

# Breast Cancer Detection From a Urine Sample by Dog Sniffing

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## Research article

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# Abstract

**Background:** Breast cancer is a leading cause of cancer death worldwide. Several studies have demonstrated that dog can sniff and detect cancer in the breath or urine sample of a patient.

**Objective:** The aim of this study is to assess whether the trained dog can detect breast cancer from urine samples.

**Methods:** A nine-year-old female Labrador Retriever was trained to identify cancer from urine samples of breast cancer patients. Urine samples from patients histologically diagnosed with primary breast cancer, those with non-breast malignant diseases, and healthy volunteers were obtained, and a double-blind test was performed.

**Results:** 40 patients with breast cancer, 142 patients with non-breast malignant diseases, and 18 healthy volunteers were enrolled, and their urine samples were collected. In 40 times out of 40 runs of a double-blind test, the trained dog could correctly identify urine samples of breast cancer patients. Sensitivity and specificity of this breast cancer detection method using dog sniffing were both 100%.

**Conclusions:** The trained dog in this study could accurately detect breast cancer from urine samples of breast cancer patients. These results indicate the feasibility of a method to detect breast cancer from urine samples using dog sniffing in the diagnosis of breast cancer.

## Introduction

Breast cancer was considered a major health issue among women, and is the second most common cause of cancer death throughout the world [1]. Early detection of the breast cancer is important for more efficient treatment. Currently, mammography (MG) is the most commonly used screening test, and has a reported sensitivity and specificity of 77% and 91%, respectively [2]. Although breast cancers can be detected during the asymptomatic phase and reduces mortality among women of certain ages [3–5], MG still has several challenges. First, prevalence of MG is not sufficiently utilized even in developed countries. The rate of check-ups for women aged 65–74 years is 16–20% and 43–46% for women aged 40–54 years in Japan [6]. Second, non-malignant lesions are also detected, which sometimes leads to unnecessary testing, treatment, and anxiety [7], and at the same time, MG is less sensitive in dense breast [8]. Furthermore, mortality reduction in women ages < 40 years has not yet been proven. Third, MG is associated with significant pain due to the relatively strong pressure applied to the breast. Fourth, there is the risk of radiation exposure especially in younger women with abnormal germline genes [9]. Given above drawbacks of MG, an alternative test with better compliance is needed to detect breast cancer in an early stage.

Cancer detection by dog sniffing (hereinafter referred to as “canine cancer detection”) is one of the candidates as a new method to detect breast cancer. Detection threshold has been shown to be as low as 1.5 parts per trillion (ppt) [10]. Trained dogs can successfully discriminate between patients with cancers

of skin [11, 12], bladder [13], lung [14–18], breast [14, 19, 20], prostate [20–22] ovary [23–25], colorectal [19, 26], liver [27], uterine cervix [28] from controls on the basis of odors in breath, urine, blood or cell culture medium. However, the canine cancer detection testing for breast cancer using human urine samples has not yet been attempted. We hypothesized that scent-trained dogs can discriminate between breast cancer patients and non-breast cancer patients using urine samples. The aim of this study was to investigate the efficacy of a canine cancer detection method using urine samples of patients diagnosed with breast cancer.

## Materials And Methods

### Patients and controls

Patients with primary breast cancer, patients with non-breast malignant diseases, and healthy control volunteers at Nippon Medical School Chiba-Hokusoh Hospital and the Jizankai Medical Foundation Tsuboi Cancer Center Hospital from January 2011 to October 2012 were enrolled. Diagnosis was based on clinical assessment using MG and/or ultrasound and confirmed preoperatively by histological examination of core needle biopsy (CNB) samples. Patients who received a surgical operation before urine sample collection, and those with other types of cancer were excluded. Patients with non-breast malignant diseases were confirmed by biopsy. For female patients, MG and/or ultrasound was performed to rule out breast cancers. Healthy volunteers were verified with systematic cancer screening tests including blood test, chest X-ray, abdominal ultrasound, MG, and gynecological examination.

### Urine sampling

Urine samples of the participants were collected with paper cups (Harn cup laminate A, Nissho Sangyo, Tokyo, Japan), and transferred to sterile test tubes (Sterile SP tube, Eiken Chemical Co., Tokyo, Japan) and each test tube was sealed with a cap. Urine samples of the breast cancer patients were collected a few days prior to surgery. The test tube samples were then stored at -20°C until 1 ml of the selected samples was used for the dog sniffing test.

### Dog and training

A nine-year-old female Labrador Retriever was provided by the St. Sugar Canine Cancer Detection Training Center in Minamiboso City, Chiba, Japan [26]. The training was performed by a professional dog trainer with a similar procedure described in the previous report [26]. Briefly, each cancer detection training session was considered complete when the dog correctly detected breath samples from a cancer patient and four controls in dozens of trials. The correct behavior was rewarded by simultaneous play with a tennis ball. Training consisted of following steps: In the first step, the dog was trained to detect a breast cancer breath sample from five breath-sampling bags with the end caps on, which included three healthy and one non-breast malignant disease breath samples. As the dog successfully accomplished this task, the healthy controls were gradually replaced with non-breast malignant disease breath samples. In the final step, the dog was trained to detect a breast cancer sample from among five samples which included

four non-breast malignant disease breath samples. This could subsequently be applied to urine samples. In this way, the dog was trained to be able to detect breast cancer patients. Under certain conditions, the dog sniffing test could not be conducted because the dog could not maintain concentration. These included weather conditions such as high temperature and high humidity in the summer.

#### Detection of urine samples from breast cancer patients

The test boxes were wooden, storage containers 27 × 30 × 20 cm in size. Each box is equipped with a 10 cm wall inside to hold a urine sample tube. So the dog does not come in direct contact with the test sample, each box was covered with a metal mesh. To conduct the test, 5 test boxes were placed in a straight line on the floor, one meter apart (Fig. 1). The sample tubes were kept separate to avoid any possibility of contamination of the control samples with volatile chemicals from the cancer samples. Double-blind testing, blinded to the dog trainer and the dog, was performed using one breast cancer sample and 4 control samples per test-run. Correct responses included (1) sitting down in front of a sample box containing a urine sample from patients with breast cancer (true positive in sensitivity calculations) and (2) only sniffing the odor of a sample and not sitting in front of a control sample (true negative). Incorrect responses included (1) sitting in front of a control sample (false positive) and (2) not sitting in front of a sample from a patient with breast cancer (false negative). Once the dog signaled in on a sample, it was given a reward. In each testing, the concentration level (high or low) of the dog was assessed and recorded. No adverse events, injury or illness to the dog was observed.

## Statistical analysis

The Kruskal-Wallis test was used to analyze the clinical characteristics of the patients and controls. The percentage of correct detection per session was calculated for each test-run. Diagnostic accuracy was calculated as the sensitivity and specificity of the dog's identification of positive urine samples compared to the histopathological diagnosis of breast cancer. Thus, sensitivity of the test is the proportion of cancer samples correctly identified by the dog while specificity is the proportion of control samples negatively indicated by the dog. A P value < 0.05 was considered statistically significant. All statistical analyses were completed using SPSS v.25 (IBM Corp., Armonk, NY, USA).

## Results

### Patients

A total of 200 participants were randomly selected in the study, and included 40 patients with primary breast cancer, 142 patients with non-breast malignancies, and 18 healthy individuals. All breast cancer patients were female. Histological diagnoses were ductal carcinoma in situ (six cases), non-specified invasive ductal carcinoma/ invasive carcinoma (33 cases), and mucinous carcinoma (one case). Pathological stages of the breast cancer patients were classified according to the Union for International Cancer Control (UICC) classification as follows: Stage 0 (ductal carcinoma in situ) for 6 cases, Stage I for 19 cases, Stage IIA for 13 cases, and Stage IIIB for 2 cases). One patient with invasive ductal

carcinoma, Stage IIIB had preoperative chemotherapy before the operation and collecting a urine sample. Non-breast malignancy patients are listed in Table 1.

Median ages of breast cancer patients, non-breast malignancy patients, and healthy individuals were 57.5 (range 28-84), 57 (range 18-88) and 52 (range 27-66) years old, respectively. Age distribution did not significantly vary among the patients and controls ( $p=0.087$ ).

Dog condition and round times before decision

A total of 40 runs were carried out. The combinations of the samples in each test-run are listed and summarized in Table 2.

In 4 out of 40 times, the dog's concentration level was low, and the remaining runs were normal. The dog's low concentration were noted for 2 days, when test-run numbers 18-22, which were the hottest days in July, were performed. On these days, the room temperature was 26.3°C to 26.8°C, and humidity was 83%. The round times before the dog's response ranged between one to three times. In further detail, the dog made one round in 14 runs, two rounds in 19 runs, and three rounds in seven runs.

Sensitivity and specificity of the detection test

Comparison of the cancer determination by dog sniffing versus pathological diagnosis among cancer patients and controls was calculated. The dog detected the breast cancer samples correctly in all test-runs (40/40). Thus, among the breast cancer patients and controls, overall sensitivity and specificity were both 100%.

## Discussion

The novelty of this study was to investigate the feasibility and efficacy of using the trained dog to detect and distinguish urine samples of breast cancer patients from a control group comprised of a variety of other malignancies and healthy volunteers. Using our established training method, the dog could be trained to detect breast cancer from urine samples, and 100% sensitivity and specificity rates could be achieved in the double-blind test series. Up to now, efficacy of urine samples has not been well clarified. Using urine samples is useful because of its simplicity and non-invasiveness. Some trained dogs were reported to discriminate between the urine of patients with urinary tract and prostate cancers from those of controls [13, 21], but this is the first study indicating the efficacy and accuracy of a dog trained to detect breast cancer from urine samples.

Originally, in 1989, the hypothesis that dog can smell a cancer odor was raised during the 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 [29]. A similar case of patient-dog interactions leading to cancer diagnoses was subsequently reported, suggesting the possibility of the existence of a cancer specific odor [30]. Initially, these "anecdotal" events were not supported by evidence.

However, the following studies have demonstrated canine cancer detection for cancer screening is promising, feasible, and safe (Table 3) [11–28].

McCulloch et al. reported that trained dogs could successfully detect breast cancers using exhaled breath samples [14]. Breath samples from 31 breast cancer patients and healthy control patients were used, and sensitivity and specificity were 0.88 and 0.98, respectively, across all stages. Sonoda et al. further investigated the utility of canine cancer detection in CRC using breath and watery stool [26]. Sensitivity and specificity in comparison with diagnosis by colonoscopy were 0.91 to 0.97, and 0.99, respectively. In order to determine whether a specific cancer odor does exist, or a particular natural scent disappears due to the cancer, a mixture of watery stool of CRC cancer patients and controls was produced, and the sample could be correctly identified by the dog. From this, it was surmised that chemical compounds from cancer could be circulating throughout the body. Next, focus was placed on whether these odors were cancer-common or cancer-specific. In several subsequent series, when one type of cancer sample was used as the standard scent, the dog was able to differentiate between other types of cancers [26, 31]. Seo et al. also reported that metabolic wastes of both breast and CRC in vitro have a common specific odor [19]. On the other hand, several types of cancers which were included as controls could be successfully identified as the targeted cancer by the sniffer dog, which is consistent with the results of this study [24]. These studies suggested that both of cancer-common scents and cancer-specific scents exist. Consequently, non-breast malignancies as well as healthy volunteers were included in the control group. The dog in this test successfully differentiated breast cancer from non-breast malignancies and healthy controls, and this concurs with previous studies [24].

The test data at this time showed a higher sensitivity and specificity compared to other previous reports. One possible reason is the environmental settings of the test-run, which allowed the dog to respond without stress. Tests were not carried out under the stressful conditions for the dog. Detection accuracy may be influenced by the condition of the dog, and therefore performance should be systematically monitored [32]. In addition, storage of the sample until testing may be pivotal in maximizing detection rate. While the effect of storage duration or method on detection accuracy was not assessed in this study, standardization of such methodology, in order to utilize this approach for a mass screening, should be considered [20].

Evidence has shown that human body emits a wide array of volatile organic compounds (VOCs), both odorous and non-odorous, depending on individual background [33]. These VOCs are emitted throughout the body, including breath, blood and urine [34, 35]. According to analysis of VOCs, different volatile patterns have been correlated with a variety of diseases including cancers [14, 33, 36, 37], which dogs can be trained to detect. Consequently, analysis of cancer specific VOCs is considered feasible. Some studies have attempted to demonstrate cancer specific VOCs by utilizing gas chromatography-mass spectrometry (GCMS) [38]. The potential of VOCs in urine, breath and blood samples to be biomarkers for an array of diseases could be demonstrated [35, 39]. However, VOCs are affected by physiological factors such as dietary and smoking habits, infections, and benign diseases [40], which GCMS cannot detect all or even nearly all chemicals present [14], nor clarify the exact chemical compounds and/or their

combinations. Combining this dog-based study with instrument-based research would be mutually beneficial for further analysis [41].

This study has limitations. Our cancer detection system relies on one trained dog. Expanding this to multiple training centers with expert trainers, multiple dogs, and over several years is desired. An effective training protocol is essential for good performance [20]. Even though dogs can be subject to the same training manner by the same trainer, inter-dog difference or poor performance due to stress have been pointed out in similar studies [10, 17].

## Conclusions

In conclusion, this study represents a novel attempt to use cancer detection dogs to distinguish between breast cancer and non-breast malignancy and healthy controls from urine samples. This method was demonstrated to be more accurate and less invasive than existing screening methods.

## List Of Abbreviations

CNB

Core needle biopsy

CRC

Colorectal cancer

GCMS

Gas chromatography-mass spectrometry

HSIL

High-grade squamous intraepithelial lesion

LSIL

Low-grade squamous intraepithelial lesion

MG

Mammography

UICC

Union for International Cancer Control

VOC

Volatile organic compounds

## Declarations

### Ethics approval and consent to participate

Participants voluntarily enrolled in this study and provided written informed consent. This study was conducted in accordance with the principles embodied in the Declaration of Helsinki, and was approved by the ethics committees of Nippon Medical School Chiba Hokusoh Hospital (IRB#320).

## Consent for publication

Not applicable.

## Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

## Competing interests

The authors declare that they have no competing interests.

## Funding

This study is funded by Research Grants of Department of Surgery, Nippon Medical School Chiba Hokusoh Hospital.

## Authors' contributions

SK, SI, MY, HT, NY, YS, and MM conceptualized and designed the study. SK, SI, MY, HT, NY, YS, and MM developed the methodology. SK, SI, MY, HT, NY, YS, and MM performed the data acquisition. SK, SI, MY, HT, NY, YS, and MM analyzed and interpreted the data. SK, SI, and MM wrote the manuscript, which was edited by all the authors who approved the final version. MM provided study supervision. All authors are guarantors of the integrity of the data collection and interpretation.

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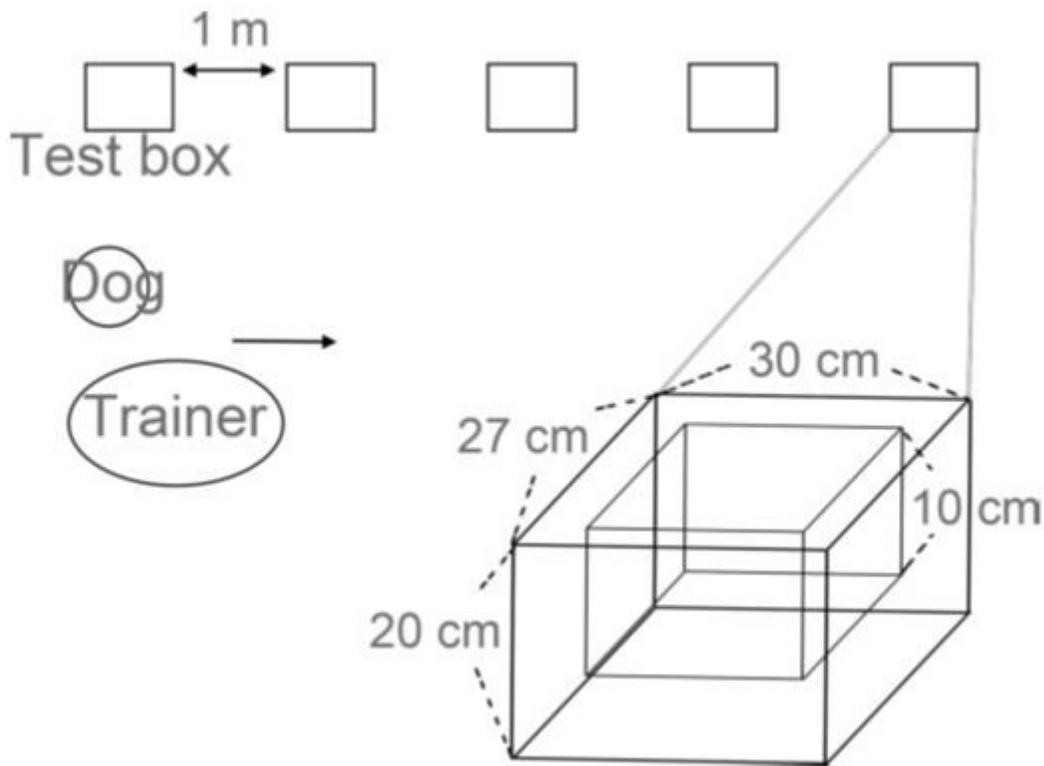
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## Tables

Due to technical limitations, table 1-3 is only available as a download in the Supplemental Files section.

## Figures



**Figure 1**

Test design. The test boxes are wooden, storage containers 27x30x20 cm in size. Each box is equipped with a 10 cm deep wall inside to hold either a breath sample bag or a urine sample tube. The 5 test boxes were placed in a straight line on the floor at a distance of 1 meter apart.

## Supplementary Files

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