Olfactory detection of human bladder cancer by dogs: proof of principle study

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Abstract

Objective To determine whether dogs can be trained to identify people with bladder cancer on the basis of urine odour more successfully than would be expected by chance alone.
Design Experimental, "proof of principle" study in which six dogs were trained to discriminate between urine from patients with bladder cancer and urine from diseased and healthy controls and then evaluated in tests requiring the selection of one bladder cancer urine sample from six controls.
Participants 36 male and female patients (age range 48-90 years) presenting with new or recurrent transitional cell carcinoma of the bladder (27 samples used for training; 9 used for formal testing); 108 male and female controls (diseased and healthy, age range 18-85 years—54 samples used in training; 54 used for testing).
Main outcome measure Mean proportion of successes per dog achieved during evaluation, compared with an expected value of 1 in 7 (14%).
Results Taken as a group, the dogs correctly selected urine from patients with bladder cancer on 22 out of 54 occasions. This gave a mean success rate of 41% (95% confidence intervals 23% to 58% under assumptions of normality, 26% to 52% using bootstrap methods), compared with 14% expected by chance alone. Multivariate analysis suggested that the dogs' capacity to recognise a characteristic bladder cancer odour was independent of other chemical aspects of the urine detectable by urinalysis.
Conclusions Dogs can be trained to distinguish patients with bladder cancer on the basis of urine odour more successfully than would be expected by chance alone. This suggests that tumour related volatile compounds are present in urine, imparting a characteristic odour signature distinct from those associated with secondary effects of the tumour, such as bleeding, inflammation, and infection.

Introduction

The hypothesis that dogs may be able to detect malignant tumours on the basis of odour was first put forward by Williams and Pembroke in a letter to the *Lancet* in 1989.[1] Their thinking arose from a consultation with a woman who claimed to have sought medical help as a direct result of her dog's inordinate interest in a skin lesion, which subsequently proved to be a malignant melanoma. Since then similar anecdotal claims of detection of skin cancer, and of malignancies of internal organs such as breast and lung, have appeared in the press and in a further letter to the *Lancet*.[2–4]

Tumours produce volatile organic compounds, which are released into the atmosphere through, for example, breath and sweat.[5–9] Some of these volatile organic compounds are likely to have distinctive odours; even when present in minute quantities, they could be detectable by dogs, with their exceptional olfactory acuity.[10–13]

Our aim was to train dogs to recognise an odour, or combination of odours (an "odour signature"), characteristic of bladder cancer but distinct from those associated with the secondary effects of the tumour, such as bleeding, inflammation, infection, and necrosis. These factors are present in a multitude of non-malignant conditions of the urinary tract and elsewhere in the body and must be ignored by the dogs if discrimination is to be attained. We assessed the dogs' abilities to detect bladder cancer, once trained, by comparison of their success rate with that expected by chance alone, in choosing one cancer urine placed randomly among six controls in blinded experiments.

Methods

Training of the dogs

Six dogs of varying breeds and ages completed a seven month period of training. The training objective was to enable the dogs to discriminate between urine from patients with bladder cancer and urine from diseased and healthy people, using samples entirely new to them, so as to preclude simple memory recognition of participants' unique odour signatures. Dogs were trained to detect one urine sample from a patient with bladder cancer placed among six control specimens.[14] Early recognition of the tumour scent was achieved by using search and find games, which were gradually replaced by discrimination phases of increasing complexity. Urine from patients with bladder cancer was presented sequentially against water, diluted urine from healthy people, undiluted urine from healthy controls, urine (containing blood) from menstruating women, and urine from patients with non-malignant active or recent urological disease or other disease. Samples were not pooled at any stage. Two of the dogs were trained and tested with dried urine samples; the remaining four dogs were provided with liquid specimens throughout.

Participant selection

We recruited patients from hospitals within the Buckinghamshire Hospitals NHS Trust and additional healthy controls from among staff and their families. Thirty six patients (23 men, age range 48-90, mean age 69; 13 women, age range 49-90, mean age 74) presenting with new or recurrent transitional cell carcinoma of the bladder gave urine before surgical intervention. We used 27 of these samples in training and the remaining nine for evaluation (see bmj.com).

ELPS *The full version of this paper appears on bmj.com*

A total of 108 diseased and healthy control participants supplied urine (54 men, age range 18-85, mean age 45; 54 women, age range 18-85, mean age 40); we used 54 samples in training and 54 during evaluation. We excluded patients with premalignant urological disease or a history of urological carcinoma. A history of other malignancy was acceptable providing the patient was now considered disease-free. All other past or current medical conditions were permissible. We made no exclusions on the basis of drugs, menstrual cycle, ethnicity, diet, alcohol consumption, smoking habits, exposure to chemicals, or findings on urinalysis (see bmj.com).

Evaluation of trained dogs

We assessed the dogs for their ability to select correctly one urine sample from a bladder cancer patient placed among six control samples (the same task as used in their training); all samples were new to the dogs. For statistical reasons, we used nine test panels, each with one positive sample and six controls, to test each dog (see bmj.com).

Statistical analysis

The primary outcome measure was the mean proportion of successes for each dog, compared with an expected value of 1 in 7 (approximately 0.143). Given the small dataset and the uncertainty of the form of the data, we estimated 95% confidence intervals by using both normal assumptions and bootstrap techniques. We applied a conditional logistic regression model to assess whether factors measured on urinalysis (such as presence of blood, leucocytes, or protein) might confound the association between participants' cancer status and selection of their urine by the dogs. We used a *t* test and rank sum test to assess the effect of the physical state of the urine.

Results

Taken as a single group, the dogs correctly selected the positive bladder cancer urine on 22 of 54 occasions (table). This gave a mean success rate of 41% (95% confidence intervals 23% to 58% under assumptions of normality and 26% to 52% using bootstrap methods), compared with 14% expected by chance.

The association between presence of cancer and selection by the dogs was slightly stronger in a multivariate conditional logistic regression model, which also included presence of blood and ketones, than in the univariate model. This indicated that the association was not due to confounding with factors measured on urinalysis. The four dogs trained on wet urine specimens (50% correct) seemed to perform better than the two dogs trained on dried samples (22% correct; P = 0.03 by *t* test, P = 0.06 by rank sum test).

Discussion

Summary of findings

Given the extraordinary claims made about dogs detecting cancer on the basis of odour,[1–4] our aim was to design and conduct a simple, yet stringent, experiment to establish whether dogs have this capability. We achieved the successful detection of urine samples from patients with bladder cancer 41% of the time (rather than the 14% expected by chance alone), providing convincing evidence that dogs do, indeed, have this ability. Multivariate analysis suggests that the dogs' capacity to recognise an odour signature characteristic of bladder cancer is independent of other chemical aspects of the urine detectable by urinalysis, such as the presence of blood.

Exactly what the chemical composition of the cancer odour signature is we can only speculate at present. Evidence from gas chromatography and mass spectroscopy studies indicates that elevated levels of formaldehyde, alkanes, and benzene derivatives occur with some cancers,[5–8] but other volatile organic molecules are probably produced as well.

Rationale for training approach

When we embarked on this project we had no relevant peer reviewed publications to refer to. The trainers on the team were experienced at teaching dogs to scent-match, but this was not the task being demanded of the dogs here. We needed them to learn to recognise an odour signature for cancer from among the hundreds present in urine, without recourse to the "pure" source of the odour. This makes it very different from training dogs to detect, for example, drugs or explosives. At the beginning of the study we considered using surplus tumour material obtained during surgery. We dismissed this, however, largely because the tissue could not be chemically fixed without irrevocably altering the smell, and the use of unfixed tissue had serious health and safety implications for the dog trainers.

Having decided that we would concentrate on urine as the source of tumour derived volatile organic compounds, we then had to consider whether to use each participant's urine sample separately or whether to pool those of the cancer patients and, separately,

Urine samples selected by the six dogs during evaluation

Run	Mongrel (age 6, M)*	Labrador (age 7, F)*	Working strain Cocker Spaniel†			Papillon (age 7, F)†	Correct
			(age 1.5, M)	(age 2, F)	(age 5, F)		
1	TCC 1	TCC 1	TCC 1	TCC 1	TCC 1	TCC 1	6
2	C 11	TCC 2	C 11	TCC 2	TCC 2	TCC 2	4
3	C 14	C 13	C 17	C 16	C 15	C 13	0
4	C 23	C 23	TCC 4	TCC 4	C 22	TCC 4	3
5	C 28	TCC 5	TCC 5	TCC 5	TCC 5	TCC 5	5
6	C 34	C 31	C 31	TCC 6	TCC 6	C 31	2
7	C 41	C 41	TCC 7	C 42	C 42	C 38	1
8	C 46	C 48	TCC 8	C 48	C 48	C 47	1
9	C 53	C 50	C 54	C 50	C 50	C 54	0
Correct	1	3	5	5	4	4	22

F=female; M=male. *Urine state=dried. †Urine state=wet.

What is already known on this topic

Canine olfactory detection of cancer has been anecdotally reported but has not, until now, been the subject of scientific scrutiny

What this study adds

Dogs can be trained to distinguish patients with bladder cancer on the basis of urine odour more successfully than would be expected by chance alone

This study provides a benchmark against which future studies can be compared

those of the controls. Although pooling might have led to a greater concentration of the desired odour signature, we foresaw some important disadvantages and pitfalls. Firstly, we had no idea whether certain foods, drinks, or drugs, for example, may obscure, interfere with, or even mimic, the odour of tumour related compounds. Only by taking detailed histories from each participant, and introducing each sample separately, could we gradually eliminate these possibilities. Secondly, pooling specimens would lead to many fewer samples being available for the dogs to smell. The very real possibility then existed that dogs would merely scent-match with known samples, rather than learn to pick out the distinctive odour signature common to the cancer urines. Lastly, and perhaps most importantly, we were concerned that "rogue" control specimens from people with undiagnosed cancer elsewhere in the body may be inadvertently added to pooled samples. We did, in fact, have an occasion during training in which all dogs unequivocally indicated as positive a sample from a participant recruited as a control on the basis of negative cystoscopy and ultrasonography. The consultant responsible for the patient was sufficiently concerned to bring forward further tests, and a transitional cell carcinoma of the right kidney was discovered.

We next had to consider the physical state of the urine when presented to the dog. We felt that air dried samples would have greater applicability in a clinical setting, by virtue of easy handling, transport, and storage. However, the overnight drying process may result in the loss of volatile organic compounds important to the overall odour signature. We therefore opted to train one cohort of dogs on wet samples and another on dried samples. When tested, the dogs trained on liquid urine performed significantly better, suggesting that the more volatile molecules are of importance in the cancer odour signature. However, the small sample sizes, together with other potentially confounding variables between the two groups of dogs limit confidence in this observation. Further work to determine the optimum physical state for the urine will therefore be needed.

Lastly, we gave careful consideration to the selection of patients and controls. During training, we exposed the dogs to urine from patients presenting with a broad range of transitional cell carcinomas, in terms of grade and stage, as we felt this would increase their likelihood of recognising the common factor or factors. We took particular care to train the dogs with control samples containing elements likely to be present in urine from patients with bladder cancer but also commonly occurring in other non-malignant pathologies. In this way, we could teach the dogs to ignore non-cancer specific odours.

Conclusion

Our approach to training was vindicated by the results achieved when the dogs were formally evaluated. Despite the fact that we had not used dogs with proved scenting abilities, and despite the inclusion of age matched diseased controls, we achieved a statistically significant success rate. Our study provides the first piece of experimental evidence to show that dogs can detect cancer by olfactory means more successfully than would be expected by chance alone. The results we achieved should provide a benchmark against which future studies can be compared, and we hope that our approach to training may assist others engaged in similar work.

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Ethical approval: South Buckinghamshire local research ethics committee approved the study.

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