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REVIEW ARTICLE

Volatile organic compounds: A promising new frontier for cancer screening

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Abstract

The late onset of cancer symptoms can cause a significant delay in diagnosis, impacting patients' prognosis and quality of life, thus prompting a need for alternative screening and detection methods. Neoplastic processes cause distinct and immediate changes to the body's metabolism, creating unique patterns in the volatile organic compounds (VOCs) produced and released through exhaled breath. For this reason, VOC profiles have emerged as diagnostic indicators for several types of malignancies, facilitating early cancer detection. Both non-invasive and accessible, the analysis of breath VOCs for cancer screening and detection has gained recognition as a new frontier in cancer diagnostics. Using exhaled breath instead of gold-standard cancer detection and screening tools that are traditionally invasive and uncomfortable for the patient could be revolutionary in improving patient compliance. Further, compared to the gold-standard tools, breath testing is relatively inexpensive, and the method of analysis, storage, and transporting the samples is simplified. Several studies have demonstrated the accuracy of VOC analysis in detecting various types of cancer, including breast cancer, colon cancer, prostate cancer, gastric cancer, and melanoma. This article summarizes the evidence supporting VOC analysis for cancer screening and detection. It reviews the clinical utility, current limitations, and necessity for standardization across all VOC screening tools to ensure the standardization and reliability of measurements. The evidence supporting breath tests to detect cancer accurately is strong, demonstrating that VOC sampling improves patient outcomes and decreases the global burden of malignant conditions by detecting cancer earlier.

Keywords: Volatile organic compounds; Breath analysis; Cancer screening; Cancer diagnostics

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1. Introduction

There is an ever-expanding interest in developing tools for accurate screening and early cancer detection. Volatile organic compound (VOC) analysis has emerged as a promising

new technique with a wide range of clinical applications (Table 1).[1-7] VOCs are by-products of biochemical reactions and are defined as carbon-containing compounds detectable as a gas at room temperature.[1] Endogenous VOCs are generated within the human body as by-products of metabolic biochemical pathways.[1-6] Once produced, the VOCs diffuse into bodily fluids, tissues, and systemic circulation.[1-3] Consequently, they can be detected in the bloodstream and transported by the circulatory system. Some VOCs are released in exhaled breath, while others are secreted in urine and feces.[1,3-6] In contrast, exogenous VOCs are introduced into the body, including smoking, dietary intake, medications, and cytotoxic treatments.[2] Metabolic changes associated with the pathophysiology of several diseases and malignancies have been shown to trigger shifts in the VOCs produced by the human body.[1-5]

Recent efforts have focused on the identification of VOCs as disease biomarkers. The hallmarks of tumor biology and the neoplastic process include sustained proliferative signaling, uninhibited growth, angiogenesis, and reprogrammed energy metabolism, leading to invasion and metastasis.[6] Hypoxia, hyperproliferation, inflammation, and reactive oxygen species result in marked shifts in both the range and concentration of detectable VOCs.[1,5,6] These neoplastic processes cause measurable, distinct, and immediate changes to the human

Table 1. Emerging applications for VOC analysis

Application	Description
Environmental exposures[117-119]	• Health risk assessment and personal exposures to environmental VOCs • Exposure to cigarette smoke, tobacco, VOCs from e-cigarettes • Workplace exposures to hazardous VOCs, fumes, smoke, and inhaled particles • Environmental risk assessment of toxicity exposure
Oncology[9,120]	• Potential applications as a screening tool for several malignancies, including colon, lung, breast, ovarian, prostate, hepatobiliary, genitourinary, head and neck, cutaneous, and gastric cancers • Can be used to estimate the burden of disease • Monitor response to treatment • Surveillance testing for disease recurrence • Represents an innovative, accessible, inexpensive, and non-invasive diagnostic point-of-care tool
Benign disease[121-126]	• Non-invasive diagnosis of inflammatory bowel disease (Crohn's disease and ulcerative colitis) • Detection and clinical monitoring of benign respiratory conditions, including asthma, pulmonary hypertension, and chronic obstructive pulmonary disease (COPD). • Detection and monitoring severity of chronic kidney and liver disease • Diagnosis of Parkinson's disease and multiple sclerosis • Monitoring glycemic controls and sequela of diabetes mellitus
Perioperative medicine[126-131]	• Prediction and early detection of anastomotic leaks in esophageal, pancreatic, and colorectal surgery • Diagnosis of post-operative pneumonia • Predicting paralytic ileus • Intraoperative monitoring, analysis of anesthetic and sedation • Diagnosis and monitoring of sepsis • Response to nutritional interventions
Drug testing[134,135]	• Detection of marijuana metabolites in urine and in exhaled breath • Detection of impact and extent of use of tobacco products, monitor response to smoking cessation • Detection of alcohol consumption • Detection of illicit drug biomarkers in exhaled breath • Assessing compliance with medical treatments • Assessing absorption and metabolism of medical treatments as well as surveillance of adverse effects
Transplant[132,133,136-138]	• Analysis of VOCs for early detection and prediction of transplant rejection • Applications in lung and hepatobiliary transplant • Diagnosis of lung allograft dysfunction • Detection of exhaled ammonia for early diagnosis of hepatic encephalopathy and monitoring response to treatment • Diagnosis of graft-versus-host disease • Detection of post-transplant acute kidney injury and monitoring response to hemodialysis
Infections[21-23]	• Monitoring respiratory infections in at-risk populations, i.e., immunosuppression, post-transplant, cystic fibrosis, and pediatrics • Differentiation between viral and bacterial respiratory infections in cystic fibrosis and COPD • Diagnosis of human echinococcosis, an infectious disease caused by helminths • Diagnosis of tuberculosis and response to treatment • Diagnosis of pneumonia and response to treatment, i.e., *Pseudomonas* and *Aspergillosis*

Abbreviation: VOC: Volatile organic compound.

body's metabolism, creating unique patterns in the VOCs being produced and released. Unique VOC profiles have demonstrated diagnostic utility for several benign and malignant conditions, enabling prediction of disease burden and response to treatment.[1-6]

Conditions with similar pathophysiological processes often exhibit similar VOC patterns (i.e., ulcerative colitis, Crohn's disease, and irritable bowel syndrome are inflammatory gastrointestinal [GI] conditions that produce similar VOC spectrums).[1,3] As such, a single VOC cannot discriminate between such disease processes. Rather, patterns of several measured VOCs have been utilized to describe distinct profiles, which have been demonstrated in proof-of-concept clinical studies to be sensitive and specific for the diagnosis of several important diseases, including malignancies.[1-5] Thus, VOC profiles represent promising oncologic biomarkers.

Breath analysis of exhaled VOCs is emerging as a non-invasive method for early cancer diagnosis. Exhaled breath is non-invasively accessible, inexpensive to sample, associated with increased patient compliance, and yields samples that are easily analyzed, stored, and transported.[1-4] Serial testing is both safe and feasible. Exhaled breath VOC analysis has the potential to be widely implemented as a simple point-of-care tool providing concurrent screening for a wide range of cancers. In addition, this technology may facilitate treatment response monitoring and post-treatment cancer surveillance.

2. Breast cancer

With over 2.3 million cases and 685,000 deaths worldwide in 2020, breast cancer is the second most diagnosed malignancy.[7,8] It remains the leading cause of cancer-related death in women.[7-9] At present, mammography is the gold-standard modality for the early detection of breast cancer, detecting cancer 1.5 – 4 years before the disease becoming clinically detectable.[10]

The impact of early, effective screening has been well established. A seminal study by Tabár *et al.*[11] demonstrated that women aged 40 – 69 participating in breast cancer screening benefit significantly from earlier intervention with decreased morbidity and mortality, compared to women who did not participate in screening programs. Patients participating in organized mammography screening have a 60% lower risk of breast cancer-related mortality within 10 years of diagnosis. The importance of timely access and compliance with breast cancer screening is highlighted by the increased morbidity and mortality of breast cancer in developing countries, where a delayed diagnosis is associated with worse outcomes compared to high- and middle-income countries.[8]

When diagnosed early, breast cancer is often curable. Improved breast cancer screening and early detection are associated with improved prognosis and decreased health-care costs. Studies exploring barriers to breast cancer screening report a combination of social, geographic, and economic factors.[12-17] Social factors, well described in the literature, include health literacy, perceived physical and emotional discomfort associated with a breast examination and mammography and cultural and religious considerations.[13,15,17] Geographic and socioeconomic factors include disparities in access to screening services for breast cancer.[13-16] There is an ongoing global need to develop inexpensive screening tests that are safe, effective, and improve patient experience. Breath analysis represents a minimally invasive point-of-care tool allowing for early cancer detection that is inexpensive and accessible. This technology may increase compliance with screening and improve access to cancer care globally.

Analysis of over 1.8 million screening mammograms in the United States between 2004 and 2008 in women between 18 and 80 years of age reported a sensitivity of 84.4% and a specificity of 90.8%. The recall rate was 9.6%, with a positive predictive value of 4.3 (Figure 1).[10] In contrast, in a small case–control study, Phillips *et al.*[12] reported a 93.8% sensitivity and 84.6% specificity in predicting the presence of breast cancer with biopsy-proven breast cancer using a prediction model with five VOCs in exhaled breath (Figure 2). This small case–control study (n = 101, with 51 patients with breast cancer) supports the potential for accurate breast cancer diagnosis using a pattern of five exhaled VOCs (1-phenylethanone, 2.3-dihydro-1-phenyl-4(1H)-quinazolinone, 2-propanol, heptanal, and isopropyl myristate) identified through gas chromatography (GC)/mass spectroscopy (MS).[12]

Patterson *et al.*[18] analyzed 308 VOCs in 20 patients with breast cancer and 20 healthy controls, using aggregate low-dimensional summaries and compound quantity clustering to predict a diagnosis of breast cancer with a sensitivity of 72% and a specificity of 64%. Similarly, Phillips *et al.*[19] employed c-statistics to identify the predictive value of individual VOCs to identify potential breast cancer biomarkers in exhaled breath. Monte Carlo simulations were then used to select the chromatographic time slices that identified breast cancer with better-than-random accuracy. The VOCs with the highest predictive values were identified. A multivariate algorithm using a combination of >30 VOCs comparing 54 women with breast cancer and 204 cancer-free controls revealed a sensitivity of 78.5%, a specificity of 88.3%, and a c-statistic of 0.89.

Li *et al.*[20] validated a predictive model using four biomarkers for breast cancer in exhaled breath (hexanal,

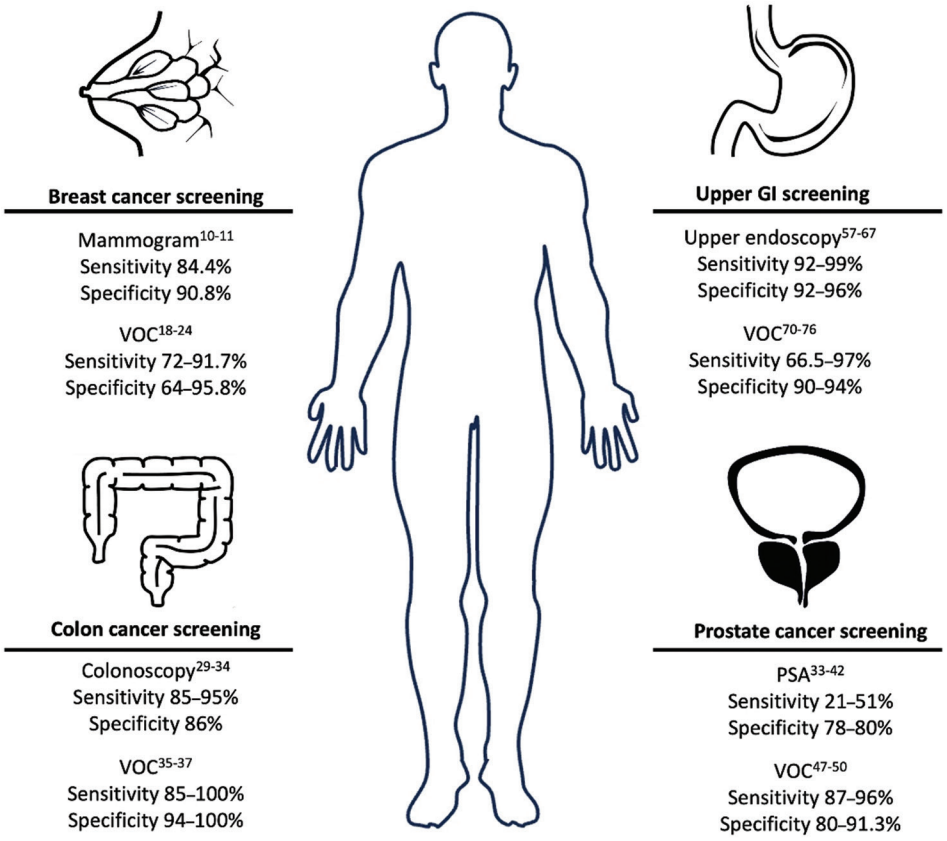

Figure 1. VOC for cancer screening and detection
Abbreviations: GI: Gastrointestinal; PSA: Prostate-specific antigen; VOC: Volatile organic compound.

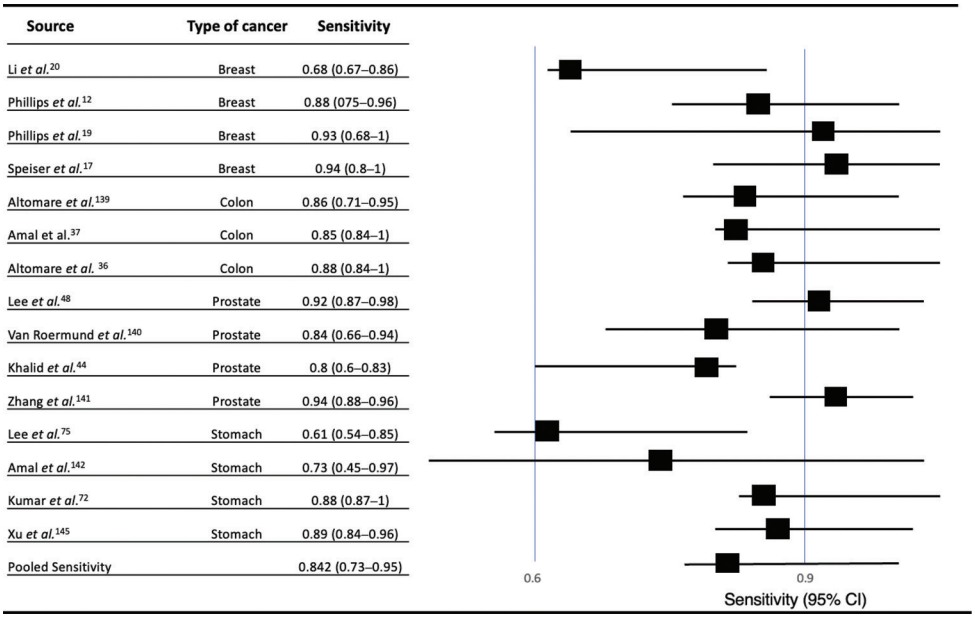

Figure 2. Forest plot of pooled sensitivity analysis

heptanal, octanal, and nonanal). A predictive model was developed using these four biomarkers to differentiate between 24 healthy controls, 17 patients with benign tumors, and 22 patients with breast cancer. Using this model, they reported an area under the curve (AUC) of 0.934, a sensitivity of 91.7%, and a specificity of 95.8%.

The biological significance of individual VOCs remains unclear. Some have been shown to be cancer biomarkers (i.e., heptanal),[21] while analogs of others have been shown to have anti-tumor properties (i.e., 2,3-dihydro-1-phenyl-4(1H)-quinazolinone).[22] Similarly, analogs of 1-phenyl-ethanone inhibit the invasion of human MCF-7/6 mammary carcinoma cells *in vitro*.[23]

Previous studies of patients with lung cancer suggest that the pattern of exhaled VOCs is associated with accelerated catabolism of otherwise benign metabolic by-products, which in turn has been correlated to the induction of cytochrome P450 enzymes.[24] The aromatase enzyme, which acts as an estrogen synthase, is a cytochrome P450 enzyme complex that acts as a catalyst for estrogen production. The induced cytochrome P450 activity associated with breast cancer may thus influence the pattern of VOCs in exhaled breath.[24] It is also likely that some VOCs found to be increased in breast cancer result from ongoing inflammatory oxidative stress, including lipid peroxidation of fatty acids.[24] Pentane, a lipid peroxidation reaction product, is well described as a VOC that is found in higher levels in patients with breast cancer.[18,24] Aldehydes, well described as increasing in the exhaled breath of patients with breast cancer, are also secondary reaction products of lipid peroxidation.

Strong evidence supports the use of exhaled VOCs to accurately detect breast cancer. While the individual molecules described may not be specific to breast cancer, it is the expression patterns that are diagnostic, leading to the description of validated unique "breathprints" that combine up to 30 exhaled VOCs. VOC analysis is intrinsically safe, painless, and inexpensive and may be superior in sensitivity and specificity when compared to screening mammograms. Confirmatory clinical studies in human populations are required to confirm these preliminary findings.

3. Colon cancer

Colon cancer is the third most common malignancy and remains a leading cause of cancer-related deaths worldwide.[25-28] There are over 1.9 million new diagnoses and 930,000 deaths annually from colon cancer.[26] The global burden of colon cancer is expected to increase by 60%, representing at least 2.2 million new cases and causing as many as 1.1 million deaths annually by 2030.[25-27]

It has been well established that early detection of colon cancer is associated with significantly better outcomes and lower health-care costs.[8,27-30] Colon cancer is typically diagnosed after the onset of symptoms through screening, colonoscopy, or stool testing. Unfortunately, over 86% of colon cancers in patients under 50 years old are symptomatic at diagnosis, associated with advanced disease and poor outcomes.[25-29] Indeed, despite strong recommendations for screening, global participation rates and compliance with screening remain as low as 1.9 – 54%.[30-34]

Colon cancer screening tools include stool-based testing to detect hemoglobin or DNA alterations suggestive of malignancy, direct visualization with endoscopy, and radiologic imaging. Stool-based screening includes immunochemical tests (fecal immunochemical test [FIT]), guaiac-based fecal occult blood tests (gFOBT), and multitarget fecal DNA testing.[34] Stool-based screening tests for colon cancer are more sensitive to the detection of cancer than pre-cancerous polyps.[30-33] FIT testing involves the evaluation of a single stool sample, with a specificity of 96.4% and a sensitivity of 73.8% for the detection of colon cancer.[29-31,33-34] It is only 23.8% sensitive for the detection of adenomas >10 mm and 7.6% for adenomas <10 mm.[29-32]

gFOBTs are 92.5% specific and 70% sensitive for the diagnosis of colon cancers, but the sensitivity is only 23.9% for adenomas >10 mm and <12.4% for smaller adenomas.[29-30] Multitarget stool DNA testing is more sensitive than other stool-based screening tests, with a sensitivity of 92.3% and a specificity of 89.8% for the detection of colon cancer.[29-34] It offers improved sensitivity for the detection of adenomas, which is reported at 42.4% for adenomas >10 mm and 17.2% for adenomas <10 mm.[29-34]

Any patient with an abnormal screening test currently requires a follow-up colonoscopy. A colonoscopy is both a diagnostic and therapeutic tool, allowing for the examination and treatment of the rectum, colon, and proximal terminal ileum. It is the definitive test for detecting pre-cancerous adenomas and CRC, with a specificity reported at 86%.[22,27,29-33] It is 75% sensitive for the detection of adenomas <5 mm, 85% for adenomas 6 – 9 mm, and 95% for adenomas >10 mm (Figure 1).[22,27,29-33] Disadvantages of colonoscopy as a screening test include patient discomfort, the inconvenience of bowel preparation, and the potential for procedural and sedation-related complications.[32] Procedural risks include the possibility of a perforated visceral organ, significant bleeding, and infection.[29-33]

Thus, there is an unmet need for a reliable, non-invasive screening test for colon cancer. The analysis of VOCs in exhaled breath has been applied to colon cancer, and while data remain sparse, studies have identified several potential metabolic biomarkers. Indeed, predictive models using combinations of 4 – 60 VOCs have been shown to be comparable to both colonoscopy and stool-based screening for the detection of colon cancer (Figure 2). However, while the individual molecules described may not be specific to colon cancer, the expression patterns are diagnostic, leading to the description of validated "breathprints," which combine clusters of exhaled VOCs.

Wang *et al.*,[35] using solid-phase microextraction-GC/MS, described increased levels of cyclohexanone, 2,2-dimethyldecane, dodecane, 4-ethyl-1-octyn-3-ol, ethylaniline, cyclooctylmethanol, trans-2-dodecen-1-ol, and 3-hydroxy-2,4,4-trimethylpentyl 2-methylpropanoate ($P < 0.05$) in the exhaled breath of patients with colon cancer. The biological significance of these molecules remains unclear. The authors hypothesize that malignancy is associated with increased oxidative stress and lipid peroxidation, which may explain the patterns of VOC expressed in the exhaled breath of patients with colon cancer.[25] Phillips *et al.*[12,19,24] published several analyses of VOC patterns expressed in various malignancies, which further support the theory that alkanes and alkane-derivatives in exhaled air may be associated with increased cytochrome P450 activity and increased oxidative stress.

Altomare *et al.*[36] demonstrated the relationship between the presence of malignancy and expressed VOCs. They discovered that a combination of 11 VOCs was diagnostic for colon cancer, with a sensitivity of 100%, a specificity of 97.92%, and an overall accuracy of 98.75% (Figure 2). The same VOC pattern discriminated between patients with a history of colon cancer who had been disease free for over a year and healthy controls with a sensitivity of 100%, specificity of 90.91%, and accuracy of 94.25%.[26] In another similar study, 418 breath samples were collected from 65 patients with colon cancer, as well as 22 with adenomas, and 122 non-cancer control cases. Using GC-MS analysis to detect four compounds of interest (acetone, ethyl acetate, ethanol, and 4-methyl octane), patients with colon cancer were distinguishable from controls with 85% sensitivity, 94% specificity, and 91% accuracy (Figure 1).[37] Their model also distinguished between advanced and non-advanced adenomas with 88% sensitivity, 100% specificity, and 94% accuracy. As such, VOC analysis offers an advantage over stool-based screening in its ability to accurately detect pre-cancerous adenoma.[37]

Given the intrinsic limitations of stool-based screening, colonoscopy remains the gold standard for the detection of pre-cancerous adenomas and the recommended evaluation following an abnormal stool-based screening test. It is an invasive test associated with patient discomfort, procedural risks, and suboptimal compliance. In contrast, early detection of colon cancer through VOC analysis would allow for non-invasive, inexpensive, and accessible screening. VOC analysis may also be superior in sensitivity and specificity when compared to screening colonoscopy.

4. Prostate cancer

Despite being the second most prevalent malignancy in men worldwide, there are currently no reliable screening tools for prostate cancer.[38-40] Prostate cancer is the third-leading cause of new cancer cases diagnosed worldwide, with approximately 1.4 million new cases diagnosed in 2020.[39] At present, a combination of digital rectal examination, serum prostate-specific antigen (PSA), and trans-rectal ultrasound-guided prostate biopsy is employed for prostate cancer.[38-41]

Serum PSA, at a cut-off of 4 ng/mL, was integrated into screening programs in the United States of America in the 1990s.[38-44] However, due to a sensitivity as low as 21% for prostate cancer and 51% for high-grade cancers, the use of PSA for cancer screening is no longer recommended in most international screening guidelines (Figure 1).[40-46] Indeed, two large screening trials failed to demonstrate a significant decrease in prostate cancer-associated mortality using PSA-based screening tests.[46,47] Moreover, with a false-positive rate as high as 20%, PSA screening has been associated with significant overdiagnosis as well as subsequent unnecessary testing/biopsies.[38-46]

Liu *et al.*[47] utilized a combination of 86 VOCs in a cohort of 43 patients with a definite pathological diagnosis of prostate cancer and 64 controls, whereby their model accurately detected prostate cancer with a sensitivity of 87.0% and a specificity of 91.3% (AOC = 0.945). Specifically, furan-3-methanol, (e,e)-octadeca-2,4-dienal, 2-ethylhexan-1-ol, and 2-undecen-1-al were most specific in differentiating cancer specimens from controls, with AUCs >0.70. Similarly, Gao *et al.*[48] measured the VOC profile of the urine headspace through GC-MS in a test cohort of 108 patients with biopsy-confirmed prostate cancer positives and compared them to controls, creating a diagnostic model with 11 VOCs, which they subsequently validated with another group of test samples, which included 53 patients with prostate cancer compared to 22 healthy controls, with a resulting AUC of 0.86. Following cross-validation, the AUC for this model was 0.92 (sensitivity = 0.96; specificity = 0.80) (Figure 1).[48]

Despite these promising results, little is known about the mechanism of production of VOCs specific to prostate cancer, and a reliable VOC profile for prostate cancer has not yet been described. Peng *et al.*[49] examined the exhaled VOC profiles of healthy controls (n = 22) compared with patients with biopsy-confirmed malignancy (breast (n = 22), lung (n = 30), colorectal (n = 26), prostate (n = 18). They describe several VOCs that, when measured, showed no overlap between controls and patients with prostate cancer (toluene, 2-amino-5-isopropyl-8-methyl-1-azulenecarbonitrile, p-xylene, and 2,2-dimethyl-decane).[49] However, this study was limited by a small sample size, and their model failed to reach statistical significance for their VOC profile for prostate cancer. The molecule sarcosine has previously been proposed as a biomarker of aggressive tumor biology in prostate cancer, and interestingly, higher levels are reported in the urine of patients with biopsy-confirmed prostate cancer (n = 44) compared to healthy controls (n = 51).[50] However, the receiver operator characteristic (ROC) for sarcosine was modest (0.71 for urine sediments; 0.67 for supernatants), which limits its potential for clinical application.[50]

In vitro studies report elevated acetaldehyde dehydrogenase activity in tumor cells, a molecule that catalyzes the oxidation of exogenous and endogenous aldehyde substrates into carboxylic acids, which may explain the finding of decreased aldehyde levels in prostate cancer VOC profiles.[46,51-54] This finding is not, however, specific to prostate cancer and has been described in colon, gastric, and breast cancer as well.[54,55] Similarly, Liu *et al.*[47] describe 2-ethyl-1-hexanol in their prostate cancer VOC profile as a known metabolite of diethylhexyl phthalate with a role in the induction of apoptosis previously implicated in the VOC profile of several other malignancies.[46,53-55] Nevertheless, VOC for prostate cancer screening and detection is promising, with excellent sensitivity and specificity profiles in studies using VOCs detected in the headspace of urine samples (Figure 1). Given the current limitations of PSA screening, further study is warranted to explore the role of VOC analysis as a non-invasive test for prostate cancer screening.

5. Gastric cancer

Gastric cancer is the fifth most common cancer worldwide, with approximately 1.09 million new cases of gastric cancer diagnosed in 2020.[56] Globally, it is the fourth leading cancer cause of death, responsible for 7.7% of all cancer-related deaths in 2020.[56] The incidence and prevalence of gastric cancer have significant variability worldwide, with most new cases of gastric cancer occurring in Eastern Asia.[56] As a result, recommendations for gastric cancer screening are varied, with some countries adopting population-based screening, while other countries reserving screening investigations for specific high-risk subgroups dependent on endemic incidence. Early diagnosis and treatment of gastric cancer results in decreased mortality. However, early-stage gastric cancer is most often asymptomatic or with symptoms similar to gastritis.[56-58] Owing to the silent or ambiguous presentation of early gastric cancer, effective screening investigations are important to ensure early gastric cancer diagnosis.

The primary method of detecting gastric cancer in the early 20th century was X-ray imaging. With the ingestion of barium contrast media, the GI tract could be assessed for abnormalities with minimal risk to patients.[59] However, the sensitivity of the single-contrast barium examination in the diagnosis of gastric carcinoma ranged from 54%[60] to an average of 75%.[61] In the late 1960s, Japanese physicians developed the gas-barium double-contrast method of X-ray imaging, which involved the ingestion of CO_2 gas-producing granules in conjunction with a barium suspension.[60-63] This method permitted visualization of the enhanced barium-saturated mucous membrane of the stomach, which was subsequently inflated with air to assess its elasticity.[62] Over time, specific techniques involving rotating the patient and timings for spot films were developed to optimize the mucosal coating of the stomach and to permit assessment of the stomach in its entirety. Sensitivity with the double contrast barium study ranged from an average of 76 – 96%; however, it has been established as superior to conventional computed tomography in localizing the diagnosis.[60,61,64]

The flexible design of the fiberoptic endoscope created in 1957 allowed for the examination of the entire stomach, overcoming the limitations of its predecessor, the rigid gastroscope.[57,65] In the early 1960s, the utility of endoscopy in the diagnosis of gastric cancer was realized as it enabled direct visualization of the gastric mucosa and allowed for biopsies to be carried out on ulcers and other suspicious areas of the stomach.[62] The sensitivity of endoscopy in the diagnosis of gastric cancer ranged from 92% to 99%, and therefore, endoscopy rapidly gained popularity for its superior diagnostic accuracy as compared to the single contrast barium meal (Figure 1).[59-61] Ultimately, endoscopy was accepted as the superior test for gastric cancer screening due to its better accuracy.[57,58,66,67] Today, endoscopy and endoscopic biopsy are accepted as the gold standard for the diagnosis of gastric cancer.[64]

Helicobacter pylori infection was identified as a major risk factor for gastric cancer in the 1980s, resulting in

the identification and eradication of *H. pylori* as a key preventative measure.[68] Endoscopy made a significant impact on gastric cancers not only by increasing the detection of early gastric cancers by enabling biopsies but also by aiding in decreasing gastric cancer occurrence by allowing for the detection and implementation of eradication therapy against *H. pylori*.[65] The limitations of upper endoscopy are primarily related to its invasiveness and resultant potential patient discomfort, as well as the associated risks of the procedure, including bleeding or perforation. As with all technical procedures, the accuracy of endoscopy can vary based on the skill and experience of the endoscopist. Endoscopy remains the gold standard in the detection of gastric cancer as it allows for the collection of biopsies for histological examination and definitive diagnosis.[69]

Before 2010, the application of human breath analysis was largely limited to urea breath testing for *H. pylori* infection, a hydrogen breath test for small bowel bacterial overgrowth, and the concentration of exhaled nitric oxide for the investigation of asthma.[70] In 2013, exhaled breath metabolites in 18 patients with biopsy-proven esophagogastric cancers were analyzed and compared to the concentrations of the metabolites in a control group of 18 patients with biopsy-proven non-cancer diseases of the upper GI tract and 17 healthy controls.[71] The study identified a significant increase in the concentration of hexanoic acid in the exhaled breath of the esophagogastric cancer patients compared to patients in the positive control and healthy control groups. In addition, there were statistically significant increases in the concentrations of phenols and their derivatives, methyl phenol and ethyl phenol, in the exhaled breath of patients with esophagogastric cancer, compared with the positive control, and healthy control groups. It was thought that these differences in concentrations were due to increased protein catabolism in gut microbiota and the upregulation of tyrosine metabolism in patients with esophagogastric cancers.

In 2015, Kumar *et al.*[72] quantified exhaled breath VOCs from 210 patients with either esophagogastric adenocarcinoma, Barrett's esophagus, benign upper GI disease such as gastritis and gastric ulcer, or a normal upper GI tract. The study identified 29 exhaled molecules of interest, including 12 VOCs present at statistically significantly higher concentrations in patients with esophagogastric cancers. The AUC using these 12 molecules to discriminate patients with esophageal and gastric adenocarcinoma from those with non-malignant conditions as well as healthy controls was 0.92 and 0.98, respectively. The authors further proposed a predictive model that differentiates patients with gastric cancer from controls. The AUC for their model was 0.92, with a sensitivity of 89.3% (95% confidence interval [CI]: 77.0 – 95.7) and specificity of 83.7% (95% CI: 74.5 – 90.9). Interestingly, *H. pylori* status and proton-pump inhibitor independently predict exhaled ammonia concentrations, identifying a key limitation of VOC screening as it remains susceptible to interference from both endogenous and exogenous factors (Figure 1).

Similarly, a recent meta-analysis published in 2021 pooled the data from five studies exploring the role of exhaled VOCs in the diagnosis of GI cancer. These studies analyzed endogenous VOCs in exhaled breath of patients with biopsy-confirmed GI cancer.[73] The pooled data analysis suggests that VOCs can be used to differentiate between gastric cancer and non-malignant gastric conditions with sensitivity of 85% and specificity of 89%, with diagnostic odds ratio and AUC values reported as 41.30 and 0.93, respectively.[73] Durán-Acevedo *et al.*[74] compared breath samples from 14 patients with gastric cancer and 15 controls. Using a novel solid-state sensor in addition to GC-MS, a significantly higher concentration of six VOCs was identified in patients with gastric cancer, leading to a predictive model that identified patients with gastric cancer with a sensitivity of 100% and a specificity of 93%. Similarly, Lee *et al.*[75] determined that four VOCs (propanal, acetamide, isoprene, and 1,3 propanediol) exhibit a gradual increase in concentration from normal control to early and advanced gastric cancer (Figure 2). Analysis of the ROC curves for these four VOCs demonstrated that the AUC for gastric cancer prediction was highest (0.842) when three or more VOCs were measured in tandem.

Intraluminal gas has also been used for VOC analysis for gastric cancer diagnosis. Yang *et al.*[76] reported on using a combination of intraluminal and exhaled gas collecting during a prospective trial involving 259 patients undergoing endoscopy to discriminate between upper GI cancer and healthy controls. Intraluminal VOC analysis was better in discriminating upper GI cancer from benign controls when compared to exhaled VOC analysis (sensitivity: 91.23% vs. 81.75%, specificity: 90.65% vs. 88.46%, and AUC: 0.930 vs. 0.877). Gastric cancer could also be detected with both intraluminal and exhaled breath VOC analysis, which discriminated this patient population versus benign controls (sensitivity: 87.04% vs. 74%, specificity: 96.99% vs. 92.31%, and AUC: 0.983 vs. 0.889).

At this time, more research is required to identify specific and reliable VOC biomarkers associated with gastric cancer to improve its diagnostic accuracy. Although several models have been shown to differentiate between benign and malignant conditions, as well as discriminate between early

and late-stage gastric cancer, exhaled VOCs lack reliable sensitivity and specificity, limiting clinical applications. Nevertheless, since exhaled VOC analysis is non-invasive and does not require sedation or tissue sampling, it remains an exciting avenue for further research.

6. Skin and soft tissue malignancies

Melanoma is the fifth most common cancer in the United States.[9] Survival is directly dependent on the stage of diagnosis, with early detection leading to improved outcomes.[77] Aside from visual skin surveillance, there are no screening tests for melanoma. Presentation often results after the detection of a new or changed skin lesion.[78] The diagnosis of early melanoma is through the biopsy of worrisome skin lesions selected by a visual assessment, which in itself remains challenging even for experienced clinicians.[78-80] Indeed, clinical diagnosis by skilled dermatologists has been estimated to be approximately 70% sensitive, and sensitivity can be improved with clinical aids such as a dermatoscopy.[80,81] More recently, the accuracy of the visual inspection was assessed in a systematic review and meta-analysis of 49 studies with a total of 34,000 skin lesions, of which 2,500 were melanomas.[81] The sensitivity and specificity of visual inspection in this analysis were 92.4% (95% CI: 26.2 – 99.8%) and 79.7% (95% CI: 073.7 – 84.7%), respectively, where the wide CI reflects significant heterogeneity in diagnostic accuracy.[81]

Melanoma-related VOCs have been found to differ from normal skin VOC expression patterns in GC studies, leading to the proposal of melanoma-specific breathprints. On a cellular level, Preti *et al.*[82] employed solid-phase micro-extraction, GC-MS, and single-stranded DNA-coated nanotube sensors to compare VOCs from normal and malignant melanocytes to identify VOCs unique to melanoma cells, including dimethyldi- and trisulfide. Similarly, Santonico *et al.*[83] utilized a gas sensor array to discriminate between benign nevi and melanoma lesions with about 80% accuracy (n = 40). Abaffy *et al.*[84] propose a dozen potential VOCs potentially derived from melanoma *in vitro*; however, many have since been shown to be environmental contaminants. The use of *in vitro* models or small tissue samples may have contributed to environmental contaminants in these studies, and as of yet, there are no convincing, characteristic VOC profiles for the detection of melanoma, despite evidence that there is a distinct volatile metabolome emanating from melanoma cells that differ from that of normal skin.

Sarcomas are defined as malignant tumors of mesenchymal origin, comprising <1% of all adult malignancies.[1] Up to 80% of sarcoma originates from soft tissue, and 20% originates from bones.[85] There are no screening tests for sarcoma nor are there characteristic signs or symptoms to facilitate diagnosis.[85-87] The diagnosis is further challenged by the multitude of subtypes and the pathology expertise required to make a correct diagnosis.[86] On expert review, up to 40% of cases were considered incorrectly diagnosed.[86-88]

The most common presenting complaint for soft tissue sarcoma is a gradually enlarging, painless mass.[85] Diagnosis is confirmed with a tissue sample and histologic examination, and radiographic imaging is used to further define the etiology of the mass, the extent of the disease, and plan treatment options.[89-92] Diagnostic delays are common and are associated with worse outcomes.[86,90] Indeed, prompt diagnosis is relevant to prognosis, as the most common prognostic factors in sarcoma are tumor size, histologic grade, and pathologic stage.[91] Recently, a cross-sectional pilot study of 59 patients described the use of electronic nose microarray technology to identify patients with an underlying diagnosis of biopsy-confirmed soft tissue sarcoma using the profile of their exhaled volatile organic molecules, and their preliminary publication reports a c-statistic of 0.85, sensitivity of 83%, and specificity of 60%.[92] Further studies are needed to establish a reproducible breathprint specific to sarcoma and to the various histological subtypes, as there is a clear need for diagnostic tools to facilitate earlier detection and reduce diagnostic delays for these malignancies.

7. Discussion

The analysis of VOCs is a promising approach for screening and diagnosing multiple tumor types. It has been shown to be non-invasive, relevant in many cancer subtypes, and has the potential to be inexpensive.[93,94] There are also several possible applications for VOC testing in cancer care. This technique could be used to triage patients with non-specific symptoms and expedite/guide the referral process from primary care to subspecialty care, improving compliance with screening and potentially decreasing the proportion of inappropriate referrals. If proven to be effective, this non-invasive technology has the potential to increase the uptake of screening, given the non-invasive nature of the test and the ease with which the samples are obtained. Moreover, given that several VOCs have been shown to reliably fluctuate based on tumor burden, there is potential for a role in monitoring response to therapy and surveillance for disease recurrence.[95-97] However, the analysis of VOCs has yet to be incorporated into clinical practice, and the approach faces several challenges to widespread implementation.

7.1. Standardization

The results of VOC testing are sensitive to the method of sample collection, patient physiology, and test environment. When measuring VOCs in exhaled breath, multiple respiratory factors may influence the concentration of certain molecules within the breath sample. There are, for example, international recommendations for the standardized measurement of nitric oxide within breath samples published by the American Thoracic Society and the European Respiratory Society, which in turn have supported the adoption of this metric as a diagnostic tool in clinical practice.[1,98] A similar framework must be proposed and implemented across all VOC screening tools to ensure the standardization and reliability of the measurements. Quality control measures will need to be implemented with established guidelines for calibration procedures, and accurate quantification analyses of VOC samples will be required to ensure reliable, high-quality, reproducible testing. The detection limits of instruments used in clinical settings for trace VOC measurements will need to be specified.

7.2. Limitations

There are several tumor factors that influence the sensitivity and specificity of VOC for cancer screening and detection, which in turn may impact the implementation of this technology in clinical practice. Tumor volume and stage, for example, are critical considerations when applying VOC analysis to cancer screening and detection. The sensitivity and specificity of VOC analysis for colorectal cancer detection have been shown to be affected by tumor size, whereby larger tumors release higher VOC concentrations, increasing the accuracy of VOC analysis.[97] VOC analysis has been shown to have a higher accuracy in detecting early-stage breast cancer compared to advanced-stage cancer, and as such, the impact of tumor volume may also vary by cancer type.[99,100] Larger tumors produce more volatile compounds, leading to a more complex VOC profile and making it more difficult to detect specific biomarkers.[100] The accuracy of VOC analysis for cancer detection can also be influenced by other factors related to tumor volumes, such as necrosis and inflammation. A study by Angioli *et al.*[101] reported that necrosis in ovarian cancer could affect the VOC profile and lead to inaccurate results in cancer detection. Similarly, a study by Rodriguez-Miguelez *et al.*[102] discovered that inflammation in breast cancer can influence the VOC signature and lead to false positives.

In addition, some malignancies may be better candidates for screening through VOC analysis. While Haick *et al.*[103] confirmed that VOC analysis could be highly sensitive and specific in detecting breast cancer, and Dragonieri *et al.*[104] demonstrated a VOC analysis protocol highly accurate for the detection of lung cancer, a study by Ge *et al.*[105] discovered that VOC analysis had low sensitivity in detecting pancreatic cancer. Moreover, the histologic subtype of the cancer may also influence the VOC profile of the malignancy, in turn affecting the sensitivity and specificity of the diagnostic test. VOC analysis has been shown to have higher accuracy in detecting adenocarcinomas than squamous cell carcinoma in lung cancer.[100] Similarly, the VOC profile of ovarian cancer varies by histological type, whereby serous tumors have a different VOC profile compared to endometrioid tumors.[106] The tumor's location within the affected organ may also impact the accuracy of the VOC analysis. The VOC profile of gastric cancer has been shown to vary by the location of the primary tumor within the stomach, whereby tumors located in the antrum produce a different VOC profile compared to those discovered in the body of the stomach.[107] Similarly, higher concentrations of VOCs are produced by lung tumors in the central airways compared to peripheral tumors.[108]

- The use of chemotherapy and radiation therapy will also influence the accuracy of VOC analysis, as adjuvant therapy changes VOC profiles produced by tumors. VOC analysis has shown lower accuracy in detecting oral cancer in patients who have received chemotherapy or radiation therapy.[109] The VOC profile of cancer has also been shown to change during adjuvant therapy, which may affect the accuracy of VOC analysis in detecting residual disease.[110,111]
- The metabolic activity of cancer cells is different at different stages of lung cancer, leading to different VOC profiles, and several recent studies have shown that the cancer stage influences the sensitivity and specificity of VOC analysis for cancer detection.[112] The VOC profiles of early-stage lung and colon cancer patients differ significantly from those of late-stage patients, and the sensitivity of VOC analysis for early-stage lung cancer detection is higher than that of late-stage cancer.[112-114] A study by Cao *et al.*[115] investigated the use of VOC analysis for early detection of gastric cancer and discovered that the sensitivity of the technique was higher for early-stage tumors than for advanced-stage tumors. Similarly, a study by Saorin *et al.*[116] reported that VOC analysis had higher accuracy in detecting early-stage ovarian cancer compared to advanced-stage cancer.
- The use of VOC analysis for cancer screening and detection is still in its early stages, and further research is needed to fully understand the impact of

tumor factors such as location, size, and histologic subtype on its accuracy. Larger tumor volumes and advanced-stage cancers may produce more complex VOC profiles, which can lead to false positives or reduced sensitivity of the technique. Moreover, the impact of adjuvant therapies such as chemotherapy, radiation, and immunotherapy on VOC release by tumor cells remains incompletely understood, further highlighting the potential limitations of VOC analysis for cancer screening and detection. Despite these challenges, VOC analysis remains a promising tool, and continued research will further refine its utility in clinical practice.

7.3. Integration into clinical practice

MS for VOC analysis is a standard technique used widely in several industries. The instrumentation has been validated over several years and is no longer in the development stage.[9] However, the accuracy and reliability of this technique for obtaining results in clinical practice have yet to be established. Furthermore, the reproducibility of the results in a clinical setting needs to be validated, reported, and optimized before implementation. Randomized control trials against the current standard of care for cancer screening and detection should be carried out before considering the integration of this tool into clinical practice. Indeed, it would be important to establish the repeatability of VOC measurements using the same analytical platform and the reproducibility of VOC measurements among instruments using different analytical platforms and/or different laboratories/centers.

7.4. Validation of VOCs as a diagnostic model

Formal trials are required to provide external validation against positive control groups and compare against current standards of care, ultimately validating the tool among the target population and the external environment where the VOC testing will ultimately take place. Validation studies are required to establish test thresholds for various cancers at various stages as well as to establish a differentiation between tumor subtypes and compare these metrics against a control test population. Subsequently, large, multicenter, blinded randomized control trials are required to validate this technology against the standard of care. Importantly, the studies will need to follow international standards for reporting using Standards for Reporting of Diagnostic Accuracy Studies guidelines.

8. Conclusion

There is strong evidence supporting the potential use of VOCs in exhaled breath for accurate cancer detection. Implementing VOC analysis for accessible screening and early detection of cancer could improve patient outcomes and decrease cancer-related deaths and the global disease burden. However, despite its immense potential, VOC analysis continues to face several implementation challenges before it can be integrated into clinical practice. Standardization of sample collection and analysis, clinical validation, and, ultimately, multicenter randomized control trials are necessary to establish the role of VOC analysis in cancer screening and detection.

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