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Inhaled insulin for the early detection of lung cancer

Early lung cancer detection may save lives but is controversial [1]. Recently a study appeared documenting improved survival of early lung cancer detected with spiral CT [2].

Biochemical methods of early lung cancer detection have been developed. For example, measurement of an autoantibody response to one or more tumor-associated antigens in an optimized panel assay provides a sensitive and specific blood test to aid the early detection of lung cancer [3].

Early lung cancer can also be detected by obtaining fluid and tissue samples. Respiratory tract material, including sputum or bronchial fluid or other pulmonary tissue or thoracic cells or regional lymph nodes, is assayed with monoclonal antibodies for antigens whose enhanced presence correlates with the development of lung cancer [4].

Surface enhanced laser desorption/ionization (SELDI) mass spectrometry has been used to identify five distinct potential lung cancer serum biomarkers with high sensitivity and specificity [5].

Very small malignant lung tumors might be detected by allowing the subject to inhale powdered insulin, preceded and followed by measurement of circulating hormones, growth factors, and receptor proteins in the blood, particularly those that lung tumors are known to produce:

- Antidiuretic hormone (ADH) is ordinarily produced in the hypothalamus and secreted from the posterior lobe of the pituitary gland. Lung tumors produce ADH. This hormone is involved in the maintenance of the extracellular fluid environment by reducing free water clearance [6].
- Adrenocorticotrophic hormone (ACTH) is the most common ectopic hormone that lung tumors produce. Like ADH, increased serum levels of ACTH in patients with lung cancer are frequent and may be detectable in up to 50% of cases [6].

- Atrial natriuretic peptide is another hormone produced ectopically by lung cancer cells, which affects renal salt and water handling. In individual patients, increased levels of atrial natriuretic peptide may contribute to hyponatremia by causing natriuresis [6].
- Parathyroid hormone (PTH) and parathyroid hormone related protein (PTHrP) are produced by malignant lung tumors [6] and can lead to hypercalcemia, most commonly in squamous cell carcinomas.

Insulin is a growth factor and causes tumor stimulation. Increased serum insulin levels are associated with an increased incidence of prostate cancer, and also a poor prognosis in prostate and breast cancer [7–9]. Moreover, Pfizer Inc. reported an increase in lung cancer among patients who used its discontinued inhaled insulin Exubera. A review of clinical trial data found there were six cases of lung cancer among 4740 patients using Exubera, compared with one of 4292 who did not take Exubera. All cases were in former cigarette smokers [10].

To diagnose lung cancer, inhaled insulin would be used to stimulate lung tumor cells to produce increased blood levels of hormones and other lung cancer markers. Subjects would undergo venepuncture, have blood collected, and receive a single dose or multiple doses of inhaled insulin. After the last insulin dose, blood would be obtained by venepuncture and measurement made of Antidiuretic hormone, Adrenocorticotrophic hormone, Atrial natriuretic peptide, parathyroid hormone, parathyroid hormone related protein, and other lung cancer serum markers. The levels of the hormones and markers would be compared pre and post insulin inhalation. If there had been a significant elevation of one or more hormones or markers after insulin inhalation, as compared to the results from controls without lung cancer, subjects would be sent for further evaluation with spiral CT scanning.

A second use of the inhaled insulin test would be to determine if a candidate for inhaled insulin therapy might be prone to develop lung cancer.

References

- [1] Marshall E. Medicine A bruising battle over lung scans. *Science* 2008;320(5876):600–3.
- [2] Henschke CI, Yankelevitz DF, Libby DM, Pasmantier MW, Smith JP, Miettinen OS. Survival of patients with stage I lung cancer detected on CT screening. *N Engl J Med* 2006;355(17):1763–71.
- [3] Chapman CJ, Murray A, McElveen JE, Sahin U, Luxemburger O, Tureci O. Autoantibodies in lung cancer: possibilities for early detection and subsequent cure. *Thorax* 2008;63(3):228–33.
- [4] Mulshine JL, Scott F, Zhou J, Avis I, Vos M, Miller MJ. Development of molecular approaches to early lung cancer detection. *Semin Radiat Oncol* 1996;6(2):72–5.
- [5] Xiao XY, Tang Y, Wei XP, He DC. A preliminary analysis of non-small cell lung cancer biomarkers in serum. *Biomed Environ Sci* 2003;16(2):140–8.
- [6] Beckles MA, Spiro SG, Colice GL, Rudd RM. Initial evaluation of the patient with lung cancer: symptoms, signs, laboratory tests, and paraneoplastic syndromes. *Chest* 2003;123(Suppl. 1):975–1045.
- [7] Hammarsten J, Hogstedt B. Hyperinsulinaemia: a prospective risk factor for lethal clinical prostate cancer. *Eur J Cancer* 2005;41(18):2887–95.
- [8] Hede K. Doctors seek to prevent breast cancer recurrence by lowering insulin levels. *J Natl Cancer Inst* 2008;100(8):530–2.
- [9] Lehrer S, Diamond EJ, Stagger S, Stone NN, Stock RG. Serum insulin level, disease stage, prostate specific antigen (PSA) and Gleason score in prostate cancer. *Br J Cancer* 2002;87(7):726–8.
- [10] Johnson A. Exuberana runs into more woes. *Wall Street J* 2008;D2.

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