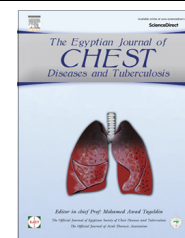




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ORIGINAL ARTICLE

Evaluation of lung cancer by estimating ferritin in exhaled breath condensate



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KEYWORDS

Lung cancer;
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 Ferritin level

Abstract *Introduction:* Early detection of lung cancer is vital to improve lung cancer survival rates and also could change the disease outcome. There is increasing interest in EBC analysis, because the method of collection is simple, non invasive, repeatable and does not necessarily require patient cooperation. This study aimed at estimating ferritin in exhaled breath condensate (EBC) in an attempt to evaluate its role as a non invasive marker for early detection of lung cancer.

Patients and methods: This study included 40 patients diagnosed as lung cancer as well as 20 patients with chronic obstructive pulmonary disease (COPD) and 20 control subjects. Ferritin level was estimated in EBC of all included subjects.

Results: The ferritin level in EBC was the highest in the lung cancer group of patients (> 60 ng/ml) in comparison to COPD patients (35–40 ng/ml). The ferritin level was the lowest in the control group. The statistical comparison of the ferritin level among the 3 groups was highly significant ($p < 0.001$).

Conclusion: The estimated ferritin level in EBC can serve as a non invasive and inexpensive marker for screening of lung cancer.

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Introduction

Lung cancer is the leading cause of cancer related mortality in the world. The American Cancer Society estimated that in 2013 the disease accounts for almost 159,500 deaths in the United States or approximately 27% of all cancer deaths in the country. Lung cancer accounts for about 14% and 12%

of all new cancer diagnoses in males and females, respectively, and nearly 70% of patients with lung cancer present with locally advanced or metastatic disease at initial diagnosis [1].

Lung cancer is a highly prevalent malignancy that is associated with substantial morbidity and mortality. Histologically, it is divided into non-small cell lung cancer (NSCLC), the more common form, and small cell carcinoma. Approximately 85% of lung tumors are NSCLC, which comprises three major histological subtypes: adenocarcinoma, squamous cell carcinoma and large-cell carcinoma [2].

Initiation and progression of lung carcinoma are the result of the interaction between genetic and environmental factors.

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Table 1 Demographic data and its comparison among the 3 studied groups.

	NSLC group no.: 40	COPD group no.: 20	Control group no.: 20	χ^2	<i>P</i>
Age groups					
< 50	4 (10%)	3 (15%)	20 (100%)	52	< 0.001
> 50	36 (90%)	17 (85%)	0		
Sex					
Female	5 (12.5%)	0	13 (65%)	28	< 0.001
Male	35 (87.5%)	20 (100%)	7 (35%)		
Smoker	35 (87.5%)	20 (100%)	2 (10%)	49	< 0.001
Non smoker	5 (12.5%)	0	18 (90%)		

Epidemiological studies indicate that cigarette smoking has a strong association, since approximately 80–90% of lung cancers are attributable to cigarette smoking [3].

Early detection of lung carcinoma could change the disease outcome; the survival rate can increase dramatically. In the effort to improve early detection, many imaging and cytology based strategies have been employed [4].

Recent attention has focused on EBC as a non invasive method for studying the composition of airway lining fluid; it contains aerosol particles in which several non volatile compounds have been identified. EBC analysis of inflammatory biomarkers; (that might reflect different aspects of lung inflammation or oxidative stress, which is an important component of inflammation) is a non invasive method which has the potential to be useful for monitoring airway inflammation in patients with respiratory diseases [5].

An interesting inflammatory marker studied recently in lung cancer is ferritin. Ferritin an iron-storing protein, was initially measured in the serum of patients affected by lung cancer and found to have increased. Elevated levels of ferritin in the serum of patients with non small cell lung cancer (NSCLC) were attributed to an inflammation rather than to body iron overload. Ferritin was also measured in samples from airways such as bronchoalveolar lavage (BAL) and bronchial secretion. The source of ferritin in airways is postulated as stemming from the transudation of serum iron into airways [6].

This study aimed at estimating ferritin level in exhaled breath condensate (EBC) in an attempt to evaluate its role as a non invasive marker for early detection of lung cancer.

Patients and methods

The present study was conducted at the Chest Department of Ain Shams University Hospitals in the period between June 2013 and January 2014. This study included a total of 80 subjects subdivided into 3 groups; Group (A) consists of forty patients diagnosed as NSCLC, Group (B) consists of twenty patients with COPD diagnosed according to the recent guidelines [7], and Group (C) consists of twenty healthy subjects recruited from the Ain Shams University hospitals and served as controls.

All the included subjects underwent detailed medical history taking, thorough clinical examination, routine laboratory investigations, plain chest X-ray postero-anterior view, and computed tomography (CT) scan of the chest.

Exhaled breath condensate collection and processing

Samples of EBC were collected as a liquid during oral tidal breathing in the seated position for 10 min using the EcoScreen (Jaeger, Hoechberg, Germany). Subjects did not wear nose clips and reported that they had ingested no liquids or solids in the previous 2 h. Sample collection was performed according to the American Thoracic Society/European Respiratory Society Task Force (ATS/ERS Task Force) guidelines [8].

Statistical analysis

Statistical analyses were performed utilizing statistical software (SPSS for Windows, version 20.0; SPSS Inc, Chicago, IL). Descriptive statistics was presented as either mean \pm standard deviation (SD) or number and percentage. Differences in measures between groups were assessed using the independent-sample *t* test for parametric data, and Mann–Whitney–Wilcoxon *U* test for non-parametric data. Statistical correlation was done using Pearson's correlation coefficient test. Receiver operator characteristic curve (ROC curve) was used to find out the best cut off value, and validity of certain variable. Statistical significance was set at $p < 0.05$.

Results

Eighty subjects participated in this study, sixty of them were admitted at the Chest Department of Ain Shams University Hospitals and the remaining twenty healthy subjects served as controls and were recruited from the pulmonary function unit of the Chest Department of Ain Shams University Hospitals. The demographic data as well as its comparison among the 3 studied groups is shown in Table 1. There was a highly significant statistical difference as regards age, sex, and smoking status.

Table 2 Distribution of histopathology in the NSCLC group.

Variables	No	%
Squamous cell carcinoma	22	55
Adenocarcinoma	18	45

Table 3 Comparison between the studied groups as regards ferritin level.

Ferritin level (ng/ml)	NSCLC group <i>n</i> = 40	COPD group <i>n</i> = 20	Controls group <i>n</i> = 20	χ^2	<i>P</i>
20–25	0	0	20 (100%)	160	< 0.001
35–40	0	20 (100%)	0		
> 60	40 (100%)	0	0		

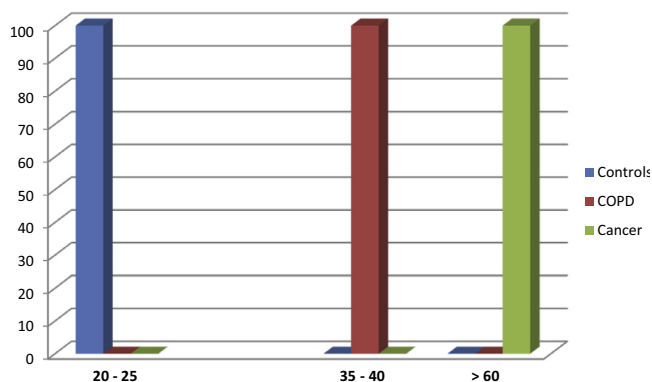


Figure 1 Ferritin level between the studied groups.

Table 4 Validity of ferritin level in the prediction of lung cancer.

Variables	%
Best cut off	40
Area under the curve (AUC)	1.00
Sensitivity	100
Specificity	100
PPV	100
NPV	100
Accuracy	100

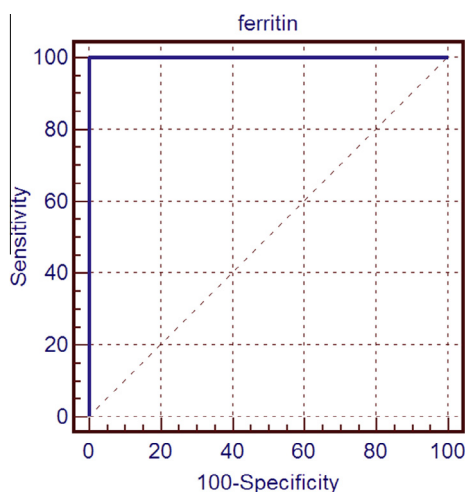


Figure 2 ROC curve.

Among the NSLC group; 55% of cases had squamous cell carcinoma, while 45% were diagnosed as adenocarcinoma (Table 2).

The comparison between the studied groups as regards ferritin level showed that 100% of the studied NSCLC group had higher ferritin above 60, while in the COPD group the level was 35–40, and in controls the level was 20–25 with a highly significant statistical difference between groups (Table 3 and Fig. 1).

The ferritin level was found to be a highly valid predictor of lung cancer at a cut-off of 40 ng/ml with a very high sensitivity and specificity (Table 4 and Fig. 2).

Discussion

Lung cancer has been the most common cancer diagnosed each year since 1985. Lung cancer had a higher incidence among males worldwide than any other cancer, followed by prostate cancer and stomach cancer. Among females, lung cancer was the fourth most diagnosed cancer, behind breast cancer, cervical cancer and colorectal cancer [9].

Aberle et al. [10] stated that the aim of lung cancer screening is to reduce lung cancer-related mortality by detecting more patients in earlier potentially curable stages. It was found in historical randomized controlled trials on the use of periodical chest X-ray and/or sputum cytology were negative, and screening based on these techniques is therefore not recommended. Low-dose computed tomography more sensitive for the detection of small nodules was studied in more recent randomized controlled trials (RCTs).

Reinhold et al. [11] found that there is increasing interest in EBC analysis, because the method of collection is simple, non invasive, repeatable and does not necessarily require patient cooperation only spontaneous breathing through either nose or mouth. The future of EBC is an immediate or in time detection of specific biomarkers to assess the presence and/or the severity of respiratory or non respiratory diseases to evaluate reactive responses of the respiratory system to exogenous toxic substances, or to assist therapeutic interventions.

Stites et al. [12] mentioned that the source of ferritin in airways in conditions such as inflammation is postulated as stemming from the transudation of serum iron into airways. Ferritin was proved to be measurable and present in high concentrations in EBC of lung diseases such as asthma and cystic fibrosis, it seldom has been studied in EBC of patients with lung cancer [13].

This study revealed that majority of NSCLC patients were males above 50 years and this is consistent with Giovanna et al. [14]. As for the COPD group of patients; all were male smokers, possibly because smoking is more common in males as well as being the most common predisposing factor for COPD. Moreover, most of NSCLC patients were smokers (87.5%) and this agreed with Giovanna et al. [14].

Results of our study showed that most of the patients were squamous cell carcinoma (55%) and 45% were adenocarcinoma and this matches with the study of Giovanna et al. [14] as they had the same results.

Results of our study showed that ferritin level in EBC of group A (NSCLC) is above 60 ng/ml and 35–40 in group B (COPD) and 20–25 in group C (control) with higher sensitivity (100%) and specificity (100%) with PPV = 100%, NPV = 100% and accuracy 100%, which represent a highly statistically significant difference between the studied groups and this is in consistent with Giovanna et al. [14] who revealed a significant statistical difference as regards the ferritin level between their two studied groups (control and NSCLC).

Finally, it is worth mentioning that this study has some limitations; first: the estimation of ferritin level in EBC in patients with other types of NSLC and SCLC was not performed. Second: the lack of the de-aeration step in EBC sampling insures the stability of the EBC values.

In conclusion, estimating ferritin level in EBC is a non invasive and inexpensive method for screening of lung cancer with sensitivity and specificity and can therefore be applied widely in Chest hospitals. Future studies should implement EBC ferritin in combination with serum ferritin and ferritin level in pleural effusion to be used as a panel for early detection of lung cancer.

Conflict of interest

None declared.

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