

Exhaled Breath Analysis for Cancer Diagnosis and Screening

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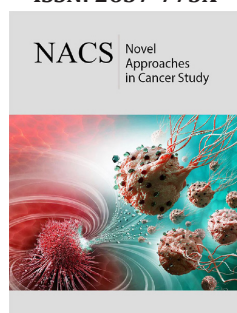
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ISSN: 2637-773X



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Submission: 📅 September 23, 2019

Published: 📅 September 30, 2019

Volume 3 - Issue 3

How to cite this article: Shao Y, Lin Y, Wang L, Mei F, Li L. Exhaled Breath Analysis for Cancer Diagnosis and Screening. *Nov Appro in Can Study*. 3(3). NACS.000562.2019.
DOI: [10.31031/NACS.2019.03.000562](https://doi.org/10.31031/NACS.2019.03.000562)

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Abstract

Background: Nowadays, cancer is still one of the main fatal disorders in the world, from which the patients suffer a lot while the burden of the families and society increased. Early recognition and treatment are crucial to reduce the death rate; however, in clinical practice, many cancers could only be recognized when it comes to a later stage. With the development and progress of the modern medical technique, more and more novel testing methods are reported and under research. Many reports showed that dogs could smell out the cancer patients, and exhaled breath test with such as the gas sensor is gradually taking an important role in cancer early diagnosis and screening. However, systematic reviews in both fields are lacking.

Objective: We conducted this review to give an overview on the applications of dog olfactory detection and/or gas analysis technique in cancer early diagnosis and screening.

Method: Chinese National Knowledge Infrastructure (CNKI) and PubMed databases up to August 31st, 2019 were searched to identify relevant studies. All studies related to dog olfactory detection and/or gas analysis products in cancer early diagnosis and screening were summarized and further analyzed. There was no limitation on language of the publication. Data were extracted from all included studies and meta-analysis was performed with Review Manager 5.3. Pooled risk ratios (RR) or mean difference (MD) with 95% CIs were used to evaluate the effectiveness of dog olfactory detection and gas analysis technique application for cancer diagnosis.

Result: 10 dog olfactory detection studies in year 2006-2019 were identified, while the meta-analysis of 2 randomized experiments in dogs showed there was no significant difference between the early cancer diagnosis accuracy of canine scent detection and biopsy-confirmed ($p > 0.05$). No clinical trials of gas analysis technique or product in human were identified, so no meta-analysis could be carried out. Different detection methods and gas analysis products for volatile organic compounds (VOCs) detection were summarized and their features, advantages and disadvantages were reported in detail.

Conclusion: The systematic review indicated that the analysis technique of VOCs from the human exhaled gas has the potential to be used for early cancer screening and diagnosis. The related techniques for VOCs detection are keeping developing, and the accuracy and specificity are continuously improved. However, more high-quality and large-scale randomized clinical trials are needed to confirm the effectiveness of exhaled gas analysis in cancer early diagnosis and screening.

Background

Cancer is one of the main diseases threatening the human life and health. Early recognition is crucial to increase the survival rate of cancer patients. However, current cancer early diagnosis faces many problems. For example, current early clinical diagnostic techniques have low specificity and sensitivity but need high cost. As the progress for the medicine, the new noninvasive and fast cancer early recognition technique has come out, which is of importance to decrease the death rate. Some research results indicate that the cancer patient could emit some special gas [1], and this provides the possibility to utilize the patient's emission gas for cancer screening, which is noninvasive, simple and sensitive. This diagnostic method has been adopted by using the trained dogs, which have the sensitive sense of smell [2]. And some research results have proven the possibility to use the dogs to realize the early diagnosis for

such as the lung cancer [3], melanoma [4], bladder cancer [5] and so on. Nevertheless, the progress for these researches is limited for the training difficulty and non-controllability of the dogs. Therefore, the artificial olfactory system technique based on gas sensor comes out. We conducted this review to give an overview on the applications of dog olfactory detection and/or gas analysis technique in cancer early diagnosis and screening.

Methodology

Literature search

We performed a comprehensive search from Chinese National Knowledge Infrastructure (CNKI) and PubMed databases up to August 31st, 2019 for all the potentially eligible studies related to dog olfactory detection and/or gas analysis products in cancer early diagnosis and screening.

Search strategy

Keywords for the search included “olfactory detection”, “dog detection”, “canine scent detection”, “scent detection” and “cancer early diagnosis” or “cancer diagnosis”. For the CNKI database, the key words were searched in Chinese characters and Pinyin. There was no limitation on language of the publication.

Data extraction and analysis

We processed and analyzed the data using the Review Manager software (Revman 5.3, provided by the Cochrane Collaboration). Random-effects models were used to calculate pooled effects. Fixed-effect models were used for combining data where it was

Table 1: Summary of dog olfactory detection studies.

No.	Year	Study Type	Country	Summary of Study	Disorder	Detection Sample	Remarks
1	2019	News report	USA	After 8 weeks of training, the Beagle was able to distinguish between serum samples from patients with malignant lung cancer and healthy controls.	Lung cancer	Blood Serum	Further isolate samples based on chemical and physical properties until specific biomarkers for each cancer are identified.
				Accuracy 97%. Double-blind study.			
2	2019	News report	USA	A click-and-click training was used to teach four beagles to distinguish between samples of normal serum and patients with malignant lung cancer.	Lung cancer	Blood Serum	Researchers speculate that dogs may be able to identify cancer samples by sniffing a biological compound.
				Accuracy 96.7% - 97.5%.			
3	2018	News report	Italy	After training, military dogs could sniff urine samples to determine whether their owners had cancer.	Prostate cancer, Bladder cancer, Kidney cancer, Lung cancer	Urine	Dogs may find abnormal physical condition of their owners according to their different odors after having cancer.
				Successfully detected urine samples from patients with different cancers, while smelled urine samples from patients with undiagnosed early cancers.			
4	2017	Literature		Dogs can sniff the skin and exhale through sniffing. Odors in odor, urine, body fluid and blood were detected for different cancers.	Lung cancer, Breast cancer, Prostate cancer, Ovarian cancer, Melanoma	Urine, Body fluid, Blood	The metabolic odors of cancer patients, such as exhaled gases, body fluids and excreta, contain specific volatile odors that healthy people do not have.

reasonable to assume that studies were estimating the same underlying treatment effect. Dichotomous data were presented as pooled Risk Ratio (RR) with 95% confidence intervals (95% CIs), while continuous data were presented as Mean Difference (MD) with 95% CIs. We performed forest plot and funnel plot analysis to test heterogeneity and assess reporting biases. $P < 0.05$ was considered statistically significant. Heterogeneity was assessed through the I^2 statistic, which estimates the fraction of variance that is due to heterogeneity and by Q test. The level of significance for the Q test was defined as $P < 0.10$.

Result

Animal study

Ten dog olfactory detection studies in year 2006-2019 were identified, details are list as in Table 1. Two studies reported the cancer diagnosis by canine scent detection in dogs [6]. The meta-analysis results showed that there was no significant difference between the canine scent detection and biopsy-confirmed groups [RR 0.84, 95% CI 0.40 to 1.79, $P=0.65$, heterogeneity $I^2=142.11$, $P<0.00001$, $I^2 = 99%$] (Figure 1). It suggested that the accuracy of canine scent detection was the same as the pathological result as gold standard for cancer diagnosis. The analysis results conducted by the fixed-effect model are considered to show an “ideal/typical intervention effect”, and the baseline differences between the groups are considered as non-statistical heterogeneity. The heterogeneity is obvious in this meta-analysis, so the random effect model should be applied.

5	2016	News report	UK	A 12-year-old British dog has been able to sniff out cancer in seconds. She has so far detected 550 cases of cancer in clinic and even saved her owner's life.	Prostate cancer, Bladder cancer, Kidney cancer	Urine	
				Accuracy 93%. Case report (animal).			
6	2015	News report	UK	The Institute has been training sniffer dogs to identify the odor of prostate tumors in urine samples.	Prostate neoplasms	Urine	Dogs can sniff out cancers because when the volatile molecules in cancerous tumors enter urine from cancerous cells, a special odor will come out.
				Accuracy 93% in detecting prostate cancer.			
7	2012	News report	Germany	Researchers spent 9 months sniffing 220 volunteers with specially trained dogs. The volunteers included healthy people, lung cancer patients and people with chronic obstructive pulmonary disease.	Lung cancer, COPD	Respiratory gases	
				4 dogs were able to make correct judgments on 71 out of 100 samples and accurately identify 93% of healthy samples from mixed samples.			
8	2012	News report	Austria	Dogs can identify cancer patients by smell, and some dogs can identify cancer patients from 120 breath samples.	Lung cancer	Respiratory gases	Dogs learn cancer information by identifying changes in a very small number of volatile components in human breath gas, but no specific chemical composition has been found.
				Accuracy 70%. A pilot studies.			
9	2007	News report	Canada	A puppy sniffed out the tumour of her owner, who has been basically cured.	Mammary cancer	Body odor	
				Case report (animal).			
10	2006	News report	USA	Professional trainers trained three Labrador dogs and two Portuguese water dogs for three weeks.	Lung cancer, Mammary cancer	Breath sample	Studies have found that there are some biochemical changes in cancer patients, and the tumor tissue will release volatile organic compounds with its own growth.
				Accuracy 99% for lung cancer patients and 98% for breast cancer patients. After counted into adjustment of whether lung cancer patients smoked or not, the accuracy rate was still 90%.			

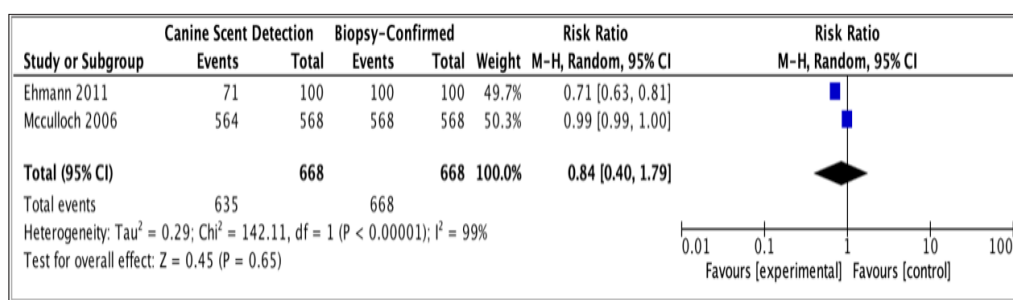


Figure 1: Preoperative

Clinical study


No clinical trials of gas analysis technique or product in human were identified, so no meta-analysis could be carried out. Different detection methods were summarized in Table 2. Gas analysis products for volatile organic compounds (VOCs) detection and their features, advantages and disadvantages were reported in Table 3. Currently, the main gas sensing technique includes electronic nose technique, exhaled breath condensate technique, gas chromatographic analysis, mass spectrum analysis, gas chromatograph-mass spectrum analysis, optical techniques and so on [7]. The electronic nose technique utilizes the redox reaction between the target gas and the sensor material. When the redox reaction happens, the characteristics of the sensor material would be changed, and this change would be reflected in the sensor's output signal. And through monitoring the output signal,

the target gas would be quantitatively detected [8]. This kind of sensor includes the metal oxide semiconductor sensor, surface acoustic wave sensor, quartz crystal microbalance sensor and so on [9]. These sensors could be arranged in arrays and combined with pattern recognition to simulate the human's olfactory system [10]. The main advantage for exhaled breath condensate technique is the detection for the generally used protein and gene type markers in the clinical diagnosis. These markers have been used for many years, and their accuracy and stability are positive. To clinician, the acceptance of this technique is higher than other ones. The gas chromatograph-mass spectrum technique separates the detected objects and using various detection equipment to quantitatively analyze and detect the separated objects. However, the high cost and difficulty in sample making limit the practical use in the clinical diagnosis for this technique [11].


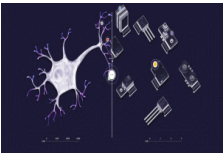


Table 2: Summary of different detection methods.

No.	Year	Study Type	Country	Summary of Study	Disorder	Detection Sample	Remarks
1	2018	Literature	India	The difference of light intensity loss caused by thoracic movement during breathing was analyzed. The respiratory frequency was calculated by data output.	Sudden infant death syndrome	Loss of light intensity during respiratory cycle	Neonatal respiratory monitor; Optical Fiber Respiratory Sensor; It can measure 10 to 130 breaths per minute with an error of 0.595% and a lag error of 0.2%. The system display threshold is 10 breaths per minute.
2	2018	Literature	Japan Tokyo	Reverse reaction of ethanol dehydrogenase (Adh): ACh is reduced to ethanol and reduced nicotinamide adenine dinucleotide (NADH) is consumed. The concentration of ACh can be quantitatively determined by fluorescence detection of NADH consumed by ADH reverse reaction.	cancer	Exhaled gas	Fiber optic biosensor (biochemical gas sensor); Gas acetaldehyde (ACh) biochemical gas sensor (biological sniffer); Breath analysis.
3	2017	Literature	China Tianjin	Proton Transfer Reaction Mass Spectrometry; Analysis of markers with high sensitivity and specificity.	Lung cancer	Patient exhaled gas	
4	2017	Literature	Israel	1404 patients and 2808 breath samples were collected to analyze the exhaled gas and diagnose the disease.	cancer	Breath samples	Nano Matrix Sensor Instrument

Table 3: Ten excellent artificial olfaction companies.

No.	Company	Country	Field	Research direction	Financing	Product Features	Product Pictures
1	Sensigent	USA	Medical diagnosis	Sensigent was formed to commercialize and market advanced technology products based on cutting edge research performed by some of the largest sensor and instrument companies. The products are used in diverse industries including Petrochemical, chemical, food and beverage, packaging materials, plastics, pet food, pulp and paper, medical research, environmental monitoring and many more.	\$60 million	The Cyranose® 320 is a fully integrated handheld chemical vapor sensing instrument designed specifically to detect and identify complex chemical mixtures that constitute aromas, odors, fragrances, formulations, spills and leaks. It is also used to identify simple mixtures and individual chemical compounds. The Cyranose® 320 is used in diverse industries including petrochemical, chemical, food and beverage, packaging materials, plastics, pet food, pulp and paper, medical research, and many more.	

2	Owlstone Medica	England	Medical diagnosis	Owlstone Medical have developed a chemical sensor on a silicon chip 100x cheaper and 1000x smaller than existing technologies: the FAIMS microchip. Owlstone Medical want to permanently change non-invasive medical diagnostics through innovative clinical projects.	€65 million	Lonestar VOC Analyzer is an easy to use analyzer for the detection of VOC biomarkers in clinical samples. ReCIVA® Breath Sampler is a reliable and reproducible way to capture VOC biomarkers in breath samples.	
3	eNose Company		Medical diagnosis	The eNose Company have developed proprietary technology for disease screening using exhaled-breath analysis. Combining fairly standard electronic components and advanced IT tools, small and robust electronic noses can be produced at low costs.		The Aeonose™ is the first electronic nose with the ability to avoid chemical calibration after manufacturing and employ a one-time, pre-production calibration instead. In that way, it is feasible to transfer an analysis model to a large number of eNoses without any difficulty.	
4	Air sense Analytics	Germany	Safety detection	AIRSENSE centers its activity on the development and manufacturing of high-quality instruments for the fields first response, public security, aviation as well as logistics and environment.		People living in towns near plants worry about air quality. AIRSENSE offers the ability to monitor large areas and thus help you make the right decisions. Other applications in the environmental and laboratory sectors include food supervision, quality assurance and odor control.	
5	Electronics Sensor	USA	Safety detection	Sensor Electronics hazardous gas detection instruments can be used to sense hundreds of different gases. From common gas types such as natural gas to exotic toxic gases like Titanium Tetrachloride.		The SEC 3000 gas detector is a unique design combining intrinsically safe and explosion proof approved standards. This toxic gas detector allows for quick and simple field installation of a calibrated sensor module into the gas detector in hazardous locations with power applied.	
6	Tell Spec		Safety detection	Tell Spec is a data company that provides predictive intelligence about food. The product combines NIR spectroscopy, bioinformatics techniques and learning algorithms to analyze consumer foods at the molecular level. Our three-part system includes the Tell spec's food sensor, a cloud-based patented analysis engine and a mobile app that work together to scan foods, identify ingredients and provide details about the food scanned.		The handheld scanner incorporates a miniature near infrared spectrometer. The internal light source focuses a beam of light through the front window into the food. Light reflected from the sample is then collected through the same window. This light is then dispersed onto a micro-mirror device and measured by an optimized detection system. This produces a digital electronic signal, known as a spectrum, characteristic of the composition of the food.	

7	Robo Scientific	England	Animal health testing	The Robo Scientific family of VOC (Volatile Organic Compound) Analyzers (derived from electronic noses) contain an array of sensors that individually respond to the vapor's producing a unique response pattern for each separate type of compound or mix of compounds.	The Model 307 is a compact, rapid response and robust identification system for volatiles and gas mixtures. The detection of the VOCs is performed using an array of the unique Robo Scientific organic semiconductor sensors. The 307 can be fitted with an array to suit your intended application and has the capability of housing between 6 and 12 individual sensors. Single VOC compounds or mixtures can be identified, after making reference measurements, by using the 'fingerprint' pattern generated from the sensors. Our sophisticated algorithms allow the instrument to be able to identify different compounds, or provides an immediate 'Good-Bad', 'Yes-No'; reaction depending upon the user's requirements and the skill of the operator.	
8	Koniku		Safety detection	Koniku is building co-processors made of biological neurons.	Nondestructive mass screening of fruits with the Koniku Kore. Fruit ripening or disease onset are not binary events. Match real world analog events with round the clock automation and nonstop volatiles sensing.	
9	Aryballe Technologies		Intelligent fragrance	Aryballe develops and manufactures bio-inspired sensors enabling groundbreaking applications in digital olfaction.	NeOse™ Pro, released early 2018, the first portable and universal odor detection device developed by Aryballe.	
10	Sensorwake		Intelligent fragrance	The product can help everyone wake up happy, relaxed and peaceful, empowered for adventures to come.	People can choose from a wide assortment of scents, like coffee, croissants, the ocean, or even the smell of money.	

Conclusion

The systematic review indicated that the analysis technique of VOCs from the human exhaled gas has the potential to be used for early cancer screening and diagnosis. The related techniques for VOCs detection are keeping developing, and the accuracy and specificity are continuously improved. However, more high-quality and large-scale randomized clinical trials are needed to confirm the effectiveness of exhaled gas analysis in cancer early diagnosis and screening.

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