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Review

An Overview on the Application of Solid Phase Microextraction in the Analysis of Volatile Organic Compounds as Potential Biomarkers of Cancer

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Abstract

The search for biomarkers of diseases, especially for the early detection of cancer, is one of the most popular research fields in biomedicine. The development of non-invasive screening techniques for the early detection of cancer is one of the greatest scientific challenges of the 21st century. Because various diseases cause to generation of biomarkers in the body, early diagnosis of diseases can be performed by analyzing these biomarkers in all body feces. Detection of volatile organic compounds (VOCs) as biomarkers of the body's metabolic processes is a new frontier in the fast, sensitive, selective and non-invasive analysis and medical diagnosis of human diseases. VOCs as biomarkers in the human body can be distinct and specific to metabolic conditions or diseases. VOCs produced as end products of cellular metabolism and are released through a variety of biological matrices such as breath, blood, saliva, urine and feces. The study of volatile metabolites in the body fluids of the patients is performed to establish "potential biomarkers" for early diagnosis and prognosis of the disease. Various genetic, epigenetic, proteomic, and metabolic markers are evaluated for early detection of cancer. One of the promising emerging methods for early detection of cancer is the analysis of VOCs. The purpose of this review is to provide insights for recent research work on the analysis of VOC-biomarker of cancers with extraction by solid phase microextraction (SPME), and how to detect VOCs in different body matrices as a potential biomarker of disease.

Introduction

Searching for biomarkers of the disease, especially for early detection of cancer, is one of the most common fields of research in biomedicine. Since various diseases cause to biomarkers generation, we can diagnose the disease early by analysis of these biomarkers, especially cancer. Screening for early detection of cancers favorably affects the survival of cancer patients. Volatile organic compound (VOCs) as biomarkers are compounds that produce and release biogenic/endogenous VOCs from physiological (pathological) processes and metabolic activities in the human body. Therefore, VOCs are considered as the systemic and local biomarkers. They can be distinct and specific to the metabolic conditions or disease, providing unique information about ongoing biochemical processes and the health of the human body.

VOCs are those organic compounds that exist as gases in the atmosphere, but are liquid or solid under normal conditions of temperature and pressure. These compounds can be present in the atmosphere at ambient temperature (vapor pressure ≥ 0.01 kPa at 20°C). In general, VOCs are less colored, have very low boiling points that allow vapors to easily enter indoor or outdoor air from liquid or solid surfaces, are mostly reactive, and are often mixed with nuisance gases. VOCs, numbering in the thousands, are ubiquitous in the environment, produced by a variety of natural and human resources, and in high concentrations are often found indoors. VOCs are found in the field of health in personal care products and medicines, skin lotions, perfumes, deodorants.[1]

Humans are extensively exposed to VOCs, and due to this fact that, some of VOCs are mutagenic, neurotoxic, genotoxic and carcinogenic, therefore, it has become a serious health concern. On the other hand, VOCs are found in healthy human body as a result of biochemical processes. Numerous VOCs have been detected in the different biological matrices including, breath (872 compounds), blood (154 compounds), breast milk (256 compounds), saliva (359 compounds), skin secretion (532 compounds), feces (381 compounds), and urine (279 compounds). Some VOCs have been identified as highly toxic or carcinogenic in nature and may have short-term and long-term effects on the human health as well as the natural ecosystem. Main toxicological effect reported

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for VOCs and their carcinogenicity classification are presented in Table 1.

Studies of laboratory animal toxicity as well as human epidemiological studies, especially in the workplace, show that there is a link between VOC exposure and adverse health outcomes such as carcinogenesis and neurological effects. Human evidence has been obtained mainly through exposure to inhalation in the workplace. Non-lethal effects include eye irritation and skin allergies. Effects on the central nervous system and carcinogenicity are the most important health effects of VOCs on the body. Among the VOCs studied, the carcinogenicity of benzene and 1,3-butadiene, is well documented. In addition, several other VOCs such as vinyl chloride, ethylene oxide, N, N-dimethylformamide, ethylbenzene, and styrene have adverse effects on human health and cause blood toxicity, and kidney damage/reproduction. Exogenous VOCs are a measure of exposure to harmful compounds in the environment. Maximum allowable of some VOC concentrations and the potential of VOCs' harm to the human health are reported in Table 2. According to the reported studies, exposure to VOCs increases the risk of congenital malformations with neural tube defects, congenital malformations of the male genital tract and wheezing/asthma in infants, respiratory diseases,[10-13] leukemia,[14] neurological disorders,[15,16] and cancer.[17-20] Prolonged exposure to low-concentration VOCs can cause respiratory illness, vision loss, and even death. Studies show that exposure to acrylamide causes damage to the central and peripheral nervous system, [21] and breast cancer.[22] Exposure to tetrachlorethylene during pregnancy increases the risk of stillbirth and placental disease.[23] Benzene, 1,3-butadiene, trichloroethylene, acrylamide, acrylonitrile, N, N-dimethylformamide, ethylbenzene, isoprene, and styrene are classified by the International Agency for Research on Cancer (IARC) as potential carcinogens.[2,20] Acrolein, croton aldehyde, toluene and xylene are classified as group 3 carcinogens (insufficient evidence).[24] Benzene is a known example, which is a cancerous nodule with a high potential to harm humans specifically (e.g., liver, kidney, spleen, and stomach) and systematically (e.g., neurological, circulatory, reproductive, immunity, cardiovascular and respiratory system).

Analysis of VOCs is a field of research in which several studies have been performed to detect, identify and quantify these compounds in various applications. The search for biomarkers of a new disease, especially for the early detection of cancer, is one of the most intense areas of research in biomedicine.[27-30] Studies show that the concentration of one or more potential biomarkers that originated from some disease can be determined in different biological samples such as urine,[31] blood serum,[32] or exhalation.[33] With recent advances in the biomonitoring of VOCs metabolites in the urine, it provides an accurate assessment of the amount of these compounds in the

Table 1. Main toxicological effect reported for VOCs and their carcinogenicity classification

Target analytes	Major health effect in humans	Carcinogenicity	Ref
Acrolein	>690 μg/m^3, eye irritation	Inadequate evidence	2
Acrylamide	400 mg/L in water, central nervous system (CNS) deficits	Probable	2
Benzene	3–32 mg/m^3, hematotoxicity	Carcinogen	2
Acetone	300 to 500 ppm, slightly irritating, nervous system damage, headache, fatigue and numbness	Inadequate evidence	3
Acrylonitrile	0.8 mg/m^3, reproductive damage	Possible	4
1-Bromopropane	Oxidative stress, genotoxic effects	Possible	
1,3-Butadiene	>11 mg/m^3, hemato-lymphopoietic, colorectal and prostate cancer	Carcinogen	
Crotonaldehyde	>1600 μg/m^3, eye, skin and respiratory irritation	Inadequate evidence	5
Isoprene	asphyxiant and CNS depressant	Possible	6
Styrene	<4.3 mg/m^3, hematological effects	Possible	7
N, N-dimethylformamide	6–20 mg/m^3, hepatic toxicity	Probable	
Propylene oxide	corneal burns, hand eczema and dermatitis	Possible	8
Formaldehyde	6 ppm, nasopharyngeal cancer, lung damage, and possibly leukemia	Carcinogen	9

Table 2. Maximum allowable of some VOC concentrations and VOCs' harm to human health[3,25,26]

VOCs	Permissible concentration in air (mg.m^{-3})	Explosion limit (vol%)	Health risks
Toluene	100	1.27-6.75	Headache, dizziness, nausea, and emphysema
Xylene	100	2.5-12.8	Anemia, leukemia, and skin irritation
Acetone	750	2.5-12.8	Eye irritation, anesthesia, headache, and cough
Acrylonitrile	20	3.0-17	Nausea, vomiting, and dyspnea
Benzene	5	1.5-8.0	Carcinogenesis, leukemia, and respiratory paralysis

body's internal load. VOC monitoring studies provide new biomarkers for assessing diseases such as airway inflammation,[34] lung damage,[35] neurological disorders,[16] immune dysfunction,[36] and cancers,[37] in populations. Due to the widespread production of these compounds, they will become a critical issue for community health in the future.

In order to increase public awareness about a particular cancer, its symptoms and diagnosis, possible causes and prevention and screening for early detection, guidelines for early diagnosis and prevention of cancer have been considered. According to the American Cancer Society's guidelines for early detection of and screening of cancers has a positive effect on the survival of cancer patients.[38]

Early detection of cancer is done by various genetic, epigenetic, proteomic and metabolic markers.[39-43] The analysis of VOCs in human exhalation is known as a cost-effective and non-invasive strategy to diagnose the disease, therefore, metabolic disorders or dysfunction in the human body can be screened by exhalation analysis. For example, benzene is an important biomarker for the early detection of lung cancer,[44] while diabetes,[45,46] can be diagnosed by detecting the concentration of acetone in the exhaled human breath.

Diagnosis of cancer in the early stages of the disease is often effective in its successful treatment.[47] Studies show that cancer cells produce unique VOC profiles that can indicate disease conditions. According to the World Health Organization (WHO) World Cancer Report in 2014, cancers are one of the leading causes of death and complications, killing 8.2 million people worldwide in 2012. About 14 million new cases were reported that year, and that number is projected to increase by 70% in the next two decade. In order to diagnose and stage the cancer, various techniques and tools such as X-ray,[48] colonoscopy,[49] mammography,[50] blood test, computed tomography,[51] positron emission ion tomography,[52] magnetic resonance imaging (MRI),[53] and ultrasonography,[54] have been used.

VOC-based diagnostic technologies can be implemented worldwide, because of the rapid monitoring and early detection and evaluation of the treatment effectiveness of high-risk populations.[55,56] To identify small amounts of these VOC biomarkers for diagnosis, in parts per million (ppm) or even parts per billion (ppb), it is necessary to develop highly sensitive, selective, low-cost devices with miniaturized sensors that not only can identify these biomarkers, but can also differentiate between health and unhealthy conditions. These types of devices can develop personal diagnoses and are fast and non-invasive, and many diseases such as cancer,[57] diabetes,[58] kidney,[58] and asthma,[59] are diagnosed by this method.[60]

A disease can be diagnosed with a specific pattern of VOCs, with little likelihood of interference with other diseases.[61,62] The frequently repetition of the VOC test in expiratory respiration may reflect the progression of cancer.

This review firstly discusses about presence of VOCs in different biological samples and available approaches for VOCs collection from sample matrices which are performed via in vitro and in vivo approaches. Then, it reviews complementary solid phase microextraction (SPME) derived analytical methods conducted to date in order to determine VOCs biomarkers of different types of cancer.

VOC biomonitoring studies in different biological samples

Disease-related VOCs produced in the body are excreted in body fluids, can migrate throughout the tissue, and may be stored in fatty areas.[63,64] These specific VOCs are more likely to be released into the bloodstream and circulate in the vascular system with blood–air partition coefficient ($\lambda_{b:a}$).[54] Non-polar VOCs with low solubility in the blood ($\lambda_{b:a}$<10(, lower blood-air separation coefficient, exchange almost exclusively in the alveoli, and polar VOCs that are more soluble in the blood ($\lambda_{b:a}$>100(tend to exchange in the airways. VOCs with 10<$\lambda_{b:a}$<100 can exchange in both the airways and alveoli.[65] Also influenced by its concentration in the blood and during their shelf life, it is located in the lungs.[66] Endogenous VOCs can be transported from the organs through the blood to the lungs and subsequently present in the exhaled breath, which changes the composition of the exhaled air and provide a unique breathing index pattern as a "mirror reflection" of disease states.[61] Diagnosis of endogenous VOCs can distinguish between various diseases, including cancers.[67]

Exhaled respiration and scalp space are often used as appropriate sources of VOC for patients and chemical fingerprinting of these compounds for early diagnosis and disease monitoring.[68,69] Endogenous VOCs are produced in the human body by altering metabolic pathways and physiological processes.[70] In cancer, the pathophysiology causes metabolic changes that alter the composition and concentration of VOC in the body.[71] Development of cancer due to one or a combination of factors such as increased oxidative stress, inflammatory stress, liver enzymes, induction of CYP450 (a group of oxidase enzymes),[72] carbohydrate metabolism, high rate of glycolysis,[73] changes protein production,[74] lactate overproduction,[75] and related lipid metabolism.[76] As a result, tumor cells produce a unique cancerous VOC profile that reflects disease conditions.[54] By exhaling, several hundred biologically produced VOC molecules can be released that can be used as biomarkers to diagnose the disease. This method can provide reliable and very valuable signs of human health. Therefore, analysis of VOCs in exhalation is known as a useful method to diagnose different types of cancer. Additionally, the exhalation breath test is painless and non-invasive, and it is suitable for children and critically ill patients.[76-79] Biomonitoring of urinary VOCs metabolites, due to its recent advances, has led to an accurate assessment the location of VOCs and the internal load of the body. New biomarkers for assessing airway

inflammation,[34] lung damage, neurological disorders,[80] immune dysfunction,[7] and cancers,[81] in populations are made by VOC biomonitoring studies.

Available approaches for VOCs collection

In recent years to investigate VOCs as cancer biomarkers, a very popular way is analysis of the exhaled breath of patients with various kinds of cancer.[82] Alternative approaches for breath analysis include the headspace analysis of cancer cells, tissues, or body fluids. All sample matrices have their advantages and disadvantages.

In vivo collection of VOCs

In vivo refers to when research or work is done with or within an entire, living organism. Examples can include studies in animal models or human clinical trials. Studies have shown that chemical changes in blood due to the presence of cancer are echoed in an alteration of the composition of VOCs in the breath of patients.[83] Therefore, it is hypothesized that abnormal VOCs produced by cancer cells are discharged via the blood stream into the endobronchial cavity and finally exhaled with breath.[76] Breath analysis, compared to blood and urine tests, is noninvasive and a sample may be easily collected at any point and in varying quantities, which makes it easy to repeat.[84] Furthermore, it does not require special storage conditions or any further work after collection. In addition, the breath matrix is a less complex mixture than urine or blood. There are approximately 200 VOCs present in a breath sample. However, they are not the same for each individual. Around 3500 different VOCs were detected in the breath of 50 people, and only 27 were found in the samples of all the subjects.

In vitro VOCs collection

In vitro is used to describe work that's performed outside of a living organism. Therefore, in this approach, cancerous cells are treated in the microenvironment and the produced VOCs by them are collected and analyzed. The investigation of VOCs produced in this approach as the source of biomarkers should hypothetically help with the dilemma of their origin, because the advantages of in vitro studies over other matrices include easier control of experimental variables and easier interpretation of results, due to the absence of factors such as gender, age and interpersonal diversity (excluding primary cell culture).[85] This approach also supplies higher reproducibility and lower cost. However, this approach does not guarantee that all of collected VOCs have endogenous origin. It is possible that, they are not generated by cancer cells and they may instead come from other origins including culture vials, extraction devices, and the sampling media.[86] According to a recently published review article by Kalluri et al,[87] it was revealed that applying in vivo and in vitro approaches for investigating VOCs as potential biomarkers of cancer have led to different results possessing poor correlations (specifically when exhaled breath has been studied as a sample matrix for detection of lung cancer(. They hypothesize that the correlation between the VOCs in the expiratory respiration of lung cancer patients and the compounds originated by lung cancer cells in vitro (approximately a quarter common to both matrices) is currently not sufficient for in vitro culture to be suitable approach for determining VOCs in exhaled breath.

These observations were attributed to this fact that, cell cultivation is conducted in a hyperoxic conditions (atmospheric oxygen concentration), which it can be regarded as a major limitation of the in vitro studies. It has been revealed that tumours grow in oxygen depleted (hypoxic) or in absence of oxygen (anoxic) conditions which is different with normal tissues.[88] Cellular oxidative stress causes to the generation of various VOCs by cells compared with hyperoxic conditions for cell culture. Studies comparing the patterns of VOCs present in the HS of cells cultured in hyperoxic and hypoxic conditions are needed to address this potential limitation of in vitro approach. The poor correlation between in vivo and in vitro studies may also arise from exogenous VOCs being included in the predictive models of cancer,[89] different extraction and detection techniques used in different studies, different experimental design, and in general a relatively lower number of in vitro studies performed to date, in comparison to the VOC studies of breath samples and biofluids.

Targeted analysis of VOCs

Another approach to solving the uncertainty of the sources of proposed VOC biomarkers focuses on the detection of hydrocarbons,[90,91] or aldehydes,[92] as biomarkers of cancer. Studies revealed that one of the main reasons of developing cancer is oxidative stress via the overproduction of reactive nitrogen species and oxygen species leading to mutations.[93] Some aldehydes are assigned to oxidative stress, which they are products of lipid peroxidation, however, the exact mechanism of their presence in body fluids and breath is not known.[94] The same mechanism underlies the emission of saturated hydrocarbons in the body.

Extraction of VOCs

Solid phase microextraction and purge and trap (PT) are the two efficient extraction techniques widely applied up to date for the extraction of VOCs as potential cancer biomarkers in both in vivo and in vitro researches. In PT which is also known as dynamic headspace extraction, an inert gas is purged into the sample matrix and the gas sample is passed through the sorbent trap and the VOCs are adsorbed on the surface of the sorbent. Afterward, the loaded analytes onto the sorbent are thermally desorbed applying an online thermal desorption device or eluted by the aid of small amounts of organic solvents. Sorbent traps are adsorbent materials packed into a small tube. The most commonly employed adsorbents for determination of VOCs are porous polymer (e.g., Tenax) or charcoal (e.g., Carbotrap) as a trapping material with varying degrees of selectivity.

Solid phase microextraction

SPME was first used in 1989 to analyze water samples by Janusz Pawliszyn.[95] SPME is a sample preparation technique, which is a flexible extraction method suitable for a variety of sample matrices.[96,97] SPME allows one to easily isolate/concentrate the desired analytics before quantification by introducing analytes to an appropriate analytical instrument. This method can be used for almost of organic compounds.[98,99] SPME is an incomplete equilibrium extraction technique because it removes only a small part of the target compound from the sample. During extraction, the sample molecules are distributed between the matrix, the main space and the stationary phase (in the case of a solid sample), or between the sample and the stationary phase (liquid and gas samples) as a result of adsorption and/or absorption on the fiber, depending on the fiber coating.[100,101] With sufficiently long extraction times, an equilibrium concentration of analyte is established between two or three phases.[101] The equilibrium time depends on the type of analyte and extraction conditions, ranging from a few minutes to a few hours.[102] The analyte distribution between the three phases (or two phases in the case of gas and liquid samples) depends on the analyte affinity for each of these phases.[103] After the defined extraction period, a sample of SPME fiber is inserted into a hot injector port in gas chromatography (GC) systems and into the suitable interface disposal chamber in the case of high-performance liquid chromatography (HPLC). SPME coupling with gas chromatography-mass spectrometry (GC-MS) is shown in Figure 1. SPME is widely used because of its advantages such as increased sensitivity and reduced transport and sample losses compared to solid phase extraction and liquid-liquid extraction. However, one of the biggest drawbacks of SPME is that breaking and tearing coatings and bending fibers can significantly reduce their overall lifespan is fiber instability.[104] Even if we change the headspace extraction (HS) to direct immersion (DI), it is still an important problem to consider. There are three SPME extraction modes: DI, HS, and membrane protected mode in which the fiber is introduced directly into the sample and into the air above the sample, and for dirty samples respectively. Some applications of SMPE for identification of a number of VOCs as biomarkers of various diseases in the human body are presented in Table 3.

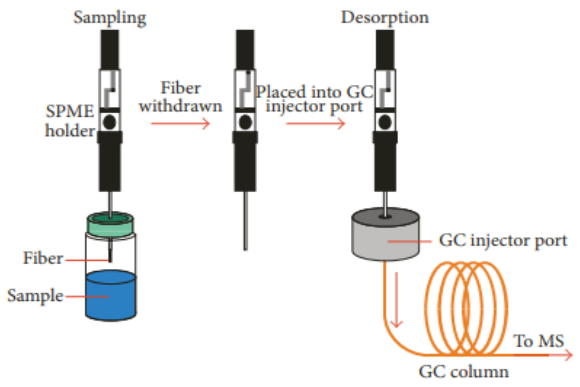

Figure 1. Diagram of analysis with head-space solid phase microextraction-gas chromatography-mass spectrometry (SPME-GC-MS).

Application of SPME for cancer diagnosis

SPME has been widely applied for determination of VOCs profile in different biological samples, due to its significant advantages as follows: SPME is a single step sample preparation method, without needing to time-consuming and laborious manipulation of analytical sample; it possesses fast and simple operation and can be easily coupled to analytical instruments such as GC and high-performance liquid chromatography (HPLC). Additionally, SPME is a non-exhaustive and equilibrium-based extraction technique, leading to no considerable change in chemical composition of the samples, creating the possibility of its application for extraction of various target compounds from living organism during in vivo studies. Up to now, SPME has been employed as an effectual tool for VOCs collection concerning different biological samples, in order to diagnose various kind of cancer.

Lung cancer detection

Lung cancer is one of the most common causes of cancer deaths worldwide, reaching 1.37 million deaths in 2008. Early diagnosis is associated with far better survival (67% 5-year survival rate) than later stage disease (23% 5-year survival rate).[126] Concerning lung cancer, Phillips et al described 22 VOCs including alkanes, alkane derivatives and benzene derivatives, showing significant differences between patients and healthy peoples.[127] According to the results of another cross-sectional study applying GC–MS, nine VOCs containing again alkanes and alkane derivatives were introduced as the best set of markers of lung cancer.[128] Studies show that to identify VOCs as possible biomarkers in lung cancer tissues, SPME combined with GC-MS followed by multivariate data analysis was used. In this study, lung tissue analysis of healthy and carcinogenic patients was successfully performed.[129] The fiber used in this analysis is polydimethylsiloxane-carboxen-divinylbenzene (PDMS/CAR/DVB). Lung tissue sampling was carried out by exposing the SPME fiber in the headspace of a 2 mL vial containing 150 mg of healthy or diseased tissue at 37°C. After 60 min, VOCs thermal desorption was conducted into the GC injector for 2 minutes at 250°C. The volatiles identified in this study are both endogenous and exogenous compounds. The obtained chromatographic data were studied by multivariate data analysis by performing principal component analysis (PCA) and linear discriminant analysis (LDA). Statistical analysis was conducted on the data set without distinction among the different types of cancer, between male and female or between smoking and no smoking people.

In another study, Thriumani et al used the HS-SPME

Table 3. SPME method in analysis of VOCs as potential biomarkers of cancer

Cancer type	Biomarker	Analyzed matrix	Analytical technique	Ref
Bladder	2,3-Butanedione; 2-Butanone;2-Pentanone; 2-Propanol; e.g.,	Urine	SPME-GC–MS	105
Lymphoma	2,6-Dimethyl-7-octen-2-ol; 2-Methylbutanal	Urine	SPME-GC–MS	106
Prostate	2,5-Dimethylbenzaldehyde; Phenylpropionaldehyde; 4-Methylhexan-3-one	Urine	SPME-GC–MS	107
Renal Cell Carcinoma	2-Oxopropanal;2,5,8-Trimethyl-1,2,3,4-tetrahydronaphthalene-1-o.	Urine	SPME-GC–MS	108
Head and Neck	2-Methyl-5-(methylthio) furan; 2-Methylbutanal; 2-Methyl-butyric acid	Urine	SPME-GC–MS	109
Lung	Not reported	Urine	HS-PTV-MS	110
Breast	2-Methyl-3-phenyl-2-propenal;3-Methyl-thiophene		SPME-GC–MS	111
Breast	1,4-Dimethylpent-2-enylbenzene;1-4-Hydroxy-3,5-di-tert-butylphenyl-2- methyl-3-morpholinopropan-1-one	Urine	SPME-GC–MS	112
Renal Cell Carcinoma	1,6 Dioxacyclododecane 7,12 dione; 1 bromo 1 (3 methyl 1 pentenylidene) 2,2,3,3 tetramethyl-cyclopropane	Urine	SPME-GC-MS	113
Colorectal	2,4- dimethylhept-1-ene, 1-pentene,2,4,4-trimethyl, Octane, 3,5-dimethyl, Nonane, 4-ethyl-5-methyl	Urine	SPME-GC × GC-MS	114
Colorectal	Toluene, ethylbenzene, benzaldehyde, octanal, benzoic acid, dodecane, tetradecane	Tissues	HS-SPME-GC/MS-SIM DI-SPME-GC/MS-SIM	115
Breast	5-Octen-1-ol, benzeneacetaldehyde, benzaldehyde, Hexadecane, tiophene, 2-pentyl	Urine	SPME-GC-MS- QTOF	116
Lung	Decane, Ethylbenzene, Propylbenzene, 1-Ethyl-2-methylbenzene, Styrene, Dodecane, Cyclohexanol	Cultured cells	SPME-GC-MS	117
Lung	Aldehydes	Exhaled breath	SPME–GC-MS	118
Renal cell carcinoma	-	Urine	HS-SPME-GC-IT-MS	119
Colorectal	phenyl methylcarbamate, ethylhexanol, and 6-t-butyl-2,2,9,9-tetramethyl-3,5-decadien-7-yne.	Blood	SPME-GC-MS-EI	120
Skin	Untargeted	Tissue	SPME-GC-MS	121
Lung	Methyl alcohol, Acetonitrile, Cyclopentane, Hexane	Breath	SPME-GC-TOF-MS	122
liver	Hexanal, 1-octen-3-ol, octane	blood	HS-SPME-GC-MS	123
Prostate	Untargeted	Urine	HS-SPME-GC-MS	124
bladder	2-pentadecanone, dodecanal, γ-dodecalactone	Tissue	HS-SPME-GC–MS	125

method and the DVB/CAR/PDMS fiber for extraction of VOCs which emitted by in vitro cultured human cells and compared with VOCs that documented as biomarker of lung cancer. In sampling, SPME coated needle exposed to headspace of cultured cell.[130] On-fiber-derived SPME sampling with GC/MS analysis has been reported to be used to measure direct C3-C9 aldehydes on exhalation to diagnose patients with non-small cell lung cancer (NSCLC). SPME combines sample extraction, concentration, and improved aldehyde stability with many advantages over conventional respiratory sampling methods.[118] The aldehydes were extracted using a 65 µm PDMS/DVB fiber.

To detect lung cancer, a study has been reported by Allafchian et al.[131] In this work, a new Au NP-thiol silane-based SPME fiber was prepared and quantitatively coupled with ion mobility spectroscopy (IMS) for the analysis of acetone, acetaldehyde and acetonitrile. IMS systems are mobile and cheaper and do not require a pre-focus process. This technique is based on ion separation based on gas phase mobility. IMS is especially used in the separation of isomers and its sensitivity is very high in the ppm rang. These compounds have been selected from many of the materials reported in the literature to diagnose lung cancer.

The detection rate of VOCs by ion mobility spectroscopy is ten-fold higher than other methods of respiratory analysis. By pairing the IMS with a multi-capillary column as a pre-separation unit, IMS offers the advantage of instant double separation of VOCs by visualization in a three-dimensional chromatogram. In a study by Westhoff et al, IMS was used to detect VOCs in the expiratory respiration of patients with lung cancer.[132] Isomer separation is useful by IMS, but one of its disadvantages is impossibility of identification of the isomeric compounds by IMS, and it is also not suitable for real-time measurement. For more information on VOCs, IMS is often paired with GC-MS.[133] GC-MS is often used to analysis of expiratory breath samples. However, separation of VOCs with this method may not be efficient enough for complex respiratory samples, even with long narrow capillaries. To improve the separation efficiency, comprehensive two-dimensional gas chromatography (GC × GC) has been developed. In GC × GC, two capillary columns are used which have different separation mechanisms and are connected to each other through a modulator. The eluted sections of the first capillary column were injected rapidly with high repetition into the second column. The separation obtained in the first column is maintained and the separation in the second column is very fast. The advantages of the GC ×

GC method are the increase in peak capacity and peak resolution compared to a conventional GC column. It has been reported that in 2014, Ma et al have developed an analytical method using the SPME technique in combination with GC × GC-flame ionization detector (FID) for preconcentration and identification of VOCs. They successfully have used this method for analysis of human exhalation and determination of biomarkers such as propanol, acetone and methanol, indicating lung cancer.[134] The collection of VOCs has been performed using the manual SPME holder and commercial SPME fiber assemblies 100 μm PDMS and 65 μm PDMS/DVB.

According to a paper published by Bajtarevic et al analysis of expiratory breath to detection of lung cancer has been performed using two methods: proton transfer reaction-mass spectrometry (PTR-MS) and SPME-GC-MS, and examined the advantages and disadvantages of both methods. It was found that PTR-MS, compared to SPME-GC-MS, does not require preconcentration and is relatively more sensitive, providing slightly more reliable results and saving time. PTR-MS is easier to manage and the number of samples reviewed by PTR-MS is much larger than GC-MS, making PTR-MS attractive and valuable. Disadvantages of the PTR-MS method include the lack of clinical estimation information and cancer diagnosis due to the lack of accurate identification of VOCs as well as the GC-MS technique. Therefore, it was suggested that PTR-MS and SPME-GC-MS are complementary to acquire more accurate, sensitive and reliable results.[135] Given the benefits of this method, in 2007 Wehinger et al have used PTR-MS to diagnose primary lung cancer by analyzing VOCs in exhaled samples and found two potentially new biomarkers for the best distinction between those with primary lung cancer and healthy individuals.[136] In other reports regarding detection of lung cancer, on-fiber-derived SPME sampling with GC-MS analysis has been reported to be used to measure direct C3-C9 aldehydes on exhalation to diagnose patients with NSCLC.

Bladder cancer detection

Bladder cancer is the 4th most common cancer among men and 13th in women. The incidence in males is about three times that in females. To investigate bladder cancer, the specific VOCs corresponded to bladder cancer may be present in the urine headspace and may be a diagnostic criterion for this particular cancer. Cauchi et al have used a non-invasive diagnostic method such as SPME-GC-MS to detect compounds such as 2,3-butanedione, 2-butanone, 2-pentanone.[105] The results revealed that bladder cancer patients have a distinct urinary volatile profile characterized by higher levels of several alkanes and aromatic compounds, and lower levels of aldehydes, ketones and monoterpenes. In order to evaluate the performance of detection method of bladder cancer, seventeen significantly altered volatiles were used, leading to 70% of sensitivity, 89% of specificity and 80% of accuracy. In another relevant research a cross-sectional study has been performed to compare the urinary VOC profiles of patients with and without bladder cancer, to obtain reliable metabolomic signatures for application as significant diagnostic and surveillance biomarkers.[137] A 50-μm-DVB-30-μm-CAR-PDMS SPME fiber was employed for sampling from the headspace of collected urine samples. It was noted that, the applied SPME fiber maximizes the number and diversity of VOCs extracted from the headspace of urinary samples, while it minimizes interfering of contaminant degradation products.

Detection of breast cancer

Breast cancer is the most common type of cancer in women, after skin cancer. Worldwide, more than 1 million women are diagnosed with breast cancer each year. It was found by Hietanen et al that, pentane concentration is increased in breath of women with breast cancer.[138] Pentane is a volatile biomarker of oxidative stress produced by lipid peroxidation of unsaturated fatty acids in cell membranes.[139] Also it was revealed by this group that, breath analysis through multivariate models containing five VOCs can accurately predict the presence or absence of breast cancer.[140]

In 2021, a study by Jiang et al have been reported.[141] In this work, hollow zeolitic imidazolate framework-7 (ZIF-7) was prepared by etching ZIF-7 with tannic acid, and then it was applied to fabrication of hollow ZIF-7 coated stainless steel fiber. The home-made SPME fiber has been successfully used for SPME followed by GC-FID to identify five biomarkers in headspace gas of human breast cancer cell lines and normal breast cell lines, in vitro. The studied VOCs in this work included isopropanol, hexanol, hexanal, acetone and decanal. SPME procedure was performed by exposing the hollow ZIF-7 coated fiber to the headspace gas of MDA-MB-231 and CCD-1095Sk cell lines in a cell culture flask with 4 mL Dulbecco's Modified Eagle Medium (DMEM) medium at 37°C. Then the fiber immediately inserted into the GC injection port at 240°C for 3 minutes for thermal desorption of extracted VOCs.

Detection of colorectal cancer

The third most common malignancy in the world is colorectal cancer. Colorectal cancer is the major cause of death relating to cancer in Europe. Early detection of colorectal cancer is vital to increase survival of patients, and exhalation analysis is a non-invasive tool for obtaining information about cancer-related changes in patients' breath regarding the concentration of VOCs. In this regard, a research by De Vietro et al has been reported,[115] in which SPME in combination with GC-MS method has been applied to determine seven selected VOCs selected from the colonic mucosa of patients with colorectal cancer, including benzaldehyde, benzoic acid, dodecane, ethylbenzene, octanal, toluene, by both head space sampling and direct immersion mode. Different SPME fibers were applied including 60 μm polyethylene glycol (PEG), 7 μm PDMS, 75 μm CAR/PDMS, 50/30 μm CAR/

DVB/PDMS, 65 µm PDMS/DVB and 85 µm polyacrylate (PA), have been used. According to the obtained results the bipolar fibers CAR/PDMS and CAR/DVB/PDMS have exhibited more extraction capability toward all the selected targets compounds.

The analysis of blood VOCs appears to have potential clinical applications for colorectal cancer screening. According to a research reported by Wang et al, SPME followed by GC-MS analytical method has been applied to analysis of VOCs as colorectal cancer biomarker in headspace of blood samples.[120] VOCs are released into the bloodstream before they are exhaled; therefore, the analysis of VOCs in blood will provide more accurate results than the analysis of VOCs in exhaled breath, considering this fact that, the composition of exhaled breath is affected by many factors, such as smoking, lung disease, and diet. In this study, blood samples were collected from 16 patients with colorectal cancer and 20 healthy controls. A 75 µm CAR/PDMS fiber has been applied in this work. For extraction of VOCs, SPME fiber was inserted into the vial and exposed to the headspace of a 2 mL blood sample for 20 minutes at 40°C. Afterward, the thermal desorption of VOCs has been performed in a GC injection port at 200°C for 2 minutes. The statistical methods including partial least-squares discriminant analysis and principal component analysis were performed to deal with the final dates. Three metabolic biomarkers including ethylhexanol, phenyl methylcarbamate, and 6-t-butyl-2,2,9,9-tetramethyl-3,5-decadien-7-yne were found at significantly lower levels in the group of colorectal cancer patients than in the healthy control group ($P < 0.01$). Additionally, significantly higher concentration of 1,1,4,4-tetramethyl-2,5-dimethylene-cyclohexane were resulted in the group of colorectal adenocarcinoma patients in comparison to the normal control group ($P < 0.05$). Compared with healthy individuals, colorectal cancer patients exhibited a distinct blood metabolic profile regarding VOCs.

Detection of gastric cancer

Gastric cancer is the fourth most common cancer in the world and it is the second cause of cancer-related death in worldwide. It remains very difficult to cure effectively, primarily because most patients present with advanced diseases. Therefore, how to find early gastric cancer cells is a great challenge for early diagnosis and therapy of patients with gastric cancer. Gastric cancer shows a lack of specific symptoms in its early stages. In addition, its clinical symptoms often do not match the corresponding stage.

The presence of some VOCs in the breathing of patients with gastric cancer has been reported by a number of research groups. It was found that, which VOCs are associated with gastric cancer. In a study published in 2018 by Mochalski et al,[142] headspace needle trap extraction (HS-NTE) as a preconcentration technique combined with GC-MS detection to identify and quantify VOCs released by gastric cancer and samples of non-cancerous tissue samples, collected from 41 patients during surgery. HS-NTE was employed to preconcentrate VOCs released by tissue samples. Two-bed 23-gauge Silcosteel-treated stainless steel needle trap device (2 cm Carbopack X and 1 cm Carboxen 1000, both 60/80 mesh) were used to trap the VOCs released by the tissue samples.

In other approach, HS-SPME sample preparation technique (applying commercial 75 µm CAR/PDMS coating) has been combined with a novel electrochemical biosensor for determination of volatile biomarkers of gastric cancer, possessing great potential in early diagnosis and the prognosis of gastric cancer in near future.[143] The identification of VOCs emitted from the headspace of the cells/medium culture was performed employing GC-MS. The Au-Ag nanoparticles-coated multi-walled carbon nanotubes were prepared as a sensing interface for detection of volatile biomarkers. According to the results, eight different VOCs were screened out between MGC-803 cells and GES-1 cells. Three compounds including nonanol, 4-butoxy 1-butanol, and 4-isopropoxybutanol, were present in the headspace of both the MGC-803 cells and the GES-1 cells, owning markedly higher concentrations in the headspace of the GES-1 cells compared with MGC-803 cells. Two volatiles such as butanone and 3-octanone were significantly detected in the headspace of the MGC-803 cells. Formic acid propyl ester, 2, 6, 11-trimethyl dodecane, and 1.4-butanediol were solely present in the GES-1 cells headspace.

In other research, for detection of gastric cancer, VOCs concentration profile was studied applying the collected expired air from patients with gastric cancer, chronic atrophic gastritis as well as from healthy peoples.[144] SPME-GC-MS and PCA statistics were applied to identify potential biomarkers of gastric cancer among VOCs. In order to extract the coexisted VOCs in expired air samples, a manual SPME holder with 75 µm CAR/PDMS fiber was inserted into the vials and exposed to the gaseous samples.

Liver cancer detection

Liver cancer is the most common fatal malignancy. It ranks fifth in the United States. Patients are often diagnosed with advanced liver cancer, which leads to poor treatment. For diagnosis of liver cancer, a research has been reported by Xue et al,[123] applying SPME followed by GC-MS detection for the determination of volatile biomarkers. In this work human blood was subjected to the analysis of VOCs. Based on the results, 47 VOCs have been detected in the headspace of blood samples, that 19 volatile compounds among of them have different levels in the liver cancer group (n = 19) and the normal group (n = 18), with statistical significance ($P < 0.05$, chi-squared test). Three volatile compounds among the 19 compounds, including 1-octen-3-ol, hexanal, and octane have been suggested as biomarkers of liver cancer with clinical diagnostic value.

Conclusion

Analysis of VOCs is a field of research in which several studies have been performed to detect, identify and quantify VOCs as reliable biomarker of different kind of cancer. According to the results reported in literature, VOCs concentration profile measured in various biological samples including expiratory breath, blood, feces, and urine are different in comparison of those of healthy control group. On the other hand, it was found that each kind of cancer has specific reliable biomarker considering different biological samples. Determination of VOC concentration in urine has been used as biomarkers of diseases such as colorectal cancer, bladder cancer and prostate cancer. Changes in the level of some metabolites in exhalation may be warning signs of diseases such as lung cancer. Therefore, diagnosing these changes is useful for diagnosing, screening, and determining the biological pathways of these diseases. SPME exhibited high accuracy, avoiding any uncertainty originated by sample evaporation losses during collection, handling, and storage. Accordingly, SPME method, which is a non-invasive and human-friendly sampling method can be coupled with highly sensitive analytical techniques such as spectroscopy and gas chromatography with mass spectrometry detection to identify and quantify VOCs, leading to accurate analysis of these compounds in all biological samples.

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Conflict of Interest

The authors certify that there is no potential conflict of interest in relation to this article.

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