Exhaled breath volatile biomarker analysis for thyroid cancer

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Compared with other types of cancer, thyroid cancer incidence rates have increased rapidly worldwide in the past few decades. In recent years, potential thyroid cancer biomarkers have been studied, but these biomarkers have neither specificity nor good positive predictive value. Exhaled breath analysis is a recently developed convenient and noninvasive method for screening and diagnosing the disease. In this study, potential thyroid cancer biomarkers in volatile organic compounds (VOCs) were detected. Exhaled breath was collected from 64 patients with histologically confirmed cases of thyroid disease (including 39 individuals with papillary thyroid carcinoma and 25 individuals with nodular goiters) and 32 healthy volunteers. Solid-phase microextraction–gas chromatography and mass spectrometry was used to assess the exhaled VOCs of the study participants. The statistical methods of principal component analysis and partial least-squares discriminant analysis were performed to process the final data. The VOCs exhibited significant differences between nodular goiter patients and normal controls, papillary thyroid carcinoma patients and normal controls, and papillary thyroid carcinoma patients and nodular goiter patients; 7, 7, and 3 characteristic metabolites played decisive roles in sample classification, respectively. Breath analysis may provide a new, noninvasive, and directly qualitative method for the clinical diagnosis of thyroid disease. (Translational Research 2015;166: 188–195)

Abbreviations: GC/MS = gas chromatography and mass spectrometry; GHB = γ-hydroxybutyric acid; PCA = principal component analysis; PLS-DA = partial least-squares discriminant analysis; PTC = papillary thyroid carcinoma; VIP = variable importance in the projection; VOCs = volatile organic compounds

INTRODUCTION

The incidence of thyroid cancer has been increasing dramatically. Compared with other types of cancer in males and females, thyroid cancer incidence rates have increased rapidly worldwide in the past few decades.[1] With the growing application of high-resolution ultrasound in clinical practice, a growing number of thyroid nodules are being detected. Although most nodules are benign, 5%–10% of them are malignant.[2] Identifying the nature of the thyroid nodules

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AT A GLANCE COMMENTARY

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Background

Compared with other types of cancer, the growth rate of thyroid cancer is very fast. In recent years, potential thyroid cancer biomarkers have been studied, but these biomarkers have neither specificity nor good positive predictive value. Exhaled breath analysis is a recently developed convenient and noninvasive method of screening and diagnosing the disease.

Translational Significance

In this study, potential thyroid cancer biomarkers in volatile organic compounds were detected. Breath analysis may provide a new, noninvasive, and directly qualitative method for the clinical diagnosis of thyroid disease.

and developing subsequent treatment have become difficult issues for clinicians and patients. The most common diagnostic method is fine-needle aspiration biopsy, which has the advantage of direct characterization and the disadvantage of invasive operation. Additionally, the success of this technique is highly dependent on the strength of the technological development and the experience of the clinician. It has a specificity of less than 75%.[3-5] In recent years, potential thyroid cancer biomarkers such as galectin-3, cytokeratin-19, and fibronectin-1 have been studied, but these biomarkers have neither specificity nor good positive predictive value.[6,7] Accordingly, the exploration of a direct and noninvasive diagnostic method is still needed to guide clinical diagnoses and the development of treatment plans.

Metabolomic approaches can identify disease-specific metabolic patterns by measuring in vivo metabolites. This technique has been widely used in studies on a variety of disease-specific biomarkers.[8-10] Yao et al used liquid chromatography coupled to an linear ion trap quadrupole mass filter orbitrap XL (LTQ Orbitrap XL, Thermo Fisher) hybrid mass spectrometer combined with a metabolomics analysis method to study metabolic changes in the serum of healthy subjects, patients with nodular goiter, and patients with papillary thyroid carcinoma (PTC).[11] The analysis showed that the main components that changed in the serum were free fatty acids such as arachidonic acid and linolenic acid, phospholipids such as lysophospholipids, and amino acids such as tryptophan, serotonin, and lysine. However, this method is invasive because it requires collecting the patient's blood.

Exhaled breath analysis is a recently developed method of screening and diagnosing the disease. Because of its convenience, noninvasiveness, good tolerance, and easy acceptability by patients, this technique has drawn increasing attention from researchers and clinicians.[12,13] Compared with normal tissue, cancerous tissue may exhibit specific metabolic patterns, and the resulting volatile metabolites will be discharged in the blood, excreted by the alveolae, and exhaled in the breath. These specific volatile metabolites can be detected and analyzed using gas chromatography and mass spectrometry (GC/MS).[14] Studies have demonstrated the specificity of volatile metabolites from patients with different cancers such as lung cancer, colorectal cancer, gastric cancer, and breast cancer.[15-18] In the present study, we used the multivariate data analysis method with GC/MS and metabolomics to compare volatile organic compounds in the exhaled breath from healthy subjects, patients with nodular goiter, and patients with PTC.

MATERIALS AND METHODS

This study was approved by the Ethics Committee of Harbin Medical University (No. 201314). A total of 64 patients who were admitted to the First Affiliated Hospital of Harbin Medical University between April and October 2012 were included in this study. To screen and identify possible noninvasive biomarkers of malignant thyroid nodules, breath samples from 39 patients with PTC (the most common type of malignant thyroid nodule) and 25 patients with nodular goiter (benign nodule), as well as 32 age and gender-matched healthy subjects, were collected, as shown in Table I. All the participants were recruited in accordance with the strict inclusion and exclusion criteria established by our research institution. In particular, the following inclusion criteria were used: (1) an age of 25–70 years and (2) agreement to participate in the study, as indicated by a signed informed consent form. The following exclusion criteria were used: (1) pregnancy, lactation, or the possibility of pregnancy; (2) the presence of a confirmed congenital disease; (3) a family history of mental illness; (4) the presence of a chronic inflammatory disease; (5) symptoms of an acute disease during the 2 weeks before the study enrollment; and (6) a history of infectious disease.

Breath collection. Breath gas sampling was performed in conjunction with the parallel collection of ambient air within 24 hours after the subjects had fasted overnight. The alveolar breath sampling procedure was performed in accordance with previous studies.[19,20] Samples were