Volatile Organic Compounds as Biomarkers: Innovations in Cancer Biosensors for Early Diagnosis

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Abstract

Timely cancer detection is crucial for improved survival rates and enhanced treatment efficacy. Volatile organic compounds (VOCs) have attracted much attention as potential biomarkers for cancer diagnosis because of their distinctive patterns linked to metabolic abnormalities in cancer cells. This review aims to examine advanced biosensor technologies that utilize VOCs for early cancer detection. This research seeks to elucidate the transformative potential of VOC biosensors in cancer therapy by analysing existing advancements, significant challenges, and anticipated advancement in the domain.

Keywords: Volatile Organic Compounds (VOCs), Cancer Biomarkers, Biosensors, AI Assisted Cancer Detection.
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Introduction

Cancer profoundly affects worldwide mortality statistics [1]. Despite breakthroughs in therapeutic procedures, a delayed diagnosis diminishes the probability of successful treatment. Imaging and tissue biopsies are recognized diagnostic techniques that are challenging, invasive, and frequently exhibit sensitivity limitations. As a result, there is an increasing demand for non-invasive, quick, and accurate diagnostic methods. Cells produce low-molecular-weight substances known as volatile organic compounds as standard metabolic byproducts. Malignant cells generate distinctive profiles of volatile organic molecules due to altered metabolic activities [2]. Blood, urine, and exhaled air may include non-invasive biomarkers known as volatile organic compounds (VOCs) [3]. VOCs must be discovered and quantified to utilise advanced biosensors for improving cancer diagnosis.

The Role of VOCs in Cancer Diagnosis

1. Metabolic Basis of VOCs

The process of metabolic reprogramming is an essential one that permits cancer cells to survive apoptosis and grow at a high rate [4]. The generation of VOC is the result of a reprogramming process that involves changes in oxidative stress, lipid metabolism, and enzyme activity [5]. This mechanism produces volatile organic molecules on purpose and is essential for the creation of chemical compounds that have a high degree of volatility. It has been found that ketones, aldehydes, and alkanes can be found in breath samples that have been collected from individuals who are afflicted with gastrointestinal, lung, and breast cancers [6].

2. Sources and Sampling of VOCs

Exhaled breath is non-invasive and easy to collect, making it a diagnostic tool. Endogenous VOCs from cellular metabolism and environmental chemicals are exhaled. Thermal desorption and gas chromatography-mass spectrometry (GC-MS) detect cancer-related VOCs [6]. The speed and precision of selected ion flow tube mass spectrometry (SIFT-MS) enable real-time monitoring and early detection [7]. Metabolic reprogramming and equilibrium require blood and serum [4]. The circulation contains volatile organic molecules from systemic and local metabolism [8]. Blood is more dependable than breath. VOCs are sensitively detected by Proton-transfer-reaction mass spectrometry (PTR-MS) and GC-MS [9]. Metabolic alterations linked to cancer progression can also be shown by the local and systemic urine metabolism alterations. Both

GC-MS and Solid Phase Micro Extraction (SPME) can detect cancer-related biochemical markers in urine's volatile organic molecules [10]. Urine can be considered as a good candidate for the long-term study because to its stability.

Biosensor Technologies for VOC Detection

Using VOCs to diagnose cancer is vital in modern medicine. The reason for this is the numerous advantages that this technology provides to its consumers. Testing vapor or skin samples for volatile organic compound (VOC) concentrations is a non-invasive alternative to biopsies [11]. Recognizing cancer-associated volatile organic compound patterns simplifies the early detection. In addition, it increases the likelihood of effective treatment and patient survival. Compared to complicated and time-consuming medical examinations, screening of volatile organic molecules is more cost-effective and adaptable. VOC recognition is a major advantage which could improve cancer prognoses and transform cancer diagnosis. Table 1 and gives a brief list of endogenous VOCs identified as various cancer biomarkers and Table 2 consolidates the comparison of various aspects of currently available biosensing technologies.

Table1: Brief list of various cancer marker VOCs

Cancer types	VOCs identified	References
Lung Cancer	Benzene, Toluene, Ethylbenzene, Xylene, Naphthalene, Styrene	[1,2]
Breast Cancer	Hexanal, Heptanal, Nonanal, Benzaldehyde, Limonene	[3,4]
Colorectal Cancer	1- octane, 2-butanone, Hexanoic acid, Indole	[5,6]
Prostate Cancer	Acetone, Isoprene, 2-octanol, Hexanal, Heptanal	[7,8]
Gastric Cancer	Ethanol, 2-propanol, 2-butanone, Ethyl acetate, Dimethyl sulfide	[9,10]
Ovarian Cancer	Ethylbenzene, Benzene, Octanal, Decanal, Nonanal	[11,12]
Liver Cancer	Dimethyl disulphide, Ethylbenzene, Hexanal, Heptane	[13–15]
Esophageal Cancer	Acetone, Ethanol, 2-propanol, Benzaldehyde	[1,16]
Pancreatic Cancer	Ethyl formate, Acetone, Isoprene, Toluene	[17,18]

Table 2: Comparison table of different biosensing technologies

Biosensing Technology	Sensitivity	Specificity	Feasibility	Reference
Electronic Noses (e-Noses)	High sensitivity for detecting a wide range of VOCs, but limited by the low concentration of VOCs in complex biological samples.	Moderate specificity, prone to cross-reactivity, which may lead to false positives /negatives due to broader detection range.	Low-cost, portable, and suitable for point-of-care applications, but may lack high accuracy.	[19, 20]
Gas Chromatography-Mass Spectrometry (GC-MS)	Excellent sensitivity, considered the gold standard for precise VOC analysis with high accuracy.	High specificity, able to distinguish VOCs with very fine differences.	Low feasibility due to its complex setup, expensive instrumentation, and time-consuming procedures.	[21, 22]
Colorimetric Sensors	Moderate sensitivity, with the	Moderate specificit	High feasibility,	[23, 24]

	ability to detect VOCs through color change. May be less sensitive than other methods.	y, often lacks the ability to distinguish between closely related VOCs.	low-cost, easy-to-use, portable, and ideal for screening in low-resource settings.	
Field-Effect Transistor (FET)-based Sensors	High sensitivity, especially when functionalized with specific receptors for targeted VOCs.	Very high specificity due to selective receptor binding to specific cancer-related VOCs.	High feasibility for portable, real-time detection, but requires customization and precision in sensor design.	[25, 26]
Optical Biosensors	Moderate to high sensitivity, depending on the system design and application.	High specificity, can be designed for selective VOC detection, though some cross-reactivity may occur.	Feasible for portable use, but requires complex instrumentation, limiting its clinical accessibility.	[27]
Surface Plasmon Resonance (SPR)	Very high sensitivity due to real-time detection of refractive index changes, ideal for detecting low concentrations.	High specificity, as SPR can detect specific interactions between VOCs and receptors. However, it can be limited by receptor availability.	Moderate feasibility; requires specialized equipment and laboratory setup, limiting its widespread use.	[28, 29]

1. Biosensors Enhanced by Nanotechnology

The electrochemical biosensor is one of the most commonly employed devices for detecting volatile organic molecules. The operation of these sensors is accomplished by allowing volatile organic compounds (VOCs) to interact with a receptor, which then results in the formation of an electrical signal that can be measured. This process is repeated until the desired outcomes are achieved. It has been demonstrated that nanomaterial electrodes, which have been the focus of recent technical advancements, can improve both the sensitivity and selectivity of an electrical signal. Zhang et al. identified VOCs specific to gastric cancer cells, such as 3-octanone and butanone, using GC-MS. An electrochemical biosensor based on Au-Ag nanoparticle-coated MWCNTs demonstrated ultrasensitive detection of these biomarkers, with detection limits as low as 0.3 ppb for 3-octanone, indicating potential for early gastric cancer diagnosis [30]. The study done by Nazir et al. identified phenol 2,2 methylene bis [6-(1,1-dimethyl ethyl)-4-methyl] (MBMBP) as a significant volatile biomarker in the breath of hepatocellular carcinoma (HCC) patients, with a minimum concentration of 2100 ppm. A hexane thiol-AuNPs modified biosensor demonstrated ultrasensitive electrochemical detection of MBMBP with a limit of detection of 0.005 mol/L, confirmed its potential for early HCC diagnosis [31]. The review by Kaya etal. highlighted in the nanomaterial-based electrochemical biosensors for the sensitive and non-invasive detection of lung and colon cancer biomarkers to enable early diagnosis and treatment. Optical biosensors can detect VOC binding by observing changes in light characteristics. The detection of cancer-associated VOCs has considerable sensitivity via methods such as surface plasmon resonance (SPR) and fluorescence-based detection [32–34].

Nanotechnology has transformed biosensor design by enhancing detection limits and facilitating downsizing [35].

Figure 1 depicts Schematic representation of the SPR-based olfactory biosensor for VOC detection [36].

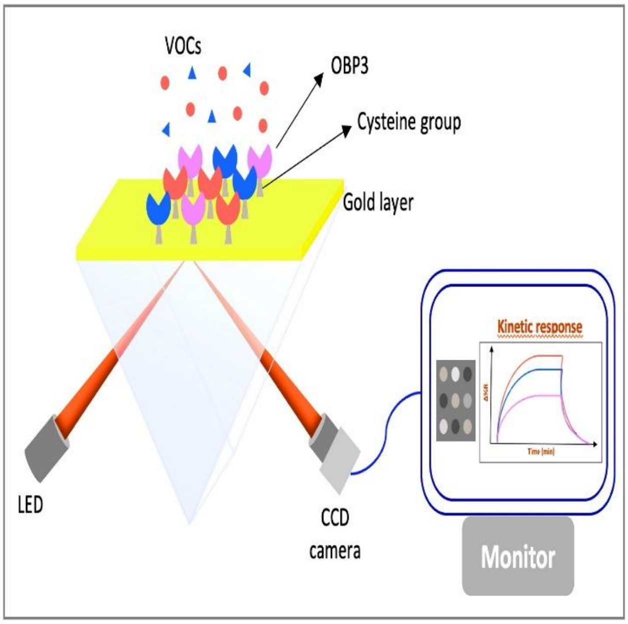

Figure 1: Schematic representation of the SPR-based olfactory biosensor for VOC detection [36].

Carbon nanotubes and quantum dots have been integrated into biosensors for the detection of VOCs at exceptionally low concentrations [37–41]. Shehada etal. developed a silicon nanowire field-effect transistor sensor capable of selectively detecting gastric cancer-related VOCs in exhaled breath while discriminating against unrelated environmental VOCs. Blind analysis of patient samples demonstrated >85% accuracy in distinguishing gastric cancer from controls, showcasing its potential for non-invasive, portable, and cost-effective cancer diagnosis [42].

2. Biosensors and Artificial Intelligence (AI)

Figure 2 schematically illustrate various medical applications of wearable biosensor design [43].

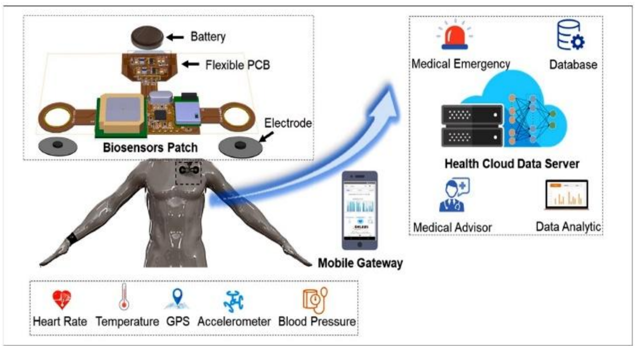

Figure 2: Schematic illustration of various medical applications of wearable biosensors [43].

The utilization of AI algorithms improves the detection of volatile organic compound patterns, hence enabling biosensors to distinguish between healthy and malignant profiles. Studies indicate that machine learning models developed using VOC datasets demonstrate considerable efficacy in precisely predicting cancer kinds. Einoch Amor etal. introduced an AI-driven nanoarray for liquid biopsy, detecting VOC patterns in blood headspace for early cancer detection and staging. The nanoarray demonstrated >84% accuracy for early detection and >97% accuracy for metastasis detection in breast, ovarian, and pancreatic cancer models, validated by mass spectrometry [44]. The study done by Johnson et al demonstrated that a DNA-decorated single-walled carbon nanotube vapor sensor array can distinguish volatile organic compound (VOC) patterns in plasma samples, achieving 95% accuracy for ovarian cancer and 90% for pancreatic cancer. The nano sensor successfully identified VOCs from early-stage cancers from the algorithm, offering a promising high-throughput diagnostic tool for these malignancies [45].

Innovations in VOC-Based Cancer Biosensors-Hybrid sensing platform, Wearable Biometric detectors, and POC devices

Many sensing modalities combined together have improved diagnostic dependability by themselves. Combining optical and electrochemical sensors has generated instruments capable of detecting a larger spectrum of VOCs [46–48]. Among popular wearable gadgets that offer continuous monitoring of VOCs can give their real-time data,and these devices are highly useful for high-risk groups specifically. Portable, user-friendly point-of- care (POC) biosensors have revolutionised cancer diagnosis [49]. Figure 3 schematically illustrates the smart phone assisted biosensors in healthcare [50].

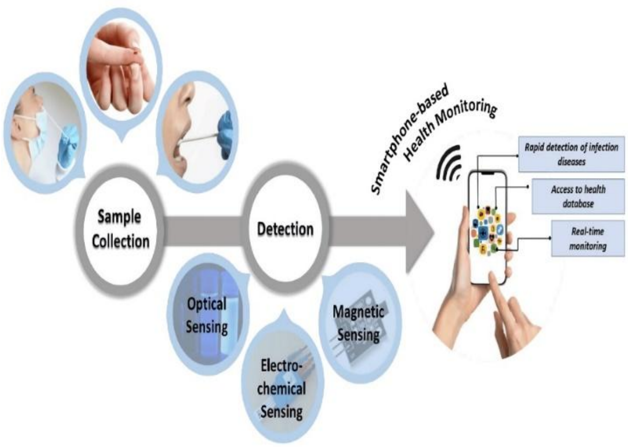

Figure 3: Schematic illustration of a POC biosensor [50]

Laboratory-level precision VOC analysis smartphone-integrated devices are among recent advances. Salimi etal. developed a smartphone-based ZnO nanosheet chemiresistive gas sensor capable of highly sensitive detection of lung cancer biomarkers such as diethyl ketone, acetone, and isopropanol in exhaled breath [51].

Challenges and future scope

Prior to VOC detection being utilised for cancer diagnosis, certain concerns need to be addressed. Standardising VOC detection is challenging. The variability in volatile organic component profiles among cancer types, biological factors, and sampling techniques makes data collection a challenging task. The issue is resolved by standardising the collection, processing, and measurement of volatile organic compounds. By standardising procedures and merging databases for VOC profiles specific to cancer, laboratories may be able to detect VOCs in the same way.

There is a possibility of false positives due to VOC interference with cancer-related VOC signals. A combination of pre-concentration and selective filtration can improve the detection of VOCs specific to cancer by reducing background interference. Developing sensors that can distinguish between environmental pollutants and volatile organic compounds (VOCs) associated with cancer, or employing sophisticated statistical or machine learning techniques to identify VOC trends, would increase our confidence in the findings. There are limitations on the clinical usage of biosensors for volatile organic molecules. Qualitative, precise, and safe products must be approved by the FDA or EMA. Development and approval can be accelerated through pre-development coordination with government entities. Thorough clinical trials demonstrating the advantages of these devices and diagnostic biosensor guidelines are necessary to resolve these challenges.

As a result of individual and environmental factors, VOC detection findings might not be repeatable using these methods. Testing and other quality control measures aid in maintaining sensor performance. Accuracy and consistency in training are guaranteed by sensor drift monitoring and correction software. Because of their sensitivity, cancer-specific volatile organic compounds (VOCs) could go undetected in biological samples. Using signal amplification or nanomaterials, biomarkers at low concentrations can be sensitively detected. Thanks to multi-modal detection, VOCs associated with cancer may be more easily located. Combining GC-MS with SPR or electronic eyes is possible.

The high price and limited availability of GC-MS make it an impractical and unproductive tool. To put a stop to this, we urgently need portable biosensing devices for point-of-care diagnostics that are both affordable and easy to transport. In locations with limited resources, these technologies could potentially become more affordable as production ramps up utilising less expensive materials. Vapour concentration monitor data is massive and difficult to evaluate. Complex VOC trends could be explained by advanced data analysis methods such as machine learning. Through the use of straightforward software, we can assist physicians in analysing data pertaining to volatile organic compounds (VOCs) and improving diagnostics by linking VOC results to imaging or biopsies.

The accuracy, reliability, and usefulness of clinical VOC-based cancer biosensors can be enhanced by avoiding or resolving these issues. Lack of approved methods for VOC collecting, storage, and analysis results in discrepancies in sample preparation that compromise diagnostic accuracy and complicate cancer diagnosis. Ambient VOCs can interfere with cancer signals, therefore complicating the biomarker's detection. Increasing sensor sensitivity will enable one to differentiate cancer-associated VOCs from ambient interference and hence address this issue. Personal medical information revealed by VOC-based diagnostics could expose privacy concerns and genetic material exploitation questions. Well-built legal frameworks guard patient records, provide informed permission, and aid to lower diagnostic bias [52]. Future VOC-based diagnostics will classify many cancer types from a single sample, hence enhancing efficiency and screening capability. For patients residing in rural areas especially, telemedicine technology with remote analysis and at-home sample collecting could increase access. Customized metabolic profile testing can help to increase the accuracy and usefulness of the operation for several patient populations by increasing sensitivity and specificity. These technologies have enormous potential; but, for full manifestation they need research, standardizing, and ethical considerations.

Conclusion

Volatile organic compounds (VOCs) present a potential avenue for non-invasive cancer diagnostics, as biosensors facilitate rapid and precise detection. Despite ongoing challenges, continuous advancements in nanotechnology, artificial intelligence (AI), and hybrid sensing platforms contribute to overcoming current limitations. To revolutionise cancer treatment, biosensors based on volatile organic compounds (VOCs) could close the gap between lab work and real-world treatments. This would consequently save lives and enhance patient outcomes.

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