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Editorial Article

Cancer-sniffing pets: what is the secret?

L. Roncati

Department of Medical and Surgical Sciences, University Hospital of Modena, Modena (Italy)

Summary

The media carry stories of patients who, thanks to early diagnosis of malignancy, claim to have been saved by their cancer-sniffing pets. It is established that the brain of a dog features a wide olfactory cortex, compared to that of humans, where the visual cortex predominates. The cat also possesses an acute sense of smell, due to its well-developed olfactory bulb and a large surface of olfactory mucosa. A series of diagnostic hallmarks of malignancy have been defined, among which tumor necrosis. It is a form of hypoxic death resulting in an accumulation of cell debris and decomposing tissue. It is well known that the decomposition process produces foul-smelling molecules, such as cadaverine and putrescine. Given their remarkable sense of smell, it is more than likely that some pets are able to detect on themselves and in their owner's body the odor of tumor necrosis deriving from aggressive cancers.

Key words: Cancer-sniffing pets; Early diagnosis of malignancy; Tumor necrosis.

All over the world, day in day out, sick people are enjoying the benefits of pet-therapy [1-6]. In parallel with this medical evidence, the media carry stories of patients who, thanks to early diagnosis of malignancy, claim to have been saved by their cancer-sniffing pets. The growing number and frequency of such claims have led to researchers advancing the theory of 'canine cancer detection'. Domestic pets, it is alleged – and above all dogs – are able to detect very low concentrations of alkanes and/or aromatic compounds generated and released by malignant tumors into the patient's breath, urine or watery stools, as well as into adsorbent materials [7-15]. It is well established that the brain of a domestic dog (*Canis lupus familiaris*) features a wide olfactory cortex, compared to that of humans, where the visual cortex predominates. Dogs are known to possess up to 56 times the number of smell-sensitive receptors present in humans; the receptors can attain a count of 280 million in selected breeds [16]. In dogs, these receptors are spread over an olfactory surface of 9.76 square centimeters (about the size of a pen-drive), whereas in humans around five million receptors occupy an area of 3.08 square centimeters, the size of a postage stamp [16, 17]. It is therefore reasonable to suppose that the sense of smell in a dog is up to 56 times more sensitive than that of a human being. In addition, the characteristic structure of the dog's nose allows the inhaled air to pass over a bony shelf, to which a multitude of odor molecules adhere. In normal breathing, the air above this shelf is not evacuated, hence the molecules build up in the nasal chambers, and the scent acquires greater intensity. As a result, the dog is able to detect even the faintest of odors [16]. The domestic cat (*Felis silvestris catus*) also possesses an acute sense of smell, due to its well-developed olfactory bulb and a large surface of olfactory mucosa. The latter occupies an area of about 5.8 square centimeters, almost twice the size of that found in humans [16]. Gynecological oncology and cancer medicine have defined a series of diagnostic hallmarks of malignancy, including: infiltrative neoplastic growth, lymphovascular and perineural invasion, an elevated mitotic cell count, a high cytoproliferative index, immune evasion, and tumor necrosis [18, 19]. On closer inspection, tumor necrosis (from the Greek νέκρωσις – death) can be defined as a form of hypoxic death deriving from high metabolic consumption by cancer cells. Rather than following the apoptotic signal transduction pathway, the uncontrolled release of cell-death products evokes an inflammatory response in the surrounding space, attracting leukocytes. This results in an accumulation of cell debris and decomposing dead tissue [20, 21]. It is well known that the decomposition process produces foul-smelling toxic molecules, such as cadaverine (pentamethylenediamine) and putrescine (tetramethylenediamine) [22-26]. These are widely recognized as being the main source of the putrid odor in decaying animal tissue, but they also account for the unpleasant smell produced by halitosis and vaginosis [27]. Given their remarkable sense of smell, it is more than likely that pets – certain canine species in particular – are able to detect on themselves and in their owner's body the odor of tumor necrosis deriving from aggressive cancers. Clearly, a tumor which occurs near to the surface of the skin would be easier to detect than one located at a deeper level. In this respect, even modern nanotechnologies seem to endorse the feasibility of cancer sniffing, since sophisticated olfactory sensors have been

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patented, and have been tested for diagnostic purposes on humans with striking results [28-32]. However, the remarkable ability of pets described above is unlikely to be of use in cancer screening models, given the time required by the pet to tune into the normal odor status of its owner, thus making it possible to pick up subtle odor changes in the future friendship. The trained molecular sniffer dogs might also be misleading due to various non-neoplastic pathologies with subsequent necrosis, such as that from gangrene, abscesses or phlegmons. In spite of these reservations, all the signs would appear to attest rudimentary "pet-diagnosis" as a scientific fact.

References

[1] Orlandi M., Trangeled K., Mambrini A., Tagliani M., Ferrarini A., Zanetti L., *et al.*: "Pet therapy effects on oncological day hospital patients undergoing chemotherapy treatment". *Anticancer Res.,* 2007, *27*, 4301.

[2] Silva N.B., Osório F.L.: "Impact of an animal-assisted therapy programme on physiological and psychosocial variables of paediatric oncology patients". *PLoS One,* 2018, *13*, e0194731.

[3] Moretti F., De Ronchi D., Bernabei V., Marchetti L., Ferrari B., Forlani C., *et al.*: "Pet therapy in elderly patients with mental illness". *Psychogeriatrics*, 2011, *11*, 125.

[4] Cherniack E.P., Cherniack A.R.: "The benefit of pets and animal-assisted therapy to the health of older individuals". *Curr. Gerontol. Geriatr. Res.,* 2014, *2014*, 623203.

[5] DeCourcey M., Russell A.C., Keister K.J.: "Animal-assisted therapy: evaluation and implementation of a complementary therapy to improve the psychological and physiological health of critically ill patients". *Dimens. Crit. Care Nurs.,* 2010, *29*, 211.

[6] Creagan E.T., Bauer B.A., Thomley B.S., Borg J.M.: "Animal-assisted therapy at Mayo Clinic: the time is now". *Complement. Ther. Clin. Pract.,* 2015, *21*, 101.

[7] Williams H., Pembroke A.: "Sniffer dogs in the melanoma clinic?" *Lancet,* 1989, *1*, 734.

[8] Church J., Williams H.: "Another sniffer dog for the clinic?" *Lancet,* 2001, *358*, 930.

[9] Willis C.M., Church S.M., Guest C.M., Cook W.A., McCarthy N., Bransbury A.J., *et al.*: "Olfactory detection of human bladder cancer by dogs: proof of principle study". *BMJ,* 2004, *329*, 712.

[10] Taverna G., Tidu L., Grizzi F., Torri V., Mandressi A., Sardella P., *et al.*: "Olfactory system of highly trained dogs detects prostate cancer in urine samples". *J. Urol.,* 2015, *193*, 1382.

[11] Cornu J.N., Cancel-Tassin G., Ondet V., Girardet C., Cussenot O.: "Olfactory detection of prostate cancer by dogs sniffing urine: a step forward in early diagnosis". *Eur. Urol.,* 2011, *59*, 197.

[12] Sonoda H., Kohnoe S., Yamazato T., Satoh Y., Morizono G., Shikata K., *et al.*: "Colorectal cancer screening with odour material by canine scent detection". *Gut,* 2011, *60*, 814.

[13] Guerrero-Flores H., Apresa-García T., Garay-Villar Ó., Sánchez-Pérez A., Flores-Villegas D., Bandera-Calderón A., *et al.*: "A non-invasive tool for detecting cervical cancer odor by trained scent dogs". *BMC Cancer,* 2017, *17*, 79.

[14] McCulloch M., Jezierski T., Broffman M., Hubbard A., Turner K., Janecki T.: "Diagnostic accuracy of canine scent detection in early- and late-stage lung and breast cancers". *Integr. Cancer Ther.,* 2006, *5*, 30.

[15] Ehmann R., Boedeker E., Friedrich U., Sagert J., Dippon J., Friedel G., Walles T.: "Canine scent detection in the diagnosis of lung cancer: revisiting a puzzling phenomenon". *Eur. Respir. J.,* 2012, *39*, 669.

[16] Moulton D.G.: "Olfaction in mammals". *Am. Zoologist*, 1967, *7*, 421.

[17] Arasaradnam R.P., Nwokolo C.U., Bardhan K.D., Covington J.A.: "Electronic nose versus canine nose: clash of the titans". *Gut,* 2011, *60*, 1768.

[18] Hanahan D., Weinberg R.A.: "Hallmarks of cancer: the next generation". *Cell,* 2011, *144*, 646.

[19] Roncati L., Barbolini G., Piacentini F., Piscioli F., Pusiol T., Maiorana A.: "Prognostic factors for breast cancer: an immunomorphological update". *Pathol. Oncol. Res.,* 2016, *22*, 449.

[20] Bredholt G., Mannelqvist M., Stefansson I.M., Birkeland E., Bø T.H., Øyan A.M., *et al.*: "Tumor necrosis is an important hallmark of aggressive endometrial cancer and associates with hypoxia, angiogenesis and inflammation responses". *Oncotarget*, 2015, *6*, 39676.

[21] Edwards J.G., Swinson D.E., Jones J.L., Muller S., Waller D.A., O'Byrne K.J.: "Tumor necrosis correlates with angiogenesis and is a predictor of poor prognosis in malignant mesothelioma". *Chest,* 2003, *124*, 1916.

[22] Liu R., Li P., Bi C.W., Ma R., Yin Y., Bi K., Li Q.: "Plasma N-acetylputrescine, cadaverine and 1,3-diaminopropane: potential biomarkers of lung cancer used to evaluate the efficacy of anticancer drugs". *Oncotarget,* 2017, *8*, 88575.

[23] Zhang X., Chen Y., Hao L., Hou A., Chen X., Li Y., *et al.*: "Macrophages induce resistance to 5-fluorouracil chemotherapy in colorectal cancer through the release of putrescine". *Cancer Lett.,* 2016, *381*, 305.

[24] Redgate E.S., Alexander D., Magra T.R., Henretty J.S., Patrene K.D., Boggs S.S.: "The effect of DFMO induced uptake of [3H] putrescine on human glioma cells". *J. Neurooncol.,* 2001, *55*, 71.

[25] Bandopadhyay M., Ganguly A.K.: "Putrescine, DNA, RNA and protein contents in human uterine, breast and rectal cancer". *J. Postgrad. Med.,* 2000, *46*, 172.

[26] Venäläinen M.K., Roine A.N., Häkkinen M.R., Vepsäläinen J.J., Kumpulainen P.S., Kiviniemi M.S., *et al.*: "Altered polyamine profiles in colorectal cancer". *Anticancer Res.,* 2018, *38*, 3601.

[27] Yeoman C.J., Thomas S.M., Miller M.E., Ulanov A.V., Torralba M., Lucas S., *et al.*: "A multi-omic systems-based approach reveals metabolic markers of bacterial vaginosis and insight into the disease". *PLoS One*, 2013, *8*, e56111.

[28] Mazzone P.: "Nanomedicine: sniffing out lung cancer". *Nat. Nanotechnol.,* 2009, *4*, 621.

[29] Barash O., Peled N., Hirsch F.R., Haick H.: "Sniffing the unique "odor print" of non-small-cell lung cancer with gold nanoparticles". *Small,* 2009, *5*, 2618.

[30] Kateb B., Ryan M.A., Homer M.L., Lara L.M., Yin Y., Higa K., Chen M.Y.. "Sniffing out cancer using the JPL electronic nose: a pilot study of a novel approach to detection and differentiation of brain cancer". *Neuroimage,* 2009, *47*, 5.

[31] Rotello V.: "Sniffing out cancer using "chemical nose" sensors". *Cell Cycle,* 2009, *8*, 3615.

[32] Fischer S.: "Sniffing for cancer: nano noses hold promise for detecting lung cancer and other diseases". *IEEE Pulse,* 2017, *8*, 20.

Corresponding Author:
L RONCATI, M.D., PhD
Department of Maternal,
Infant and Adult Medical and Surgical Sciences
Institute of Pathology
University Hospital of Modena, Policlinico
Viale del Pozzo, 71 - 41124 Modena (Italy)
e-mail: emailmedical@gmail.com