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Odors and cancer: Current status and future directions

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ABSTRACT

Cancer is the second leading cause of death in the world. Because tumors detected at early stages are easier to treat, the search for biomarkers—especially non-invasive ones—that allow early detection of malignancies remains a central goal to reduce cancer mortality. Cancer, like other pathologies, often alters body odors, and much has been done by scientists over the last few decades to assess the value of volatile organic compounds (VOCs) as signatures of cancers. We present here a quantitative review of 208 studies carried out between 1984 and 2020 that explore VOCs as potential biomarkers of cancers. We analyzed the main findings of these studies, listing and classifying VOCs related to different cancer types while considering both sampling methods and analysis techniques. Considering this synthesis, we discuss several of the challenges and the most promising prospects of this research direction in the war against cancer.

1. Introduction

Cancer is the second leading cause of death in the world, after heart disease, with an estimated nine million deaths in 2020 [1,2]. In 90% of cases, cancer-related deaths are attributable to metastasis, not to primary tumors [3,4]. To reduce mortality in cancer patients, it is therefore important to detect malignancies as early as possible [5], before metastasis and establishment of tumor cells at distant sites. Early diagnosis of cancer has indeed been shown to greatly increase the effectiveness of treatments, which in return reduces mortality and morbidity [6]. However, early cancer detection remains a difficult task for several reasons, a major one being that tumor progression is often an elusive process: patients may display symptoms such as fatigue, weight loss [7], or pain only at already advanced stages of the disease. Thus more than ever, the development of tools and biomarkers for early cancer detection holds tremendous hope for early treatment.

Cancer diagnosis today relies on a variety of clinical settings, including radiography, computerized tomography, magnetic resonance imaging, positron emission tomography, endoscopy, ultrasound, thermography, cytology, and biopsy (reviewed in [8,9]). Apart from these

clinical techniques, there are molecular tools based on both genomic and proteomic signatures of cancer [10]. All of these existing technologies and methods are effective; however, several of them are invasive, expensive, time-consuming, or limited to facilities in large hospitals [11–13]. Thus, there is a great interest in finding biomarkers linked to cancer that could be detected with less invasive and less expensive measures. Since the mid-1980s, increasing attention has been devoted to exploring the relevance of volatile organic compounds (VOCs) emitted by the body as potential biomarkers of cancers.

The study of human smell for detecting diseases is not new. Indeed, the first to have used human scent as sign of disease was Hippocrates, around 400 BCE, who asked his students to smell the breath of their patients as a potential indicator of disease [14]. With advances in analytical techniques such as gas chromatography, many studies on VOCs in humans [15,16] have been carried out with great potential for the detection of biomarkers in many diseases. Volatile organic compounds are emitted from the whole body and can be analyzed from exhaled air, feces, saliva [15], skin [15,17–19], urine [15,20], and blood [21]. Since the beginning of the 20th century, the number of studies linked to variations in VOCs emitted by humans to detect diseases has

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been steadily increasing, whether they concern parasitic diseases such as malaria [22] or chronic diseases [23] such as asthma [24], diabetes [25], or tuberculosis [26], or even to the recently unfolding COVID 19 pandemic [27]. The study of VOCs can also be used in the context of disease diagnosis in both wild animals, e.g., *Mycobacterium bovis* infection in badgers and cattle [28] and domesticated animals, such as respiratory infections of bovine [29]. This allows a less invasive approach in animals, where medical examinations can be highly stressful and where disease detection is mostly done post mortem [30].

Concerning malignant pathologies, several studies published over the last few decades have been conducted on volatile organic compounds emitted by cancer patients in the hope of developing a non-invasive way to detect early cancers [31–33]. These studies yielded several publications for different types of cancers, in particular for lung cancer (for reviews, see [31,34,35]). Different sources of VOCs emission have been considered, such as exhaled air [36,37], urine [38], or even cell culture [39]. Various analysis techniques have been employed, including gas chromatography–mass selective detection (GC-MS) [40,41], proton transfer reaction–mass spectrometry (PTR-MS) [42], and electronic nose techniques [43]. However, most review papers that focused on the qualitative analysis of the topic have not been able to reach a consensus on the number and identity of VOCs that would allow (early) cancer diagnosis [36,44,45]. We therefore decided to conduct an in-depth review of the various approaches and techniques that have so far been employed across the fields of cancer and chemical ecology. By conducting a comprehensive review and meta-analysis of the literature, we quantify the number of compounds that may have a role in cancer detection, taking into account the different sampling and analysis techniques. Finally, we provide some recommendations on how to improve our capacity at identifying relevant VOCs biomarkers for cancer.

2. Materials and methods

2.1. Literature review

Our systematic database review was conducted by searching published articles on PubMed (<https://pubmed.ncbi.nlm.nih.gov/>), Web of Science (www.webofknowledge.com), and Google Scholar (<https://scholar.google.com/>) that contained the following terms: (“cancer” AND “VOC” OR “volatile organic” OR “odor detection”). Much of the information on the generalities of different cancers was found on the American Cancer Society site (<https://www.cancer.org/>). We took into account all the studies that have analyzed the chemical composition of odor profiles from human cancerous patients. The literature included articles published in English from 1984 and until August 2020, excluding systematic reviews, meta-analyses, case report studies such as experimental treatments designed to modify odors (e.g. induced oxidative stress), studies performed on animals, as well as studies that investigated the ability of diverse animals to smell cancer.

For each study, we extracted the following data: type of cancer studied, sample type (e.g., exhaled air, urine...), year of publication, analytical methods, numbers of compounds detected, and the name of the volatile compounds that were shown to be specific to cancer odors. Each compound found in the literature was verified using the National Institute of Standards and Technology (NIST) (<https://www.nist.gov/>) and Pubchem databases (<https://pubchem.ncbi.nlm.nih.gov/>) to ensure that compound annotations were consistent. We categorized publications based on the analytical method used. Gas chromatography–mass

spectrometry (GC-MS) included all the analyses conducted with TD-GC-MS (thermal desorption–gas chromatography–mass spectrometry) and/or GC-TOF-MS (gas chromatography/time-of-flight mass spectrometry). Studies dealing with electronic nose techniques were grouped under the term e-nose [46]. We grouped rarely used techniques in a category called “other”: FT-ICR-MS (nanoelectrospray Fourier transform ion cyclotron resonance mass spectrometry) [47], TD-SPI-MS (thermal desorption–single photon ionization–mass spectrometry) [48], TDLS (tunable diode laser spectrometer) [49], and H-NMR (proton nuclear magnetic resonance) [50].

2.2. Statistical analyses

We used multiple correspondence analysis to investigate the underlying structure of the dataset, which was fully categorical. The aim was to investigate whether the various chemical compounds reported in the literature formed groups based on some categorical variables. This would help to identify experimental conditions in which they would be more likely to be detected. We included the year of publication (expecting that certain molecules would only be detected in recent years due to technological improvement in detection methods), the reference of each paper (to test for potential effects of publications reporting a large number of molecules), the cancer type (expecting different molecules to be observed for different cancers), and the detection methods (expecting different molecules would be detected with different methods). All analyses were carried out with R software v. 4.0.3 [51], and the multiple correspondence analysis was computed using the FactoMineR [52] and factextra [53] packages.

3. Results

A total of 208 publications were identified as being studies on the characterization of cancer using VOCs (Table 1).

Studies that used e-nose do not include chemical identification of VOCs, so lists of potential compounds that may discriminate between healthy persons and cancer patients were available in 142 of these studies. Among the 208 publications, 13 had not only studied a single cancer but had also compared patients with different types of cancers to healthy patients [89,99,202,205,210,113,139,162,169,180,184,185,187]. Eight other publications used different sampling techniques or different analysis techniques in the same study [44,55,56,58,86,102,107,187].

3.1. Diversity of cancers and methodologies

We found 208 studies that were carried out on different types of cancers with different sampling techniques and different analysis methods. Altogether, 142 publications (70% of the total publications referenced) investigated VOCs emission from different body parts. The first study exploring the potential of VOCs as cancer biomarkers was published in the mid-80s [171]. However, this study focused only on a single compound (emission of methane) in the exhaled air of patients displaying a colorectal cancer. The first investigation that carried out a comprehensive study on a large spectrum of VOCs between healthy individuals and individuals with lung cancer was published in 1985 [76]. There was an increase in the number of publications on the topic during the 2000s, thanks to advances in new technologies for odor sampling and analyses (Fig. 1), yielding an average of 15 publications per year since 2010.

Table 1

Studies on cancer volatiles according to cancer type, sample type, and analysis technique. The numbers in brackets refer to the number of publications for each category.

Type of cancer	Sample	Analysis technique	Reference	
Lung (118)	blood (4)	GC-MS (3)	[54–58]	
		LC-MS (1)	[54]	
	cell culture (17)	GC-MS (11)	[59,60,69,61–68]	
		e-nose (2)	[70,71]	
		PTR-MS (1)	[72]	
	exhaled breath (93)	SIFT-MS (3)	[73–75]	
		GC-MS (48)	[21,40,80–89,44,90–99,56,100–109,57,110–117,58,76–79]	
		e-nose (43)	[32,34,119–128,83,129–138,89,139–148,94,149–151,99,106,108,113,118]	
		GC-IMS (4)	[152–156]	
		Other (3)	[47,49,157,158]	
	pleural effusion sample (2)	PTR-MS (3)	[90,101,159]	
GC-MS (2)		[160,161]		
sweat patches (1)		GC-MS (1)	[162]	
tissue (4)		GC-MS (4)	[44,86,102,107]	
urine (4)		GC-MS (4)	[163–166]	
Colorectal (26)		exhaled breath (11)	e-nose (6)	[89,113,167–170]
			GC-MS (8)	[41,89,113,171–175]
	fecal (5)	e-nose (1)	[176]	
		GC-MS (4)	[174,177–179]	
	saliva (1)	GC-MS (1)	[180]	
	sweat patches (1)	GC-MS(1)	[162]	
		e-nose(1)	[181]	
	urine (7)	FAIMS (1)	[182]	
		GC-MS (6)	[5,50,182–185]	
		H-NMR (1)	[50]	
	Breast (21)	blood (1)	GC-MS (1)	[186]
cell culture (5)		GC-MS (2)	[187,188]	
		IMS (1)	[189]	
		SIFT-MS (2)	[190,191]	
exhaled breath (11)		GC-MS (9)	[89,192–199]	
		e-nose (4)	[89,195,200,201]	
urine (4)		LC-MS (1)	[202]	
		GC-MS (4)	[184,185,202,203]	
saliva (1)		GC-MS (1)	[204]	
Bladder (8)		exhaled breath (2)	e-nose (2)	[113,169]
			GC-MS (1)	[113]
	urine (6)	e-nose (3)	[205–207]	
		GC-MS (2)	[208,209]	
Gastric (11)	exhaled breath (10)	SIFT-MS (1)	[210]	
		GC-MS-MS(6)	[113,162,175,211–213]	
		e-nose(4)	[113,175,214,215]	
		TD-SPI-MS (1)	[48]	
		SIFT-MS (2)	[216,217]	
Gastro-esophageal (2)	sweat patches (1)	GC-MS (1)	[162]	
	exhaled breath (1)	SIFT-MS (1)	[218]	
	urine (1)	SIFT-MS (1)	[187]	
Head and neck (11)	exhaled breath (9)	e-nose (7)	[99,113,139,169,219–221]	
		GC-MS (4)	[99,113,219,222]	
	sweat patches (1)	GC-MS (1)	[162]	
	saliva (1)	GC-MS (1)	[223]	
Kidney (2)	exhaled breath (1)	e-nose (1)	[113]	
		GC-MS (1)	[113]	
Leukemia (3)	sweat patches (1)	GC-MS (1)	[162]	
	cell culture (2)	GC-MS (2)	[224,225]	
Liver (4)	urine (1)	GC-MS (1)	[184]	
		GC-MS (1)	[226]	
	blood (1)	GC-MS (1)	[226]	
		cell culture (2)	GC-MS (2)	[227,228]
Lymphoma (2)	exhaled breath (1)	e-nose (1)	[227]	
		GC-MS (1)	[229]	
		GC-MS (1)	[162]	
Malignant Pleural Mesothelioma (6)	sweat patches (1)	GC-MS (1)	[162]	
		urine (1)	GC-MS (1)	[184]
Melanoma (3)	exhaled breath (5)	e-nose (2)	[230,231]	
		GC-MS (2)	[232,233]	
		IMS (1)	[156]	
		GC-MS (1)	[234]	
Ovarian (5)	cell culture (1)	e-nose (1)	[235]	
		GC-MS (2)	[235,236]	
		GC-MS (2)	[235,236]	
Pancreas (1)	skin (2)	GC-MS (2)	[235,236]	
		e-nose (1)	[235]	
		GC-MS (1)	[235]	
Prostate (11)	exhaled breath (4)	e-nose (4)	[113,237–239]	
		GC-MS (2)	[113,237]	
Prostate (11)	urine (1)	LC-MS (1)	[202]	
		GC-MS (1)	[202]	
Prostate (11)	sweat patches (1)	GC-MS (1)	[162]	
		GC-MS (1)	[162]	
Prostate (11)	exhaled breath (4)	e-nose (4)	[89,113,240,241]	
		GC-MS (1)	[162]	

(continued on next page)

Table 1 (continued)

Type of cancer	Sample	Analysis technique	Reference
Stomach (2)	sweat patches (1) urine (6)	GC-MS (2)	[89,113]
		GC-MS (1)	[162]
		e-nose (3)	[205,242,243]
	exhaled breath (1)	GC-MS (2)	[244,245]
		SIFT-MS (1)	[210]
		GC-MS (1)	[246]
Thyroid (1)	saliva (1)	GC-MS (1)	[180]
	tissue (1)	GC-MS (1)	[246]
	exhaled breath (1)	GC-MS (1)	[247]

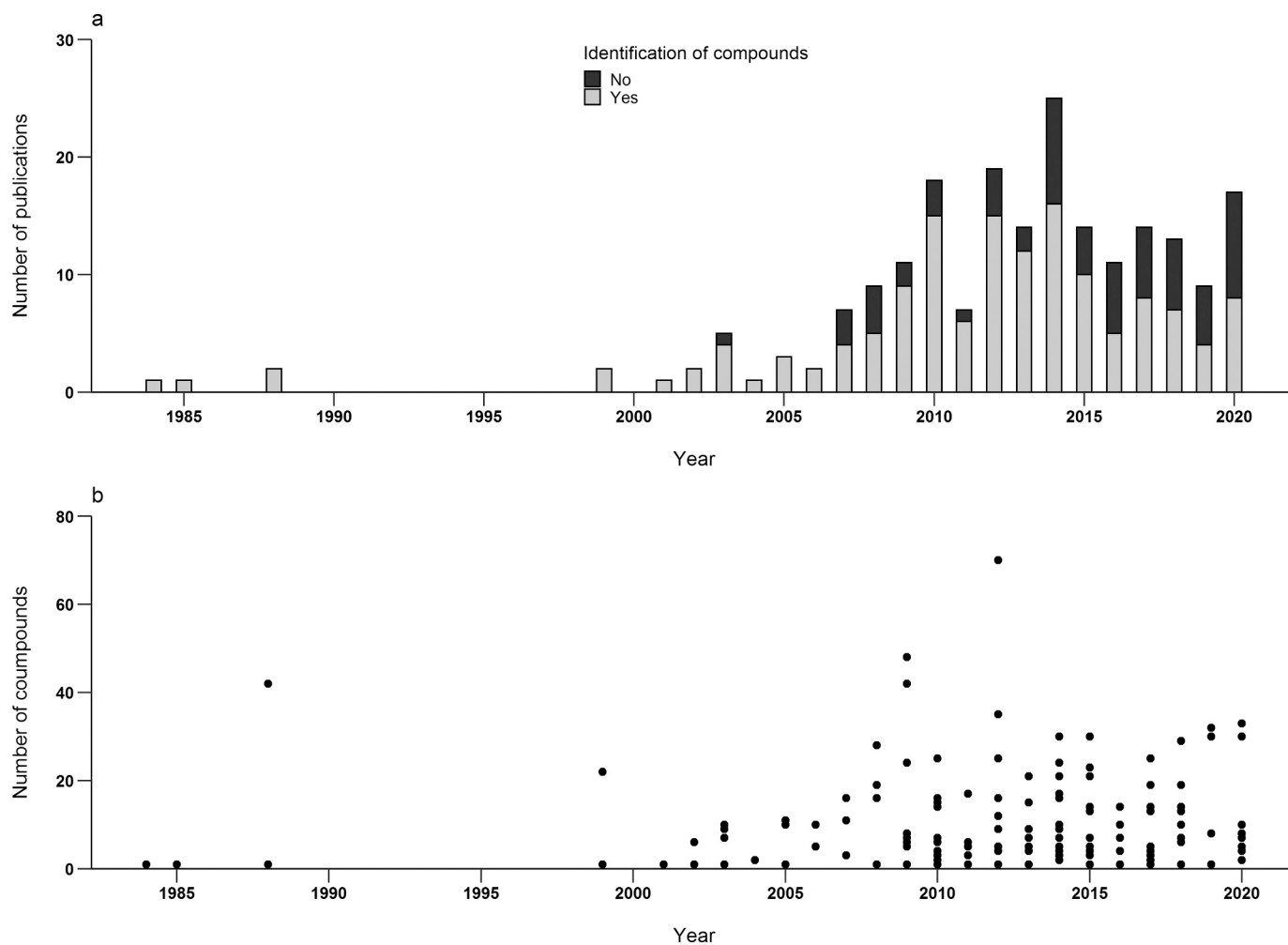


Fig. 1. a) Evolution of the yearly number of papers published from 1984 through August 2020 that investigated volatile organic compounds (VOCs) released by cancerous samples. Gray bars: compounds were identified; black bars: compounds were not identified. b) Number of compounds identified per study according to the year of publication.

There was also an increase in the number of publications that did not carry out compound identifications. Studies that did not identify compounds were generally those that used the electronic nose technique or those that simply aimed at differentiating between healthy people and those with cancer without identifying the compounds involved. The *E*-nose technique has become more frequently used since 2003. The first publication was on lung cancer [118], after which an increasing proportion of publications used this technology. As a consequence, there was a decrease in the number of studies attempting to identify cancer-related compounds into the mid-2010s. Among the publications that identified discriminating compounds, there was great heterogeneity in

the number of compounds detected. Some detected only 10 compounds or fewer, while others reported up to 70 compounds [66]. In this latter publication, the large number of compounds detected was due to the fact that authors collected odor samples from cell cultures at different incubation times and observed different new compounds through time. The large variation in the number of compounds isolated may be because some studies used different analysis techniques, for example GC-MS (Gas Chromatography–Mass Spectrometry) and LC-MS (Liquid Chromatography–Mass Spectrometry), or different samples, such as exhaled air and cell culture, which increases the number of compounds that can be detected.

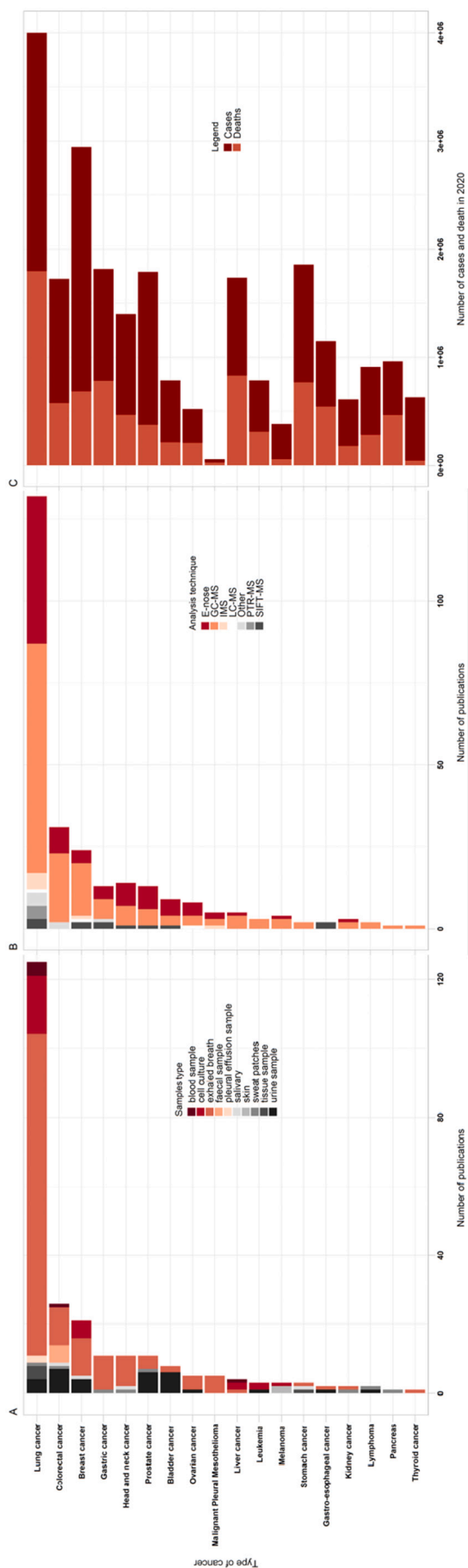


Fig. 2. Number of publications per type of cancer according to the sample source examined (A) the chemical analyses used (B). The graph C gives the number of cases and deaths for each cancer in 2020 [1].

These 208 publications included 18 different types of cancers, with a predominance for lung cancer (Fig. 2). Since the seminal publication on lung cancer [76], 118 studies have been published on this cancer, accounting for almost 60% of the studies. A seven hundred eighty four different studied cancers were colorectal cancer, with 26 papers (12,5% of publications), and breast cancer, with 21 papers (10% of publications). The other types of cancer studied represent together 72 papers (35% of publications). The second most common cancer affecting only men [1], prostate cancer, accounts for only 11 articles (5% of the publications). Among the cancers affecting only women, apart from breast cancer, only ovarian cancer has been studied (five papers, 2,5% of publications). Three other cancers were studied, gastric cancer (11 publications), head and neck cancer (11 publications), and bladder cancer (8 publications), which represent 4–5% of publications. Finally, leukemia, melanoma, and kidney cancer, were covered in fewer than 1% of publications, with only one or two articles focusing on the specific cancer. Altogether, the 208 publications finally represented 237 “studies”, when considering the different types of cancer in these publications.

Samples were from nine different areas, with the chemical analysis of exhaled breath being largely dominant compared to other body parts. Exhaled air sampling has been used to detect almost all the cancers listed in our review, except for leukemia, lymphoma, melanoma, and liver and pancreatic cancer. Exhaled breath analysis is a non-invasive technique that allows the observation of by-products from biochemical processes in the body [248]. It is a rapid and easy method with many advantages compared to other diagnostic techniques, such as bronchoscopy for lung cancer or other medical imaging [39]. It is non-invasive and painless—the patient is just asked to blow into a machine, similar to a stress test with a pulmonologist. The method can be used as often as necessary without restriction, allowing frequent patient follow-ups.

Following exhaled air, the two most often used samples were cell cultures and urine samples, with 27 and 25 papers (13% and 12% of publications), respectively. Becker [38] suggested that urine has more advantages than breath for the search of volatile biomarkers, and thus must be considered as a better method for non-invasive cancer detection. The other seven types of samples represent fewer than 10% of publications (only 1 to 2.5% for each sampling technique), indicating that these body extracts, e.g. tissue samples or sweat patches, were largely under-represented in the literature. Skin samples (melanoma) and saliva samples (colorectal and stomach cancer) were used in fewer than 1% of publications. Pleural effusion samples are used exclusively for the study of lung cancer, and this technique was used in only one publication [160]. This technique involves the removal by thoracentesis (needle aspiration) of fluid from a pleural effusion.

To carry out odor sampling on the different VOCs emission routes that we referenced above, different techniques were used. The most common, SPME (solid-phase microextraction) was developed in 1995 [249]. The first publication using this technique dates from 2003 [119]; it coupled SPME to a SAW (surface acoustic wave) sensor array, a type of electronic nose. SPME fiber is more frequently coupled to GC-MS. Apart from SPME fiber, studies used sorbent traps, glass tubes, or Tenax sorbent tubes. To analyze these samples, different analysis techniques using various high-performance equipment were employed, with GC-MS being the most frequently used technique (128 papers, 61.5% of publications) (Fig. 2). The GC-MS technique has been used on all types of cancer except gastroesophageal cancer, which was studied only by selected ion flow tube mass spectrometry (SIFT-MS). The e-nose was used in 75 publications (36%). This method was designed to imitate the mammalian olfactory system with an instrument designed to obtain repeatable measurements. This technique does not necessarily require the identification of VOCs to characterize people as being healthy or with cancer [46]. The electronic nose technique has been used with cancers that had been studied with other techniques; the seven least-studied cancers (kidney, leukemia, gastroesophageal, lymphoma, stomach, pancreatic, and thyroid cancer) have never been studied with this technique (Fig. 2). The ion flow tube mass spectrometry (SIFT-MS) [250] and proton

Table 2

The 28 most common compounds cited in the 142 studies on cancer odors. Only volatile compounds that were reported in more than 10 studies are shown. Origin (natural or not natural) and occurrence of compounds in the studies are given.

Compound	Number of publications N (%)	Compound origin ¹	Possible contamination source	Cancer Type / Number of publications (N)			
				Lung (83)	Colorectal (18)	Breast (16)	Other cancer (46)
Hexanal	27(19)	Natural: fatty acid derivative		19	3	1	11
Acetone	25(17.6)	Natural: fatty acid derivative		15	5	3	11
Styrene	20(14.1)	Not natural: industrial origin (manufacture of polymers and copolymers)	Ambient air, cigarette smoke, food packaging	16	1	1	9
Ethanol	20(14)	Natural: fatty acid derivative		11	4	1	11
Xylene	19(13.4)	Not natural: solvent used in industry and medical technology	Ambient air, cigarette smoke. Printing, rubber, paint, and leather materials	11	4	1	14
Toluene	19(13.4)	Not natural: industrial solvent, gasoline, chemical products	Ambient air, cigarette smoke, vehicle exhaust, consumer products	16	3	1	14
2-Butanone	19(13.4)	Natural: shikimate pathway		14	1	1	4
Isoprene	18(12.7)	Natural: mevalonate or methylerythritol 4-phosphate pathway		14	1	1	7
Ethylbenzene	18(12.7)	Not natural: petrochemical industry (polystyrene, gasoline additive, rubber, paints...)	Ambient air, water, cigarette smoke, consumer products	14	3	1	13
2-ethyl-1-hexanol	18(12.7)	Not natural: industrial origin (production of plasticizer phthalate, fragrance for cosmetics)	Ambient air, plastics, cosmetics	13	2	3	14
Nonanal	18(12.7)	Natural: fatty acid derivative		9	5	1	17
Phenol	18(12.7)	Not natural: plastic manufacture, antiseptic	Indoor air, water	5	3	5	13
Benzene	15(10.6)	Not natural: industrial chemical, chemical precursor	Gasoline vapors, vehicle emissions, cigarette smoke, food packaging	13	0	1	1
2-Propanol	15(10.6.0)	Not natural ² : solvent for coatings or industrial processes, pharmaceutical applications, rubbing alcohol...	Indoor air, household and commercial products (cleaners, disinfectants, cosmetics, solvents...)	11	2	1	2
Cyclohexanone	14(9.9)	Not natural: industrial chemical precursor to polyamides (nylon), solvent for plastics, rubbers, waxes	Indoor air, cigarette smoke	8	1	2	3
Heptanal	13(9.2)	Natural: fatty acid derivative		8	2	2	8
Decanal	13(9.2)	Natural: fatty acid derivative		7	4	0	9
Benzaldehyde	13(9.2)	Natural: shikimate pathway		9	1	1	2
Decane	13(9.2)	Natural: fatty acid derivative		9	1	1	2
Undecane	12(8.5)	Natural: fatty acid derivative		8	4	1	13
Dodecane	12(8.5)	Natural: fatty acid derivative		5	3	2	2
Acetaldehyde	12(8.5)	Natural: fatty acid derivative		10	1	0	2
1-Propanol	12(8.5)	Natural: fatty acid derivative		10	0	0	1
Hexane	11(7.7)	Natural: fatty acid derivative		9	0	1	1
2-Methylpentane (isohexane)	10(7.0)	Not natural: industrial solvent, gasoline, chemical intermediate	Gasoline vapors, indoor air	10	1	0	6
Pentane	10(7.0)	Not natural: solvent. Possible endogenous origin (lipid peroxidation)	Indoor air	10	0	0	0
p-Cresol (4-methylphenol)	10(7.0)	Natural: by-product of tyrosine metabolism		1	5	2	3
Cyclohexane	10(7.0)	Not natural: industrial solvent	Air / water contaminant	5	2	1	2

¹ Origin of compounds: the name of the biosynthetic pathway is given for compounds naturally produced by living organisms while details for industrial origin are given for compounds that are not natural.

² Possible natural origin of isopropanol: [255, 256]

transfer reaction mass spectrometry (PTR-MS) [251] techniques were used in 11 (5.3%) and in four (2%) publications, respectively. Because these techniques are based on chemical ionization and only molecular ions can be generated, compounds with identical molecular masses after ionization cannot be distinguished from each other with this technique. Another technique, ion mobility spectrometry IMS [252,253], was used in seven (3.4%) publications. Finally, the LC-MS technique [254], which involves liquid chromatography (LC) coupled to mass spectrometry (MS), was only mentioned in 1% of the publications: one on lung cancer from a blood sample [54] and another on urine from two cancers, breast and ovarian [202].

3.2. Volatile compounds associated with cancer

A total of 784 different compounds were isolated and identified

across the 142 references—all cancers combined—as being compounds that distinguish between healthy people and those with cancer. Of these compounds, 190 compounds were detected in more than one study. Table 2 lists the 28 most commonly occurring compounds from these studies: they occurred in at least 10 studies out of the 142. Fig. 3 indicates whether the concentration of those compounds decreases or increases / appears or disappears as cancer develops.

In total, 16 of the 28 compounds are of natural origin, including nonanal, hexanal, acetone, and ethanol. Compounds such as styrene, xylene, toluene, and ethylbenzene are pollutants found in the ambient air or cigarette smoke; these are not produced by the body but are still found in certain types of samples, such as exhaled air [113], cell culture [65,66], sweat patches [162], and urine samples [209]. We found all these compounds in at least three different odor source samples and at least nine of the 18 cancer studies (Fig. 4). In some studies, certain

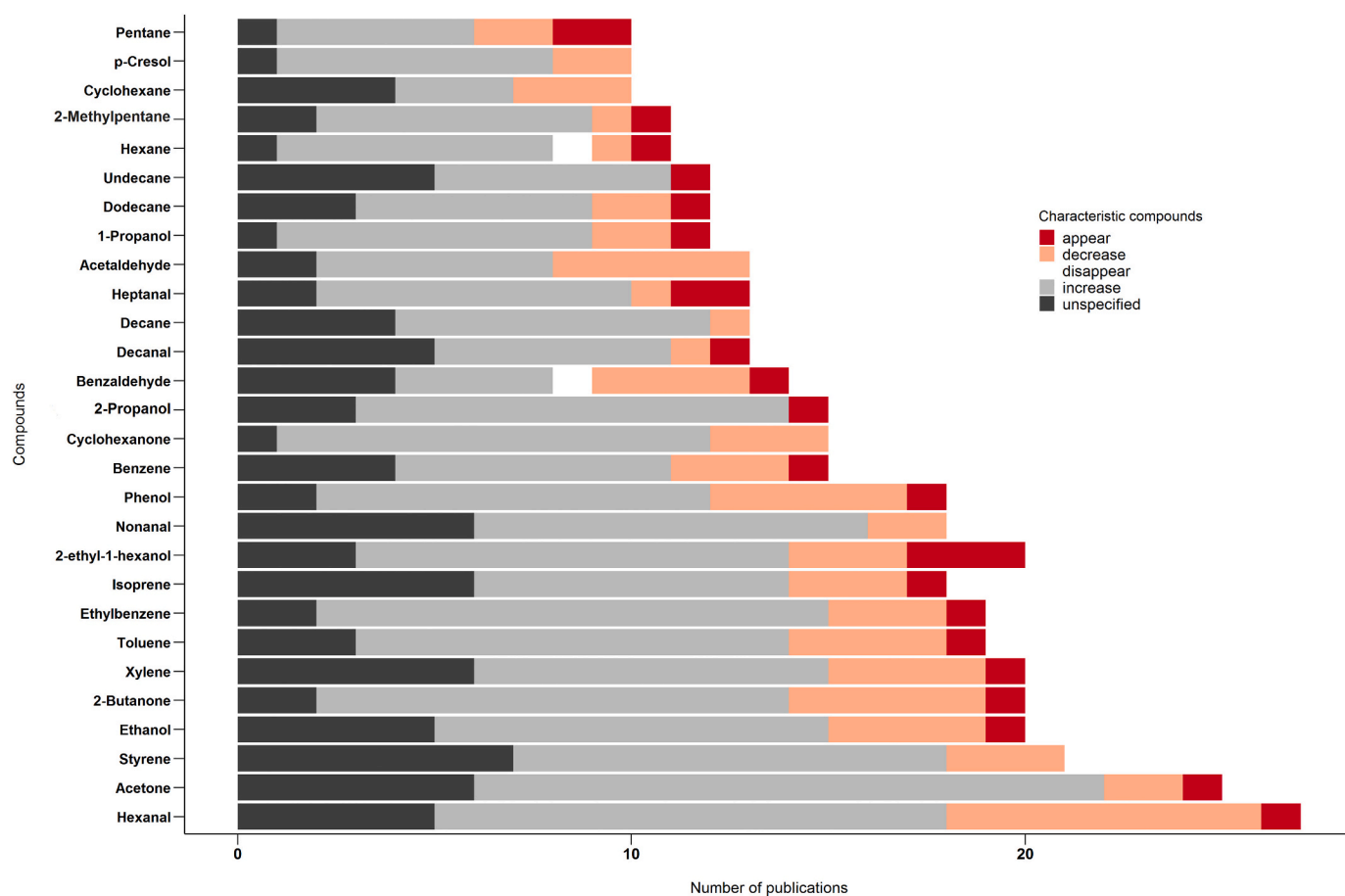


Fig. 3. Occurrence and variation characteristics of the 28 most common volatile compounds found to be associated with cancer.

compounds were specific to cancer patients, while in others they were present in both healthy and sick individuals but at different levels. Full details for these two situations and for each cancer types are given below. In some cases, the compounds were mentioned to allow differentiation between the healthy and cancer group, without indicating whether their concentration increased or decreased. In most cases, the 28 compounds tended to increase, or were sometimes only detected in cancer patients.

a) Lung cancer

Lung cancer is the third most common cancer in humans, but it is the most prevalent cause of cancer death worldwide [257]. Lung cancer includes different clinical types of pathology, with the main types of lung cancer being small-cell lung carcinoma (SCLC) and non-small-cell lung carcinoma (NSCLC). NSCLC is divided into three major histologic types: adenocarcinoma, squamous cell carcinoma, and large-cell carcinoma [258]. Different types of lung cancers are linked to different mutations that lead to the activation of oncogenes, the inactivation of tumor suppressors, and defects in the maintenance of chromosomal integrity. Depending on the type of lung cancer, it is not necessarily the same mutated genes that cause the tumor. For example, K-RAS mutations are detected almost exclusively in adenocarcinoma [259]. Because different types of lung cancers exist, it could be expected that different volatile profiles may occur. However, most studies did not consider the stage of cancer development or the type of cancer.

Analyses of volatiles from lung cancer represent 60% of the publications on cancer odors, with a total of 118 studies, of which 79 carried out individual compound identifications. A total of 458 different compounds were identified, but only 116 compounds have been recorded in

more than a single publication. Five compounds were found in at least 15 publications (i.e., 10%): hexanal, toluene, styrene, ethylbenzene and acetone. These compounds are not just found in lung cancer, e.g., hexanal was also detected in breast cancer [198] and colorectal cancer [162]. Forty four studies found that these five compounds may help distinguish between cancer patients and healthy individuals; the differentiating effect in 30 studies is associated with increased concentrations of these compounds in cancer patients while 11 studies found decreased concentrations. These five compounds are found in different types of samples (Table 1), such as exhaled breath, urine, tissue, blood, cell culture, and sweat patches. For three compounds—hexanal, styrene and ethylbenzene—decreased levels were observed in four publications studying cell cultures [59,63,65,66], but increased levels were found in 22 publication in other types of samples. Among 28 compounds identified, none was specific to lung cancer, except 1-propanol and pentane. 1-propanol has been found exhaled breath samples (10 studies) and from cell cultures odors (1 study) of lung cancer patients. In 9/10 publications, these compounds were found to increase or appear in cancer patients. Eighteen percent (10 out of 55 studies) of all publications on lung cancer that sampled exhaled breath have detected 1-propanol. Pentane has been found in 10 publications, 9 on exhaled breath and one on cell culture. Such as 1-propanol this compound was observed to increase or appear in most publications (8 out of 10 studies).

b) Cancer of the digestive system

Cancers of the digestive system include colorectal, stomach, gastric, gastroesophageal, pancreatic, and liver cancer. Among these cancers, colorectal is the third most common cancer in men and the second in women, and it represents 9% of all cancer deaths [257]. As previously

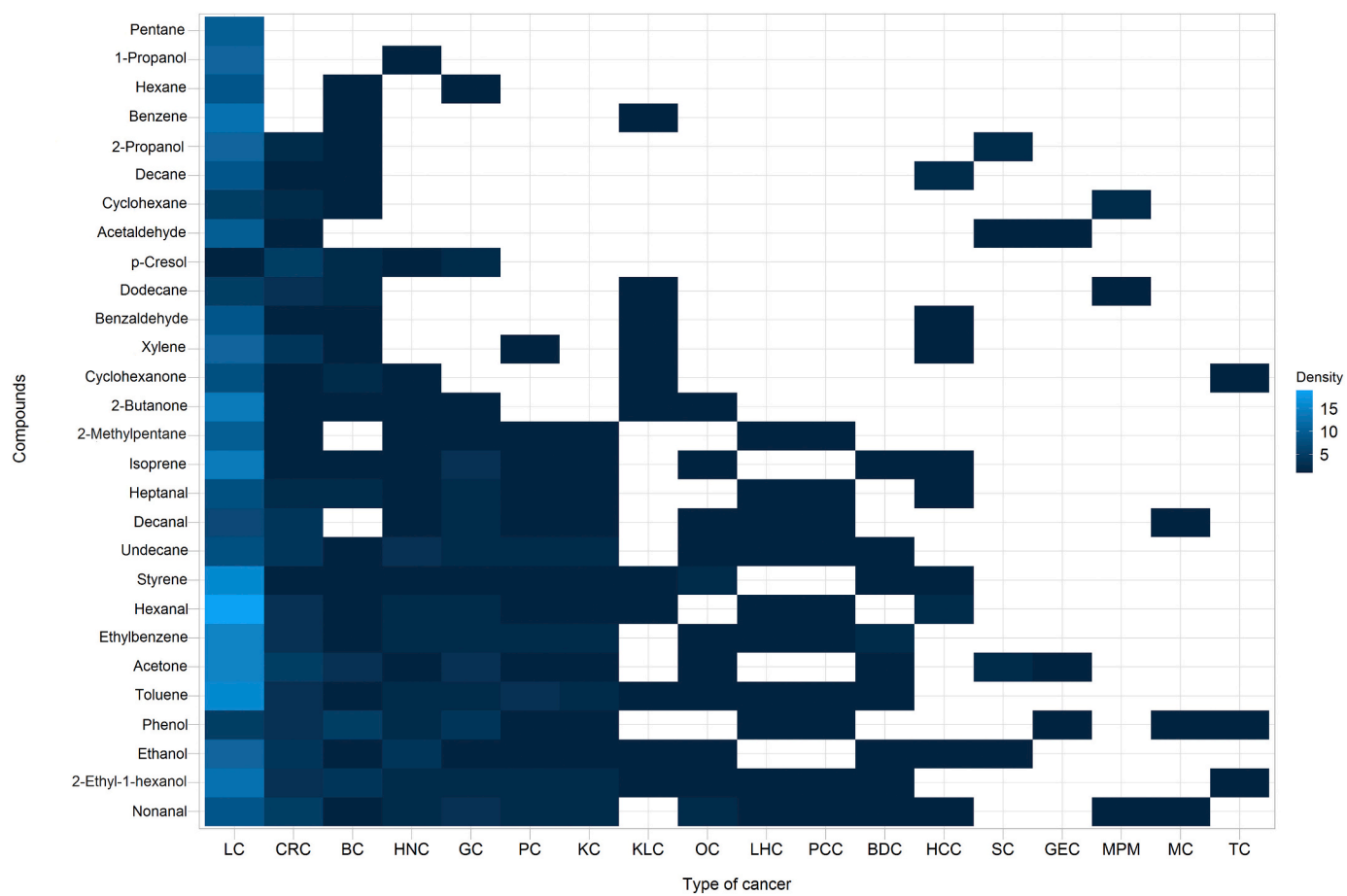


Fig. 4. Occurrence of the 28 most common volatile compounds associated with cancer for each type of cancer and the number of studies by cancer type for which each compound was found. LC: lung cancer; CRC: colorectal cancer; BC: breast cancer; HNC: Head and neck cancer; GC: gastric cancer; PC: prostate cancer; KC: kidney cancer; KLC: Leukemia; OC: ovarian cancer; LHC: Lymphoma; PCC: Pancreas cancer; BDC: Bladder cancer; HCC: Liver cancer (Hepatocellular carcinoma); SC: stomach cancer; GEC: gastro-esophageal cancer; MPM: malignant pleural mesothelioma; MC: melanoma; TC: thyroid cancer.

indicated, colorectal cancer is also the second most studied cancer for the identification of VOCs. With colorectal cancer, 95% of cases are adenocarcinomas and usually begin with adenomatous colon polyps. These polyps may then develop into malignant tumors following a series of genetic mutations [260]. These developments can be prevented if an intervention is made to excise polyps. It is therefore critical to find a technique to detect polyps and lesions before they become malignant.

Analyses of volatiles from individuals with colorectal cancer represent almost 10% of the publications; this includes 26 studies, 20 of which performed VOCs identification. Two hundred compounds were isolated and identified, but 170 were detected only once. The 200 compounds were isolated from six different types of samples: fecal, exhaled breath, urine, sweat patches, blood and saliva. Of the 28 compounds appearing in Fig. 4, 24 compounds were found in studies on colorectal cancer. Nine compounds (styrene, xylene, ethylbenzene, nonanal, dodecane, undecane, 2-propanol, 2-ethyl-1-hexanol and decanal) increase in cancer patients, other compounds increased or decreased depending on the publication. All these 24 compounds have been found in other types of cancer and are not unique to colorectal cancer (Fig. 4). The exception was p-cresol, which was found only in the urine: increased levels were observed in three publications [50,183,261] and decreased levels were reported in other publications [5]. This compound was found in four out of five publications for this cancer;

analyses were performed on urine.

For gastric cancer, the second-most studied digestive cancer, nine publications identified 62 compounds by investigating two types of samples, exhaled breath and sweat patches. Among the list of 25 compounds, sixteen were found in gastric cancer but only in two or three publications. Only phenol common to colorectal cancer which increases in cancer patients was found in four publications studying exhaled air [48,216,217] and sweat patches [162]. Two studies [187,216] found increased levels of p-cresol in the exhaled breath of gastric cancer patients.

Four studies investigated odor emissions linked to liver cancer, and no common compound was found among the four studies. Two discriminant compounds were found in two publications: decane was found to increase in cancer patients [226,229] while hexanal was found to decrease [228]. Of the 25 compounds most reported across publications, only nine were found in liver cancer (Fig. 4).

Very few studies have been carried out for other digestive cancers: two for gastroesophageal and stomach and one for pancreas. In gastroesophageal cancer, only one compound, hydrogen sulfide, was found in the two publications. Compounds identified in other cancers such as acetone or phenol were also identified in these studies [187,218]. These two publications did not use the same techniques and sampled urine [187] and exhaled air [218], which may explain the differences in the

compounds found. In total, 14 compounds were found in these two publications. For stomach cancer, we found only five compounds in two publications [180,246], and only two compounds were identified in both publications, acetone and 2-propanol. Two studies on stomach cancer were conducted on different sample types, exhaled breath and tissue [246] and saliva [180]. Acetone and 2-propanol were found with these three sample types; concentrations increased in exhaled breath and tissue, but concentrations were not specified in the article using saliva. The only publication on the pancreas was published in 2020 [162], but this study considered only two patients with pancreatic cancer and also included other cancers. The identified compounds were common to other cancers, such as colorectal or lung cancers.

c) Breast cancer

Breast cancer is the most frequently diagnosed cancer in women worldwide, with more than two million new cases per year, and it is the first cause of cancer death in women, with 626,700 deaths world-wide (data from 2018, [257]). Despite current diagnostic techniques based on mammograms and biopsy when mammograms shows breast change, breast cancer is often fatal when detected too late [262]. Despite the importance of finding early breast cancer biomarkers, only 8% of studies looking at odors linked to cancer have studied breast cancer. Among the 19 studies that investigated volatile emissions associated with breast cancer, 113 compounds were isolated and identified. Only four types of samples were used to study breast cancer odors: exhaled breath, urine, salivary and cell culture. Twelve compounds are common among these 16 studies, and only five of the 28 common compounds were not found for breast cancer (1-propanol, decanal, acetaldehyde, 2-methylpentane, pentane). Among the compounds identified in this cancer, only phenol was found in five publications [185,188,203,204,263] and 2-ethyl-1-hexanol in four publications [188,195,203,264] while all other compounds were only common to one or two publications.

d) Reproductive cancers: ovarian and prostate cancer

Ovarian cancer is one of the most lethal cancers in women (184,000 deaths in 2018 [257,265]), three out of four cases are diagnosed in advanced stages [266]. The principal cause of ovarian cancer lethality is the absence of valid screening programs and its rapid spread through the peritoneal surface. There is currently no screening test for the early detection of ovarian cancer, and new means of detection that could be more precocious and less invasive—such as VOCs analyses—would be of great value. Nevertheless, only five studies explored this direction for this cancer. Of these, only three identified compounds since the two other studies used the electronic nose. Two of the studies were carried out on exhaled air [113,237] and the other on urine [202]. Only nine of the 25 common compounds were cited as compounds detecting patients with ovarian cancer. Among these nine compounds, styrene and nonanal were common to both publications on exhaled breath. Different compounds were found in urine: androstenedione, 3-methyluridine, and 1-methyladenosine.

Prostate cancer is the second most frequently diagnosed cancer in men, with an estimated 1,3 million new cases and 395,000 deaths in 2018; it is the fifth leading cause of cancer death in men worldwide [257]. Like ovarian cancer, prostate cancer has been poorly investigated for VOCs: only 11 publications, of which only five attempted to identify specific VOCs. Two publications have examined exhaled breath [89,113], two considered urine samples [210,245] and one was based on sweat patches [162]. Of these five publications, 45 compounds were identified, 15 of which were in the list of 28 compounds. Toluene is the only compound found in three publications [89,113,162], and was

shown either to increase in cancerous samples [89,113] or to decrease [162].

e) Other cancers

● Bladder

Bladder cancer mainly occurs in older people. Most people (9/10) with this cancer are over 55, and the average age at diagnosis is around 73 years of age. Most bladder cancers start in the innermost lining of the bladder, which is called the urothelium or transitional epithelium. The more the cancer grows inside or through the layers of the bladder wall, the more difficult it is to treat as it invades the tissues of the bladder. To detect this cancer, urinary cytology and cystoscopy imaging are carried out, and the definitive pathological diagnosis is made by the transurethral route with a biopsy of the bladder. These examinations are highly invasive [267,268]. Finding a less invasive diagnostic technique, such as VOCs from urine, is thus highly sought. Eight studies were published on bladder cancer, six using urine samples, but two also examined exhaled air. Among these eight publications, only three focused on the identifying compounds, while the others used the electronic nose. Two publications looked for biomarkers in urine [209,210], and the third [113] used exhaled breath and considered different cancers. Another study [210] also investigated several cancers, including prostate and bladder cancers, and looked only at changes in the levels of a single compound, formaldehyde, which seems to increase in people with cancer. In two other publications [113,209], only one compound, ethylbenzene, was found in common.

● Head and neck squamous cell carcinoma

The term head-and-neck cancer (HNC) refers to a group of various types of tumors originating from various anatomical structures, including soft tissues, craniofacial bone, salivary glands, mucous membranes, and skin [269]. Most head and neck cancer cases (90%) are squamous cell carcinomas (HNSCC). Despite advanced diagnostics and treatment methods, this cancer family is often fatal; it is the sixth most common cancer worldwide, killing 450,000 people in 2018 [257,270]. The diagnostic technique for HNSCC is invasive panendoscopy, which consists of rigid esophagoscopy, rigid tracheobronchoscopy, direct laryngoscopy, hypopharyngoscopy, and inspection and palpation of the oral cavity and oropharynx with subsequent biopsy for histopathology examination under general anesthesia [220]. Only 11 publications investigated VOCs in this cancer, and only seven identified compounds. Only three samples were tested, exhaled breath, salivary and sweat patches. Eighty seven compounds were identified in these studies, but only two compounds were found in common, ethanol [113,219,222,223] and undecane [107,217,220].

● Kidney

Kidney cancer starts in the kidney, a pair of bean-shaped organs that remove excess water, salt, and wastes from blood in the renal arteries [271]. This cancer, like pancreatic cancer and lymphoma, has appeared in publications that studied several cancers at the same time [113,162]. These two publications have examined exhaled breath [113] and sweat patches [162]. Five compounds were in common in these two studies, which belong to the list of 28 compounds (Table 2): undecane, toluene, nonanal, ethylbenzene and 2-ethyl-1-hexanol.

● Leukemia

Leukemia is a group of cancers that usually starts in the bone marrow and leads to high numbers of abnormal and dysfunctional white blood cells. Only three studies were carried out on this type of cancer, one on human leukemia cell lines (THP1) [225] that detected seven potential biomarker compounds, including styrene and 2-ethyl-1-hexanol, which increased in cancer patients, and 2-butanone, which decreased. The other publication focused on myeloid leukemia [224], which is one of the most common hematologic malignancies. This study explored two cell lines (lymphoma cell line JEKO and acute mononuclear leukemia cell line SHI-1) that differed from the cell lines studied in the other publication [225]. The two cell lines do not have the same compounds: nine compounds were found for cell line JEKO and eight for cell line SHI-1. These include compounds already identified in other cancers, such as toluene, xylene, ethanol, and hexanal. All the compounds mentioned were found in other publications on other cancers except dodecane, 3,7-dimethyldodecane. One study [184] was conducted on the urine of patients with different types of cancers, including leukemia, colorectal cancer, and lymphoma. Four compounds were found to differentiate between healthy individuals and cancer patients. Among these three publications, no compounds were found in common. .

● Lymphoma

Lymphoma, like leukemia, is a cancer of the blood. It includes cancer of the lymphatic system, which is characterized by the excessive proliferation of lymphocytes in the ganglia. The main symptom is an increase in node size, and diagnosis is based on biopsy of the affected lymph nodes. Lymphoma is one of the ten most common cancers in the world [265]. Lymphoma has been investigated for VOCs in two publications that also studied other types of cancers [162,184]. Investigations were conducted on sweat patches [162] and on urine samples [184]. In urine samples, two compounds, 2-methyl-3-phenyl-2-propenal and 3-heptanone, were observed to increase significantly in the cancerous group [184].

● Malignant pleural mesothelioma

Malignant pleural mesothelioma is an aggressive tumor originating from the pleural lining of the thorax. It is causally associated with previous asbestos exposure [272]. Despite the ban on asbestos in 2005 across the European Union, it remains present in certain buildings, and the latency period for the cancer to appear following asbestos exposure is 40–50 years [272]. Thus, incidence is increasing despite the ban on asbestos. In addition to its high incidence rate, this cancer has a five-year survival rate of less than 5%. This very poor prognosis highlights the importance of early detection [273]. Five publications investigated volatiles from malignant pleural mesothelioma. Two studies identified 10 compounds from the exhaled air of patients [156,232], while three others [156,230,231] used the electronic nose. No compound was common to the two publications [156,232].

● Melanoma

Melanoma is the deadliest form of skin cancer because it can quickly spread to other parts of the body. Only two out of three publications identified compounds associated with melanoma [234,236], and it was only studied in cell culture. Twenty-three compounds were identified in these two publications, but no compound was common to both publications.

● Thyroid

Thyroid cancer starts in the thyroid gland, which makes hormones that help regulate metabolism, heart rate, blood pressure, and body temperature. The prevalence of this cancer has seemed to increase compared to other types of cancer, mostly because the use of high-

resolution ultrasound allows better detection of thyroid nodules [265]. Although most nodules are benign, 5–10% can become malignant [274]. To evaluate their level of malignancy, the most common diagnostic method is fine-needle aspiration biopsy, which has the advantage of direct characterization, but it remains an invasive operation [275]. Only one study focused on thyroid cancer by examining the composition of exhaled breath between normal persons and patients with thyroid disease [247]. Seven volatile compounds were found characteristics of thyroid cancer. Considering the list of 28 compounds (Table 2), only 2-ethyl-1-hexanol and phenol were identified in thyroid cancer.

3.3. Multiple correspondence analysis

The multiple correspondence analysis only explained 4.1% of the variance of the dataset. This indicates that, overall, there are very few compounds in the dataset that are specific to certain publications, cancer types, year of publication, or detection method. This also suggests that many VOCs can be detected using multiple methods. If this is the case, it could lead to the discovery of potential biomarkers that can be relatively easily detected using the wide range of machines available in pathology laboratories and hospitals.

4. Discussion

Our review demonstrates that, despite extensive research focused on identifying VOCs as potential signatures of cancers in recent years, this topic remains in its infancy and no definitive answers currently exist. Two important results also emerge from this review. First, even though many similar studies on the same cancer type found distinct volatile patterns and showed highly variable discriminant compounds, we could still establish a list of 28 compounds (Table 2) that were detected in most studies. These molecules were shown to be frequently present in the volatile emissions of various samples belonging to individuals with cancer. Second, the nature of the 28 compounds commonly associated with cancer is intriguing. Twelve of the 28 molecules are not natural compounds, i.e., they are compounds of exogenous origin that cannot be produced by any living organism, and the presence of these industrial compounds in biological samples inevitably raises questions concerning their origin. Several hypotheses can be proposed to explain this finding, ranging from body contamination, pollution associated with sampling, and/or misidentification. The other compounds of natural origin in this list are all common compounds regularly found (and even systemically found for a few, such as nonanal) in odor samples from animals or plants, or from other headspace sampling [276–279]. No particular or specific volatile compound(s), whenever considering quantitative or qualitative changes associated with cancer, emerged from all the studies reviewed here.

Regarding these molecules, several important questions remain unanswered: i) To what extent are changes in compound profiles linked to the tumor growth itself or to other metabolic disorders associated with tumor formation? ii) What are the biochemical pathways involved in the changes of volatile emissions—at least for natural compounds—that are associated with cancer? iii) What is the origin of the exogenous industrial chemical compounds in biological samples? Given that compounds such as styrene, xylene, toluene, and ethylbenzene are all classified as strong human carcinogens [280,281], is their presence in the volatile emissions of cancer individuals a consequence or cause of cancer?

Although many of the studies that investigated cancer volatiles have found promising discriminating compounds, none of the 28 most common compounds identified in these studies can be hypothesized to be produced and emitted by tumor growth itself. It currently remains uncertain what kind of metabolic disorders, such as those already recorded [282] can be involved in generating particular components that will finally emanate from the body as volatile compounds associated with cancer. Some authors have proposed biochemical processes, such as

accelerated oxidative stress linked to tumor growth, may result in the production of particular compounds [283,284].

The presence of exogenous compounds in odor profiles has often been validated by multiple authors without providing an explanation of their origin; conversely, other authors have eliminated these apparently aberrant data [90]. A few authors tentatively proposed reasons for their presence as potentially relevant volatile biomarkers [264,283]. Compounds such as benzene, toluene, ethylbenzene, and xylene (so-called BTEX compounds) are ubiquitous volatiles, almost always present in GC profiles from any kind of odor collection [285,286]. Their presence in the human body, for example in fatty tissues, may originate from multiple sources, such as regular exposure to cigarette smoke, indoor air, occupational environment, and pollution [287–289]. It seems reasonable to think that patients with lung cancer may eventually display higher levels of BTEX compounds than healthy patients in their breath because such compounds have likely accumulated in their body over time and also have known carcinogenic effects [290].

Another volatile compound often isolated from cancerous samples is 2-ethyl-1-hexanol, a potential candidate for a cancer biomarker [160,188,195]. Even though some explanations for an endogenous origin have been tentatively proposed in these studies, it remains to be demonstrated how a ubiquitous phthalate metabolite, known to be a common pollutant [291,292], may have a biomarker value.

For all these reasons, it is important to consider with caution the compounds with exogenous origin (Table 2) before assigning them as potential disease biomarkers. There is an urgent need to explore the biochemical processes that may explain why such contaminants can be emitted differently between cancer and healthy patients.

Of the 28 compounds recorded here, only two have been found in a single type of cancer, i.e., lung cancer: 1-propanol and pentane. 1-propanol is an endogenous and primary alcohol, usually detected in the exhaled air or even organ tissues [102]. Given the apparent specificity of this compound to lung cancer, more investigation would be necessary, with particular focus on the molecular pathways that contribute to its production. Regarding pentane, its endogenous presence in exhaled breath has been hypothesized to result from an increase peroxidation of fatty acids in patients with severe lung disease [293,294]. Further studies will have to confirm whether these compounds are biomarkers exclusive of lung cancer.

Apart from the 28 compounds found in the majority of cancers, other compounds were also detected in particular families of cancers affecting related organs; for example, p-cresol was only found in colorectal cancer [5,50,183,184] and gastric cancer [48,162,216,217], which are both digestive cancers. These compounds are endogenous, and higher levels are found mainly in urine samples of cancer patients. The compound p-cresol (4-methyl phenol) is a shikimic malodorous product with a typical fecal odor, and it has been isolated in volatile emissions from diverse mammal feces [295] and particularly human feces [296,297]. The modification of compounds emitted by the microbiome could be a sign of the impact of cancer on bacteria in our bodies. In the case of digestive cancers, this could result from an alteration in the important microbiome community present in this compartment of the body. However, it is surprising that p-cresol was identified mostly in the urine and was not found in studies using feces. In any case, the elevated concentration of this compound in the urine of patients with digestive cancers might be a good indicator of this type of malignancies. In summary, among the many compounds studied so far, 28 were found in most studies investigating VOCs and cancer. Two compounds stood out: 1-propanol was only associated with lung cancer while p-cresol could be of interest in the detection of digestive cancer (colorectal and gastric).

Despite these first promising advances, major problems need to be resolved before generalizations can be made and VOCs routinely used as a diagnostic tool of cancers by clinicians. First, we need to understand the reasons for the high heterogeneity between the results from different studies, namely whether such differences are biologically relevant or are merely artifacts, and whether better standardization of the

methodologies could be achieved. For example, in lung cancer, three compounds (hexanal, ethylbenzene, and styrene) were shown to vary differently when distinct samples were used. The concentrations of these compounds were observed to decrease in cell culture studies, but their levels increased for samples originating from breath, urine, tissues, or blood. This observation suggests that VOCs emitted by cancer cells do not behave in the same way when they originate from living organisms or are recovered from cell culture. A critical review [298] explained differences in the volatile patterns between breath samples and in vitro cell cultures by the age of the patient, environmental temperature, medication, disease stage, or comorbidities of each patient. Their review only focused on lung cancer and included two sampling techniques, but the possible variation due to such parameters could be generalized to most studies on cancer and odors. A standardized protocol for each cancer type should be proposed and applied in clinical settings. For instance, in the light of previous works, it seems that the most relevant sample for lung cancer is exhaled breath since lung cancer directly affects the respiratory system; in addition, the technique has proven its effectiveness, is currently used, and is not invasive. For other cancers, exhaled air might be less relevant since it may not be indicative of the physiological status of the impacted organ. Different sample types can be more applicable than others for different types of cancers, e.g., tissue for melanoma, feces for digestive cancer, urine for the kidneys, and blood for leukemia and lymphoma. VOCs measured from cell cultures may also have diagnostic value; however, because of the potential differences between analyses performed on cells versus patients, it is likely necessary to consider both sources of information.

The present synthesis also reveals that some cancers are more studied than others, for instance, lung cancers are over-represented while others like thyroid, pancreas, kidney, and lymphoma are underrepresented and/or never studied alone. Other cancers, such as bone or cervical cancers, have never been studied. For example, since cervical cancer is induced by papillomaviruses, it would be interesting to explore if the mere presence of the virus modifies odors and how these VOCs change when cells become cancerous. It is all the more surprising that no study has been done on this cancer because research has shown that dogs were able to detect other cancers, e.g. cervical cancer, with a sensitivity and specificity greater than 90% [299].

Animal models are particularly promising for studies of cancer-associated VOCs, since they offer the possibility of controlling numerous variables that add noise (e.g., age of individuals, age at which cancer starts its growth, sex, alimentation, reproductive status), and hence theoretically could help to isolate appropriate biomarkers [300]. These kinds of studies, especially those using genetically modified models for which cancer induction is controlled by the investigators, will also help to determine precisely how changes in VOCs co-vary in magnitude with tumor growth as well as the extent to which VOCs are altered before cancer can be detected. Such longitudinal studies are lacking at the moment. Studies using a mouse model mostly investigated the terminal stage of lung cancer [66,301,302]. Only two studies [303,304] examined changes in VOCs during cancer development in a mouse model. Experiments on mouse models [303,304] generally inject cancer cells into the animals, thus limiting the possibility of observing the natural evolution of cells within an organ as well as the precise timing odor changes over tumor progression. The mouse model seems a good way to study these variations and better understand them, although because mice do not emit the same compounds as humans, it is impossible to extrapolate the results even with genetically modified mouse models that develop human cancers. However, this approach may also allow to estimate at what cancer growth stage different variations of compounds can be observable. Furthermore, standardized rigorous protocols can be developed to assess the best sampling techniques for each cancer. Finally, the mouse model approach could allow the study of mechanisms that generate these modifications as well as ways to decipher the biochemical pathways involved in all cancer development and progression. Indeed, as long as the mechanism

controlling VOCs modification is poorly understood, it will be difficult to know how it occurs within a patient and to predict how VOCs change with disease progression.

The mechanistic and biochemical links between VOCs variation and cancer progression are not currently understood. Different research directions have been proposed and further explorations are needed. For instance, it has been suggested [305] that aberrant protein synthesis associated with melanoma growth may have produced a specific odor (to which a dog responded). Regarding breath, other authors [79] considered that oxygen free-radical activity may increase in cancerous cells. This process would degrade cell membranes by lipid peroxidation and convert polyunsaturated fatty acids to volatile alkanes that may be the main odorous cancer markers in exhaled breath. More recently, it has been hypothesized that cancer odor is a product of alterations in the major histocompatibility complex (MHC) [306].

Finally, an important point to consider for the future of this discipline is the need for comparative analyses that consider not only different cancers, i.e., on different organs, but also other (non-malignant) pathologies. Identifying VOCs as biomarkers of pathologies is not feasible for early cancer diagnosis. Given that most—if not all—pathologies are to some extent associated with body odor modifications, this point is crucial. Nakhleh et al. (2017)[113] studied 17 different diseases using an artificially intelligent nanoarray and detected 13 compounds, including some that were also found in other cancer studies (e.g., ethylbenzene, nonanal, styrene, toluene, and undecane). None of these compounds can be solely considered as a biomarker, but variations in volatile patterns may help to identifying specific diseases. Our review showed that no particular group of compounds emerged for any type of cancer. With artificially intelligent techniques, such as electronic nose, it is possible to examine small variations within a set of compounds. The sensitivity and specificity (i.e., the proportion of correctly identified healthy and sick people) are reported to be greater than 90% in some publications [94,99,122,140]. The use of noses, whether animal or electronic, can be considered as a very promising technique for the detection of odor variation linked to cancer. With appropriate learning, animals such as dogs and mice can detect with close to 100% sensitivity and specificity individuals with lung, breast [307], colorectal [308], and bladder cancer [309]. In addition to dogs and mice, the use of insects as a disease detector seems also possible. The antennal responses (i.e. without associative training possibility) of *Drosophila* to mammary epithelial cells from different types of breast cancer cells has been tested [310].

Other authors [303] showed that the nematode *Caenorhabditis elegans* was able to discriminate between human odor samples from cancerous and healthy patients. The response of *C.elegans* olfactory neurons to urine from cancer patients was significantly stronger to cancerous odors than to controlled odors, with a sensitivity and specificity of 95%. Furthermore, animals seem to be able to detect cancer at early stages [304,311], which would indicate the promising potential of odor analysis for early diagnosis of cancer. A very promising aspect of odor analysis in the context of cancer diagnosis could be to develop and establish an individual monitoring system, similar to the concept of regular mammography in breast cancer. For instance, we suggest long-term monitoring of odor profiles throughout an individual's life while carrying out imaging or other clinical examinations in parallel. This would allow the retrospective establishment of links between odor alterations with cancer initiation or progression.

5. Conclusion

1) Despite an increasing number of publications in the field of cancer-related odors over the last 20 years, with 208 publications referenced, this subject is still in its infancy and no definitive answer currently exists. The increasing enthusiasm in the field observed in the recent years gives hope that these techniques will be able to diagnose cancers earlier. The use of new techniques, such as electronic

noses in compelling compound identification seems to be increasingly developed. At the moment most studies have focused on a few cancers and mainly with the same sampling method (exhaled breath).

- 2) More than 700 different compounds have been isolated and identified in these publications. Here, we propose a detailed list of the 28 most common compounds. Among these most cited compounds, 12 are exogenous compounds of industrial origin. Their presence in biological samples raises questions concerning their origin, and hypotheses or explanations should be proposed before such compounds could be considered as potentially relevant volatile biomarkers.
- 3) While many compounds were isolated in several types of cancer, a few compounds were found in one type of cancer, e.g. 1-propanol and pentane for lung cancer and p-cresol for 2 types of digestive cancer, colorectal and gastric cancer. However, further studies are needed to confirm the specific value of such compounds as a cancer biomarker.
- 4) Finally, the search for VOCs as the signature of cancer is more than ever a stimulating and promising research direction, but it requires a much larger global research effort to go beyond the descriptive phase. In particular, biologists need the assistance of qualified chemists to avoid compound misidentification or error of interpretation. An effort should also be made to extend the list of cancers explored with this approach, using a variety of techniques.

Author's contribution

FG collected the data in the 208 publications, analyzed them with AMD and wrote the paper. LD, FT and BU conceived the original idea, supervised the project, discussed the results and contributed to the final manuscript. JM supervised the chemical ecology aspects.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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