Woof! Smells like cancer

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A keen sense of smell, the ability to pick up distant sounds, an intelligence that allows for rigorous training and a fierce loyalty towards their 'masters' set dogs apart from other domesticated animals. Dogs have been bred for various behavioural and morphological traits for decades, and highly efficient breeds that specialize in certain tasks have been created. Whereas the German Shepherd is highly rated as a police dog for its ability to track down criminals by following odour trails, the Doberman or Rottweiler serves as an excellent guard dog, the Australian Kelpie is highly adept as a herding dog, used to muster livestock, terriers are excellent companions for hunting mammals, whereas a retriever is indispensable for bird hunters. Though many dog breeds are raised for their usefulness, toy dogs like the chihuahua, the pomeranian or the pug are bred solely as family dogs, pets maintained for the pleasure of their company, and attractiveness. However, these dog breeds are also good as watchdogs, though they cannot act as guard dogs. They usually bark aggressively when unfamiliar people enter the premises of the house where they live, and thus are good at alerting family members about the presence of possible intruders.

The obvious ability of dogs to identify individual humans is largely dependent on their sense of smell. It is known that the exploratory olfactory behaviour of pet dogs differs based on whether a human is known to them or not[1]. Pet dogs are usually closely associated with children in the family, and they have been shown to distinguish between dummies wearing clothes from familiar and unfamiliar children[2]. This suggests that dogs depend heavily on the sense of smell for their interactions with known humans. The ability of dogs to detect specific human odours is so strong that they are known to match odours from different body parts (hand scent to elbow scent, trouser pocket scent to hand scent) to identify humans, and this is used by the police to identify criminals from scented objects left behind at a scene of crime[3]. While the bloodhound is an excellent search and rescue dog, typically used for locating hidden and missing objects and people, beagles are used in airports and other public places for sniffing baggage for non-permitted items like drugs and explosives. Trained dogs that can sniff out decomposing bodies are called cadaver dogs. In a controlled laboratory experiment, Oesterhelweg *et al.*[4] put fresh pieces of carpet with two recently deceased corpses, and then the 'contaminated' carpet pieces were mixed with uncontaminated ones to test the ability of three cadaver dogs maintained by the State Police of Hamburg. The dogs demonstrated excellent sensitivity (75–100) and specificity (91–100) for identifying the contaminated carpet pieces, with an accuracy ranging from 92% to 100%. The errors were higher for cases where the carpet pieces had been exposed to the corpses only for 2 min, but were reduced when the dogs were tested for carpet pieces contaminated for 10 min.

A close-up of a dog's nose.

A special nose

Why are dogs such efficient sniffers? The dog's brain is dominated by the olfactory cortex. The olfactory bulb, which is a part of the brain responsible for transmitting information about smell from the nose to the brain, is about 40 times larger in dogs than in humans, relative to the total brain size. Olfaction in mammals is chiefly the function of the olfactory epithelium which lines the nasal cavity, and bears olfactory neurons that have olfactory receptors (ORs). In dogs, there are 125–220 million ORs which bind to specific volatile odourant molecules. The ORs in mammals are coded by the largest subfamily of genes – the olfactory subgenome. The ORs were first characterized in rat[5], and since then they have been detected in many vertebrate species, including humans[6]. Glusman *et al.*[7] have identified nearly 1000 OR genes in the human genome, only about a third of which seems to be functional, whereas the rest are pseudogenes[7,8], i.e. DNA sequences that resemble functional genes but are not functional themselves. Interestingly, dogs and humans have a similar repertoire of OR genes, but while about 18% of the OR genes in the dog genome are pseudogenes, this fraction is as high as 63% in humans[9]. Thus the dog olfactory epithelium can express up to 20 times more ORs than humans, which allows dogs to detect odourants at a much lower concentration than humans[10,11]. The identification and recognition of odourant molecules is achieved through a combinatorial code – a given chemical molecule can bind to several receptors, and the receptors in their turn can bind to different molecules. This combinatorial code can be highly complex, with some odourants being potentially recognized by 20 different receptors[12]. Now imagine the possibility of the spectrum of odourants that the dog brain might decipher, given its immensely large supply of olfactory receptors, and their ability to identify odourants by such a set of combinations.

Can dogs smell human maladies?

Dog owners often tend to attribute special behaviours to their pets, although they may not always have any scientific evidence. One such special ability attributed to dogs is their perception of imminent death in the family. Many dog owners also claim that their pets are capable of predicting heart attacks and epileptic seizures. In fact, dogs can be trained to identify external signs of an oncoming seizure in their owners and alert them by pawing or barking; such dogs are known as seizure-alert and seizure-response dogs. However, this idea has been strongly contested by Gregory L. Krauss of the John Hopkins University School of Medicine, who is an epilepsy specialist medical doctor. He carried out a systematic study with seven patients to demonstrate that seizure-alert dogs do not always react to epileptic seizures, but they respond to seizures caused by psychological conditions[13]. In a survey conducted on 212 dog owners with medically diagnosed type-1 diabetes, Wells *et al.*[14] reported a behavioural response of the pet to at least one episode of hypoglycaemia of the owner in 65.1% cases, with 31.9% of the animals responding to 11 or more events. Most dogs tried to attract the owner's attention by barking, licking, nuzzling, etc., whereas a smaller proportion registered fear-response like trembling, running away from the owner, and/or hyperventilating. As the dogs were not trained to respond to a change in the blood sugar levels of their owners, these behavioural responses were intrinsic. This suggests that dogs may indeed have a natural tendency to sense changes in the physiological conditions of their owners.

Dogs smell cancer

A woman had a blemish on her upper leg which was diagnosed by her doctor and was declared to be quite a harmless mole, not worth removing. Though she was content with the diagnosis, her dog, a half Border Collie and half Doberman Pinscher, was not. She insisted on pushing her nose up her owner's skirts and pants and sniffing the mole. Initially the woman considered this to be bad behaviour on the part of her pet and bad training on her part. But the dog continued to sniff, and one day, when the owner was wearing shorts, the dog tried to snip off the mole. As she had never tried to bite before, and also did not react to any of the other moles on her body, the woman was worried and consulted a dermatologist. The mole was excised and sent for a biopsy; the result was positive – it was a malignant melanoma that would have soon spread and killed her if it had not been excised. Williams and Pembroke[15] reported this incident in *The Lancet* in 1989. They wrote, 'This dog may have saved her owner's life by prompting her to seek treatment when the lesion was still at a thin and curable stage.' However, research in this field did not proceed for the next decade. In September 2001, Church and Williams[16] wrote a letter to *The Lancet* reporting a similar case of a 66-year-old man who had an eczema patch on his thigh, which had grown slowly over 18 years, and had been given only topical treatment. The family got a pet Labrador named Parker in 1994, and after two years the dog began to push persistently against the man's trouser legs and sniffed at the eczema. When the eczema was excised, it was diagnosed to be a basal cell carcinoma. After the excision, Parker did not show any interest in the area[16]. It was quite obvious that both the dogs had smelled the cancer in the skin lesions of their owners, which had bothered them. These anecdotal incidents have triggered research in the field of cancer detection by dogs, and the results are impressive.

Can dogs really smell cancer?

The first scientific report on dogs detecting cancer in laboratory tests was published by Willis *et al.*[17]. The group trained six dogs of various breeds and ages over 7 months to distinguish between urine samples from patients with bladder cancer and healthy people. The dogs were then subjected to the test of identifying one urine sample from a patient with bladder cancer from a set of seven samples, of which six were controls, i.e. urine samples from healthy people. The dogs correctly identified 22 out of 54 samples, achieving a success rate of 41%, which was much higher than the 14% expected by chance alone. The dog's capacity to recognize a characteristic bladder cancer odour was independent of other chemical aspects of the urine detectable by urinalysis. Two months later, Pickel *et al.*[18] reported the results of a test on two dogs that could detect melanoma. They trained the dogs to identify melanoma tissue and then tested them by hiding melanoma tissue samples on the skin of healthy volunteers. Both dogs were successful in locating the cancerous tissue. When the dogs were tested with real patients, they could successfully identify clinically diagnosed melanoma locations. One dog was also able to report melanoma at a skin location which had not been diagnosed clinically, but on further histopathological examination, the dog's report was confirmed to be correct. These reports set the stage for more rigorous research to test the extent of accuracy with which dogs can detect cancer in humans.

Though the early reports showed that dogs could distinguish between samples from healthy and cancer-affected people, be it in the urine or in the skin, the success rates were not impressive. The first experimental evidence for highly accurate detection of cancer by dogs was reported a couple of years later. Five dogs were trained to identify breath samples from breast and lung cancer patients, and then they were tested for the ability to detect breath samples from cancer patients. In each trial, only one cancer sample was used with four healthy samples, arranged in a random order, and the dog had to identify the cancer sample by sniffing. The test protocol was similar to that used by Willis *et al.*[17], but in this case both single blind (the dog handler was unaware of the identity of the sample but the experimenter was aware) and double blind (both the dog handler and the experimenter were blind to the status of the sample) tests were carried out. In the single blind test, if the dog sniffed out the cancer sample correctly, the experimenter rewarded the dog with food. However, in the double blind set up, this was not possible. The results were similar in both sets. The overall sensitivity of canine scent detection was 0.99, and specificity was also 0.99 for lung cancer, whereas these values were 0.88 and 0.98 respectively, for breast cancer. The high sensitivity in case of lung cancer was comparable to chest X-ray in detecting early-stage lung cancer, and the high specificity compared favourably to CT scan in ruling out lung cancer. In case of breast cancer, the high sensitivity and specificity were comparable with mammography for detecting or ruling out breast cancer, as the case may be. Interestingly, the dogs performed equally efficiently with both early and late-stage cancer samples, which suggests that they could possibly be used to understand the mechanism for early stage cancer detection through odour specificity[19].

Though these results are promising, a similar study with urine samples of patients with breast and prostate cancer provided different results. Only two out of six dogs tested with breast cancer samples and two out of four dogs tested for prostate cancer samples mixed with samples from healthy people performed better than expected by chance alone for specificity and none did better than the expectation for sensitivity. However, the authors concluded that the use of more rigorous training methods and better handling of urine samples would perhaps have produced better results. Interestingly, a few months later, another paper published on ovarian carcinomas reported different results. The authors trained a dog to distinguish different histopathological types and grades of ovarian carcinomas, including borderline tumours from healthy samples. Then they conducted a double blind test in which the dog achieved 100% sensitivity and 97.5% specificity to ovarian carcinomas[20]. While the earlier report by Gordon *et al.*[21] is discouraging, the results obtained by Horvath *et al.*[20] are highly encouraging. However, the latter study sample was only one dog, which could have had particularly good olfactory capabilities.

The latest study in the field of odour-based detection of cancer has been on colorectal cancer (CRC)[22]. The National Cancer Institute, USA, reports 102,900 cases of colon and 39,670 cases of rectal cancer in 2010 alone. There have been 51,370 deaths due to CRC in the US in 2010 (www.cancer.gov). CRC is a major threat to the population, and currently the most economic and non-invasive screening method available for CRC is the faecal occult blood test (FOBT). If CRC is detected by FOBT, patients can undergo total colonoscopy, leading to a reduced incidence and mortality of CRC. However, the positive predictive value of FOBT is about 10%, and this definitely is not adequate. Sonoda *et al*.[22] used watery stool samples obtained by suction during colonoscopy and breath samples from the beginning to end of exhalation to train a 8-year-old female Labrador for cancer detection. The training was carried out in three steps: in the first step, breath samples from a patient with oesophageal cancer and four controls were used. First the dog smelt a standard sample of oesophageal cancer from a paper cup and then tried to find a match from a set of five paper cups, of which only one had the test sample. A similar training session was conducted with lung cancer samples after one day and gastric cancer samples after two days.

The second phase of training lasted for a month. Here, breath samples containing oesophageal, lung and gastric cancer smells originating from the same patient as in the first phase were chosen randomly. In the third phase, the dog was given one kind of sample as the standard, and was asked to identify another type of cancer smell from the set of sample bags provided. The dog was trained to detect a wide range of cancers: oesophageal cancer, breast cancer, lung cancer, gastric cancer, pancreatic cancer, hepatocellular carsinoma, cholangiocarcinoma, CRC, prostate cancer, uterine cancer, ovarian cancer and bladder cancer. Thirty-seven samples from patients with CRC and 148 samples from control volunteers were used for the experiment with breath samples, and for watery stool samples there were 33 from patients with CRC and 132 from control volunteers. When the dog's judgement was compared with colonoscopy-confirmed diagnosis, the overall sensitivity for the canine scent detection was 0.91 for breath samples and 0.97 for watery stool samples, and the overall specificity was 0.99 in both cases. The accuracy of canine scent detection was even higher for early stages of cancer, and was not confounded by current smoking, benign colorectal disease or inflammatory disease. The authors conclude that there is no specific smell for a type of cancer, and cancer-specific chemical compounds may be circulating in the body, since the dog could detect cancer from both breath and watery stool samples. These odour materials may become important in designing better cancer diagnostic tools in the future[22].

Dogs in the clinic

I have discussed several anecdotal as well as experimental reports that provide strong evidence for the ability of dogs to detect cancer. In the two cases where the pet dogs bothered their owners by constantly sniffing at a skin anomaly that eventually was confirmed to be cancerous, suggests that dogs are able to detect cancer by its odour and responded to it instinctively, as these pet dogs did not have any prior training for cancer detection. However, anecdotal evidences cannot be taken at face value for scientific research, and hence the need for controlled experiments. The experimental evidence for cancer detection by dogs has gradually begun to accumulate. The latest study by Sonoda *et al.*[22] on CRC is quite impressive, especially because the dog was trained only with breath samples, and was still able to detect CRC in watery stool samples with 97% sensitivity and 99% specificity. However, these are data on a single dog, and further studies are required to establish the robustness of the conclusions.

Given that dogs are such efficient sniffers and are routinely used for detection by the police and intelligence departments, can they be used for cancer detection too? This question becomes all the more relevant when we see numbers like 10% positive predictive value for FOBT versus the high sensitivity and specificity of the dog. Some people argue that the use of dogs for cancer detection could also provide a stress-free, painless test as opposed to biopsies. Then why are we not training more dogs for cancer detection and doing away with tests like FOBT? It has been argued that the feasibility of using dogs for detecting cancer in the clinic is quite low, for several reasons. First, it would be difficult to convince people that a dog can be as efficient, sometimes even more so than any existing physical/biochemical test. Second, not every person likes dogs, and for some it might be unacceptable to visit a clinic that maintains dogs on its staff list. Even some dog lovers might object to this simply on grounds of health and hygiene. Third, training and maintaining a dog is expensive, and dogs do not live forever. So not only would there have to be a constant supply of dogs that are perfectly trained for cancer detection, but there would also be the problem of variability between dogs. There would be a range of efficiency that would make it difficult to decide the level of accuracy of judgement of the dog, unless tested by some parallel method, which in turn would kill the purpose of using the dog in the first place. These arguments do not sound convincing enough, given the advantage of using the dog over biopsy or FOBT. The real reason is probably much simpler: it is not easy to convince people to allow their medical fates to be determined by a dog, rather than by a tangible, trusted method like a biopsy. Not many of us would want to undergo a painful surgery or take chemotherapy because a dog lay down on the floor after sniffing a breath sample.

Are we then bothered about the cancer detection ability of dogs simply because of academic interest? Though an interest in understanding the cognitive abilities of the dog is a good enough reason to study this behaviour in them, the interests of most researchers who have devoted time to this problem is not just academic. Though it is not feasible to use dogs as cancer-detecting agents in the clinic, it might be possible to design an instrument that mimics the dog nose that detects cancer. In order to do so, we first need to have strong proof in favour of this ability in dogs, and then we need to probe deeper to understand what odourants they might be perceiving and how. Though research in this field is still in its infancy, we are already close to the goal. A team of scientists from Israel has been successful in designing a microarray of nanosensors modelled on the dog's nose that can differentiate between 'healthy' and 'cancerous' breath samples, and also between breath samples from patients having different types of cancer[23]. Dr Hossain Haick, who led the team, was named one of the 'ten most promising Israeli young scientists' in 2010 for this work. When we indeed have a robot nose for cancer detection in our clinics, many dog lovers across the globe will surely raise a toast to man's best friend!

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