Printed in the Republic of Korea
ANALYTICAL SCIENCE & TECHNOLOGY
Vol. 38 No. 2, 106-122, 2025
https://doi.org/10.5806/AST.2025.38.2.106

Review

Systematic review and meta-analysis of volatile organic compounds (VOCs) for breast cancer screening using the PRISMA approach

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(Received April 1, 2025; Revised April 12, 2025; Accepted April 17, 2025)

Abstract: Breast cancer remains one of the most health challenges among women globally. Early detection significantly improves patient conditions and survival rates. Volatile organic compounds (VOCs) which are low molecular weight byproducts released through biological processes have gained a great attention as potential non-invasive biomarkers for cancer diagnosis. This systematic review was conducted using the PRISMA approach to analyze recent studies on utility of VOCs in breast cancer screening. A total of 1,340 studies were initially retrieved from Google Scholar, of which 30 studies were selected for in-depth analysis. The results indicate that eight VOCs were among the most frequently reported out of a total 268 identified through the studies. The eight frequent VOCs associated with breast cancer found in various biological samples such as breath, blood, urine, cell, and saliva were phenol, 2-ethyl-1-hexanol, acetic acid, p-cresol, octanoic acid, 2-pentylfuran, guaiacol, 4-tert-butylphenol. In review, significant variability was present in sampling methods, headspace solid phase microextraction conditions, analytical techniques, and identified VOCs across studies. To enhance VOC-based cancer diagnosis toward clinical utilization, future research should focus on standardizing analytical protocols, improving VOCs' selectivity, and exploring machine learning-based classification models. This review underscores the significant potential of VOC-based diagnostics while emphasizing the need for further validation and standardization of methodological methodologies.

Key words: breast cancer, biomarker, volatile organic compounds (VOCs), non-invasive, PRISMA

1. Introduction

Breast cancer remains one of the most prevalent malignancies among women worldwide including in South Korea. According to the Korean Statistical Information Service (KOSIS), approximately 30,000 women were newly diagnosed with breast cancer in 2021, and the number has been steadily increasing over the past decade.[1] The majority of breast cancer cases occur in women aged 40 and above with a notable rise in incidence among women in their 30s and even late 20s, indicating a shift toward earlier onset[1,2] underscores the urgent need for early screening accessible to younger and asymptomatic individuals. Early diagnosis of cancer is critical for the improvement of patient survival rates and treatment interventions.

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Numerous studies have shown that early detection significantly increases the chances of successful outcomes and reduces healthcare costs.[3-5]

Conventional diagnosis methods for breast cancer include imaging techniques, a breast biopsy, HER-2/neu detection assay, blood-based assay. Images of breast could be obtained by radiating X-ray (mammography), a proton density of the tissue (magnetic resonance image, MRI), and using radioactive tracer emitting gamma rays (molecular breast imaging, MBI). A breast biopsy is a medical procedure to take a small piece of tissue from the breast to test it. It is simultaneously conjunction with clinical breast examination and breast imaging for diagnostic accuracy. The HER-2/neu detection assay identifies the presence of HER-2 protein overexpression in breast cancer cells. A blood-based assay detects circulating biomarkers such as DNA, RNA, protein or metabolites.[6]

Traditional diagnostic methods often involve invasive procedures such as biopsies or imaging-based techniques that can be expensive, uncomfortable, or inaccessible in certain clinical settings. In recent years, interest has grown in developing non-invasive diagnostic approaches that utilize biomarkers derived from biological samples. Volatile organic compounds (VOCs), emitted as metabolic byproducts, have emerged as promising candidates for non-invasive cancer diagnostics.[7,8]

VOCs are a diverse group of organic chemicals with low molecular weight that readily evaporate at room temperature. They could be detected in exhaled breath, urine, sweat, blood, and tissue. In the context of breast cancer, VOCs are increasingly recognized as valuable alternative biomarkers because they are strongly associated with tumor-related metabolic alterations, oxidative stress, inflammation processes, and host–microbiome interactions.[9] Breast cancer cells undergo profound metabolic reprogramming such as altered glycolysis, lipid metabolism, and amino acid turnover. These changes could result in the production of distinct VOC profiles often referred to as “cancer volatilomes”.[10-12] For example, increased levels of aldehydes, ketones, alcohols, and fatty acid derivatives have been detected in the breath or serum of breast cancer patients. These VOCs are often byproducts of lipid peroxidation, cytochrome P450-mediated detoxification, or gut microbial fermentation, all of which are altered in cancerous states. In addition, oxidative stress as a hallmark of cancer progression leads to the generation of specific VOCs such as alkanes and furan derivatives. Some phenolic VOCs and short-chain fatty acids may also reflect changes in the tumor microenvironment or immune activity. The breast tissue's proximity to adipose-rich and hormone-sensitive regions makes it particularly reactive to systemic metabolic and inflammatory cues, which can modulate the VOC profile. VOCs may reflect physiological and pathological changes in the body and tumor-related metabolic alternatives can generate distinct VOC profiles.

Among these matrixes, most VOC-based cancer studies to date have primarily focused on breath and urine because of their accessibility and established sampling protocols.[13] Although sweat and skin secretions offer non-invasive and continuous sampling potential, they remain underexplored in cancer VOC research even though analytical methods have been optimized for gaseous or liquid samples, leaving a methodological gap in the development of VOC analysis tools still exist tailored to alternative sample types. A broader inclusion of diverse sample matrixes in VOC studies may enhance diagnostic accessibility and increase patient compliance, especially in the context of large-scale screening programs.[14]

Despite the clinical significance of breast cancer, VOC-based research in this area remains limited compared to other cancers such as lung or gastrointestinal cancers.[15] Much of the existing VOC literatures have more focused on these metabolically active tumors than breast cancer-specific VOC profiles. Expanding research in this area could contribute to the development of novel diagnostic approaches for breast cancer and potentially improve outcomes through earlier detection. Among the various analytical methods used in VOC research, gas chromatography (GC) remains one of the most widely applied techniques due to its high sensitivity and resolution.[16] Headspace gas chromatography (HS-GC) is particularly advan-

tageous for VOC analysis because it allows for the detection of volatile compounds without the need for direct contact with complex biological matrixes.[17] This reduces matrix interference and preserves sample integrity. However, limitations include the requirement for precise temperature and equilibrium control, and relatively longer sample preparation times compared to direct injection techniques. Nonetheless, HS-GC continues to be a powerful tool in cancer VOC research due to its reproducibility and capacity for coupling with mass spectrometry for compound identification.[18]

This review systematically identifies and evaluates studies on breast cancer-related VOCs using the PRISMA(Preferred Reporting Items for Systematic Reviews and Meta-Analyses) framework, with the aim of providing a comprehensive assessment of current non-invasive analytical strategies. Specifically, we investigate sampling and analytical methods, highlight key methodological trends, and propose considerations for the development of protocols in VOC-based breast cancer diagnostics. In addition, we address existing limitations in the field and suggest future research directions to advance the clinical utility of VOC analysis in early detection and cancer monitoring.

2. Systemic Review using PRISMA

This review follows the PRISMA guidelines to ensure a systematic and reproducible analysis. PRISMA is a standardized framework designed to improve the transparency and completeness of reporting in systematic reviews and meta-analyses. It provides a 27-item checklist and a four-phase flow diagram to guide authors in structuring and reporting their reviews in a

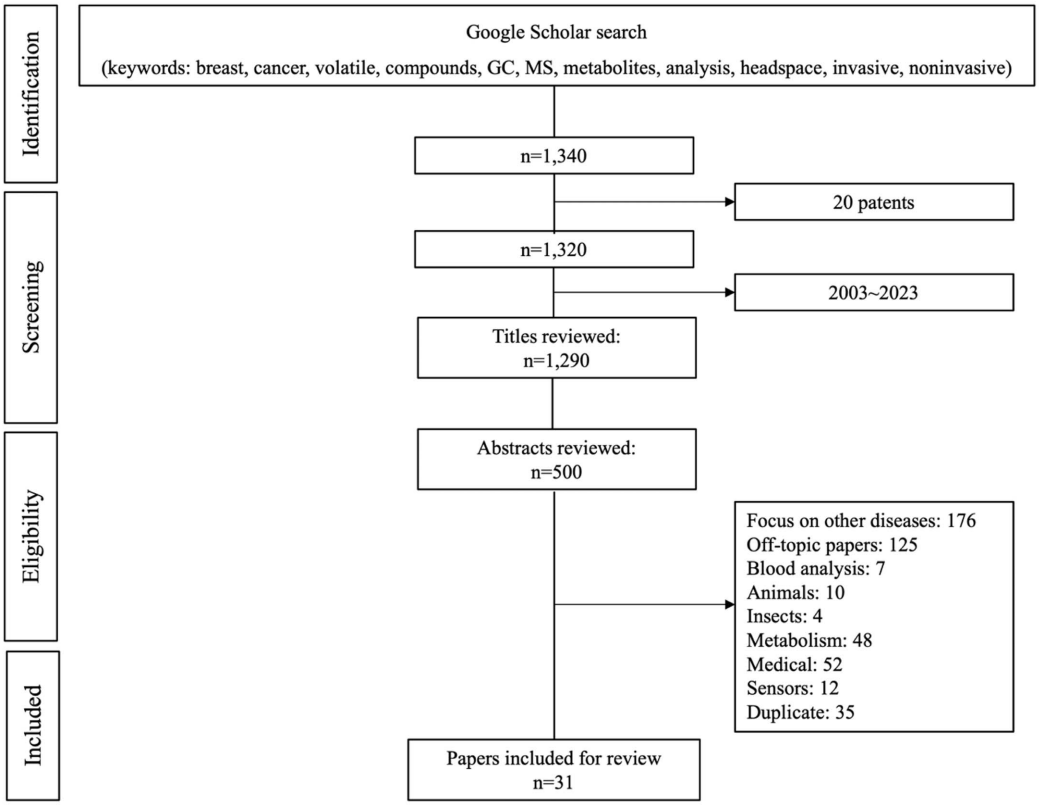


Fig. 1. The flow chart of PRISMA.

methodologically rigorous manner.[19] In this review, PRISMA was conducted in the following order: identification, screening, eligibility, and included.

Google Scholar was selected as the search engine for this PRISMA-based systematic review. For identification, the keywords of 'breast, cancer, volatile, compounds, GC, MS, metabolites, analysis, headspace, invasive, noninvasive' were used. As a result, 1,340 studies were initially identified. After excluding 20 patents, the remaining 1,320 studies published between 2003 and 2023 were re-evaluated. The titles of 1,290 studies were screened to eliminate unrelated studies, and it reduced the selection to 500 at screening step. In eligibility process, the abstracts of these 500 studies were further reviewed leading to the exclusion of 176 studies that focused on other cancers, 125 studies that were not directly related to the primary topic, 7 studies that analyzed blood samples instead of VOCs, 14 studies that focused on animal or insect models, 48 studies related to metabolomics rather than VOC profiling, 52 medical-based studies that lacked analytical chemistry approaches, and 12 studies that primarily investigated sensor technology rather than VOC detection. Duplicate studies were also excluded during the eligibility process. Following this process, 30 studies were included for detailed analysis (*Fig.* 1).[20-83] Quality assessments were independently conducted by two reviewers (J.K. and Y.P.). Any disagreements in study inclusion were resolved through discussion with a third reviewer (S.B.).

3. Identified VOCs and Their Analytical Methods

The selected 30 studies were further examined to compile key methodological details related to VOC sampling and analytical methods for breast cancer (*Table* 1).

3.1. Types of VOCs and samples

A total of 268 VOCs were reported across the selected studies. When classified based on chemical structure, alkenes were the most frequently reported accounting for 20.9 % of all VOCs followed by ketones (15.7 %), alkanes (14.6 %), alcohols (12.3 %), carboxylic acids (12.3 %), aldehydes (7.5 %), aromatic compounds (5.6 %), esters (4.5 %), sulfides (1.9 %), and amines (1.5 %). Additionally, heterocyclic compounds, ethers, and alkaloids each comprised 0.7 %, while pyridines, amides, and alkynes each accounted for 0.4 % (*Fig.* 2).

Among the VOCs identified, the eight most frequently reported compounds were cited in at least four and up to seven different studies. These eight VOCs including phenol, 2-ethyl-1-hexanol, acetic acid, p-cresol, octanoic acid, 2-pentylfuran, guaiacol, 4-tert-butylphenol with their chemical classification, names, CAS numbers, molecular weights, structures, frequencies in which they were reported, and sample matrixes have been compiled in *Table* 2. The eight VOCs summarized in *Table* 2 exhibit distinct olfactory properties that are relevant to both sensory evaluation and their biological or environmental origins. Phenol was the most frequently mentioned VOC across the literature. Among these compounds, alcohols were the most prevalent, comprising 63 % followed by carboxylic acids at 25 %, and aromatic compounds at 12 %. All eight VOCs were detected in urine and 2-ethyl-1-hexanol and octanoic acid also identified in cell cultures and urine, while phenol and acetic acid were found in breath, cell cultures, saliva, and urine.

Phenol emits a sharp, medicinal, and smoky odor, often associated with antiseptic or burnt wood characteristics. Its relevance with breast cancer would be estrogenic activity linked to inflammation and microbial metabolism. 2-Ethyl-1-hexanol possesses a slightly sweet, oily scent with plastic-like undertones, commonly perceived as synthetic or industrial. Acetic acid is characterized by a strong, pungent, vinegar-like aroma that is widely recognized and highly volatile.

p-Cresol presents a barnyard or fecal odor, with tar-like notes often linked to animal waste and body odor. Similarly, octanoic acid (caprylic acid) has a rancid, fatty, and sweaty scent profile, typically associated with sebum and human body odor. 2-Pentylfuran contributes a green, beany, and nutty

Table 1. Summary of sampling and analytical methods obtained from 30 references

Sampling method			Analytical method			Reference
Matrix (total*)	Number of samples	Age	SPME fiber**	Instrument	Number of VOCs***	
Breath (7)	22	20-75	PDMS/DVB	GC/MS	5	74
	276	21-74	-	GC/MS	14	67
	203	18-80	75 mm thick	GC/MS	7	70
	63	>18	-	GC/MS	4	72
	201	>18	-	GC/MS	8	63
	51	42	-	GC/MS	5	59
	258	55±7	-	GC/MS	28	11
Cell (12)	12	-	DVB/CAR/PDMS(50/30)	GC/MS	6	12
	-		DVB/CAR/ PDMS	GC/MS	8	66
	-	-	CAR/PDMS	GC/MS	20	68
	4	-	-	GC/MS	2	65
	-	-	DVB/CAR/PDMS	GC/MS	4	69
	6	-	DVB/CAR/PDMS	GC/MS	13	77
	60	44-85	CAR/PDMS(75)	GC/MS	4	51
	60	44-85	CAR/PDMS	GC/MS	17	56
	5	-	ZIF-7	GC-FID	5	84
	4	-	-	SESI-MS	17	57
	6	-	-	SIFT-CI/MS	1	61
	2	-	-	SIFT-CI/MS	1	60
Urine (10)	8	28-69	PDMS(100), PA(85), PDMS/ DVB(65), DVB/CAR/PDMS (50/30), CAR/PDMS(85,75)	GC/MS	80	82
	53	38-83	DVB/Car1000/CarX (NTME)	GC/MS	30	80
	37	-	DVB/CAR/PDMS	GC-MS QTOF	20	81
	-	-	DVB/CAR/PDMS	GC-MS QTOF	45	78
	14	54±8	CAR/PDMS(75)	GC/MS	65	75
	43	-	DVB/CAR/PDMS	GC/MS QTOF	36	73
	6	31-74	PDMS (100), PA (85), DVB/CAR/ PDMS (50/30), CAR/PDMS (75), CW/DVB (70), PDMS/DVB (65).	GC/MS	26	79
	10	44-85	PDMS/DVB (65), DVB/CAR/PDMS (50/30), CAR/PDMS(75)	GC/MS	30	64
	17	44-85	CAR/PDMS	GC/MS	70	56
	4	48±8	-	GC/MS	100	62
Saliva (1)	66	25-76	CAR/PDMS	GC/MS	8	76

–: not available
*total: number of total studies
**SPME: solid phase microextraction (PDMS: polydimethylsiloxane; CAR: carboxen; DVB: divinylbenzene; ZIF: zeolitic imidazolate framework; PA: poly(acrylic acid); CW: carbowax; Car: carborane)
***VOCs: volatile organic compounds

aroma, commonly attributed to lipid oxidation processes and plant-derived volatiles. Guaiacol, a methoxyphenol, is known for its distinctive smoky and woody aroma with subtle vanilla-like sweetness; it is widely used in flavoring compounds such as roasted coffee and smoked meats. Finally, 4-tert-butylphenol is perceived

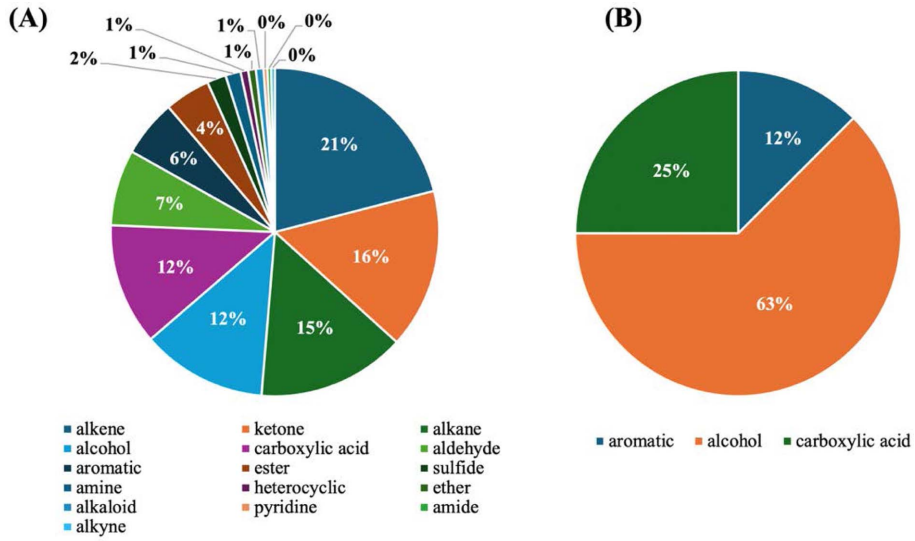
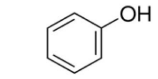
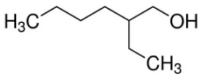
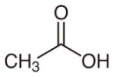
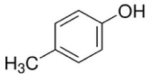
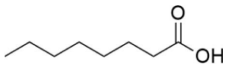
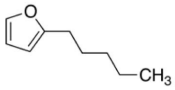
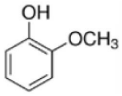
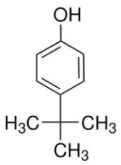


Fig. 2. Analysis results of the distribution of (A) 268 VOCs and (B) selected 8 VOCs.

Table 2. 8 VOCs related to breast cancer (frequency ≥ 4)

Chemical type	Name	CAS No.	M.W (g mol^{-1})	Structure	Frequency	Matrix
Alcohol	Phenol	108-95-2	94.11		7	B[a], C[b], U[c], S[d]
Alcohol	2-Ethyl-1-hexanol	104-76-7	130.23		6	C, U
Carboxylic acid	Acetic acid	64-19-7	60.05		5	B, C, U, S
Alcohol	p-Cresol	106-44-5	108.14			U
Carboxylic acid	Octanoic acid	124-07-2	144.21			C, U
Aromatic	2-Pentylfuran	3777-69-3	138.21			U
Alcohol	Guaiacol	90-05-1	124.14		4	U
Alcohol	4-tert-Butylphenol	98-54-4	150.22			U

a) B = breath, b) C = cell, c) U = urine, d) S = saliva

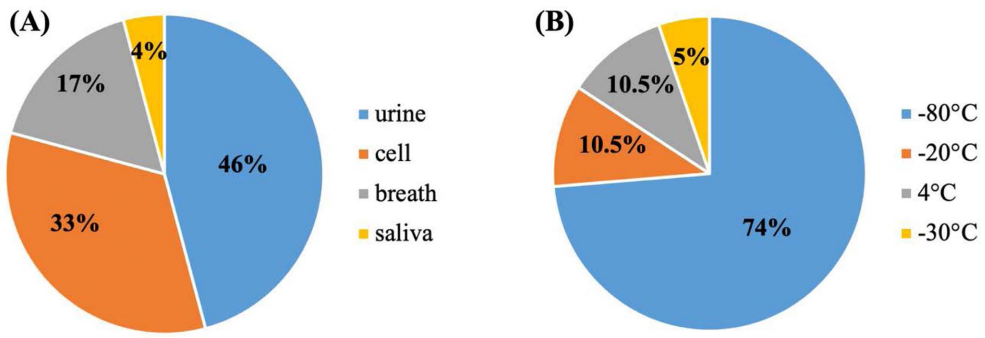


Fig. 3. Analysis results of (A) sample matrix and (B) storage temperature.

as mildly sweet but exhibits a synthetic, rubber-like odor frequently linked to industrial materials and certain perfumery applications.

In summary, while several of these compounds contribute pleasant or food-related aromas (e.g., guaiacol, 2-pentylfuran), others are associated with unpleasant or biologically derived odors (e.g., phenol, p-cresol, octanoic acid), and some with artificial or environmental exposures (e.g., 2-ethyl-1-hexanol, 4-tert-butylphenol). These odor characteristics provide insight into their potential roles as biomarkers or sensory indicators in environmental or biomedical contexts. These findings would highlight the diversity of VOCs associated with breast cancer and their potential as diagnostic biomarkers.

3.2. Sampling methods

The key parameters were matrix and number of samples, temperature of sample storage, age and BMI of breast cancer patient. An analysis of sample matrixes used in the reviewed studies revealed that urine was the most commonly utilized accounting for 46 % of studies. This was followed by cell samples (33 %), exhaled breath (17 %), and saliva (4 %). Although cell samples were the second most frequently used sample type, their applicability in clinical settings is limited as they do not fully account individual metabolic variability. As a result, their diagnostic accuracy in real-world applications remains uncertain. There were very few studies that explored non-invasive sampling methods such as skin secretions or sweat. It highlights the need for further research in these areas to expand the applicability of VOC-based breast cancer diagnosis.

The number of samples used in each study varied significantly ranged between 2 and 256. The age of sampled patients were also varied between 18 and 85. Most studies did not specify body mass index (BMI) as an inclusion criterion, except one study. It restricted the BMI range between 17 and 28, while another limited participants to those without hypertension or diabetes. Regarding sample storage temperatures, 74 % of studies reported that -80 °C was the most frequently used. Additionally, -20 °C and 4 °C were each used in 10.5 % of studies, while -30 °C was reported in 5 % of cases (*Fig.* 3).

3.3. HS-SPME conditions

Solid-phase microextraction (SPME) is a widely adopted sample preparation technique for the extraction and preconcentration of volatile and semi-volatile organic compounds in complex biological matrixes.[84] The technique relies on a coated fiber, typically made of fused silica and embedded with polymer, which is exposed to the sample matrix or its headspace. Analytes partition between the sample and the fiber coating based on their physicochemical properties. After the extraction phase, the fiber is transferred directly into the heated injection port of a gas chromatograph, where the analytes are thermally desorbed for subsequent analysis (*Fig.* 4).[85] SPME offers several advantages, including high sensitivity, minimal sample preparation, low solvent consumption, and compatibility with automation. It is especially

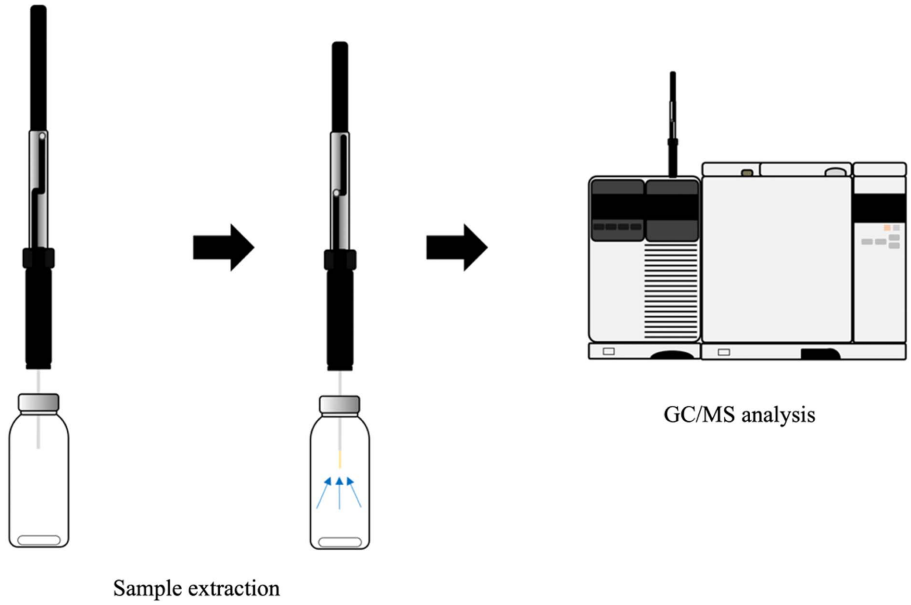


Fig. 4. Operation procedure of headspace-solid phase microextraction (HS-SPME).

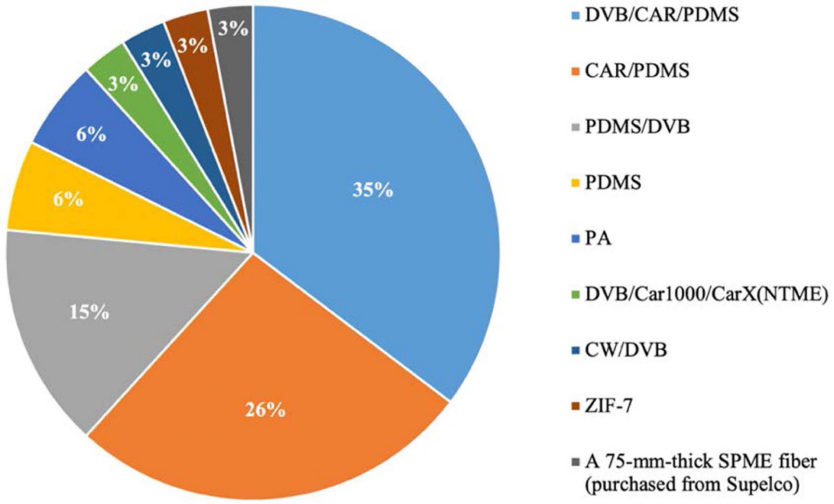


Fig. 5. Analysis results of type of SPME fiber.

useful for VOC analysis in breath, urine, and cell culture media, where matrix interferences can otherwise complicate direct injection techniques.[86] The efficiency of SPME depends on various factors such as fiber coating type, extraction temperature and time, agitation, and sample pH or salinity. Because of its simplicity and effectiveness, SPME has become an essential technique in VOC biomarker discovery and has been frequently applied in cancer-related VOC studies, including those targeting breast cancer.[87]

Key parameters included the type of SPME fiber, the temperature and time of saturation, adsorption, and desorption, as well as the chromatographic column and analytical instrument employed. The comparative results of these conditions are summarized in *Figs.* 5 and 6. The most commonly used SPME fiber was the moderately polar DVB/CAR/PDMS (Divinylbenzene/Carboxen/Polydimethylsiloxane), accounting

for 35 % of studies. Carboxen is a porous carbon-based sorbent with a high surface area, widely used in SPME fibers for its strong affinity toward small and volatile analytes, particularly in trace-level of VOC analysis.[88] The low-polarity CAR/PDMS (Carboxen/Polydimethylsiloxane) was used at 26 %, the non-polar PDMS/DVB (Polydimethylsiloxane/ Divinylbenzene) at 15 %, and the non-polar PDMS (Polydimethylsiloxane) and polar PA (Poly(acrylic acid)) at 6 % each, respectively. Other fiber types including DVB/Car1000/CarX (Divinylbenzene/ Carborane-Silica(1000)/Carborane-Silica(X)), CW/ DVB (Carbowax/Divinylbenzene), and the non-polar ZIF-7 (Zeolitic imidazolate framework-7) were used in 3 % of the studies (*Fig.* 5). Car1000/CarX fiber is composed of carborane–silica composites which was designed to enhance the adsorption of a wide range of volatile and semi-volatile organic compounds, particularly under low-polarity and thermally stable conditions.[89] Most studies utilized commercially available SPME fibers (e.g., DVB/ CAR/PDMS, CAR/PDMS, PDMS/DVB, PDMS, PA). However, given the lack of detailed information of SPME fibers for breath samples, it is reasonable to infer that breath sample was collected from the sampling bag and injected into the analytical instrument directly.

The sample volume used for analysis varied significantly among studies ranging between 5 μL and 1 L. The large variation in sample volumes might be attributed to differences in sample matrixes. Breath samples typically required larger volumes, while cell samples were generally processed in smaller volumes than gas samples. To enhance VOC extraction efficiency, 32 % of the studies added sodium chloride (NaCl), while others incorporated additives such as hydrochloric acid (HCl), protease inhibitors, and doxorubicin. Doxorubicin (DOX) is one of the most widely used and effective chemotherapy drugs, often administered alone or in combination with other agents. It has a broad spectrum of activity and is commonly used to treat both solid tumors and hematologic cancers, including breast cancer, sarcomas, and pediatric malignancies.[90] In addition to additives, 29 % of the studies adjusted the sample pH to a highly acidic range (pH 1~3). Sample pH was mostly controlled with the HCl solution to optimize VOC extraction. Most urine samples were treated with NaCl as it was, as NaCl was added to enhance VOC extraction efficiency from water-based matrixes.[91] In contrast, pH adjustment was commonly performed to cell samples, as pH plays a critical role in the extraction efficiency and stability of VOCs in cellular matrixes.[92]

The SPME saturation temperature was primarily set at 60 °C in 67 % of studies by considering the boiling points of VOCs which generally range between 50 °C and 100 °C. The saturation time was predominantly 30 min accounting for 80 % of studies. The SPME adsorption conditions varied based on the analytical instruments and columns used in different matrixes. However, adsorption at 60 °C was most common, which reported in 28 % of studies followed by 37 °C (22 %), 50 °C (22 %), 40 °C (17 %), 38 °C (6 %) and 200 °C (5 %). Adsorption time was 30 min in 30 % of studies while 75 min (20 %), 60 min (15 %), 20 min (10 %), 45 min (10 %), 10 min (5 %), 40 min (5 %), and 50 min (5 %) were also reported. A distinct trend was observed in the selection of saturation and adsorption temperatures between cell and urine samples. For cell samples, saturation and adsorption were predominantly performed at temperatures below 50 °C reflecting their thermally labile nature, whereas urine samples, which are more thermally stable, were generally processed at temperatures above 50 °C. For complete desorption of the adsorbed VOCs from the fiber, 90 % of studies conducted desorption at 250 °C while 5 % used 200 °C and 270 °C. The desorption time was 5 min and 6 min in 22 % of studies followed by 2 min (17 %), 10 min (17 %), 12 min (11 %), 0.5 min (6 %), and 3 min (5 %) (*Fig.* 6).

3.4. Detection and characterization of VOCs

Among the analytical instruments used for VOC analysis, gas chromatography/mass spectrometry (GC/ MS) was the most commonly employed, accounting for 77 % of studies. GC has been widely adopted

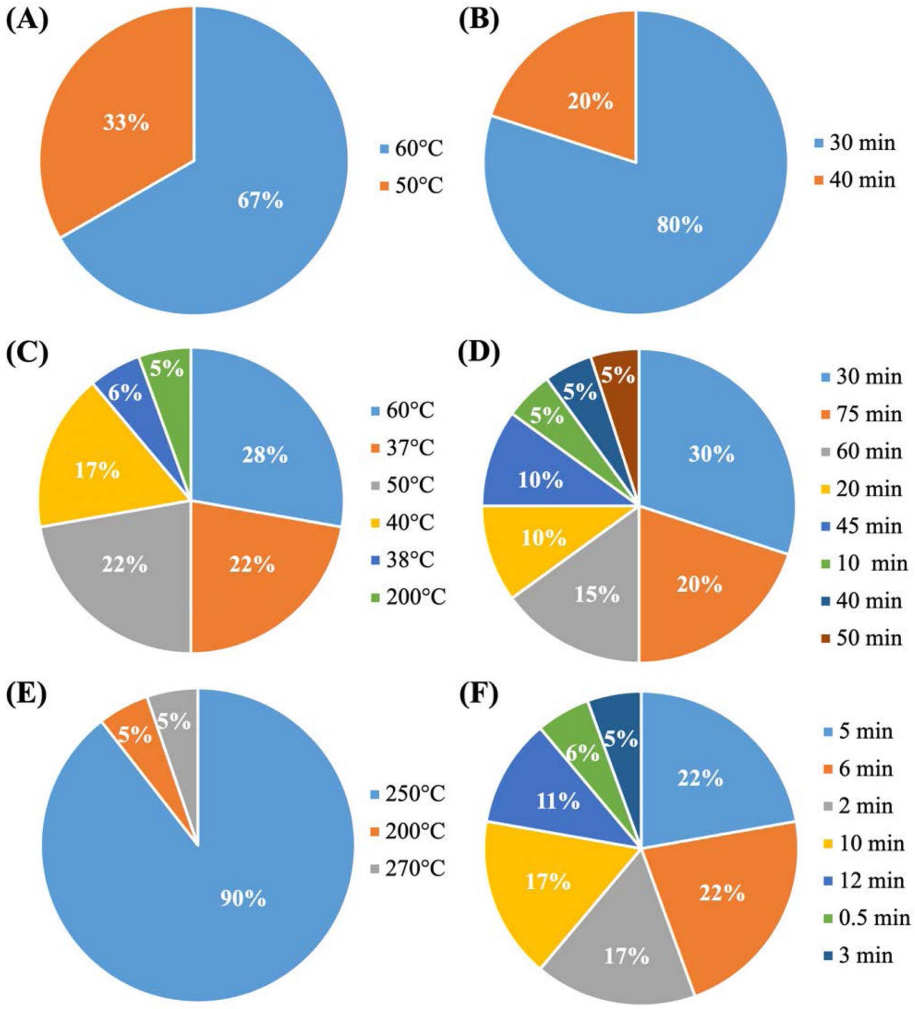


Fig. 6. Analysis results of (A) saturation temperature, (B) saturation time, (C) adsorption temperature, (D) adsorption time, (E) desorption temperature, and (F) desorption time.

analytical technique that separates volatile compounds through differential partitioning between a stationary phase and a mobile gas phase to enable high-resolution analysis of complex mixtures.[93] Because of its high sensitivity, reproducibility, and capability for VOC identification, the combination of chromatographic separation with mass spectrometric detection allows for accurate qualitative and quantitative analysis of low-abundance VOCs, making it particularly well-suited for biomarker discovery in cancer research. This technique enables the separation of complex mixtures and the detection of VOCs at trace levels, even in biologically noisy matrixes such as urine or breath.[94] Moreover, GC/MS offers a robust platform for inter-laboratory comparability when standardized protocols are applied.[95] Gas chromatography/mass spectrometry-quadrupole time-of-flight (GC/MS-QTOF) was used in 10 %, selected ion flow tube-chemical ionization/mass spectrometry (SIFT-CI/MS) was used in 7 % of cases, while gas chromatography-flame ionization detector (GC-FID) and secondary electrospray ionization-mass spectrometry (SESI-MS) were applied in 3 % of studies. GC/MS-QTOF offers high mass accuracy and resolution, making it suitable

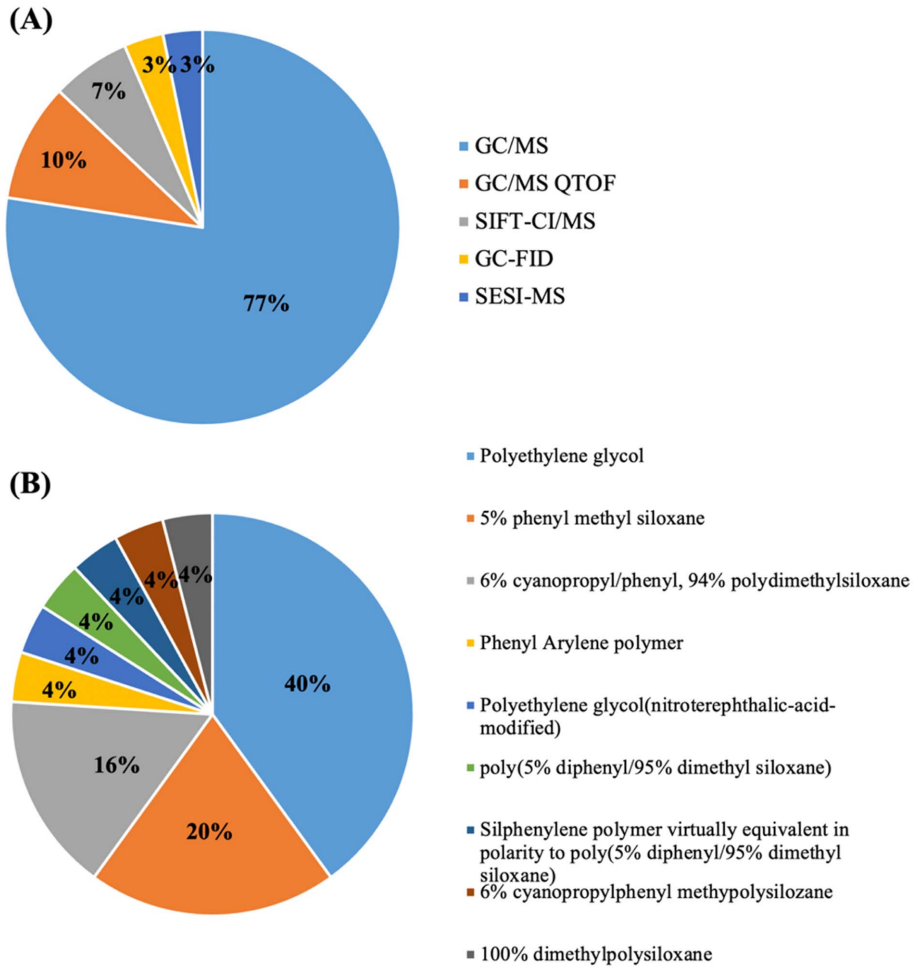


Fig. 7. Analysis results of (A) analytical instruments and (B) column stationary phase.

for untargeted VOC profiling and the identification of novel biomarkers.[96] Compound identification in GC-based methods is typically achieved by comparing acquired spectra against established mass spectral libraries, such as the NIST database.[97]

The stationary phases of the GC columns used in these studies also varied significantly. Polyethylene glycol (PEG), a polar stationary phase, was the most frequently used, accounting for 40 % of studies. Columns with a 5 % phenyl methyl siloxane was used in 20 % of studies and columns with 6 % cyanopropyl/phenyl/94 % polydimethylsiloxane was 16 %. Other stationary phases included 6 % cyanopropylphenyl methylpolysiloxane, poly(5 % diphenyl/95 % dimethyl siloxane), nitroterephthalic-acid-modified polyethylene glycol, phenyl arylene polymer, silphenylene polymer (with polarity equivalent to poly(5 % diphenyl/95 % dimethyl siloxane)), and 100 % dimethylpolysiloxane, each of which was used in 4 % of studies (*Fig.* 7).

3.5. Challenges and limitations of VOC-based breast cancer diagnosis

Despite the potential of VOCs as biomarkers for breast cancer, several challenges must be addressed. The lack of standardization in sampling and analytical methods, and data interpretation hinders reproducibility and comparability among studies. A review of 30 studies reveals substantial variability in sample storage

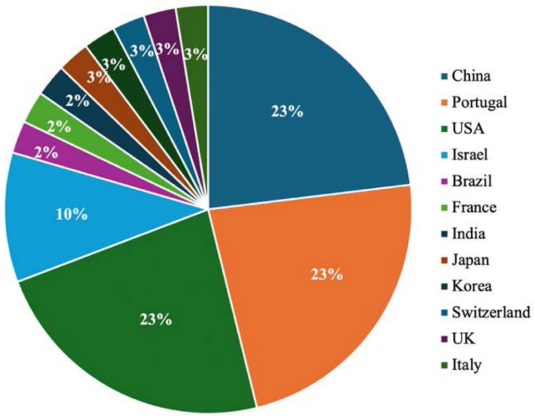


Fig. 8. Analysis results of country.

temperature, saturation, and adsorption temperatures and times during analysis depending on the matrix of sample. These inconsistencies highlight the need to establish standardized analytical methods to each sample matrix. Additionally, external factors such as diet, lifestyle, medication use, and environmental exposures can significantly influence VOC profiles, making it difficult to distinguish disease-specific biomarkers.[98,99] Notably, the majority of studies were conducted in limited countries such as China, Portugal, and the United States (*Fig.* 8). To better compare VOC patterns across different populations and support the development of standardized biomarkers, further research is necessary. Another major limitation is the lack of large-scale clinical validation, as many identified VOC biomarkers have not yet been rigorously tested for diagnostic reliability and specificity. Although GC/MS was the most commonly used instruments in the studies reviewed, its clinical implementation faces significant challenges. High-resolution techniques such as GC/MS and SIFT-CI/MS require costly and specialized equipment and expertise, which limits their accessibility and practicality. To overcome these limitations, future research should prioritize the establishment of standardized methodologies, the expansion of clinical studies, and the integration of advanced data analysis approaches to enhance the reliability and applicability of VOC-based breast cancer diagnosis.

4. Future Directions for VOC-Based Breast Cancer Screening

4.1. Diagnostic accuracy and standardization of analytical methods

While numerous VOCs have been suggested as potential biomarkers for breast cancer, their diagnostic performance remains uncertain because of the limited clinical validation and inconsistent methodologies. Many studies differ in critical parameters such as sample type (e.g., breath, urine, or cell cultures), SPME fiber selection, adsorption temperatures and times, and chromatographic systems. These variations contribute to inconsistent results and limit cross-study comparability. To improve diagnostic reliability, future research should aim to validate candidate VOCs in large, diverse populations and establish standardized methods for sampling, sample preparation, and analysis. It includes defining consistent storage conditions, extraction procedures, and implementing rigorous quality control measures such as internal standards, blank samples, and instrument calibration. Establishing methodological consensus will not only enhance reproducibility but also support multi-center collaborations and facilitate the clinical translation of VOC-based diagnostics.

4.2. Integration of machine learning for VOC pattern analysis

Given the complex and multivariate nature of VOC datasets, conventional statistical tools often fall short in capturing subtle patterns associated with disease states. Machine learning (ML), a subset of artificial intelligence that enables systems to learn patterns from data and make predictions without being explicitly programmed, offers a powerful approach to uncover nonlinear relationships and classify VOC profiles with high accuracy.[100] Algorithms such as support vector machines (SVM), random forest (RF), and artificial neural networks (ANN) have already demonstrated promising results in classifying cancer samples based on VOC signatures.[101] SVMs are effective for high-dimensional data and operate by finding the optimal hyperplane that separates classes.

RF is an ensemble method that constructs multiple decision trees to improve classification performance and reduce overfitting. ANNs mimic the structure of the human brain and are particularly powerful for modeling complex, nonlinear relationships. To utilize the full potential of ML, we should focus on collecting large, high-quality datasets that include diverse sample types and standardized measurements. This will allow for effective training and validation of predictive models. Additionally, explainable AI techniques should be applied to provide insights into the decision-making process of these models, so that it increases their interpretability and clinical trustworthiness. Combining ML with other omics data, such as genomics or metabolomics, could further enhance the specificity and sensitivity of breast cancer detection. Ultimately, the integration of machine learning into VOC research holds the potential to revolutionize early cancer diagnostics by enabling real-time, non-invasive screening tools.

4.3. Expanding research on breast cancer-specific VOCs and their metabolic pathways

Despite the growing interest in VOC-based cancer diagnostics, studies specifically focused on breast cancer VOCs remains limited compared to other cancer types such as lung or colorectal cancer. Moreover, the metabolic pathways responsible for the production and alteration of VOCs in breast cancer are still poorly understood. Elucidating these pathways is essential for validating VOCs as biologically meaningful biomarkers rather than incidental findings. Future investigations should integrate metabolomic profiling and pathway analysis to trace the biochemical origins of key VOCs associated with breast cancer. This will require interdisciplinary collaboration among analytical chemists, biochemists, and clinicians to bridge the gap between chemical signatures and biological mechanisms. Furthermore, in vitro and in vivo models should be used to simulate VOC production under various conditions such as tumor progression, treatment response, and hormonal influences. A deeper understanding of the metabolic context of VOCs will aid in identifying biomarkers with higher disease specificity and reduce the likelihood of false positives.

5. Conclusions

This systematic review comprehensively assessed studies on breast cancer-related volatile organic compounds (VOCs) selected through the PRISMA methodology, with a focus on non-invasive sampling and analytical methods. Our analysis revealed that GC/MS, particularly when paired with HS-SPME was the most widely employed platform for VOC analysis. However, there is a notable lack of methodological consistency across studies, including variation in sample matrixes (breath, urine, cell), SPME fiber selection, sample preparation conditions (such as pH adjustment and salt addition), and extraction temperatures and times. These discrepancies present a significant barrier to inter-study comparability and limit the clinical translation of findings. While certain VOCs, such as phenol, 2-ethyl-1-hexanol, and acetic acid, were frequently reported in association with breast cancer, their diagnostic utility has yet to be validated through large-scale, multi-institutional studies. Additionally, the geographic distribution of studies remains concentrated in a few countries, suggesting a need for greater global representation to capture ethnic and environmental variability in VOC analysis. Notably, research on alternative non-invasive matrixes such as sweat or skin secretions remains limited in spite of their potential to facilitate easy and continuous sampling in real-world settings. The field would benefit from standardized analytical protocols and broader clinical validation including integration with machine learning approaches that can extract meaningful diagnostic patterns from complex VOC datasets. Linking VOCs to metabolic pathways could also improve biological interpretability and assist in identifying cancer-specific signatures. Ultimately, while VOC-based diagnostics for breast cancer are still in development, this review underscores their potential as a scalable, patient-friendly approach to early detection and disease monitoring and provides that current methodological challenges are addressed

through collaborative and multidisciplinary research efforts.

Acknowledgements

This study was supported by the National Research Foundation of Korea (Project No: RS-2023-00252784217820409900001) and by a sabbatical year (2023-2024) from Seoul Women's University.

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