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Editorial

Towards zero lung cancer

Edited by: Peifang Wei

Lung cancer is the leading cause of cancer-related deaths worldwide and the third leading cause of death among population in China.[1] Over the past 30 years, the incidence of lung cancer in China has been continuously increasing. It is estimated that there are currently 0.8 to 1 million newly diagnosed cases of lung cancer in China each year.[2] And this number is expected to continue increasing for a period. On the other hand, in recent years, there has been a shift in the staging of lung cancer due to the widespread use of CT scans in China, with an increasing proportion of stage I lung cancer. This trend is consistent with the situation in the United States since the 21st century. It is expected that the overall survival rate of lung cancer in China will continue to improve.[3] Ordered by the technological maturity, this article is based on the ongoing work of our team and presents specific pathways and prospects for the prevention and control of lung cancer (Fig. 1).

Establishing precise early screening tools and strategies

The majority of lung cancer is a slowly developing disease with a wide "window of opportunity" ranging from curable (no metastasis) to incurable stages. Early detection and effective intervention during this window can completely prevent deaths caused by lung cancer. CT screening can detect the majority of early-stage lung cancers located within the lung parenchyma (while bronchoscopy is required for cancers originating from the mucosa). Previous studies such as National Lung Screening Trial (NLST) and Nederlands-Leuvens Longkanker Screenings ONderzoek (NELSON) have demonstrated that CT screening reduces long-term lung cancer-related mortality in high-risk populations.[4,5] Our team's CT mass screening project conducted in Guangzhou has also indicated a 63% reduction in lung cancer-related mortality compared to non-screened individuals, which is the largest reduction ever reported. This may be attributed to the inclusion of more curable individuals in the mass screening and more proactive tracking and intervention measures.[6]

However, CT screening has a significant drawback. Its high sensitivity leads to a high false positive rate, which can exceed 96% and result in a substantial amount of overdiagnosis and overtreatment. [4] In China, 20–30% of high-risk lung nodules surgically removed are found to be benign lesions. More and more intermediate-to-low-risk lung nodules received additional repeated examinations, causing significant waste of societal resources. Therefore, we are actively developing auxiliary diagnostic tools to mitigate the risk of overdiagnosis, including imaging artificial intelligence (AI) and liquid biopsy. These include the world's first circulating tumor DNA (ctDNA) high-throughput methylation diagnostic tool, which identifies 100 lung cancer-specific methylations obtained through massive screening.[7] This model achieves an accuracy rate of 85%, and when combined with imaging AI, its accuracy rate increases to 91%.[8] However, these tools cannot entirely alleviate individuals' anxiety regarding lung nodules.

Therefore, we propose a more rational approach to screening, employing efficient and cost-effective non-invasive methods such as liquid biopsy, exhaled breath analysis, saliva testing, and others, as alternatives to CT screening. These biomarker-based tools need to possess high sensitivity to ensure the detection of any potential lung cancer without missing any cases, while specifically identifying lung cancers that truly require intervention, excluding benign lung nodules and indolent cancers that do not necessitate intervention, such as *in situ* carcinoma and some minimally invasive carcinoma. Currently, there are several investigational techniques that hold promise in achieving this objective, including fragmentomics based on low-depth whole-genome sequencing, T cell receptor (TCR) sequencing for blood-based detection, as well as metabolomics approaches utilizing samples such as oral-pharyngeal secretions, saliva, and exhaled breath. We are currently organizing a clinical trial to explore the feasibility of replacing CT screening with these alternative non-invasive biomarkers. Meanwhile, the portability of testing equipment and the establishment of fast detection methods (such as antibodies or clustered regularly interspaced short palindromic repeats [CRISPR] test strips) will help popularize screening in various types of institutions (such as physical examination centers, community hospitals, etc.), and even on-site testing. This could potentially transition from passive screening approaches to proactive outreach testing, addressing the current challenge of low response rates in centralized screening.

Previously, due to cost-effectiveness considerations, particularly the false positive rate of CT, most lung cancer screenings were targeted towards high-risk individuals. However, the definition of high-risk population lacks sensitivity. In our previous lung cancer screening program in Guangzhou, we observed that individuals who did not meet the criteria for high-risk as defined by National Comprehensive Cancer Network (NCCN) and Chinese expert consensus still had a considerable lung cancer detection rate, with a higher proportion of stage I lung cancer cases. Once we implement screening methods that are more accurate and have lower false positive rates than CT, we can conduct population-wide screening to detect all potential cases of lung cancer.

Developing feasible early intervention and prevention strategies

For early-stage lung cancer, minimally invasive intervention treatments such as video-assisted thoracoscopic surgery (VATS), percutaneous ablation, and stereotactic body radiation therapy (SBRT) have been utilized to achieve minimal trauma. Compared to tradi-

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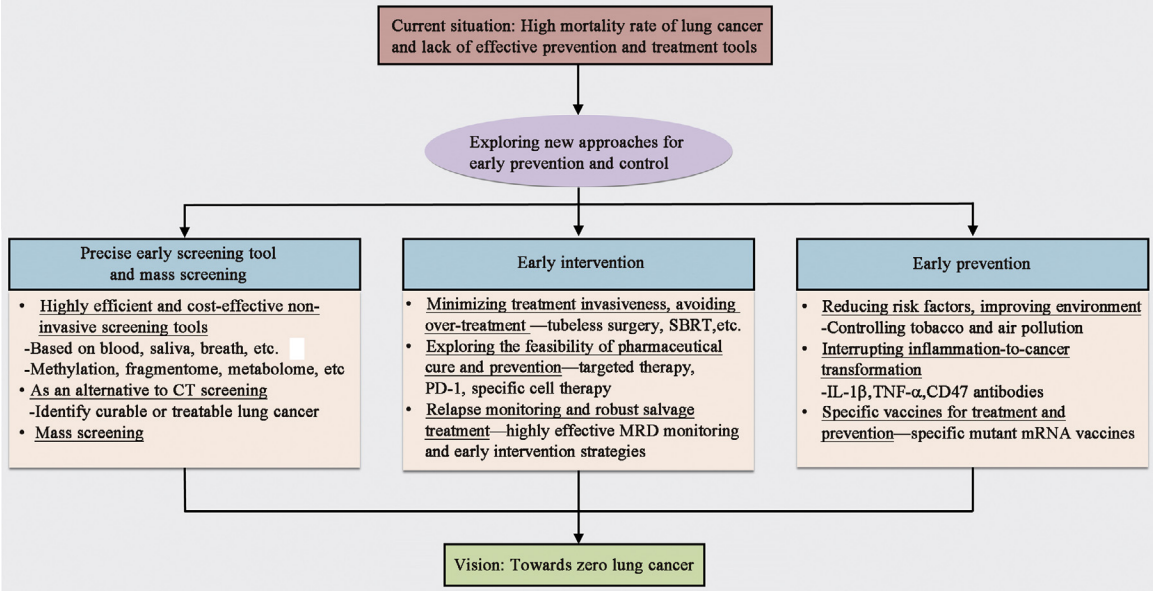

Fig. 1. Towards zero lung cancer. CT: Computed tomography; IL-1β: Interleukin-1β; MRD: Minimal residual disease; mRNA: Messenger RNA; PD-1: Programmed death-1; SBRT: Stereotactic body radiation therapy; TNF-α: Tumor necrosis factor-α; VATS: Video-assisted thoracoscopic surgery.

tional open surgery and intubation anesthesia, He et al[9-11] showed that tubeless VATS (without endotracheal intubation, chest tube, and urinary catheter) significantly reduces the treatment-related trauma, enabling a larger population, including the elderly, to undergo curative surgery. As cancer is a systemic disease, pharmacological treatment also plays a crucial role. We have pioneered the exploration of the efficacy of *EGFR* targeted therapy, programmed death-1 (PD-1) immune checkpoint inhibitors, and other immunotherapeutic drugs in stage 0 lung cancer,[12-14] and developed corresponding imaging AI tools for predicting gene mutation types of small lung nodules.[15] Among them, AI prediction of *EGFR* mutation in stage 0 lung cancer demonstrated a 60% effectiveness rate in *EGFR*-mutated patients when treated with first-generation EGFR-TKIs, consistent with previously reported drug sensitivity. PD-1 inhibitor has also shown certain activity in some immunogenic stage 0 lung cancers. Moreover, PD-1 inhibitor not only serves as a therapeutic agent for treating tumors but also exhibits early inhibitory effects on tumor occurrence and even anti-aging functions, making it a potential candidate for universal drug exploration. Considering the challenge of obtaining pathological tissues for early-stage small nodule lung cancer, we propose new diagnostic criteria that utilize imaging AI and liquid biopsy, combined with multidisciplinary discussions, to perform qualitative characterization and classification of lesions, thereby selecting appropriate drug treatments.

On the other hand, early intervention encompasses secondary and tertiary prevention, with early identification and prevention of recurrence being particularly crucial. We have observed that stage I lung cancer can achieve complete recurrence prevention through adjuvant therapy, whereas the success rate for stages II-III is lower.[16] Due to the inability of imaging techniques to detect minimal lesions, functional-based tools such as minimal residual disease (MRD) detection based on ctDNA become essential.[17] We are currently developing MRD detection tools that can simultaneously provide qualitative and locational information to guide more precise postoperative adjuvant therapy. Furthermore, it is necessary to improve the probability of curative salvage treatment. In cases where early screening is inaccessible or when facing rapidly progressing lung cancer, robust salvage measures are required. The current or upcoming approaches for lung cancer treatment include immunotherapy, T-cell receptors (TCRs)-T/chimeric antigen receptor-modified T (CAR-T) cell therapy, boron neutron capture therapy (BNCT), antibody-drug conjugates (ADCs), proteolysis-targeting chimeras (ProTACs), gene editing, and other modalities. Currently, PD-1-based therapy has achieved a treatment response rate of approximately 20%.[18-22] In the future, implementing various combinations of these approaches can significantly increase the chances of curative salvage therapy. Furthermore, the future outlook for treatment development aims to achieve ultimate precision by utilizing high-throughput omics technologies (such as genomics, transcriptomics, proteomics, and microenvironmental analysis) for precise subtyping of individual cells and even organelles. Subsequently, based on the genetic features and phenotypic characteristics of each individual, finely tailored and personalized precision treatment strategies can be customized.

Actively mitigating lung cancer risk factors and reducing the incidence of lung cancer associated with long-term chronic inflammation stimulation

Smoking is the most well-established risk factor for lung cancer, but it only explains a fraction of lung cancer cases, such as central airway lung cancer and certain Kirsten rat sarcoma viral oncogene homologue (*KRAS*)-mutant adenocarcinomas.[23,24] In recent years, there has been an increase in the incidence of non-smoking-related peripheral lung cancer, which is associated with pollution in the industrialized era. Our alveolar cells have not evolved defense mechanisms against exposure to fine particulate pollution. Therefore, controlling tobacco use, and reducing environmental pollution such as PM2.5, harmful gases, microplastics, etc., can help reduce the formation of these types of lung cancer.[25-28] Indoor air purification and promoting the elimination of harmful pulmonary deposits may contribute to primary prevention of lung cancer and all chronic respiratory diseases. In recent years, substantial evidence has revealed key signaling pathways involved in the transformation of chronic inflammation into cancer, such as Interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), and others.[29-35] Therefore, anti-inflammatory drugs such as IL-1β monoclonal antibodies, aspirin, and others have been proven or suggested to have preventive effects against lung cancer.

Moreover, the elucidation of distinct lung cancer susceptibility genes and their underlying mechanisms holds the potential to elucidate cases of lung cancer with strong familial associations, particularly those involving multiple primary lung cancers. Such findings can further inform molecular-based screening approaches. In addition, we are developing

universal vaccines targeting specific lung cancer-specific antigens (registration number: ChiCTR2300071001). Effective and mass-produceable vaccines can aid in future preventive interventions for high-risk population, reducing the occurrence of certain specific types of lung cancers. Moreover, their utilization in conjunction with standard therapies can enhance immune clearance efficacy and improve rates of treatment response.

Through the research and implementation of precise early screening, effective intervention, and reduction of inducements, along with the establishment of a nationwide screening network and the seamless integration of science and technology with policy, we anticipate achieving zero mortality from lung cancer in the near future. Our goal is to transform lung cancer into a disease that can be effectively controlled, similar to tuberculosis, and change its status as a leading cause of death, making the title of “number one killer” for lung cancer a thing of the past.

Conflicts of interest

None.

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