climate classification.) Although only a small portion of the surface of the globe is subjected to this weather, many cities with productive sleep research centers share this climate (eg, Boston, Massachusetts; New York, New York; Philadelphia, Pennsylvania; Milan, Italy; Sao Paulo, Brazil; Hong Kong, China). It is possible to attempt to replicate the data in the same climate or to do a worldwide study.

It is feasible to undertake an initiative to analyze global polysomnographic data. Sleep laboratories from any part of the planet can send the polysomnography reports to us in databases containing full meteorologic data or at least daily relative air humidity. The mathematicians at our university are capable of extending the cosinor analyses to larger databases.

One opportunity to test immediately the seasonality of polysomnographic records may emerge from data Ramos-Xavier and colleagues already have. The epidemiologic study published in 2010 by Tufik and colleagues probably allows answering one doubt from our study. Patients with the most severe cases of sleep apnea may seek the sleep laboratory in the winter not exclusively because winter-related upper airway conditions such as colds or allergies might have worsened their apnea symptoms but simply because it is more convenient for them to take the time to seek treatment in the winter. The population-based sample from Sao Paulo was recruited using a probabilistic three-stage cluster sampling technique. Therefore, if the volunteers in the Tufik and colleagues’ study undergoing polysomnography randomly over the year have apnea-hypopnea indexes that fit a cosinor model, stronger evidence will be attained of the climatic influences on sleep apnea.

Besides seasonality of obstructive sleep apnea severity, we observed seasonal variation of some polysomnographic measurements that may be worth analyzing in larger samples. For instance, cardiac arrhythmias on polysomnography also have an acrophase over the year have apnea-hypopnea indexes that fit a cosinor model, stronger evidence will be attained of the climatic influences on sleep apnea.

The potential for complication from thyroid nodule biopsy via EBUS-TBNA is highlighted in the following case. A 49-year-old woman was referred for EBUS-TBNA of asymptomatic mediastinal adenopathy with a history of low-grade endometrial sarcoma resected through hysterectomy 3 months prior. At the time of surgery, small-volume mediastinal adenopathy and lung nodules were identified. On follow-up CT imaging, adenopathy had increased in size. A thyroid nodule was also identified (Fig 1A). Thus, the patient underwent airway inspection (normal) and EBUS-TBNA. Sampling of a 9-mm subcarinal lymph node yielded noncaseating granuloma consistent with sarcoid-like lymphadenopathy on two passes, and follow-up CT imaging 3 months later identified stable disease. The thyroid nodule was also sampled through EBUS-TBNA, and cytologic analysis identified colloid consistent with a benign nodule. The patient presented to the ED 8 days later with fever and swelling and pain in her neck. Ultrasonography of her neck identified a thyroid abscess, which was drained (Fig 1B). She was treated with IV antibiotics, and repeat ultrasound-guided drainage was required 48 h later. Thyroid aspirate cultures grew Streptococcus mitis and mixed gram-positive and gram-negative organisms sensitive to penicillin. Mycobacterial staining and cultures of the abscess and mediastinal lymph node were negative. She was discharged without recurrence of symptoms, and follow-up thyroid function testing was normal.

The standard modality of sampling thyroid nodules is through ultrasound-guided fine-needle aspirate (US-FNA) with a low complication rate. US-FNA is aseptic; however, it is not possible to maintain the sterility of an EBUS-TBNA needle through the human mouth and oropharynx. Thyroid nodules visible by endobronchial ultrasound are present close to the proximal trachea below the vocal cords, an area prone to contamination of the oropharynx. Infectious complications postulated to be secondary to oropharyngeal contamination have been described previously. Until randomized comparisons of EBUS-TBNA with standard and safe procedures such as US-FNA of the thyroid are carried out, bronchoscopists should proceed with caution in expanding the use of EBUS-TBNA, especially in the proximal airway prone to oropharyngeal contamination. Retrosternal thyroid nodules beyond the reach of US-FNA are an ideal cohort for further investigation.

**Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration of Thyroid Nodules**

**Pushing the Boundary Too Far?**

To the Editor:

Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) helps bronchoscopists attain cytologic specimens from sites beyond the airway with accuracy, ease, and safety. Research has flourished, and publications have included reports of biopsying not only lymph nodes for lung cancer staging, but also lung and mediastinal masses, TB-infected lymph nodes, cysts, and thyroid nodules.

The potential for complication from thyroid nodule biopsy via EBUS-TBNA is highlighted in the following case. A 49-year-old woman was referred for EBUS-TBNA of asymptomatic mediastinal adenopathy with a history of low-grade endometrial sarcoma resected through hysterectomy 3 months prior. At the time of surgery, small-volume mediastinal adenopathy and lung nodules were identified. On follow-up CT imaging, adenopathy had increased in size. A thyroid nodule was also identified (Fig 1A). Thus, the patient underwent airway inspection (normal) and EBUS-TBNA. Sampling of a 9-mm subcarinal lymph node yielded noncaseating granuloma consistent with sarcoid-like lymphadenopathy on two passes, and follow-up CT imaging 3 months later identified stable disease. The thyroid nodule was also sampled through EBUS-TBNA, and cytologic analysis identified colloid consistent with a benign nodule. The patient presented to the ED 8 days later with fever and swelling and pain in her neck. Ultrasonography of her neck identified a thyroid abscess, which was drained (Fig 1B). She was treated with IV antibiotics, and repeat ultrasound-guided drainage was required 48 h later. Thyroid aspirate cultures grew Streptococcus mitis and mixed gram-positive and gram-negative organisms sensitive to penicillin. Mycobacterial staining and cultures of the abscess and mediastinal lymph node were negative. She was discharged without recurrence of symptoms, and follow-up thyroid function testing was normal.

The standard modality of sampling thyroid nodules is through ultrasound-guided fine-needle aspirate (US-FNA) with a low complication rate. US-FNA is aseptic; however, it is not possible to maintain the sterility of an EBUS-TBNA needle through the human mouth and oropharynx. Thyroid nodules visible by endobronchial ultrasound are present close to the proximal trachea below the vocal cords, an area prone to contamination of the oropharynx. Infectious complications postulated to be secondary to oropharyngeal contamination have been described previously. Until randomized comparisons of EBUS-TBNA with standard and safe procedures such as US-FNA of the thyroid are carried out, bronchoscopists should proceed with caution in expanding the use of EBUS-TBNA, especially in the proximal airway prone to oropharyngeal contamination. Retrosternal thyroid nodules beyond the reach of US-FNA are an ideal cohort for further investigation.

### References


Figure 1. A, Contrast-enhanced axial enhanced CT scan through the thoracic inlet demonstrates a 2-cm, homogenously low-attenuation nodule in the right lobe of the thyroid accessible to ultrasound fine-needle aspiration (arrow). B, High-frequency transverse ultrasound image of the neck demonstrates a predominantly hypoechoic fluid-containing lesion in the right lobe of the thyroid. There is slight nodularity of the medial wall (arrows), and the lesion measured slightly larger than on a previous CT scan. Aspiration of this lesion revealed purulent material.

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REFERENCES


Intronic Boundary Mutation rs430397 Cannot Affect Alternate Splicing and Is an Indecisive Risk Factor for Non-small Cell Lung Cancer

To the Editor:

We thank Dr Merrick1 for his editorial comments on our article2 in CHEST (June 2012) on an intronic polymorphism (rs430397) in the glucose-regulated protein 78 (GRP78) gene and pharmacogenomics in non-small cell lung cancer (NSCLC) treated with platinum-based therapy. Alternative splicing is an important mechanism for gene expression, expanding the coding capacity of a single gene to allow production of different protein isoforms, which can have very different functions. For validating the hypothesis that intron/exon boundary polymorphism rs430397 affects alternative splicing, we performed resequencing of cDNA polymerase chain reaction products with forward primer AAAAGAAGACG-GGCAAAG and reverse primer AGCCACCAACAGAACA. The latter is also the sequencing primer. In 60 blood samples of healthy control subjects, 45 hepatocellular carcinoma samples, and 66 NSCLC samples, we have not found evidence of functional splicing. Nonetheless, we still agree with Dr Merrick’s opinion that it will be of significant importance to study the impact of the rs430397 variant on protein localization, isoform generation, cell function, and so forth.

Again, this variant is also associated with hepatocellular carcinoma risk and prognosis.2 As a stress-inducible endoplasmic reticulum calcium-binding chaperone, GRF78 is used extensively as a biologic marker for onset of the unfolded protein response as well as a unique model for deciphering the mechanisms whereby endoplasmic reticulum stress upregulates nuclear gene expression.4 Here, we studied the possible association of rs430397 and NSCLC risk in China. An association analysis was carried out in the samples described.2,5 This study was approved by the ethics committee...