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The Last Word

Thinking Outside the Box About Screening for Ovarian Cancer: The Nose Knows!

Ovarian cancer is the ninth most common malignancy and fifth most common cause of cancer-related deaths in women.[1] At least 80% of patients with this malignancy are diagnosed at a late stage, and despite advances in treatment, aggressive surgery and toxic chemotherapy are necessary to cure even a small percentage. Treatment approaches for patients diagnosed with earlier stages of ovarian cancer are far less morbid and more successful; thus, efforts have been made to increase the rate of early diagnosis through large population-based screening programs.

Unfortunately, due to the lack of both sensitive and specific testing approaches for early-stage disease, these have been largely unsuccessful.[2–4] Most recently, early results from the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial, sponsored by the NCI, were reported at the 2011 ASCO Annual Meeting and subsequently published in the *Journal of the American Medical Association*.[5] The report showed that the interventions used in the investigation were ineffective at improving long-term survival.

We desperately need new approaches to screening for ovarian cancer. We may also need to "think outside the box."

Some recently reported "out of the box" investigations for ovarian cancer screening focus on man's, and possibly woman's, best friend. Horvath et al.[6] initially demonstrated that a Riesenschnauzer dog could be trained to discriminate between ovarian cancer and nonmalignant tissue in petri dishes with nearly 100% sensitivity and specificity. The same laboratory subsequently showed that the characteristic odor was present in the peripheral blood of patients with ovarian cancer.[7] An electronic version of the detector was then developed, but it was not as sensitive or specific as the biologic four-legged version.[8]

Literature reporting on the ability of dogs to recognize malignant tissue has been published in the past few years. The original report by Williams and Pembroke[9] in 1989 described a patient who became concerned about a cutaneous lesion because her dog was interested in that particular lesion but none of the other lesions on her skin. Excision revealed a malignant melanoma. Subsequent articles reported canine ability to distinguish not only other cutaneous lesions, but also bladder,[10] lung,[11] colon,[12] prostate,[12] and breast[13] cancers.

The most recently published reports discuss a dog's ability, with training, to distinguish malignant ovarian tissue from normal nonmalignant ovarian tissue. In one report, a Schnauzer was able to accurately differentiate between malignant and nonmalignant ovarian tissue with 100% sensitivity and 97.5% specificity.[6] The only error occurred when the dog was presented a tissue sample containing malignant metastatic endometrial cancer. A subsequent study compared the dog's olfactory ability to distinguish the blood of patients with ovarian cancer from that of patients without malignancy, noting similar sensitivities and specificities.[7]

Subsequent trials again attempted using an electronic nose, which had been designed to detect low concentrations of volatile chemicals. The success rate of the manufactured nose was lower, however, with 84.4% and 86.8% sensitivity and specificity, respectively.[8] Similar findings were reported for electronic noses in a study of breath exhaled from patients with lung cancer compared with control subjects.[14]

Researchers hypothesize that that the tumors produce volatile chemicals yet to be identified. The dogs' sensitive olfactory senses are able to detect these compounds more accurately than our best current electronics.[15]

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Although they may seem odd, pursuing these biologic approaches does have certain advantages. First, this type of tumor detection involves no radiation exposure, which eliminates one concern of many for those who are concerned with radiation risks associated with large-scale population cancer screening. This low-tech approach is also associated with substantially lower costs. Patient confidentiality also ceases to be a concern (aside from the human technicians), because dogs cannot disclose protected health information.

Despite the unusual nature of this screening, now may be the time for us to try to overcome the inherent difficulties in designing prospective clinical trials using animals, including training enough of them. Experience has proven that dogs can be trained in sufficient numbers to be used for detection of illicitly transported drugs. Similarly, dogs are regularly trained to be the eyes and ears of the blind. Perhaps now is the time for a colleague's prediction to come true. Her response to the original manuscript reporting these observations was,"Now instead of a CAT scan, I will have a DOG scan?" Perhaps we might better define this as a "modern PET scan."

References

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. CA Cancer J Clin 2012;62:10–29.
2. Olivier RI, Lubsen-Brandsma MA, Verhoef S, van Beurden M. CA125 and transvaginal ultrasound monitoring in high-risk women cannot prevent the diagnosis of advanced ovarian cancer. Gynecol Oncol 2006;100:20–26.
3. Menon U, Gentry-Maharaj A, Hallett R, et al. Sensitivity and specificity of multimodal and ultrasound screening for ovarian cancer, and stage distribution of detected cancers: results of the prevalence screen of the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS). Lancet Oncol 2009;10:327–340.
4. Rossing MA, Wicklund KG, Cushing-Haugen KL, Weiss NS. Predictive value of symptoms for early detection of ovarian cancer. J Natl Cancer Inst 2010;102:222–229.
5. Buys SS, Partridge E, Black A, et al. Effect of screening on ovarian cancer mortality: the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening randomized controlled trial. JAMA 2011;305:2295–2303.
6. Horvath G, Jarverud GA, Jarverud S, Horvath I. Human ovarian carcinomas detected by specific odor. Integr Cancer Ther 2008;7:76–80.
7. Horvath G, Andersson H, Paulsson G. Characteristic odour in the blood reveals ovarian carcinoma. BMC Cancer 2010;10:643.
8. Horvath G, Chilo J, Lindblad T. Different volatile signals emitted by human ovarian carcinoma and healthy tissue. Future Oncol 2010;6:1043–1049.
9. Williams H, Pembroke A. Sniffer dogs in the melanoma clinic? Lancet 1989;1:734.
10. Willis CM, Church SM, Guest CM, et al. Olfactory detection of human bladder cancer by dogs: proof of principle study. BMJ 2004;329:712.
11. Ehmann R, Boedeker E, Friedrich U, et al. Canine scent detection in the diagnosis of lung cancer: revisiting a puzzling phenomenon. Eur Respir J 2012;39:669–676.
12. Sonoda H, Kohnoe S, Yamazato T, et al. Colorectal cancer screening with odour material by canine scent detection. Gut 2011;60:814–819.
13. Slupsky CM, Steed H, Wells TH, et al. Urine metabolite analysis offers potential early diagnosis of ovarian and breast cancers. Clin Cancer Res 2010;16:5835–5841.
14. Dragonieri S, Annema JT, Schot R, et al. An electronic nose in the discrimination of patients with non-small cell lung cancer and COPD. Lung Cancer 2009;64:166–170.
15. Lesniak A, Walczak M, Jezierski T, et al. Canine olfactory receptor gene polymorphism and its relation to odor detection performance by sniffer dogs. J Hered 2008;99:518–527.