

Smell, lung cancer, electronic nose and trained dogs

Abstract

Lung cancer (LC) represents a problem of high magnitude for the medical systems due to its morbidity and mortality, also because of the huge human and economical efforts and costs that it catalyzes. Only in Europe, the average life-time cost of lung cancer patients ranges between €46,000 and €61,000 per patient.

Secondary prevention, which consists in mass-screening of the high-risk population, could result of high benefit. For this aim to become a reality in the future, a potentially inexpensive and non-invasive approach for LC (pre)diagnosing is emerging. Such possibility relies on the detection of volatile biomarkers emitted from cell membranes. Tumor growth is accompanied by gene changes that may lead to oxidative stress, and the per oxidation of the cell membrane species causes volatile biomarkers to be emitted. Some of these biomarkers appear in distinctively different mixture compositions, depending on whether a cell is healthy or cancerous. These volatile biomarkers can be detected, among others, through the analysis of the exhaled breath, because the cancer-related changes in the blood chemistry are reflected in measurable changes to the breath through exchange via the lung. Importantly, these volatiles or their metabolic products are transmitted to the alveolar exhaled breath through exchange via the lung even at the very onset of the disease.

There are several methods that can be applied to analyses the exhaled breath for the identification of a specific pattern of volatile biomarkers related with the target medical condition. The feasibility of three strategies, and the possible synergic effect of their concomitant application as a powerful pre-estimation tool for mass-screening of LC high-risk population:

- i. Spectrographic techniques such as Gas-Chromatography coupled to Mass-Spectrometry (GC-MS), which relies on reference libraries of analyses mass spectra to structurally identify and track the analyses in gaseous samples.
- ii. Electronic-nose (e-nose), which consists in a matrix of chemical gas sensors specifically trained for the target application by means of a pattern recognition algorithm.

Keywords: lung cancer, non-invasive, breath analysis, volatile biomarkers, gas chromatography/mass spectrometry, electronic nose, trained dogs, smell, metabolomics

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Introduction

Globally, lung cancer (LC) is the most widespread cancer for men and the third one for women,¹ and represents the most common cause of death from cancer worldwide.² In Europe, approximately 400,000 new cases of LC are diagnosed every year, and almost 350,000 deaths are produced during the same period of time.³ In the case of Spain, LC incidence reaches 20,000 new cases per year, and the 5years survival rate is situated somewhere around 10-12%.⁴

The conventional LC diagnosis methods used nowadays by the medical centers such as bronchoscope biopsy, pulmonary puncture, chest radiography and computer tomography scanning, occasionally miss tumors, are not free of complications and are very costly.⁵ Although it was demonstrated recently that low dose helical computed tomography provides very encouraging results in terms of excellent accuracy and early detection of the disease,⁶ this technique is extremely expensive and it is impossible to be introduced for mass-screening of high-risk population with the human and economic resources available nowadays.

Health-care strategies are every time more directed towards the use of non-invasive techniques, such as those employing the

metabolic profile concept, which reflects the internal biochemical processes produced inside the human body.⁷ The metabolic profile can be extracted from a series of biological samples: breath, blood, urine, sweat and skin. The detection, in exhaled breath samples, of a volatile organic compounds (VOCs) pattern that is linked with a disease condition, represents a novel approach that overcomes many constraints of the conventional diagnostic techniques.^{8,9} Actually, breath analysis offers several advantages: the breath samples are non-invasive and easy to obtain, the breath contains less complicated volatile mixtures than either serum or urine, while breath testing has the potential for direct and real-time monitoring. Moreover, the volatile biomarkers are transmitted to the alveolar exhaled breath through exchange via the lung even at the very onset of the disease, which offers the possibility to detect the disease at an early stage, when it is still localized and easier to treat.

This method has been explored in different fields of medicine such as respiratory medicine, uremia and oncology.⁸⁻¹⁰ Importantly, every disease has its own volatiles fingerprint, therefore the presence of the target disease would not be masked by other diseases.¹¹

One of the methods commonly used to identify disease related volatile biomarkers in the breath is based on employing analytical

chemistry equipment such as Gas-Chromatography coupled to Mass-Spectrometry (GC-MS), which relies on reference libraries of analytes mass spectra to structurally identify and track the VOCs in gaseous samples.¹² The first study regarding the identification in the exhaled air of LC patients of several VOCs associated with this disease using the GC-MS was published in the '80s.¹³ Since then, >100 different VOCs were identified in the breath of patients with lung cancer.¹⁴ These comprise seven families of compounds, such as hydrocarbons (alkanes, branched-chain alkanes and branched-chain alkenes), primary and secondary alcohols, aldehydes and branched aldehydes, ketones, esters, nitriles and aromatic compounds.¹⁵ Patient's classification is then realized through the statistical analysis of the selected volatile biomarkers in the breath. This way, for example, it was possible to discriminate between LC patients and healthy controls, independently of their smoking habits, with 80% sensitivity and 100% specificity.^{16,17}

In another study, using a set of 13 volatile biomarkers, it was obtained 72% sensitivity and 94% specificity for the identification of LC patients in a population comprising 36 LC patients, 25 patients with chronic obstructive pulmonary disease (COPD), 35 smokers and 50 non-smokers.¹⁸ An alternative method to this conventional technique is based on the so-called "electronic-nose" devices (e-nose). Bio-inspired, an e-nose system performs odor detection using an array of cross-reactive chemical sensors, where every constituent sensor from the array provides a different response upon exposure to a gaseous sample.¹⁹ Sensors combined responses are used to establish odor-specific response patterns by applying pattern recognition algorithms and classification techniques. Thus, the e-nose system is trained for the selective detection of a target odor. The identification of any unknown sample is performed by comparing the pattern generated by the e-nose upon exposure to the unknown odor with the patterns stored in its database.²⁰ In this strategy, a special attention must be paid to the sensing materials of the chemical sensors. Because of the high humidity content in the exhaled breath (>70% relative humidity (RH)), sensors materials should have hydrophobic characteristics in order to be sensitive to very low VOC concentrations in the presence of rich water content. The possibility to discriminate LC patients with e-nose devices has been recently demonstrated by several studies.²¹⁻²³ For instance, trained e-nose devices were able to identify the breath samples of patients with lung cancer and distinguish them from healthy controls,²⁴ as well as from patients having the three next most widespread primary cancers (colon, breast and prostate cancer).^{21,24} In another study, the classification accuracy between LC patients and patients with head-and-neck cancer (highly correlated with tobacco smoking) achieved 100%, while the discrimination between LC patients and healthy controls was 96%.²⁵ On the other hand, a research study performed on a population of 30 volunteers (10 LC patients, 10 COPD and 10 healthy controls), provided 85% accuracy for the discrimination between LC and COPD patients, and 80-90% accuracy between LC patients and healthy controls.²⁶ A completely different strategy to identify specific odors consists in training dogs for this purpose. It was known from Ancient times that breath's smell could be associated with internal diseases. For example, Hippocrates associated in his treatise on breath aroma and diseases an unpleasant fishy smell of the breath with advanced liver disease, a urine-like smell with failing kidneys and the sweet and fruity odor of acetone with uncontrolled diabetes.²⁷

Nevertheless, a dog sniffing is by far the most exceptional in odors identification, which contributed to the use of trained dogs in different

applications such as survivals search and rescue in the case of natural disasters or for finding concealed drugs in airports, to name just a few examples. The enormous value of dogs for human's health assessment has also been evidenced. It was demonstrated that the dogs may serve as an early warning system for certain types of medical disorders, including cancer, oncoming seizures or hypoglycemia.²⁸ The first report regarding the hypothesis that dogs may be able to detect malignant tumors on the basis of odor was published in 1989.²⁹ Other studies have reported that dogs can successfully identify several types of cancer.³⁰

The capability of trained dogs to identify the exhaled breath of LC patients has been also reported. The discrimination of LC patients in a study population comprising 220 volunteers with LC, COPD and healthy controls, employing four dogs trained for this purpose, achieved 71% sensitivity and 93% specificity,³¹ while in another study the sensitivity and specificity obtained with five trained dogs on a study population of 55 LC patients and 83 controls was 99%.³² However, in spite of the promising results obtained individually by the previously enumerated techniques, each one of them presents its own disadvantages. Thus, the number of the volatile biomarkers identified by GC-MS highly depends on the detection limit of the specific GC-MS unit employed, while the lack of normalization and standardization has led to significant variations in the VOC profiles and/or concentrations between the different studies reported in the literature.¹⁵ The e-nose approach increases the variety of compounds to which the sensing system is sensitive, but the sensors can present several problems such as drift and aging, which limits the lifecycle of the e-nose device. Regarding the use of trained dogs, their behavior can be affected by subjective factors such as momentary motivation or friskiness.

Nevertheless, the synergic effect of the three methodologies, which has not been considered till now, could have significant benefit as a pre-estimation tool for mass-screening of LC high-risk population.

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Conflict of interest

The author declares no conflict of interest.

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