Breath test for breast cancer using the BREATHLINK*

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To evaluate the BreathLinkTMin women with breast cancer and in cancer-free controls, in order to identify their breath VOC profiles and to develop multivariate predictive algorithms that can identify women with breast cancer.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Observational invasive

Summary

ID

NL-OMON38138

Source
ToetsingOnline

Brief title
Point of care breath test for breast cancer

Condition

- Other condition
- Breast neoplasms malignant and unspecified (incl nipple)

Synonym
breast cancer

Health condition

vrouwen met een normaal mammogram en vrouwen met een afwijkend mammogram gevolgd door biopsie, PA benigne of borstkanker

Research involving
Human

Sponsors and support

Primary sponsor: Menssana Research inc
Source(s) of monetary or material Support: MAASTRO cancer foundation

Intervention

Keyword: breast cancer, breath test, diagnostic, remote diagnosis system

Outcome measures

Primary outcome

Targeted outcome: ROC curves for multivariate predictive algorithms that will

predict a woman*s membership in one of the following categories:

1. Breast cancer negative

2. Breast cancer positive

ROC curves in the breast cancer positive group will be stratified for disease

stage with information about the tumors genetic background, with C-statistic,

sensitivity, specificity and confidence intervals.

Secondary outcome

not applicable

Study description

Background summary

1.Evidence for breath biomarkers of breast cancer
Clinical studies have shown that volatile biomarkers of breast cancer are excreted in the breath. In a pilot study of volatile biomarkers of oxidative stress a breath test for identified breast cancer with 93.8% sensitivity and 84.6% specificity6, 7. In a recent validation study8, volatile organic

compounds (VOCs) in the breath of 54 women with biopsy-proven breast cancer and 204 cancer-free controls were analyzed using automated thermal desorption/gas chromatography/mass spectroscopy (ATD/GC/MS). Chromatograms were converted into a series of datapoints by segmenting them into 900 time slices (8 s duration, 4 s overlap) and determiningtheir alveolar gradients (abundance in breath minus abundance in ambient room air). MonteCarlo simulations identified time slices with better than random accuracy as biomarkers ofbreast cancer by excluding random identifiers. Patients were randomly allocated to trainingsets or test sets in 2:1 data splits. In the training sets, time slices were ranked according theirC-statistic values (area under curve of receiver operating characteristic), and the top ten timeslices were combined in multivariate algorithms that were cross-validated in the test sets. Monte Carlo simulations identified an excess of correct over random time slices, consistent with non-random biomarkers of breast cancer in the breath. The outcomes of ten random data splits (mean (standard deviation)) in the training sets were sensitivity = 78.5% (6.14), specificity = 88.3% (5.47), C-statistic = 0.89 (0.03) and in the test sets, sensitivity = 75.3% (7.22), specificity = 84.8 (9.97), C-statistic = 0.83 (0.06). These findings demonstrated that volatile biomarkers in the breath identified breast cancer with accuracy comparable to a film or digital mammogram.

2.Scientific basis of breath biomarkers in breast cancer

The time slices and VOCs identified as biomarkers were not unique to patients with breast cancer, but were also observed in the cancer-free controls in greater or lesser abundance. Previous studies of breath biomarkers of disease yielded similar findings: in patients with lung cancer, breath biomarkers were apparently generated by accelerated catabolism of normal metabolic products, consistent with cancer-associated induction of cytochrome P450 enzymes. A similar mechanism may account for the volatile biomarkers of breast cancer, associated with altered metabolism of estrogen (figure 1). Estrogens promote the proliferation of both normal and neoplastic breast epithelium cells, and their role as breast carcinogens has been confirmed by epidemiological studies. The carcinogenic role of estrogens is supported by the finding that aromatase is expressed at a higher level in human breast cancer tissue than in normal breast tissue. Aromatase (estrogen synthase) is the cytochrome P450 enzyme complex that catalyzes estrogen production by converting C19 androgens to C18 estrogens. Other cytochrome P450 enzymes are also activated in breast cancer, including CYP1A1, CYP1B1 and CYP3A4. Cytochromes P450 are hemoproteins encoded by a superfamily of genes nearly ubiquitously distributed in different organisms from all biological kingdoms. The reactions carried out by P450s are extremely diverse and contribute to bioconversion of xenobiotics, alkanes, terpenes and aromatic compounds. Since normal human metabolism generates a wide variety of VOC products including alkane products of oxidative stress 16, the induced cytochrome P450 activity associated with breast cancer may have modulated the composition of VOCs excreted in the breath. In addition, a number of the VOCs identified as candidate biomarkers of breast cancer included alkanes (e.g. tridecane, dodecane) and methylated alkane derivatives, which are

products of oxidative stress produced by lipid peroxidation of polyunsaturated fatty acids. Increased oxidative stress has been implicated as a risk factor in women with breast cancer and increased breath pentane, another alkane, has been reported in women with breast cancer

3.Clinical Perspective on breath testing
A brief history of breath testing: In the18th century, Lavoisier developed a breath test for carbon dioxide in the breath. This was the first chemical probe of metabolism, and it provided the first evidence that foodstuffs are oxidized in the body. During the 19th century, colorimetric breath tests detected ethanol in alcohol drinkers, and acetone in diabetics with ketoacidosis. Radiolabeled drugs in the 20th century enabled new breath tests for digestive disorders including H. pylori infection and pancreatic insufficiency. In 1971, Linus Pauling reported a new analytical technique: microanalysis of volatile organic compounds (VOCs) in the breath, and the remarkable discovery that normal human breath contains a large number of different VOCs in very low concentrations. He made this discovery by freezing breath VOCs in a tube chilled with acetone and dry ice, then analyzing the concentrated sample using the then-new technology of GC. Subsequent studies have shown that a sample of human breath contains hundreds of different VOCs, mostly in picomolar (10-12 M) concentrations.
Breath VOC assays in the laboratory:Laboratory-based assayshave been employed for proof-of-principle studies, and biomarker discovery. Breath VOC samples are collected at the clinical study with a breath collection apparatus (BCA):
Breath VOC samples are captured onto sorbent traps that are sealed hermetically and sent to the laboratory for analysis by ATD/GC/MS (Figure 3). This methodology has enabled the first-ever large multi-center clinical studies of breath testing.
Breath biomarkers of oxidative stress: Power plants, biological or man-made, commonly produce toxic byproducts. Mammalian life is sustained by the energy produced in mitochondrial power plants which also convert oxygen to toxic and potentially lethal byproducts. Oxygen is the final acceptor of electrons in oxidative metabolism, but electron leakage from the mitochondria in the form of reactive oxygen species (ROS) inflicts oxidative stress, a constant barrage of oxidative damage to DNA, proteins, lipids and other biologically important molecules27 (Figure 2). Oxidative stress has been implicated as a pathologic mechanism in aging and several diseases, but it has proved difficult to measure its intensity in vivo. Various markers of oxidative stress have been proposed, including malonaldehyde and conjugated dienes in the blood, and alkanes and in the breath. Increased breath alkanes, particularly ethane and pentane, have demonstrated increased oxidative stress in breast cancer, rheumatoid arthritis, heart transplant rejection, acute myocardial infarction, schizophrenia and bronchial asthma.

Study objective

To evaluate the BreathLinkTMin women with breast cancer and in cancer-free

controls, in order to identify their breath VOC profiles and to develop multivariate predictive algorithms that can identify women with breast cancer.

Study design

Study Design
A 12 month multi-center, unblinded study in humans using breath assays to evaluate the BreathLinkTM to determine breast cancer biomarkers

Study burden and risks

Procedures:
Patient Screening
a. Healthy subjects scheduled for a screening-mammogram (= group 1) or subjects with an abnormal mammogram who've had a breast biopsy (= group 2) are screened to ensure they satisfy the inclusion/exclusion criteria.
b. Informed Consent
c. Medical and medication history
d. Clinical Report Form

Breath Test
1 Breath test using the BreathLinkTM

Safety Variables:
BreathLinkTM: disposable mouthpiece and bacterial filter
List any Adverse Events that occur within 24 hours of breath sample collection.
Compliance with sample collection according to protocol, only by qualified personel

Study Devices
BreathLinkTM

Duration of Subject Participation
The total time allocated to the study will not exceed 10 minutes.
* Breath tests in Group 1 (screening mammogram) will be performed prior to screening mammography.
* Breath tests in Group 2 A (post-biopsy, abnormal mammograrm and benigne biopt) will be performed after breast biopsy.
* Breath tests in Grooup 2B (post-biopsy, abnormal mammogram and breastcancer) will be performed in the window between biopsy and start treatment.

Contacts

Public

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Group 1
1. Breath sample collected during 7-day period prior to screening mammography.
2. Patient has no prior history of cancer.
3. Patient understands the study and is willing and able to give signed informed consent to participate.
4. Patient agrees to provide the results of their mammogram
5.Female, age >< = 18 years.
Group 2 A and 2B
1. Breath sample is collected after breast biopsy and before possible initiation of cancer treatment.
2. Patient agrees to provide the results of their mammogram if available.
3. Patient agrees to provide the results of their breast biopsy.
4. Patient understands the study and is willing and able to give signed informed consent to participate.
5. Female, age >< = 18 years.

Exclusion criteria

Group 1
1. Previous history of breast cancer.
2. Previous history of cancer at any other site.
3. Previous history of breast biopsy.
4. Previous history of abnormal mammogram.
5. Previous history of palpable breast mass.

Group 2:
1. Previous history of breast cancer.
2. Previous history of cancer at any other site.

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	06-09-2012
Enrollment:	100
Type:	Actual

Ethics review

Approved WMO

Date:	04-04-2012
Application type:	First submission
Review commission:	MEC academisch ziekenhuis Maastricht/Universiteit Maastricht, MEC azM/UM (Maastricht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL35924.068.11