Vol.3.Issue.2., 2015

Bulletin of Pharmaceutical and Medical Sciences (BOPAMS)
A Peer Reviewed International Journal http://www.bopams.com

REVIEW ARTICLE

INTERNATIONAL STANDARD SERIAL NUMBER
E-ISSN 2341-4103

CANINE OLFACTORY DETECTION OF CANCERS IN HUMANS –AN UNTAPPED COST EFFECTIVE AND ACCURATE BIO -TECHNOLOGY TOOL

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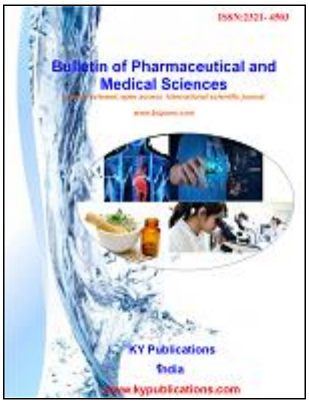

ABSTRACT

There is a global rise of incidence of cancer and cancer related deaths in the last two decades which is only showing an upward trend. Detection of cancers has become a huge burden on the health care cost of countries owing not only to the cost of the equipments needed for the detection but also the false positives and negative results. The role of animals to detect cancer efficiently through smell has been known for a while and there is scientific literature to support this. We look here in this paper at the potential possibilities of use of animals in routine diagnostics of cancers.

INTRODUCTION

Medical science has come a long way in the last century and half, from being predominantly based on the subjective skills that were guided by the intuitive capacity of the physician, called 'clinical acumen' in common parlance, to a greater reliance on the ever expanding repertoire of diagnostic tools which add an objective component to the process of identifying health problems and handling them. This had lead to the myriad use of these diagnostic techniques, which have time and again been proven to be of utmost value in specific case diagnosis, their efficacy ratified by epidemiological research.

So now the physician is encouraged to call upon the services of the wide array of investigation tools in order that his/her case identification is as precise as possible with current available techniques. Though this augurs well for the science of identification of health problems, it has lead to a lot of infrastructural problems. It becomes ethically imperative that when the knowhow is available then it be made universally available and accessible to the public in a democratic way of functioning. This places a lot of pressure on the health care delivery system with newer and better diagnostic tools constantly being improvised by cutting edge research. So it is necessary that progress in this field be focused on developing and discovering methods that can make use of already available resources in an innovative way.

As life form, as Homo sapiens, on this biosphere we call as earth, we are co-habituated and assisted by a variety of other species in our needs of day to day survival and comfort. These animal friends of ours have been serving us in a variety of ways (from assistance to subsistence) from the beginning of civilization. But their role as diagnostic help has hitherto been explored with any seriousness.

Rising global burden of cancer

"Global burden rise of incidence of cancer is 14.1 million new cases and 8.2 million cancer deaths in 2012 compared to 12.7 million and 7,6 million respectively in 2008. By 2015 GLOBOCAN 2012 predicted 19.3

million new cases would be added per year. More than half of all cancer (56.8%) and cancer deaths (64.9%) in 2010 occurred in developed countries in the world[1]". Most commonly diagnosed cancer worldwide were those of lung 1.8 million (13%) breast 1.7million (11.9%) colorectal 1.4 million (9.3%). Common causes of cancer deaths were carcinoma of lung -1.6 million (19.4%) liver- 0.8 million (9.1%) stomach - 0.7 million (8.8%).

Breast cancer estimates have increased by 20%, mortality by 14%. Breast cancer is the most common cause of death among women, most frequently diagnosed cancer among women in 140/184 countries worldwide. Cancer cervix fourth most common after breast, colorectal and lung and 266,000 deaths in 2012 worldwide. 70% of global burden falls in the lower level of development, more than 1/5th of all new cases diagnosed in India[1].

Economic implications:

In India on an average a patient spends 2 to 10 lakhs on cancer treatment. Halfway of the investment for oncology set up is used for technology and equipment[2].

Sniffing the problem out

Around 400 BC, Hippocrates recognized the diagnostic usefulness of body odors and reported on several disease-specific odors emanated from urine or sputum[3]. Since the 1980s, devices that electronically mimic the human olfactory system, called the 'electronic nose', have been developed and repeatedly improved. In the 1990s, a Gas Chromatography -Mass Spectrometry - olfactometer GC-MS-olfactometer (GC-MS-O) was developed, that can identify characteristic odorous compounds that are in low abundance in a complex mixture of volatile organic compounds (VOCs) from various biological samples. Electronic noses employ several gas sensors that are combined with a pattern recognition system to analyze and characterize sample-derived complex VOCs without separation of the mixture into individual components[3].

Sense and Sensitivity of Olfaction

Humans mostly experience the environment through sight, the canines rely more on smell and odors' and relies less on vision.[4] An average dog has over 200 millions scent receptor compared to only about 5 million in humans. Canine nose (C nose) detection threshold is as low as parts per trillion.

Dogs, for example, require an average volatile organic compound (VOC) concentration of less than 0.001 part per million. E-noses on the other hand have a detection threshold of 5 to 0.1 parts per million (ppm), although like animals different types of Enoses have different affinity for different volatiles. In comparison, humans have a detection threshold, on average, ranging from 0 to 80 ppm, again depending on of the type of substance.[4]

Early detection of cancer is a desirable goal and predicts longer survival. Investigations like chest X ray (CXR), sputum cytology –have many false negative results while Computed tomography (CT) shows increased false positive results. Mammography screening detects not only cancerous lesions, but also non cancerous lesions leading to unnecessary testing treatment, and anxiety: in addition mammography fails to detect cancer in women with dense breast tissue.

Hundreds of volatile organic compounds (VOCs) are emitted from the human body, and the components of VOCs usually reflect the metabolic condition of an individual. Recent progresses in analytical techniques allow rapid analyses of disease-specific VOCs derived from breath, blood, skin and urine can be used as diagnostic olfactory biomarkers of infectious diseases, metabolic diseases, genetic disorders and other kinds of diseases. [3]

The first to hypothesize that dogs could detect cancer through smell were Williams and Pembroke in 1989. They had a patient whose dog was constantly licking and trying to bite a mole on her leg and upon removal in turned out to be melanoma.[4]

The authors Michael & McCulloch used a food reward-based method of training 5 ordinary household dogs to distinguish, by scent alone, exhaled breath samples of 55 lung and 31 breast cancer patients from those of 83 healthy controls. Among lung cancer patients and controls, overall sensitivity of canine scent detection compared to biopsy-confirmed conventional diagnosis was 0.99 (95% confidence interval [CI], 0.99-

1.00) and over- all specificity 0.99 (95% CI, 0.96-1.00). Among breast cancer patients and controls, sensitivity was 0.88 (95% CI, 0.75-1.00) and specificity 0.98 (95% CI, 0.90-0.99). Sensitivity and specificity were remarkably similar across all 4 stages of both diseases. They observed that *t*raining was efficient and cancer detection was accurate. In a matter of weeks, ordinary household dogs with only basic behavioral “puppy training” were trained to accurately distinguish breath samples of lung and breast cancer patients from those of controls [5].

The high mortality rate associated with ovarian carcinoma is mainly owing to late diagnosis. Horvath G et al in 2008 reported a study where they taught a dog to distinguish different histopathological types and grades of ovarian carcinomas, including borderline tumors, from healthy control samples. Double-blind tests showed 100% sensitivity and 97.5% specificity. Moreover, the odor of ovarian carcinomas seems to differ from those of other gynecological malignances such cervical, endometrial, and vulvar carcinomas.[6]

Overall sensitivity of canine scent detection compared to biopsy confirmed conventional diagnosis was 0.99. 95% (CI) overall specificity 99%.

Ordinary household dogs with only basic, behavioral puppy training were trained to accurately distinguish breath samples of lung and breast cancer patients from those of contact.

In patients with colorectal cancer (CRC) and controls, the sensitivity of canine scent detection of breath samples compared with conventional diagnosis by colonoscopy was 0.91 and the specificity was 0.99. The sensitivity of canine scent detection of watery stool samples was 0.97 and the specificity was 0.99. The accuracy of canine scent detection was even higher for early-stage cancers. Canine scent detection was not confounded by current smoking, benign colorectal disease, inflammatory disease, infection or the presence of human haemoglobin or transferrin[7].

The potential of animals appears to be underestimated, understudied and, consequently, underused in the medical field. In the six cancer studies with dogs reviewed here, for example, median sensitivity and specificity were 94% and 98%, respectively. Although no direct comparison studies have been performed, dogs appear to outperform Enoses, since median sensitivity and specificity of the Enoses in the seven cancer studies was only 75% and 92%, respectively [4].

Enose and C nose

‘Enose in the broadest sense of the word includes applications such as chemical gas sensors, gas chromatography, optical sensor systems, infrared spectroscopy, and mass spectrometry. Enose studies have mainly focused on lung diseases and malignancies such as ovarian, bladder, and lung cancer. There are many types of Enoses with a large variety of underlying techniques; results from one type of Enose are not (easily) generalisable to another. Also, Enoses are relatively expensive.

Breast cancer is the most prevalent malignancy amongst women in the Western world. A study including detection dogs was performed, where sensitivity and specificity of dog detection (C nose canine nose) was 88% and 98%, and Enose reached 94% and 74%, respectively. A more recent Enose study analyzed 258 breath samples and found a sensitivity of 75% and a specificity of 85%, supporting the notion that Enoses do not reach the same diagnostic accuracy as dogs[4].

The smelling ability of animals holds promise as a detection tool. The studies reviewed by Bijil and et al 2013 suggest that animals are often as accurate as or even superior to standard diagnostic methods .[4]

What future holds

Canine olfactory detection of cancers could be a cost effective bio technological application in the diagnosis of cancers in human. Each animal needs special training, from two weeks to 2 years, which requires specific expertise and may be time-consuming. After this training phase, animals need individual performance assessment, and regular practice to maintain their skills at least once in six months. Even the ordinary dogs could be trained with basic puppy training. Unlike with enoses, smoking, infection ,presence of blood or benign lesions do pose as confounding factors in the diagnosis. Once they are trained, the accuracy of detection of cancers by dogs is of the highest order for screening as of now and reproducible, all for the cost of a cookie or a toy as a reward.

Early detection of cancer not only improves survival and quality of life but also obviates the need for sophisticated therapeutic interventions thus saving the cost of equipments and therapeutic costs incurred in oncology .The afflicted could be spared of the financial, physical and emotional trauma that these patients would undergo with the sensitivity of the modern equipments available as of date.

It is pertinent to consider active implémentation of a cost effective and high accuracy of the application in the field of medical diagnostics .It may be worthwhile to consider and initiate bachelor and postgraduate courses in dog training , as a part of laboratory diagnosis biotechnology, and Applied animal behaviour science courses as in the developed countries .Further research may be encouraged by the government and health care providers .

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