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REVIEW

Circulating tumour-derived DNA and RNA markers in blood: a tool for early detection, diagnostics, and follow-up?

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Summary
Background: Lung cancer is the most common cause of cancer death in developed countries. The prognosis is poor with only 10—15% of patients surviving 5 years after diagnosis. This dismal prognosis is attributed to the lack of efficient diagnostic methods for early detection and lack of successful treatment for metastatic disease. Within the last decade, rapid advances in molecular biology and radiology have provided a rational basis for improving early detection and patients' outcome. A non-invasive blood test effective in detecting preneoplastic changes or early lung cancer in high risk individuals has been perceived as a holy grail by cancer researchers.
Methods: The introduction of polymerase chain reaction (PCR)-based technology in the late 1980s and its refinement over the last 10 years have allowed us to detect and quantify extremely small amounts of tumour-derived nucleic acids. This has led to an increased knowledge of the molecular pathogenesis of lung cancer and a basis for the use of DNA and RNA markers in blood for early cancer detection, diagnostics, and follow-up. Common genetic alterations in lung carcinogenesis are already well known. We reviewed published literature on DNA and RNA in plasma or serum in lung cancer patients up to 2004, with particular emphasis on reports published since 1995.
Results: Twenty-two clinical studies have evaluating the role of DNA and RNA aberrations in the blood of lung cancer patients. A total of 1618 (range 10—163/study) cases and 595 (range 10—120/study) control cases were evaluated, and overall plasma/serum abnormalities were found in 43% (range 0—78%) of cases and 0.8% of healthy controls. For (1) total DNA and gene expression levels, 61% (range 53—71%) of cases and 0.9% of controls; (2) oncogene mutations, 16% (range 0—30%) and 0%; (3) microsatellite alterations, 46% (range 24—71%) and 21% (controls with non-malignant pulmonary disease); (4) promoter methylation, 42% (range 5—73%) and 0%; (5) tumour-related RNAs, 54% (range 39—78%) and 6%. In general,

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the studies contain small series of lung cancer patients and even smaller or missing case control groups.
Conclusion: The analysis of circulating DNA or RNA in plasma is a promising non-invasive diagnostic tool, requiring only a limited blood sample. Its wide applicability and potential importance will possibly lead to increasing clinical impact in the near future. However, large prospective clinical studies are needed to validate and standardise any tests for DNA or RNA alteration in plasma or serum of high risk individuals or patients with established lung cancer.

Contents

1. Introduction

In the western world, lung cancer is one of the most common cancers and the leading cause of cancer deaths. In the US, lung cancer accounts for more deaths than prostate cancer, breast cancer, and colorectal cancer combined [1]. The high mortality rate is related to the low cure rate (6—15%), which in turn is related to the lack of adequate screening and early detection measures. Only 15% of lung cancer patients are diagnosed at an early stage [2]. The lung cancer cure rates have been relatively unaltered for 40 years, and further substantial increase is not to be expected with the current treatment modalities. The most promising way to improve this dismal prognosis is by means of early detection.

About 90% of the lung cancer cases are caused by cigarette smoking [3—5]. Primary prevention measures aimed at decreasing tobacco exposure are extremely important. But even if interventions reduced cigarette smoking dramatically, today's smokers will have a significantly increased lung cancer risk for the next 20—40 years. Thus, in addition to primary prevention, secondary prevention such as early detection measures will be important tools for reducing lung cancer deaths.

The aim for early detection is to identify lung cancer at a stage early enough to be curable by surgery. The problem has, hitherto, been lack of valid screening methods. There are no consensus or established methods to screen smokers or other high risk individuals for lung cancer. Previous studies of sputum cytology or annual X-rays showed no benefits in lung cancer mortality reduction [6—9]. Nevertheless, low resolution lung CT screening of high risk individuals (heavy smokers)