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The possibility of inventing new technologies in the detection of cancer by applying elements of the canine olfactory apparatus

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A B S T R A C T

In order to find better tools in the diagnosis of cancer in an earlier and more precise manner, researchers have explored the use of volatile organic compound (VOCs) as a way to detect this disease. Interestingly, the canine olfactory apparatus was observed to detect cancer in two anecdotal reports. After the description of these events, researchers began to study this phenomenon in a structured way in order to assess the ability of canines in detecting cancer-related VOCs. Due to the fact that some of these studies have shown that the canine olfactory apparatus is highly proficient in the detection of cancer-related VOCs, in this article we assess the possibility of constructing a bioelectronic-nose, based on canine olfactory receptors (ORs), for the purpose of diagnosing cancer in a more sensitive, specific, and cost effective manner than what is available nowadays. Furthermore, in order to prove the feasibility and the need of the proposed apparatus, we searched for the following type of articles: all of the studies that have examined, to our knowledge, the ability of dogs in detecting cancer; articles that assess the dog olfactory receptor (OR) gene repertoire, since a central part of the proposed bioelectronic nose is being able to recognize the odorant that emanates from the cancerous lesion, and for that purpose is necessary to express the canine ORs in heterologous cells; examples of articles that depict different devices that have been built for the purpose of detecting cancer-related VOCs, so as to assess if the construction of the proposed apparatus is needed; and articles that describe examples of already constructed bioelectronic noses, in order to demonstrate the existence of a technical precedent and thus the plausibility of the proposed device.

Introduction

In medicine, the odor of patients has been a great tool in the diagnosis of some diseases. For example, it is known that ancient Greeks were the first to harness the odor of patients and their corporal fluids as a way to diagnose certain pathologies [1]. Based on this ancestral knowledge, in the last decades scientists have been searching more precise and less invasive ways for the detection of several diseases. Therefore, the research to detect and identify some volatile organic compounds (VOCs), which are a source of odors, as a way to develop new diagnostic methods, has been of great importance to medical sciences [2–4]. VOCs are molecules capable of volatilizing at room temperature and are the product of different metabolic pathways [5,6]. The National Aeronautics and Space Administration along with the Jet Propulsion Laboratory and Caltech were one of the pioneers in the development of a sensor that could detect these volatile organic compounds [7,8]. Furthermore, Krishna Persaud was one of the first individuals that proposed the utilization of these sensors in order to detect certain disease processes [9–11].

In cancerous cells, a change in the rate of oxidative stress, lipid peroxidation, and gene sequences leads to abnormalities in the biochemical pathways of these cells and thus to the production of specific VOCs [12]. Based on the last information published by GLOBOCAN in 2008, the cancer types with the highest incidence are breast cancer (10.9%), prostate cancer (PCa) (7.1%), lung cancer (LC) (12.7%) and colorectal cancer (9.8%), while the cancer types with the largest mortality are LC (18.2%), stomach cancer (9.7%), liver cancer (9.2%) and colorectal cancer (8.1%) [13].

In an effort to diagnose this disease in earlier stages and thus to reduce its mortality, several diagnostic tests have been used. Nevertheless, in the detection of cancer these tests present several drawbacks. For example, mammography in women ages 40–49 has a lower sensitivity and specificity when compared with older women [14]; in LC low dose spiral CT scan has not been able to reduce mortality in patients who are affected by this disease

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[15]. Moreover, because the current algorithms and diagnostic methods in the diagnosis of LC are not very precise most patients are diagnosed in late stages of this disease and less than 20% of diagnosed individuals are eligible for curative surgery [16].

To increase the likelihood of detecting cancer in earlier stages, with a greater specificity, sensitivity, and efficiency to what is already mentioned in the literature, and due to the ability of dogs to detect cancer-related VOCs; we assess the possibility of inventing a bioelectronic nose (a combination of a biological recognition part, olfactory receptors (OR), and a non-biological sensing platform) based on the canine olfactory apparatus [5,6,17–25].

In order to prove the feasibility of the proposed bioelectronic nose, we searched throughout the literature for the following type of articles: (1) all or most of the articles that have assessed the ability of dogs in detecting cancer, so as to evaluate if this skill portrayed by canines is good enough in order to translate it into a bioelectronic nose. (2) Articles that assess the dog olfactory receptor (OR) gene repertoire, since a central part of the proposed bioelectronic nose is being able to recognize the odorant that emanates from the cancerous lesion; and for that purpose we consider that is necessary to express in heterologous cells the canine olfactory receptors that are responsible for detecting the cancer-related VOCs. In order to achieve such purpose is essential to know and understand the dog OR repertoire. (3) Examples of articles that depict different devices that have been built for the purpose of detecting cancer-related VOCs, so as to assess if the construction of the proposed apparatus is needed. (4) Articles that describe examples of already constructed bioelectronic noses, which have used ORs expressed in heterologous cells as the biological sensing element of the apparatus, in order to demonstrate the existence of a technical precedent and thus the plausibility of the proposed device.

Theory

Canine clinical findings

The observation that dogs are proficient in smelling cancer was perceived by Sir Hywel Williams and Andres Pembroke. In a letter to *The Lancet* they reported that one of their patients sought a consultation with them due to the great interest that her dog showed in a skin lesion on one of her legs. It was later excised, analyzed and proven to be a malignant melanoma. Years later, it was published that another patient was diagnosed with skin cancer, this time basal cell carcinoma, when he sought a consultation with his primary care physician after he noticed that his dog was paying special interest to a lesion that was previously diagnosed as eczema [26]. After these events, the scientific community started to pay attention to the ability of dogs in identifying cancer-related odors and the possible impact that this fact could have in the clinical practice. Thus, scientists began to study this remarkable ability of dogs in a more meticulous way [5,6,17–24].

Bladder cancer

In 2004 Willis et al. published a study looking to verify empirically the olfactory acuity of dogs in the detection of bladder cancer. In the study, six dogs were used in order to detect the cancerous compounds in urine samples of patients presenting recurrent transition cell carcinoma of the bladder against a control group of healthy patients. The study showed that the dogs correctly selected the urine from the patients with bladder cancer with a success rate of 41% [17].

Willis et al. in 2010 published another study in which he and his collaborators used four dogs in order to evaluate if the canine olfactory apparatus reacts to cancer-related VOCs or to inflammatory-related odors. They accomplished the mentioned purpose, by separating the controls into those that were completely healthy and those that that had one or more minor dipstick findings or any other non-cancerous urological pathology. Furthermore, the authors did not exclude any patient from the study upon the presence of confounders (i.e., medications, menstrual cycle, alcohol consumption, smoking habits, etc.). For the dogs as a group the calculated sensitivity was 64%, while the calculated specificity ranged from 92% for the best-performing dog, down to 56% for the worst-performing dog. The investigators did not find any significant variation in the performance of dogs relative to tumor grade [18].

Melanoma

Pickel et al. published a study that had the purpose of assessing the possible existence of certain VOCs that could have a usage in the clinical practice as biomarkers for the detection of melanoma; in order to detect these VOCs, the authors proposed the usage of a biological detector: the canine olfactory system.

For the study, two dogs were used alongside seven patients presenting melanoma (the stage and type of the melanoma varied among the patients). One of the dogs sniffed all of the patients, and it localized the lesion in six out of the seven patients; while the other dog only sniffed four out of the seven patients, and it localized the lesion in three out of the four patients. Additionally, different sub-tests were performed which revealed that dogs were capable of identifying and recognizing the smell of melanoma samples even when presented with distractors commonly found in a clinical environment (i.e., adhesive bandages, gauze, latex gloves, etc.) [19].

Lung cancer

McCulloch et al. performed a study, in which they tried to prove if canines could detect LC and breast cancer through their sense of smell. The authors performed the study with the aid of five dogs and breath samples. In regard to LC; the canines were capable of discerning among LC patients and controls with a sensitivity of 99% and a specificity of 99%, regardless of the stage of the disease [5].

Another study was performed by Ehmann et al. that evaluated the ability of dogs to identify LC. For the study, four dogs were used along with breath samples from patients and controls. Patients with chronic obstructive pulmonary disease (COPD) were used as controls and patients were not excluded from the study on the basis of tobacco smoking, food ingestion and the intake of drugs.

The authors calculated a sensitivity of 90%, a specificity of 72% and a positive and negative predictive value of 86% and 78%, respectively. Furthermore, the staged and type of LC varied among patients and it was concluded that these factors did not have an influence in the ability of the dogs to detect LC. Additionally, the author's state that LC was detected regardless of the presence of COPD, tobacco smoke and food odors; thus it can be established that inflammatory process does not intercede in the ability of dogs in detecting cancer-related VOCs. Nevertheless, 9/112 drugs were identified as potential confounders [23].

Breast cancer

As mentioned before, McCulloch et al. performed a study in order to demonstrate if the canine olfactory ability could be helpful in detecting lung and breast cancer. For breast cancer, the calculated sensitivity was 88% (95% CI 75–100%) and the calculated specificity was 98% (95% CI 90–99%) [5].

By using urine samples and four dogs, Gordon et al. assessed whether dogs could identify breast and prostate cancer-related VOCs. The authors state that the dogs' choices of breast