Analysis of Volatile Organic Compounds in the Exhaled Breath for the Diagnosis of Lung Cancer

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Abstract: Volatile organic compounds are able to be detected in the exhaled breath by a variety of sensing techniques. These volatiles may be produced by cellular metabolic processes, or inhaled/absorbed from exogenous sources. Lung cancer cells may produce and process these compounds different than normal cells. The differences may be detectable in the breath. The following manuscript will review the evidence supporting the premise that a unique chemical signature can be detected in the breath of patients with lung cancer, discuss the results of studies using mass spectrometry and nonspecific chemical sensing techniques to detect the unique lung cancer signature, and speculate on the advancements that must occur to develop a breath test accurate enough to be clinically useful.

Key Words: Breath test, Volatile organic compounds, Mass spectrometry, Diagnostic test.

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Lung cancer is a major public health problem in the United States and worldwide. In 2008 there will be an estimated 161,840 deaths from lung cancer in the United States.[1] This exceeds the number of deaths from breast, prostate, colon, and pancreatic cancer combined.[1] Despite the identification of at risk individuals, screening studies using imaging and sputum analysis have yet to demonstrate a reduction in lung cancer specific mortality. Thus, lung cancer is frequently diagnosed at an advanced stage when treatment is less effective. Currently, the diagnosis of lung cancer is made from a biopsy taken of a lung nodule or mass found during the evaluation of symptoms or as a result of unrelated imaging. Advances in computed tomography (CT) imaging have led to an epidemic of small lung nodules being detected. The evaluation of these nodules is costly, typically requiring serial imaging, and provoking undue anxiety. A simple to use, inexpensive, noninvasive, and accurate lung cancer test would be a major advance in the management of lung cancer and the evaluation of lung nodules.

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There is a growing literature on the analysis of volatile organic compounds (VOCs) in the exhaled breath for the diagnosis of lung cancer. A breath test that is capable of accurately diagnosing early stage lung cancer has tremendous potential utility as part of a screening or diagnostic algorithm, and in the evaluation of small lung nodules. This manuscript will outline evidence supporting the potential for development of such a test, and speculate on the advances that need to occur to make it a reality.

Volatile Organic Compounds in the Breath

Exhaled breath is largely composed of nitrogen, oxygen, carbon dioxide, water, and inert gases. Trace components—volatile substances that are generated in the body or absorbed from the environment—present in the nmol/l–pmol/l (parts per billion volume—parts per trillion volume) range make up the rest of the breath. The exogenous volatiles are inhaled into and absorbed through the lungs or absorbed through the skin. They originate from many solvents and petroleum based products. The endogenous volatiles are generated by the cellular biochemical processes of the body. Thus, measurement of VOCs in the breath can provide a window into the biochemical processes of the body.

Several classes of VOCs can be measured in the exhaled breath (Table 1). These include saturated and unsaturated hydrocarbons, oxygen-containing, sulfur-containing, and nitrogen-containing compounds. Saturated hydrocarbons (e.g., ethane, pentane, and aldehydes) are formed during lipid peroxidation of fatty acid components of cell membranes, triggered by reactive oxygen species (ROS). They are felt to be markers of oxidative stress. Smaller quantities may be produced by protein oxidation and colonic bacterial metabolism. They have a low solubility in the blood and hence are excreted in the breath within minutes of their formation. Unsaturated hydrocarbons are also detected in the exhaled breath. One example, isoprene, is formed along the mevalonic pathway of cholesterol synthesis. Oxygen-containing compounds such as acetone are found in the breath. Acetone is produced by decarboxylation of acetoacetate which is derived from lipolysis or lipid peroxidation. Sulfur containing compounds found in the breath can be generated by incomplete metabolism of methionine in the transamination pathway. Nitrogen containing compounds can be elevated in the breath of subjects with liver impairment or uremia. The origin of many endogenous VOCs is not known. Additional work needs to be performed to learn about the important biochemical pathways for all of the volatiles that can be detected.[2]

TABLE 1. Classes of Volatile Organic Compounds in the Breath

Class of VOC	Example	Example of Mechanism of Production
Saturated hydrocarbons	Ethane, pentane, aldehydes	Lipid peroxidation of fatty acid components of cell membranes–triggered by reactive oxygen species
Unsaturated hydrocarbons	Isoprene	Mevalonic pathway of cholesterol synthesis
Oxygen-containing	Acetone	Decarboxylation of acetoacetate from lipolysis or lipid peroxidation
Sulfur-containing	Ethyl mercaptane, dimethylsulfide	Incomplete metabolism of methionine
Nitrogen-containing	Dimethylamine, ammonia	Elevated in liver impairment and uremia

The first report detailing the identification of VOCs in the breath of healthy subjects was published in 1971. Approximately 250 separate VOCs were identified.[3] More recently, gas chromatography–mass spectrometry (GC-MS) analysis of VOCs in the C4-C20 range in the exhaled breath of 50 normal individuals found the average number of VOCs was 204 per person. In total 3481 different VOCs were identified with 27 common to all subjects.[4] Others have reported changes in the quantity of VOCs produced when supplemental oxygen is administered to healthy subjects,[5] differences in smokers versus nonsmokers,[6] and differences with age.[7]

Rationale for the Study of Breath VOCs in Lung Cancer

For the pattern of breath VOCs of patients with lung cancer to be unique, the biochemical processes that lead to their generation or metabolism must be different in lung cancer patients than in those without lung cancer.

The following are a few examples of differences in the biochemical processes of lung cancer cells:

- ROS are increased by cigarette smoke. The VOCs produced as a result of lipid peroxidation from these ROS can be metabolized by cytochrome P450 (CYP) mixed oxidase enzymes. Polycyclic aromatic hydrocarbons in tobacco smoke may induce CYP enzymes. For example, polymorphisms are present for the inducibility of CYP-1A1. Easy inducibility seems to be more common in individuals with lung cancer. The susceptible genotype has been associated with higher disease recurrence rates and lower survival rates.[8] Thus, the activation of CYP enzymes in individuals with lung cancer may accelerate the degradation of VOCs that are produced as a result of oxidative stress.
- Adenosine monophosphate-activated protein kinase (AMPK) is a key cellular energy sensor. When cells are faced with energy stresses, such as in tumor microenvironments, AMPK functions to restore energy balance. When active, AMPK functions to inhibit synthetic pathways and stimulate catabolic pathways in an effort to restore levels of adenosine triphosphate.[9] Activated AMPK leads to decreased lipogenesis and increased fatty acid oxidation, which can alter the production of VOCs. AMPK activation has been reported in tumor xenografts.[10] LKB1, the upstream kinase of AMPK, is a tumor suppressor known to be mutated in Peutz–Jeghers syndrome. Mutations in LKB1 have also been reported in 30–50% of lung large cell and adenocarcinoma cell lines.[11–13] Fibronectin, a tumor matrix protein, has been found to inactivate LKB1/AMPK signaling pathways.[14] Differences in AMPK activation may lead to differences in the production or metabolism of VOCs.
- The expression of the antioxidants manganese superoxide dismutase and catalase is different in lung cancer tissue than in normal tissue.[15] This may influence the VOCs identified in the breath.

Other support for this concept exists in the literature:

- One study investigated the production of volatile compounds from the head-space gas of two cancer cells lines (SK-MES, CALU-1) in vitro using selected ion flow tube mass spectrometry (SIFT-MS). They found that acetaldehyde was produced at concentrations above physiologic. The concentration of acetaldehyde was proportional to the number of cells in the medium.[16]
- Another study has looked at the origin, distribution, and metabolism of exhaled volatiles by comparing blood volatiles to those in the breath of 10 healthy controls and 10 individuals with stage I lung cancer. They found 25 total compounds that had previously been reported in the breath of lung cancer patients. High levels of hexanal and heptanal were measured in those with lung cancer but not in healthy controls. These compounds were also detected in the breath of the subjects with lung cancer but not the breath of the controls. They concluded that the VOCs in the breath originate in the blood.[17]
- Other investigators studied VOCs from the headspace of lung cancer cell media. VOCs from the culture medium of lung cancer cells differed from virgin culture medium and differed from that of control cell cultures (bronchial epithelial cells, tastebud cells, osteogenic cells, and lipocytes).[18]

The above rationale and support has stimulated investigators to analyze patterns of breath VOCs to determine their potential as a diagnostic test for lung cancer. Two groups of sensor systems have been used for this purpose—mass spectrometry systems and nonspecific gaseous chemical sensing devices.

Studies Using Mass Spectrometry

Several studies have compared patterns of VOCs in lung cancer patients to various control groups using mass spectrometry (Table 2). Two of the most recent studies are described here.

TABLE 2. Studies of Gas Chromatography-Mass Spectrometry for the Evaluation of Breath Volatile Organic Compounds in Lung Cancer

Author	Year	Cancer Subjects	Control Subjects	No. VOCs in Model	Model Accuracy	Validation Accuracy
Gordon et al.[19]	1985	12	17	3	93%	NA
O'Neill et al.[20]	1988	8	0	9	NA	NA
Preti [21]	1988	10	16	2	NA	NA
Phillips et al.[22]	1999	60	48	22	81.50%	71.7% sens, 66.7% spp*
Phillips et al.[23]	2003	67	132	9	89.6% sens, 82.9% spp vs. healthy controls, 37.4% spp in lung disease controls	85.2% sens, 80.5% spp vs. healthy controls†
Corradi et al.[24]	2003	14	43	NA	NA	NA
Poli et al.[25]	2005	36	110	13	NA	72.2% sens, 93.6% spp
Phillips et al.[26]	2007	193	211	16	86.7% sens, 79.4% spp	84.6% sens, 80% spp
Chen et al.[18]	2007	29	20	11	NA	86.2% sens, 69.2% spp
Wehinger et al.[27]	2007	17	170	2	NA	54% sens, 99% spp‡

*Leave one out methodology used for validation (not an additional data set).

†Volatile organic compounds of interest determined prior to testing (not a separate model and validation set).

‡Relevant volatile organic compounds chosen from whole group, with validation performed by splitting the same group into model and test groups with multiple iterations (not an additional data set).

Sens, sensitivity; spp, specificity.

In 2005, a study was reported comparing concentrations of 13 VOCs (seven aliphatic and six aromatic compounds) from the breath of early stage non-small cell lung cancer patients (36 subjects) with asymptomatic smokers (35 subjects), control nonsmokers (50 subjects), and subjects with mild to moderate chronic obstructive pulmonary disease (COPD) (25 subjects). In addition, samples were collected in 26 subjects both before and after resection of their tumor. After 60 minutes of rest, study subjects performed a single slow vital capacity breath through a one-way valve into a Teflon bulb that trapped the final 150 ml of exhaled breath. Exhaled VOCs were extracted by means of a solid-phase microextraction fiber then analyzed by GC-MS. Levels of the studied VOCs were higher in the cancer group, COPD group, and asymptomatic smoker group than in the nonsmoker controls and ambient air. Multinomial logistic regression was used to predict the subject category from the VOC concentrations. There was an overall accuracy of 82% with a sensitivity and specificity for lung cancer of 72.2 and 93.6%, respectively. The concentration of only two VOCs (isoprene and decane) decreased significantly after resection. This report added to the literature by trying to standardize breath collection techniques, enrolling early stage lung cancer patients, and comparing them to controls with otherwise similar characteristics.[25]

In 2007, results of breath analysis from 193 untreated lung cancer patients and 211 control subjects participating in a lung cancer screening trial who had negative chest CT scans were reported. There was no difference in age, sex, or smoking history between the two groups. In addition, 80 postlung cancer resection patients were studied. All subjects breathed normally for 2 minutes into a breath collection device designed to sample alveolar air. The VOCs from 1 liter of alveolar air and a separate 1 liter of ambient air were collected on sorbent traps and analyzed via automated thermal desorption with GC-MS. The subjects were divided in a 2:1 fashion into a training set and prediction set. Multiple pattern recognition statistical techniques were used to analyze the results with a fuzzy logic model proving to have the best discriminatory capabilities. With this model 16 VOCs, mainly alkane derivatives, were found to be statistically different between the groups. Alveolar gradients were calculated for these VOCs. In general, they were lower in the breath of cancer subjects than controls. Fuzzy logic calculated typicality scores for cancer and control groups in the training set based on the VOC levels and interactions. These were applied to the prediction set. If a subject's typicality score was closer to the cancer group then the test was labeled as suggesting cancer was present. Using this method the test had a sensitivity of 84.6% and specificity of 80% with an area under the curve of 0.88. The results were validated using a leave-one-out model that showed a sensitivity of 80% and specificity of 81% for an area under the curve of 0.88. The robustness of the results was suggested by finding similar results from 20 iterations of the analysis using randomly chosen training and prediction sets. There was no difference in the results across stages 1–4. Smoking status did not affect the results. In the 80 subjects who had completed resection for lung cancer the test was positive for lung cancer in 77 (96.3%) leading the authors to speculate that the VOCs were coming from other tissues that shared metabolic changes suggestive of cancer. In 45 subjects who were eliminated from the main group (31 with primary or recurrent lung cancer, 14 with metastatic cancer, mesothelioma, or a benign tumor), all 45 were felt to be positive for cancer on the breath test.[26]

The results of the GC-MS studies are promising but the accuracies are not yet high enough to be clinically useful. The benefits of the GC-MS systems are that they are very sensitive and can detect specific VOCs and measure their concentrations. The downside is that the systems are expensive, they require some expertise to use, and the breath contents need to be captured then transported to the devices. Thus, these systems are not ideal as point-of-care tests.

Studies Using Non-Specific Gaseous Chemical Sensing Devices

Recently, gaseous chemical sensing and identification devices have been developed that are able to detect a single (or patterns of) odorant molecule(s) such as VOCs. These devices have used a variety of sensor arrays including conductive polymers, nonconductive polymer/carbon black composites, metal oxide semiconductors, fluorescent dye/polymer systems, quartz microbalance sensors coated with metalloporphyrins, polymer coated surface acoustic wave devices, and chemoresponsive dyes. The premise with most of these systems is that absorption of gases onto the sensor system causes a change in the conductivity, mass, vibration, or color of the sensor, thus altering its' output. The systems generally consist of an array of sensors, which can be tuned to their task. The composite output of the array requires multivariate statistical techniques to analyze the patterns of output produced (a "smellprint"). The sensitivities of these devices to various chemical groups and concentrations vary with the particular sensing technology. Some report sensitivities in the parts per billion range. A few of these sensors have been studied as diagnostic tests for lung cancer (Table 3).

The first report of the use of a gaseous chemical sensing device for the diagnosis of lung cancer appeared in 2003. The authors used a quartz microbalance sensor system. The output of these sensors is the variation of oscillating frequency of the sensor. As molecules adsorb to the surface of the sensor, the mass of the sensor changes, leading to variation in the oscillating frequency. The sensors are given different chemical sensitivities by coating their surface with chemicals that bind to VOCs. In this study, eight different metalloporphyrins were used to give the quartz sensors different chemical sensitivities. The study population included 35 individuals with lung cancer, nine with previously resected lung cancer (two of which were studied before resection as well), and 18 healthy controls. Analysis of this output was reported to show near 100% correct classification of lung cancer and 94% classification of healthy controls. The model that was developed was not validated on additional patient groups.[28]

Another report of the use of a gaseous chemical sensing device to diagnose lung cancer was published in 2005. This study used a carbon polymer sensor system with 32 separate sensors. The system's output is the reversible change in resistance across each sensor as various chemicals adsorb to the surface. The chemical sensitivity of each sensor is unique because of the chemical diversity of the sensor materials. This study was performed in two phases, a training phase and a validation phase. In each phase subjects inhaled filtered air then exhaled from total lung capacity into a Mylar bag. Each sample was analyzed five times. In the training phase, the study population included 14 lung cancer patients, 19 subjects with α-1 antitrypsin deficiency, six with chronic beryllium disease, two with COPD, and 20 healthy controls. Analysis suggested that the sensor output from lung cancer subjects was distinguishable from healthy controls whereas the output from other disease groups was not. This did not vary by cell type, stage of cancer, smoking status, or forced expiratory volume in 1 second. A support vector machine algorithm was created from this training group and applied to a separate population of subjects for validation. In this group there were 14 lung cancer patients (six with small cell carcinoma), 12 with COPD, two with resected lung cancer, 11 with asthma, seven with pulmonary hypertension, and 30 healthy volunteers. The model identified 85% of the samples accurately for an overall sensitivity of 71.4% and specificity of 91.9%.[30]

A study was published in 2007 using colorimetric sensor array technology. The sensor used by this system had 36 spots composed of different chemically sensitive compounds (e.g., metalloporphyrins) impregnated on a disposable cartridge (Figure 1). The colors of these spots change based on the chemicals they come in contact with. In this study, individuals with lung cancer, other lung diseases, and healthy controls performed tidal breathing of room air for 12 minutes. During this time they exhaled into a device designed to draw their breath across a colorimetric sensor array. A scanner documented color changes occurring on the array over time. The color changes for each individual were converted into a numerical vector. The vectors were analyzed statistically to determine if lung cancer could be predicted from the sensor responses. 143 individuals participated in the study, 49 with non-small cell lung cancer, 18 COPD, 15 idiopathic pulmonary fibrosis, 20 pulmonary arterial hypertension, 20 sarcoidosis, and 21 healthy controls. A prediction model was developed using observations from 70% of the subjects. This model was able to predict the presence of lung cancer in the remaining 30% of the subjects with a sensitivity of 73.3% and specificity of 72.4%. There was no difference based on age, sex, smoking status, or stage of lung cancer. Twenty-one subjects with small indeterminate lung nodules were studied, one of which was lung cancer. The sensitivity of the model was 100% with a specificity of 60% when applied to this group.[31]

TABLE 3. Studies of Gaseous Chemical Sensing Devices for the Evaluation of Breath VOCs in Lung Cancer

Author	Year	Cancer Subjects	Control Subjects	Sensor System	Model Accuracy	Validation Accuracy
DiNatale et al.[28]	2003	35	18	Quartz microbalance	NA	90.3%*
Chen et al.[29]	2005	5	5	Surface acoustic wave	NA	80%
Machado et al.[30]	2005	28	109	Carbon-polymer array	71.6%	sens 71.4%, spp 91.9%
Mazzone et al.[31]	2007	49	94	Colorimetric sensor array	85.9%	sens 73.3%, spp 72.4%

*Leave one out methodology used for validation (not an additional data set).
Sens, sensitivity; spp, specificity.

FIGURE 1. Example of colorimetric sensor used in Ref. 31. Chemoresponsive dyes are impregnated on the disposable cartridge. The dye colors change based on the chemicals that adhere to them.

The benefits of the gaseous chemical sensing devices over GC-MS are that they are relatively inexpensive, and easy to use for point-of-care testing as they are made of reusable or disposable sensors. They have been criticized for their lack of ability to identify the specific chemical compounds within the breath that are different between those with and without lung cancer. In addition they may not be sensitive enough to detect all of the potentially important VOCs in the breath.

How Accurate Does the Test Need to Be?

The accuracy of the breath test required for it to be clinically useful depends on the purpose of the test. A breath diagnostic for lung cancer could be used as part of a lung cancer screening program or in the diagnosis of indeterminate lung nodules. If used as part of a screening program you would like the test to raise the probability of malignancy in the population that receives a positive test high enough to avoid many CT scans and unnecessary biopsies while ensuring that very few individuals with lung cancer are missed. For example, in CT screening trials of high risk individuals the prevalence of malignancy (i.e., on the initial screen) is approximately 1.5%. Thus for every 200 CT scans, three people are diagnosed with lung cancer and 197 additional scans are performed. A breath test would be useful if it could raise the probability of lung cancer in anyone having a CT scan so that fewer CT scans would be performed in those without lung cancer, yet allow the screening program to miss very few with lung cancer. To have one cancer identified for every 10 scans performed the specificity of the breath test would need to be between 85 and 90%. To ensure that only one of every 1000 patients with a negative breath test has lung cancer (and thus could have benefited from having a CT scan) the sensitivity of the test must approach 95%. For the incidence screens (i.e., the yearly follow-up chest CT scans), only 0.5% of at risk subjects are found to have lung cancer. Thus only one of 200 CT scans performed finds lung cancer. To have one cancer for every 10 scans performed on the incidence screen the specificity of the test must now exceed 95%. For only one of every 1000 negative breath test results to occur in a patient with lung cancer, the sensitivity of the test must be 85% or better (Tables 4 and 5).

If the test is used to diagnose lung cancer from indeterminate lung nodules you would like the test to be accurate enough to influence clinical decisions for a wide range of patients (Table 6). For example, for a given patient you might suggest resection of the lung nodule if the probability of malignancy was 90% or greater and follow-up with serial imaging if the probability of malignancy was less than 10%.

TABLE 4. Test Characteristics for the Prevalence Screen of a Lung Cancer Screening Program

Sensitivity	Specificity	LR	PPV	NPV
95	95	19	22.4	99.92
	90	9.5	12.6	99.92
	85	6.3	8.8	99.91
90	95	18	21.5	99.84
	90	9	12.1	99.83
	85	6	8.4	99.82
85	95	17	20.6	99.76
	90	8.5	11.5	99.75
	85	5.7	7.9	99.73
80	80	4	5.7	99.6

CT screening studies of high risk individuals (e.g. smokers over age 55) have found a prevalence of lung cancer of approximately 1.5% (i.e. 67 patients have CT scans for every 1 cancer diagnosed on the initial screen). To raise the prevalence in those who would require imaging to 10% or greater (i.e. 10 patients would have a CT scan for every one cancer diagnosed on the initial screen) a breath test would have to have a specificity of near 90%. A sensitivity of at least 90% would mean most with lung cancer will not be missed.

LR, likelihood ratio; PPV, positive predictive value; NPV, negative predictive value.

TABLE 5. Test Characteristics for the Incidence Screen of a Lung Cancer Screening Program

Sensitivity	Specificity	LR	PPV	NPV
95	95	19	8.7	99.97
	90	9.5	4.6	99.97
	85	6.3	3.1	99.97
90	95	18	8.3	99.95
	90	9	4.3	99.94
	85	6	2.9	99.94
85	95	17	7.9	99.92
	90	8.5	4.1	99.92
	85	5.7	2.8	99.91
80	80	4	2.0	99.87

CT screening studies of high risk individuals have found an incidence of lung cancer of approximately 0.5% (i.e. 200 patients have CT scans for every one cancer diagnosed on yearly follow-up screens). To raise the incidence in those who would require imaging to close to 10% (i.e. 10 patients would have a CT scan for every one cancer diagnosed on yearly follow-up screens) a breath test would have to have a specificity of greater than 95%. A sensitivity of at least 90% would mean most with lung cancer will not be missed.

LR, likelihood ratio; PPV, positive predictive value; NPV, negative predictive value.

TABLE 6. Test Characteristics for the Diagnosis of Lung Cancer from Indeterminate Lung Nodules

Sensitivity	Specificity	PoTP 90%	PoTP 10%
95	95	32.1	67.7
90	90	50	50
85	85	61.2	38.8
80	80	69.2	30.7

When evaluating a patient with a lung nodule, clinical and radiographic features are used to predict the likelihood of malignancy in the nodule. An adjuvant test would be most useful if it raised the probability of malignancy to the point where additional testing would not be needed (e.g. 90%) or lowered the probability of malignancy to the point where follow-up alone was appropriate (e.g. 10%). The above table shows the pretest probability necessary to reach these thresholds for different sensitivities and specificities of the test. For example, to raise the post-test probability to 90% or greater with a test that is 95% sensitive and specific the pretest probability must be at least 32.1%, whereas the pretest probability would need to be at least 69.2% to have a post-test probability of 90% or greater if the test was only 80% sensitive and specific. Similarly, to lower the probability of malignancy to 10% or less after testing, the pretest probability must be 67.7% or less for a test that is 95% sensitive and specific. For a test that is 80% sensitive and specific to lower the probability of malignancy to below 10% the pretest probability could be no more than 30.7%. To be useful clinically the test being developed should be a minimum of 90% sensitive and specific. PoTP 90%-values in this column indicate the pre-test probability necessary for the post-test probability to be 90% or greater if the test is positive, PoTP 10%-values in this column indicate the pre-test probability necessary for the post-test probability to be 10% or less if the test is negative.

Prebreath test probabilities of malignancy would be determined using traditional clinical and radiographic features of the nodule. A breath test that is 95% sensitive and specific could raise the probability of malignancy to greater than 90% if the pretest probability was 32.1% or greater, whereas the pretest probability would need to be at least 69.2% to have a post-test probability of 90% or greater if the test was only 80% sensitive and specific. Similarly, to lower the probability of malignancy to 10% or less the pretest probability could be 67.7% or lower for a test that is 95% sensitive and specific but would have to be 30.7% or lower if the test was just 80% sensitive and specific.

How Accurate Can the Test Be?

An unusual line of evidence has suggested that breath analysis can be improved to the point of clinical utility. A group of investigators studied the ability of dogs to detect lung cancer. They enrolled 55 patients with lung cancer and 83 healthy volunteers in their study. The dogs were trained to identify the samples from cancer patients by using 27 of the lung cancer patients' samples and 66 of the healthy controls. In double-blinded testing using the remaining subjects samples, the dogs were able to detect lung cancer with a 99% sensitivity and specificity.[32]

How to Improve the Test Accuracy

Technical and procedural advances will help to improve and clarify the accuracy of breath testing for lung cancer:

- The unique pattern of VOCs in the breath of lung cancer patients needs to be further characterized. Studies using MS have used different VOC patterns for their models (Table 2). Advances in the ability of chemical sensing devices to detect VOCs at lower concentrations in near real-time is occurring.[33–35]
- Information about the unique pattern of VOCs in the breath of lung cancer patients, gathered from advanced sensing systems, can be used to refine point-of-care testing devices.
- The pattern of breath VOCs for different lung cancer histologies and other tumor characteristics should be clarified.
- Breath collection methods should be standardized so that the most important portion of the breath can be identified and a consistent sample of that portion is easy to obtain (e.g., alveolar breath).
- A standard approach to controlling for ambient VOCs should be adopted.
- Testing of the devices that are developed should occur in populations similar to those in whom the test will be applied.

Summary

The analysis of VOCs in the exhaled breath of individuals with lung cancer has the potential to develop into a useful investigational and clinical tool. Advances in analytic techniques will allow us to more accurately identify the unique constituents of the breath. This could translate into a better understanding of the pathobiology of lung cancer while assisting with its' clinical management.

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