluating the role of immunotherapy in this setting.

Pre-Neoplasia and Its Role in Prevention

In contrast to the dramatic explosion of knowledge on cancer genomics from recent technological developments, much work is still needed in the study of pre-neoplasia. Nonetheless we have seen advances over the past year to consolidate and expand further the pioneering work performed previously in this field.[32] Duruisseaux and Esteller[33] undertook and published a comprehensive review of epigenetic DNA hypermethylation of key genes, such as cyclin dependent kinase inhibitor 2a (*CDKN2A*), death associated protein kinase (*DAPK*), O-6-methylguanine-DNA methyltransferase (*MGMT*), retinoic acid receptor beta (*RARb*), *RASSF1A*, and *hTERT*, during the process of progression from normal cells to carcinoma. This article can be a valuable resource to researchers keen on exploring the role of epigenetic disruptions in lung cancer carcinogenesis to realize the full potential these markers may hold in the future for predicting risk, early diagnosis, and potential treatments. Another important development has been the identification of altered gene expression profiles in 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)–exposed normal appearing mouse airways, partly modulated with smoking status in human airway, and the finding that a candidate human bronchial gene classifier is also enriched in the mouse airways.[34] This potentially allows the use of such murine models to not only understand human lung carcinogenesis but to also help select the most promising chemoprevention agents for human clinical trials. Also in 2018, Pan et al.[35] provided a detailed description of methods which can be used for obtaining repeated airway brushings in live mice, that is, mimicking bronchoscopy in humans, to help increase the research utility of experimental preneoplastic mouse models. Again, the novelty of such a mouse model, which replicates what is done in humans, lies in the potential of using such murine models to accelerate testing of a wider range of candidate chemopreventive agents and to better select those most likely to be impactful in prerequisite clinical trials. Furthermore in this topic, research by Kobayashi et al.[36] has indicated that a subset of KRAS- or BRAF-mutated ground-glass nodules may undergo spontaneous regression, a paper introduced by the legendary pathologist Dr. Adi Gazdar.[37] Such observations confirm the wide spectrum of behaviors among ground-glass nodules and offer the promise of new innovations that can perhaps initiate natural regression of such disease. The potential for cure by prevention cannot be underestimated. It is therefore clear that there has been steady progress in lung preneoplasia research over the past year with the hope of translation to human benefit through prevention and/or early diagnosis.

Lung Cancer Early Detection

Risk Assessment

Screening for lung cancer through LDCT is different from other screening programs such as those in breast cancer or colorectal cancer where everyone above a certain age group can be eligible. LDCT screening is more

of a process than just a test. It is a sensitive tool, but has implications for downstream investigations including further imaging, biopsies, and surgery. To maximize benefits and minimize potential harms, accurate risk assessment is needed to identify individuals with sufficient risk most likely to benefit from LDCT screening. Emerging data suggests the USPSTF- or NLST-like criteria of age and smoking pack-years alone are suboptimal for identifying high-risk individuals for LDCT screening.[38] Only an estimated 40% of lung cancer patients in the U.S. and Canada would meet the USPSTF screening criteria (patients 55 to 80 years old who had smoked at least 30 pack-years and not starting screening after 15 years of smoking abstinence) had screening been available before diagnosis.[39] Age and smoking pack-years criteria also do not take into account racial and ethnic differences. This is important as, for example, African Americans have a higher incidence of lung cancer after adjustment for important predictors such as smoking.[40] USPSTF risk selection criteria therefore does not address health disparities among different ethnicities.[41]

Lung cancer risk prediction tools can potentially increase the sensitivity and positive predictive value of screening selection criteria, reducing the number needed to screen to avert one lung cancer death and improve cost-effectiveness. There are at least 22 lung cancer risk prediction tools published.[42] One of the most accurate prediction models is the Prostate, Lung, Colorectal and Ovarian trial risk model 2012 version ($PLCO_{m2012}$) model that has been externally validated internationally.[43] The $PLCO_{m2012}$ model addresses other risk factors besides age and smoking such as ethnicity, chronic obstructive pulmonary disease (COPD), family history of lung cancer, and socioeconomic status. Retrospective studies suggest the sensitivity to identify ever-smokers at high risk of lung cancer for screening can be improved to as high as 80% using such tools.[43] However, in a prospective study in a Canadian population with newly diagnosed lung cancer between 2016 and 2018, the sensitivity of the $PLCO_{m2012}$ model was 63%, compared to 45% using the USPSTF criteria, suggesting additional work must be done to improve the accuracy of risk prediction tools in ever-smokers.[44] Another important question to address in the future will be how to select the most appropriate risk prediction model to use. There are now two RCTs in progress to address this question and prospectively compare different risk prediction models, the International Lung Screening Trial (ILST) and the Yorkshire Lung Screening Trial (YLST), with results expected in coming years. Interim analysis of ILST, presented at WCLC 2018, suggests $PLCO_{m2012}$ outperforms USPSTF criteria with a 15.9% higher proportion of lung cancers.[44,45]

The worldwide burden of lung cancer is significant and projected to increase in coming years, especially in East Asia because of the significant population size, the high stable incidence rates in males, and the significant upward incidence trends in females.[46,47] Additionally, a significant proportion of lung cancers in East Asian countries are in never-smokers with a female predominance.[48] Currently, there are no validated risk prediction tools for never-smokers or specifically for Asian populations. The incorporation of other risk factors such as outdoor and household air pollution and genetic susceptibility may improve the accuracy of lung cancer risk prediction among Asian populations. Preliminary findings from Myers et al.[49] suggest there is significant association between cumulative outdoor air pollution exposure and lung cancer in female never-smokers as well as a significant association between air pollution and Asian ethnicity in never-smokers of both sexes. Such findings may be important in the development of future risk prediction models relevant to these populations.

An accurate risk assessment tool is important not only for lung cancer screening but also for chemoprevention trials. Despite a rapidly increasing understanding of the mechanisms of lung carcinogenesis, the prevention of lung cancer has proven to be complicated. To date, no phase III chemoprevention trial has shown benefit and some trials have in fact shown harm in current smokers.[50] The availability of accurate lung cancer risk assessment as well as accurate lung nodule malignancy probability tools could allow the use of lung cancer incidence as a primary endpoint, instead of intermediate lung cancer biomarkers, when testing for promising chemopreventive agents within a lung cancer screening setting using a smaller sample size and within a shorter time frame than conventional phase III trial designs.[51]

Image-Based Screening

Screening for lung cancer through LDCT has been a highly relevant and keenly debated topic in thoracic oncology over the past 12 to 18 months. Although LDCT screening is already available in some parts of the world, primarily the United States, it has yet to be established elsewhere. In Europe, the majority have been awaiting the final mortality results of the NELSON study, a large RCT powered to detect a reduction in lung cancer mortality at 10 years.[52] The final results of the NESLON trial were presented at the plenary session of the WCLC in September 2018 showing a 26% mortality reduction in males (95% confidence interval [CI]: 0.60–0.91, $p = 0.003$) and 39% in females (95% CI: 0.35–1.04, $p = 0.0543$) at 10 years.[5] This, combined with the pre-existing evidence from NLST, provides robust evidence

that LDCT screening for lung cancer in high-risk populations reduces disease-specific mortality. Subsequently the IASLC, the largest global organization dedicated to the study of thoracic malignancies, released a position statement strongly recommending widespread implementation of LDCT lung cancer screening.[53] The presented NELSON results also showed how stringent nodule management algorithms can reduce the rate of indeterminate and positive screening scan results, with a rate of 9.3% and 2.2% respectively, thereby reducing potential harms of screening.[5] Additionally, the 10-year results of the Italian MILD study were also presented at the same congress and revealed a 39% overall reduction in lung cancer–specific mortality (0.59; 95% CI: 0.38–0.92).[54] Final publications of both these studies are still awaited and expected in the near future. A further significant development from Europe was the publication of the European Union (E.U.) position statement on lung cancer screening.[55] This detailed document, co-authored by several experts with previous experience in lung cancer screening trials, provides a comprehensive summary of the evidence for LDCT screening while at the same time highlighting matters still needing to be addressed before widescale implementation across the continent. The statement concludes with nine recommendations to guide the implementation of lung cancer screening in Europe and expresses strong support for LDCT screening by suggesting planning for implementation to start within 18 months. Several pilot studies and programs are already underway in Europe, primarily in the United Kingdom, implementing lung cancer screening for their local populations.[56-58] A common methodological approach between these pilot programs is the novel use of lung health checks (LHC) whereby ever-smokers are invited to have an assessment, which can include a symptoms history, spirometry, and tobacco addiction treatment, from which only those most likely to benefit are offered LDCT screening. This selection is performed through the incorporation of the previously discussed lung cancer risk prediction models into the LHCs. This approach, combined with substantial public and primary care engagement, has shown improved participation rates compared with previous larger screening trials, especially among high-risk socioeconomically deprived populations previously described as hard-to-reach, and resulted in high lung cancer detection rates (Table 1). The Manchester program, which used the use of mobile CT units to access some of the most deprived areas of the city, reported a lung cancer detection rate of 4.4% across two screening rounds of which 80% were early stage (I-II). Furthermore, having adopted the latest British Thoracic Society nodule management guidelines, the Manchester investigators report an overall false-positive rate of 3.5% (0.8% in the second round), defined as a proportion of the screened population as a whole, and a benign surgical resection rate of 2.5% (one case).[59,60] The encouraging results from these pilot studies have led to strong support from NHS England with a recent announcement of plans to rollout similar programs across the country.[61]

In Asia, LDCT lung cancer screening is still under consideration as the incidence of lung cancer among never-smokers is higher compared to Europe and North America.[62,63] As discussed above, an estimated 10% to 30% of the lung cancers in Asia occur in never-smokers, more so among females, and therefore countermeasures for lung cancer in nonsmokers and light smokers are important.[64,65] A population-based cohort study aimed to evaluate the effectiveness of lung cancer screening using LDCT was conducted in Hitachi, Japan. The study targeted the general population, including non-/light smokers, aged 50 to 74 years, and investigated for lung cancer incidence and mortality as well as all-cause

Table 1. Baseline Results From United Kingdom–Based Lung Cancer Screening Pilot Studies

Pilot	LDCT Screening Criteria	LHC Participation	Lowest SES Quintile (%)	Proportion Screened With LDCT (%)	Baseline Cancer Detection Rate (%)	Early Stage (I-II) (%)
Manchester	$PLCO_{m2012} \geq 1.51\%$	9926 invited, 26.3% attended[a]	75	56	3.0	80
Liverpool[b]	LLP $\geq$ 5%	13,761 invited, 40% attended	81	35	1.9	76
London[b]	NLST; LLP $\geq$ 2.5%; $PLCO_{m2012} \geq 1.51\%$	1997 invited, 50% attended	55	76	4.3	71

[a]Maximum capacity reached.
[b]Ongoing programs.
LDCT, low-dose computed tomography; LHC, lung health check; Manchester, The Manchester Lung Health Check Pilot; Liverpool, Liverpool Healthy Lung Project; London, Lung Screening Uptake Trial; SES, socioeconomic status; $PLCO_{m2012}$, Prostate, Lung, Colorectal and Ovarian trial risk model 2012 version; LLP, Liverpool Lung Project risk model; NLST, National Lung Screening Trial.

mortality from both LDCT and chest x ray screening. The study showed a 23% increase in lung cancer incidence and a 51% reduction in lung cancer–specific mortality with LDCT compared to chest x ray. Additionally, there was a 43% reduction in all-cause mortality associated with LDCT screening.[62] In Korea, a pilot study of the Korean Lung Cancer Screening Project (K-LUCAS), a population-based single-arm trial targeting high-risk populations (aged 55 to 74 years, $\geq$30 pack-year smoking history, smoked within the last 15 years) was conducted to evaluate the feasibility of implementing Lung Imaging Reporting and Data System (Lung-RADS) for LDCT screening.[66] In this pilot study, 256 participants underwent LDCT screening and Lung-RADS was used to categorize the findings. Overall, the distribution of results between Lung-RADS categories 1, 2, 3, and 4 were 57%, 35.5%, 3.9%, and 3.5%, respectively. Positive findings (category 3-4) were exhibited in 7.4% of participants. Lung cancer was diagnosed in one participant (stage IA, SCLC). Between 2017 and 2018, the K-LUCAS project expanded to enroll 8000 participants a year at 14 institutions nationwide. As of November 2018, 13,491 participants have undergone LDCT screening with a scan positivity rate of 15.3%. A total of 69 lung cancers have been diagnosed of which 69.5% were early stage (I-II). Subsequently, the Korean Ministry of Health and Welfare announced that a nationwide lung cancer screening with LDCT will start in July 2019.[67] Although there have been multiple lung cancer screening cohort studies in Asia, no large-scale RCT has ever been conducted to date. A Chinese study, The China National Cancer Early Screening (CHANCES) Trial: Lung Cancer and Colorectal Cancer, is expected to launch in the spring of 2019 with the primary aims of (1) investigating the efficacy of LDCT lung cancer screening in the reduction of lung cancer mortality in high-risk population, (2) evaluating the effectiveness of different screening intervals, and (3) identifying an optimal protocol for lung cancer screening in a Chinese population.[68]

Another eagerly discussed topic within image-based lung cancer screening is the incorporation of modern technology. Improving the accurate detection of pulmonary nodules, reducing the rate of false-positive results and improving the work efficiency of radiologists are three major challenges for the implementation of LDCT screening. Artificial intelligence, machine learning and deep learning technologies have made rapid progress in recent years. Several recent studies have shown that all three technologies can significantly improve the detection rate of pulmonary nodules, including both nonsolid and part-solid nodules, reduce the rate of missed cancer diagnosis, and shorten reporting times of radiologists.[69-72] After the detection of pulmonary nodules, such equipment can also assist with both segmentation and accurate size measurements.[69,71] Furthermore, these technologies have been shown to have the potential to assist with risk stratification of pulmonary nodules, distinguishing between benign and malignant nodules, as well as reducing unnecessary workup in a lung screening population.[73-77] Further data is expected over the coming year regarding the use of technology within lung cancer screening protocols.

Screening and Smoking Cessation

Successfully incorporating smoking cessation into lung cancer screening programs is expected to reduce lung cancer mortality over and above that achieved by lung cancer screening alone and also has the potential to improve cost-effectiveness.[78,79] Widely regarded as a potential teachable moment, LDCT screening offers a critical opportunity to promote smoking cessation and reduce further lung cancer morbidity and mortality.[80,81] One concern, particularly in those who receive a negative screening scan result, is the moral hazard of providing a "license to smoke," also referred to as a "health certificate effect."[82-84] While addressing smoking cessation in the setting of lung cancer screening in the United States is required by the Centers for Medicare and Medicaid Services, widely recommended by national preventive health experts and other related professional organizations and societies, best practices for integration and implementation of evidence-based tobacco treatment in the context of lung cancer screening are not well defined.[81,85] Data from the larger lung cancer screening trials have shown mixed results with regard to the impact of screening on smoking habits. NELSON data suggested a possible negative impact on smoking as screening was associated with a lower prolonged abstinence rate compared to the control group (14.5% versus 19.1%; odds ratio = 1.40, 95% CI: 1.01–1.92; $p < 0.05$).[86] The Danish DLCST trial showed no significant positive or negative impact on smoking cessation from screening.[87] Encouragingly, recent data from the UKLS trial has shown a positive impact of screening on smoking cessation with quit rates of 14% versus 8% at 1 year and 24% versus 21% at 2 years in the intervention versus control arms, respectively. The impact was especially encouraging in those with a positive CT result.[88] Overall, rates of smoking cessation vary greatly across lung cancer screening settings and there is consensus that merely undergoing LDCT itself has little effect on smoking cessation.[89,90] Screening sites vary in readiness and there are several reported barriers for delivering high-quality tobacco treatment.[91,92] Small pilot studies testing smoking cessation interventions in the context of lung cancer screening show promising results.[93-95] There are several new initiatives examining cost-effective implementation of tobacco treatment in

routine cancer care. The U.S. National Cancer Institute has established the SCALE collaboration, a network of randomized clinical trials testing various tobacco treatment models in the context of lung cancer screening.[96] Although data collection is ongoing, several of these trials have recently published their clinical protocols and study designs.[97,98] In summary, despite the strong endorsement that high-quality lung cancer screening should include integration of evidence-based tobacco treatment, the optimal approach for delivering feasible, cost-effective, and sustainable cessation interventions in the context of LDCT screening remains largely unknown. Patient, provider, and systems levels barriers exist and await further needed research on implementation processes and outcome.

Breath-Based Screening

Noninvasive biomarkers such as breath volatile organic compounds (VOCs) and exhaled breath condensate (EBC), consisting of both VOCs and non-VOCs, are interesting to evaluate in a lung cancer screening setting. Cancer alters the metabolism of patients, for example, by increasing glycolysis and oxidative stress and the induction of cytochrome P-450 (CYP450) enzymes, which in turn alters the VOC and non-VOC compounds in exhaled breath.[99] Trained canines have been shown to be able to discriminate lung cancer breath samples from healthy individual and patients with COPD, but the number of patients with solitary pulmonary nodules (SPNs) or stage I disease have been low in previous studies.[100-104] A study specifically focusing on SPNs (30 patients, 79 controls) was presented at WCLC 2018 and showed a sensitivity of 97% and specificity of 99% (Table 2).[105] These results are similar to previously published studies which have included stage I-IV disease.[100-104] As dogs need to be trained individually and separately, and can have "off" days, bioengineered platforms are preferred. Technical standards and pitfalls of both VOC and EBC were discussed in depth in the recently published European Respiratory Society technical standard.[106] Previous EBC and VOC studies have already shown promising results for lung cancer detection and were well summarized in three recent reviews.[104,107,108]

VOC analysis and interpretation is usually based on either evaluation of specific molecules by, for example, gas chromatography–mass spectrometry or pattern recognition of complex mixtures, also referred to as "eNoses"; therefore, specific VOC compounds do not need to be identified.[109] In 2018, several studies were presented or published on this topic and are also summarized in Table 2.[101,105,110-117] With the exception of one study (de Vries et al.[110]), they all included patients with a suspicion of or proven lung cancer. The percentage of patients with early-stage disease varied between 12% and 79%.[101,105,111-117] In the study that included patients without a suspicion of lung cancer, exhaled breathprints were collected from 639 patients with COPD who were managed according to standard care and the incidence of lung cancer was monitored at 1 year after sampling. The study showed a sensitivity of 80% and a specificity of 90% for lung cancer prediction.[110] The LuCID-study (NCT02612532) is an ongoing trial that includes people who are referred for a lung cancer diagnostic workup. VOCs are analyzed by the ReCIVA breath sampler and the primary outcome is an improved area under the curve for the optimal lung cancer detection diagnostic algorithm. The study aims to include 4000 participants overall, and as of the last update at WCLC 2018, 1972 persons have been included.[118] Finally, proteomics analysis on EBC has shown an area under the curve of 0.82 for discriminating lung cancer patients (n = 48, 6 with stage I-II) from healthy controls (n = 49).[119] In 2018, two studies evaluating EBC microRNAs for lung cancer detection were presented at WCLC 2018 (Table 2).[120,121]

Biofluid-Based Screening

Biomarkers of risk for lung cancer also have the potential to improve early detection beyond the use of imaging. MicroRNAs (miRNAs) control the expression of key driver genes associated with tumorigenesis in several cancer types and can be detected as stable circulating molecules in body fluids. Deregulated miRNAs have been identified as potential biomarkers in plasma from cancer patients. Circulating miRNAs have been assessed as a candidate for early disease detection in lung cancer. In a study presented at the WCLC 2018, 38 plasma samples from patients with lung adenocarcinoma and squamous cell carcinoma and 21 healthy controls from a screening population were profiled for an 800-miRNA set using the Nanostring Counter platform. Validation was performed in an independent sample set of 40 patients and 40 controls, paired by age and sex, using TaqMan quantitative real-time polymerase chain reaction. A subset of 149 miRNAs were significantly overexpressed in patient plasma compared to controls, most common of which were associated with the controlling the expression of tyrosine kinase, transcription factors, and immune system–related genes associated with lung tumorigenesis. In addition, three distinct miRNA signatures with 12 unique miRNAs were identified in the discovery set and validated in the independent sample set.[122] These results contribute to the identification of circulating plasma miRNAs as potential biomarkers for early disease detection in lung cancer.

Table 2. Summary of Breath-Based Screening Approaches

Author	No. Total Patients / % NSCLC	% Stage I-II NSCLC	No. and Type of Controls	Type Breath Test	Sensitivity (%)	Specificity (%)	NPV (%)	PPV (%)	AUC of ROC
Dogs									
Guirao et al.[105]	30 / 100	100	18 COPD 61 healthy	1 Sniffer dog	97	99	99	97	0.985
Fischer-Tenhagen et al.[101]	9 / All lung cancer, not specified	NA	10 healthy	2 Sniffer dogs (A & B)	A: 100 B: 89	A: 80 B: 40	A: 100 B: 80	A: 82 B: 57	NA
eNoses /VOCs									
Van de Goor et al.[117]	60 / 85	12	107	Aeonose	TS: 83 VS: 88	TS: 84 VS: 86	TS: 90 VS: 92	TS: 74 VS: 78	0.84
Tirzite et al.[116]	252 / 86	34	122 Healthy, 101 benign lung disease	Cyranose 320	S-: 96 S+: 96	S-: 91 S+: 92	S-: 96 S+: 94	S-: 91 S+: 94	NA
Huang et al.[111]	56 / 98	79	188 Hospitalized for other reason	Cyranose 320	LDA: 75 SVM: 83	LDA: 97 SVM: 86	LDA: 90 SVM: 93	LDA: 90 SVM: 93	LDA: 0.91 SVM: 0.90
Krauss et al.[115]	55 / all lung cancer (30 untreated, 25 in CR)	NA	25 Healthy 24 COPD	Aeonose	94 (Untreated vs. healthy control), "all CR also positive"	84 (Untreated vs healthy control)	NA "COPD also positive"	NA	0.95
Janssens et al.[112]	56 / all lung cancer	NA	28 COPD	MCC/IMS	77	86	65	92	0.85
De Vries et al.[110]	35 COPD patients that developed lung cancer <1 year of inclusion	NA	639 COPD	SpiroNose	80	90	NA	NA	0.91
Kort et al.[114]	107 / 100	NA	200 Healthy	Aeonose	All: 78 AC: 82 SCC: 85	All: 57 AC: 53 SCC: 78	All: 74 AC: 80 SCC: 95	NA	All: 0.73 AC: 0.74 SCC: 0.80
Kort et al.[113]	18 / all SCLC	NA	75 Healthy	Aeonose	89	80	97	52	0.86
EBC									
Spivack[121]	89 / 100	Predominantly	88 Smokers	RTube collection, 40 miRNA panel analysis	NA	NA	NA	NA	miRNA: 0.64-0.76 CM: 0.84 miRNA+CM: 0.86
Pattnaik et al.[120]	NA / 100	NA	NA	RTube collection, Quantimir qPCR	NA, "miRNAs differentially expressed in NSCLC"	NA	NA	NA	NA

COPD, chronic obstructive pulmonary disease; AC, adenocarcinoma; SCC, squamous cell cancer; NPV: negative prediction value; PPV: positive prediction value; AUC: area under the curve; ROC: receiver operating curve; VOC: volatile organic compounds; NA: not available; TS: training set; VS: validation set; S-: non-smoking; S+: smoking; LDA: linear discriminant analysis; SVM: support vector machine analysis; CR: complete remission; EBC: exhaled breath condensate; CM: clinical model; miRNA: microRNA

Lung EpiCheck is a plasma-based test that detects lung cancer–associated hypermethylation changes in six markers in circulating free DNA using real-time polymerase chain reaction. In a recent study, EpiCheck was performed on 689 patient samples (367 patients in the training set, 322 patients in the test set), of which 283 patients had established cancer, and the rest served as controls. The algorithm for calculating EpiScore as well as the threshold for positivity were decided based on the training set and then tested on an independent test set. Specificity and sensitivity of EpIcheck performance score was 94% and 74%, and 91% and 74% in the training set and test set, respectively.[6] These results require further validation but provide an early glimpse into the promise of plasma-based biomarkers as a screening tool for lung cancer.

Lung Cancer Diagnostics and Early Treatment

Advances in Diagnostic Methods

SPNs identified through imaging requiring further assessment can be a significant burden to health care providers, both medically and economically, and should prompt discussion and relevant assessments depending on size, appearance, and location.[123,124] Noninvasive biomarkers may support nodule assessment in the future, although their implementation requires longitudinal validation.[7] A definitive diagnosis requires tissue sampling which can be achieved mostly by bronchoscopy or transthoracic biopsy. Treatment with surgery or radiotherapy without tissue sampling can also be considered but needs to be carefully weighed against procedural risks in a multidisciplinary team. Transthoracic needle aspiration plays a significant role in the investigation of pulmonary nodules due to its widespread availability and relatively low invasiveness. The diagnostic accuracy of transthoracic needle aspiration depends on the size and location of the lesion, as well as operator technique, and decreases from more than 90% to 25% when the nodule size decreases to less than 1 cm.[125] For nodules less than 2 cm, the total diagnostic accuracy of a CT-guided biopsy is approximately 77%, whereas for nodules measuring 0.5 cm to 0.7 cm in diameter, sensitivity decreases to approximately 50%.[126]

The investigation of peripheral lung nodules remains a challenge. Traditional bronchoscopy has poor performance in locating and acquiring the required tissue from peripherally positioned nodules (sensitivity, 20% to 84%). Ultrathin bronchoscopy (UTB), with an outer diameter of 3 mm and an inner working channel diameter of 1.2 mm, allows examination beyond that of the conventional bronchoscope. A recent study for peripheral pulmonary lesion investigation in 310 patients, combining either UTB or thin bronchoscopy, which has an external diameter of 4 mm, with endobronchial ultrasound (EBUS), fluoroscopy, and virtual bronchoscopy (VB) showed a higher diagnostic yield in UTB versus thin bronchoscopy (74% versus 59%; $p = 0.044$).[127] Additionally, bronchoscopy may also be guided by virtual systems. VB is a computer-guided bronchoscopy simulation facilitated by preprocedural CT imaging. The diagnostic yield by UTB in combination with CT and VB is reported to be 65.4% to 81.6%.[128] Combining EBUS with a guide sheath and VB results in a diagnostic yield of 63.3% to 84.4%, whereas combining x ray fluoroscopy and VB has a diagnostic yield of 62.5% to 78.7%. The overall performance of VB in a recent literature review was reported to be 73.8%, reduced to 67.4% for lesions less than or equal to 2 cm.[129] Electromagnetic navigation bronchoscopy (ENB) is an image-based technology that uses VB and facilitates approaching peripheral lung lesions by means of electromagnetic fields.[130] There are two commercially available systems that provide ENB: i-Logi (Covidien, Minneapolis, Minnesota) and SPiNDrive (Veran Medical Technologies, Inc., St. Louis, Missouri). A meta-analysis for the diagnostic yield for lung cancer of ENB showed a sensitivity of 71.1% (95% CI: 64.6–76.8) and a negative predictive value of 52.1% (95% CI: 43.5–60.6).[131] Radial probe endobronchial ultrasound may overcome some of the limitations that exist with the previously discussed methods as it allows real-time imaging of the target peripheral nodule and, in the hands of an experienced bronchoscopist, can show a sensitivity of 70%.[129] One of the main limitations of flexible bronchoscopy is an inability to access and sample nodules that are eccentrically positioned without an airway to approach them. To overcome this, a novel navigational approach known as bronchoscopic transparenchymal nodule access (BTPNA) has been developed and recently described.[132] Currently, BTPNA relies heavily on operator experience and equipment; further data are still required and awaited. Robotic bronchoscopy systems are also being evaluated, and may offer an alternative approach that can potentially overcome the above limitations.[133]

There are several novel methods of investigating smaller but suspicious pulmonary nodules. The best approach depends on several factors including location of the nodule, presence or absence of a bronchus sign, availability, operator experience, risk, and patient preference.

Conclusion

Despite significant advances in the management of lung cancer, it remains the most common cause of cancer-related mortality with poor overall survival outcomes globally. There continues to be an urgent need for

the development of better prevention and early detection strategies. Over the past year, results of the NELSON and MILD trials have reinforced pre-existing evidence that screening high-risk populations with LDCT can lead to mortality reduction. The subsequent release of the IASLC position statement strongly recommending LDCT screening for lung cancer is an indicator that we might be on the brink of widespread implementation. Beyond screening, there has been a dramatic increase in dual and poly-tobacco use with the recent emergence of other tobacco products, including e-cigarettes. Although the long-term effects of poly-tobacco use on lung cancer remains unclear, there is an acceptance that efforts to reduce the use of combustible cigarettes will result in a decline in lung cancer morbidity and mortality. In 2018, we witnessed results suggesting, for the first time, superiority in the use of e-cigarettes compared to nicotine replacement therapy as a method for smoking cessation. While these results are very encouraging, more research is clearly needed to develop suitable policies for appropriate and safe implementation of e-cigarettes as a smoking cessation adjunct. Encouragingly, there continues to be significant interest and ongoing research in the topics of pre-neoplasia and chemoprevention, as outlined in this review. The identification and development of various forms of biomarkers continues to be an exciting area of lung cancer research and results over the past 18 months have provided us with an early glimpse into the promise of such biomarkers as a future tool in the screening, diagnosis, and management of lung cancer. At the same time, with ongoing advancements in technology, great strides are being made in the development of new and improved diagnostic methods for investigation of early-stage lung cancer. Successful implementation of new smoking cessation methods, screening, and improved lung cancer diagnostics holds great promise for an exciting future where lung cancer is both a preventable and a curable disease.

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