CHAPTER 53

INCIDENCE AND SCREENING OF NON SMALL CELL LUNG CANCER

Şeyda ÖRS KAYA [1]
Funda CANSUN [2]

Lung cancer is the most common cancer andthe leading cause of cancer-related deaths worldwide. [1]There are two main types of lung cancer; small cell and non-small cell lung cancer.Non-small-cell lung cancer (NSCLC) consists of approximately ~85% of primary lung cancers, the most common subtypes beingadenocarcinoma (ADC) and squamous cell carcinoma (SCC) [2].

Environmental and lifestyle factors have been proven to affect the subsequentdevelopment of lung cancer, of which cigarettesmoking is the most important. Smoking is estimated to account for 85% to 90% of lung cancers.[3] Cancer development risk is associated with the extent of smoking and exposure to other carcinogenic factors, suchas asbestos. Other factors associated with increasedlung cancer risk include ionizing radiation, as found in patients with a history of Hodgkinlymphoma[4] or breast cancer[5]; environmentaltoxins, such as secondhand smoke,radon, and toxic metals (arsenic, chromium, andnickel); and polycyclic aromatic hydrocarbons.[3] History of pulmonary fibrosis, humanimmunodeficiency virus infection, andalcohol consumption have also been identified as risk factors for lung cancer.[6,7]

Interestingly, Lung cancer incidence and mortality rates are the highest in the developed countries. In contrast, lung cancer rates in underdevelopedareasare estimatedto be lower. However, many developingcountries have inadequate data collecting and reporting systems; therefore, many lung cancer cases go unreported, obscuringthe disease's real incidence.[8]

According to The WorldHealth Organization (WHO), estimations, lung cancer death rates worldwide will continue to rise, mainly due to an increase in global tobacco use.[9]Becausewomen had an increasing smoking pattern, lung cancer death rates decreasedmore than a decade after they decreasedin men.[10]Researches focusing on lung cancer incidence in non smokers revealed that women are more likely than men to have non-smoking-associated lung cancer. [11]

Regarding ethnicity, the incidence of lung cancer,although declining for both white and blackmen, is approximately 20% higher for blackmen.[12] On the contrary, the lowest incidenceandmortality rates are seen in Asian-Americans,Pacific Islanders and Hispanic women.[13] Race-relateddifferences are the result of complexinteractions between socioeconomic status,occupational exposures, and lifestyle.

LUNG CANCER SCREENING

The time taken for lung cancer to develop is variable. It takes several years for cancer to devel-

[1] Assoc. Prof., Dr Suat Seren Chest Diseases And Chest Surgery Training And Research Hospital
[2] MD, Dr Suat Seren Chest Diseases And Chest Surgery Training And Research Hospital

The identification of oncogenic driver alterations that underlie small inhibitors' sensitivity has led to a growing interest in identifying additional targetable oncogenes in non-small cell lung cancer. Although the therapeutic impact of discovering these alterations has now been widely demonstrated, the epidemiological data associated with each of these biomarkers remained insufficient. The concept of "oncogene addiction" refers to tumor-cell dependence on the specific activity of an activated or overexpressed oncogene. The main oncogenic drivers in thoracic malignancies are mutations of *EGFR*, *KRAS*, and *ALK*, which are most often reported in adenocarcinomas. However, additional molecular targets have been highlighted recently: *i.e., BRAF*mutations, *HER2* and *PIK3CA*, and new translocations, such as *ROS1* and *RET*. Therapeutic strategies target to inhibit these signaling pathways, among which are monoclonal antibodies and tyrosine-kinase inhibitors.

While the new markers primarily are aimed to be in use in therapeutic strategies, studies are targeting to obtain screening tests such as detecting tumor presence via examining HnRNP A2 / B1 in sputum or analyzing exhaled air. The antigens can be detected in serum or plasma via ELİSA (p53, NYO-ESO-1, CAGE, GBU 4-5, Annexin, SOX-2) and can be used in diagnostic tests in patient groups at risk [21]. In another study, the protein group (C-reactive protein, prolactin, hepatocyte growth factor) andfour biomarkers, including the NYO-ESO-1 antigen, have been examined,ultimately relative to the carcino-embryogenic antigen they are more susceptible to lung cancer, and combining these antigens with LDCT can contribute to screening programs[22]

The detection of real-time micro RNA's(miRNA) in circulation by PCR isamong the remarkable works of recent years.

The stability of miRNAs and their unique structure in cancerous tissue provide advantages. miRNA's fount to have high diagnostic value in patients identified with LDCT and yet asymptomatic[23]

Another exciting research of our day is the volatile biomarkers. Volatile organic compounds (VOCs), a diverse group of carbon-based chemicals in exhaled breath, sweat, or urine, provide information about human health status. Different patterns of VOCs have been correlated with various diseases and syndromes such as cancer [24], asthma [25], cystic fibrosis [26], diabetes [27], tuberculosis [28], chronic obstructive pulmonary disease [29], heart allograft rejection [30], and irritable bowel syndrome [31].

Ehman et al. have conducted interesting researches; exhalation samples of 220 volunteers (healthy individuals, confirmed lung cancer patients, or chronic obstructive pulmonary disease (COPD)) were presented to sniffer dogs following a rigid scientific protocol. Lung cancer was identified with an overall sensitivity of 71% and a specificity of 93%.[32]

The role of VOCs in clinical diagnosis and therapeutic monitoring is expected to become increasingly significant due to recent advances in the field.

Although the advancement of technology has made significant steps in treatment, screening tests, and early diagnosis, we believe that there will be exciting new developments in which artificial intelligence will be added.

REFERENCES:

1. Shibuya K, Mathers CD, Boschi-Pinto C, et al. Global and regional estimates of cancer mortality and incidence by site: II. Results for the global burden of disease 2000. BMC Cancer 2002;2:37.
2. Youlden DR, Cramb SM, Baade PD. The International Epidemiology of Lung Cancer: geographical distribution and secular trends. J Thorac Oncol 2008; 3:819–831.
3. Alberg AJ, Samet JM. Epidemiology of lung cancer. Chest.2003;123(1 suppl):21S-49S.
4. Lorigan P, Radford J, Howell A, Thatcher N. Lung cancer after treatment for Hodgkin's lymphoma: a systematic review. LancetOncol. 2005;6(10):773-779.
5. Huang YJ, Huang TW, Lin FH, Chung CH, Tsao CH, Chien WC.Radiation therapy for invasive breast cancer increases the risk ofsecond primary lung cancer: a nationwide population-basedcohort analysis. J Thorac Oncol. 2017;12(5):782-790.

6. Hubbard R, Venn A, Lewis S, Britton J. Lung cancer and cryptogenic fibrosing alveolitis: a population-based cohort study.Am J Respir Crit Care Med. 2000;161(1):5-8.
7. Kirk GD, Merlo C, O' Driscoll P, et al. HIV infection is associatedwith an increased risk for lung cancer, independent ofsmoking. Clin Infect Dis. 2007;45(1):103-110.
8. Sartorius B, Sartorius K. How much incident lung cancer was missed globally in 2012? An ecological country-level study.Geospat Health. 2016;11(2):396.
9. Dela Cruz CS, Tanoue LT, Matthay RA. Lung cancer: epidemiology, etiology, and prevention. Clin Chest Med. 2011;32(4):605-644.
10. Kohler BA, Ward E, McCarthy BJ, et al. Annual report to thenation on the status of cancer, 1975-2007, featuring tumors ofthe brain and other nervous systems. J Natl Cancer Inst. 2011;103(9):714-736.
11. Lung cancer incidence in never-smokers; *J Clin Oncol*. 2007 February 10; 25(5): 472 478. DOI:10.1200/JCO.2006.07.2983.
12. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. CA Cancer J Clin. 2010;60(5):277-300.
13. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA CancerJ Clin. 2018;68(1):7 30.
14. 1. NCI: SEER Cancer Statistics Review; 1996-2002.
15. Goldstraw P, Crowley J, Chansky K, GirouxDJ, Groome PA, Rami-Porta R, et al. TheIASLC Lung Cancer Staging Project: proposalsfor the revision of the TNM stage groupingsin the forthcoming (seventh) edition of theTNM classification of malignant tumors. JThorac Oncol 2007;2:706-14.
16. Felten MK, Knoll L, Schikowsky C. Is it useful to combine sputum cytology and low-dose spiral computed tomography for early detection of lung cancer in formerly asbestos-exposed power industry workers? *Journal of Occupational Medicine and Toxicology*. 2014. 9:14. DOI:10.1186/1745-6673-9-14
17. Kaneko M, Eguchi K, Ohmatsu H, KakinumaR, Naruke T, Suemasu K, et al. Peripherallung cancer: screening and detection with low-dosespiral CT versus radiography. Radiology1996;201(3):798-802.
18. International Early Lung Cancer Action ProgramInvestigators, Henschke CI, YankelevitzDF, Libby DM, Pasmantier MW, Smith JP, MiettinenOS. Survival of patients with stage Ilung cancer detected on CT screening. N EnglJ Med 2006;355(17):1763-71.
19. Aberle DR, Adams AM, Berg CD, Black WC,Clapp JD, Fagerstrom RM, et al. NationalLung Screening Trial Research Team. Reducedlung-cancer mortality with low-dosecomputed tomographic screening. N Engl JMed 2011;365:395-409.
20. FDA-NIH Biomarker Working Group. *BEST (Biomarkers, EndpointS, and other Tools) Resource.* Silver Spring, Food and Drug Administration, 2016.
21. Boyle P, Chapman CJ, Holdenrieder S, MurrayA, Robertson C, Wood WC, et al. Clinicalvalidation of an autoantibody test for lung cancer.Ann Oncol 2011;22(2):383-9.
22. Ma S, Wang W, Xia B, Zhang S, Yuan H,Jiang H, et al. Multiplexed serum biomarkers for the detection of lung cancer. Biomedicine2016;11:210-8.
23. Alipoor SD, Adcock IM, Garssen J, Mortaz E,Varahram M, Mirsaeidi M, et al. The roles ofmiRNAs as potential biomarkers in lung diseases.Eur J Pharmacol 2016;791:395-404.
24. H. J. O'Neill, S. M. Gordon, M. H. O'Neill, R. D. Gibbons, and J. P. Szidon, "A computerized classification technique for screening for the presence of breath biomarkers in lung cancer," *Clinical Chemistry*, vol. 34, no. 8, pp. 1613–1618, 1988.View at: Google Scholar
25. B. Ibrahim, M. Basanta, P. Cadden et al., "Non-invasive phenotyping using exhaled volatile organic compounds in asthma," *Thorax*, vol. 66, no. 9, pp. 804–809, 2011. View at: Publisher Site | Google Scholar
26. M. Barker, M. Hengst, J. Schmid et al., "Volatile organic compounds in the exhaled breath of young patients with cystic fibrosis," *European Respiratory Journal*, vol. 27, no. 5, pp. 929–936, 2006.View at: Publisher Site | Google Scholar
27. M. Phillips, R. N. Cataneo, T. Cheema, and J. Greenberg, "Increased breath biomarkers of oxidative stress in diabetes mellitus," *Clinica Chimica Acta*, vol. 344, no. 1-2, pp. 189–194, 2004.View at: Publisher Site | Google Scholar
28. M. Phillips, R. N. Cataneo, R. Condos et al., "Volatile biomarkers of pulmonary tuberculosis in the breath," *Tuberculosis*, vol. 87, no. 1, pp. 44–52, 2007.View at: Publisher Site | Google Scholar
29. C. O. Phillips, Y. Syed, N. M. Parthaláin, R. Zwiggelaar, T. C. Claypole, and K. E. Lewis, "Machine learning methods on exhaled volatile organic compounds for distinguishing COPD patients from healthy controls," *Journal of Breath Research*, vol. 6, no. 3, Article ID 036003, 2012.View at: Publisher Site | Google Scholar
30. M. Phillips, J. P. Boehmer, R. N. Cataneo, et al., "Heart allograft rejection: detection with breath alkanes in low levels (the HARDBALL study)," *Journal of Heart and Lung Transplantation*, vol. 23, no. 6, pp. 701–708, 2004. View at: Publisher Site | Google Scholar
31. I. Ahmed, R. Greenwood, B. de Lacy Costello, N. M. Ratcliffe, and C. S. Probert, "An investigation of fecal volatile organic metabolites in irritable bowel syndrome," *PLoS ONE*, vol. 8, no. 3, Article ID e58204, 2013.View at Publisher Site | Google Scholar
32. Canine scent detection in the diagnosis of lung cancer: revisiting a puzzling phenomenon; Eur Respir J 2012; 39: 669–676 DOI: 10.1183/09031936.00051711