

EBC in lung cancer: which future?

Tho the Editors:

Sirs,

Lung cancer still remains the leading cause of cancer death in Europe and in many countries worldwide [1]. Lung cancer is typically silent early in its course and is usually diagnosed late, when treatment is often inefficient. Sadly, major efforts of these last few years to screen for lung cancer with the use of chest radiography, cell sputum examination, CT imaging (high and low-dose) and PET have been carried out with at enormous costs, also in terms of health care resources, and with poor results [2, 3].

With the recognised importance of the molecular aspect of lung tumours highlighted by the recent introduction of the parameter "B" in the TNM staging, interesting prospectives in early lung cancer screening are being awaited from the *molecular analysis* of distrectual samples coming from cancer [4]. An increasing interest in this regard is being directed towards the exhaled breath condensate (EBC).

The complete non-invasiveness of the collection method of this sample makes the latter more readily accepted by healthy subjects who are at risk of a tumour, such as smokers, as well as by patients affected by lung cancer, who are likely to already be exhausted, not only by their condition, but also by the considerable number of exams they have had to undergo. Furthermore, the use of the EBC in lung cancer studies is rightly encouraged in the light of its low expensiveness of cost for the Health Service.

EBC was introduced in the study of lung cancer only 15 years ago, resulting in more than 30 publications of attractive international scientific papers. After an initial interest in soluble tumour marker dosage, the curiosity of oncologist researchers was directed to the "omics" (genomic, proteomic and metabolomic) alterations recently identified in lung tumour and considered as new-fangled markers of the condition [1, 5-8].

In 2004, the possibility to analyse somatic DNA alteration in the EBC, as demonstrated by Gessner (6), opened the doors of genomic's application to the EBC, allowing for the small preliminary studies on p53 and EGFR gene mutations, microsatellite alterations on chromosomes 3 and 19, methylation of DAPK, RASSF1A and PAX5 beta promoters [1, 5-9].

At regards proteomics, there is certainly a great interest in this promising line of inquiry in the wake of its demonstrated ability to detect proteins in EBC. However, there has been no published research on the proteomic EBC profile of lung cancer patients and healthy controls, which can probably be put down to the difficulties still remaining with tools of proteomics and with the confounding variables that may interfere with protein analysis [9].

Great expectations are also awaited from the metabolomics applied to EBC, although a study on lung cancer still hasn't come out.

Regarding the possibility to study gene expression in EBC, it failed due to the fact that no research group has been able, until now, to extract RNA from this sample.

In conclusion, what is the future of EBC application in lung cancer?

To answer this question we must first keep in mind that the EBC is accompanied by limits, such as the lack of an appropriate standardisation, the absence of reference values for most markers analysed, not to mention a low sensibility of assays that still confine it to the research field [10].

Secondly, notwithstanding the identification of often new non-invasive soluble and "omic" lung cancer markers in EBC, it is important to consider that a single biomarker will never be proved to be useful in screening and monitoring of lung cancer, as only the combination of specific and sensitive markers could help defining the fingerprint of lung cancer patients.

Therefore, before one can speak about the future of EBC in lung cancer, one needs to overcome the EBC limits and to recognise and to standardise a valid panel of exhaled lung cancer markers.

We believe that the progress made in these directions could allow for the identification a specific, fast, inexpensive and non-invasive breath-signature to be used in clinical applications for early and "personalised" screening, diagnosis and treatment monitoring of lung cancer. This is similar to what happens for helicobacter pylori, for carbohydrate malabsorption and for DPD-deficiency.

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