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Bladder cancer detected via amplified gene in cells found in urine

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Counting the copies of a specific gene in cells gathered from a urine sample may provide a simple, noninvasive way to detect bladder cancer, a team led by researchers at The University of Texas M. D. Anderson Cancer Center reports in the *Journal of the National Cancer Institute*.

When the telltale gene, *Aurora kinase A*, is numerous and overexpressed in urothelial cells, errors during cell division follow, the team also found. The new cells have too few or too many chromosomes, instead of the normal pairs of 23 chromosomes.

"Abnormal chromosome counts are the most fundamental feature - the signature - of human cancers," said senior author Bogdan Czerniak, M.D., Ph.D., professor in M. D. Anderson's Department of Pathology. "We have further clarified the role that the *Aurora kinase A* gene (AURKA) plays in this misaggregation of chromosomes in bladder cancer.

"As a biomarker, *Aurora kinase A* can detect bladder cancer in voided urine with high degrees of sensitivity and specificity," Czerniak said.

Bladder cancer is the fifth most common cancer in the United States, with an estimated 68,000 new cases and about 14,000 deaths annually. It is usually diagnosed after a patient has symptoms by biopsy of tissue removed during a cytoscopic examination of the bladder or microscopic analysis of cells found in the urine.

FISH finds gene, ferrets out bladder cancer

The team used fluorescence in situ hybridization (FISH) to count copies of the gene in urothelial cells from the bladder culled from urine samples. A blinded analysis of samples from 23 bladder cancer patients and seven cancer-free controls showed the AURKA biomarker identified all 23 cancer cases and correctly characterized six of the seven controls as not having bladder cancer.

The biomarker test was validated in urine samples from a separate group of 100 bladder cancer patients and 148 controls. Blinded analysis showed the biomarker accurately identified 87 of the cancer cases and characterized 96.6 percent of the controls as cancer-free, producing only five false positives.

Cytological analysis was conducted on additional samples from 59 of the cancer cases. Microscopic examination of the cells identified 48 of the 59 cancers (81.4 percent). Nine of the 11 cases mischaracterized by cytology were correctly identified by the FISH *Aurora kinase A* test. "It appears that the biomarker is better than cytological analysis of cells isolated from urine," Czerniak said.

"Our next step is to develop a U.S. Food and Drug Administration approved, commercially available test," Czerniak said. That will require independent validation in prospective, multi-institutional clinical trials. If approved, the test could detect new and recurrent cases earlier, leading to increased bladder preservation and improved survival.

Greater *Aurora kinase A*, more chromosomal confusion

In a series of experiments that led to the urine tests, the scientists demonstrated that *Aurora kinase A* overexpression is tightly associated with chromosomal misaggregation, and both occur most heavily in the

most aggressive forms of bladder cancer.

The gene encodes a protein important to orderly cell division and equal segregation of chromosomes. *Aurora kinase A* is a critical protein involved in the duplication, maturation and distribution of centrosomes, which function during cell division to assure the two daughter cells receive the normal 23 pairs of chromosomes.

Current study co-author Subrata Sen, Ph.D., associate professor in M. D. Anderson's Department of Molecular Pathology, and colleagues showed in 1998 that AURKA is an oncogene that is overexpressed and amplified in many types of human cancers, contributing to creation of abnormal centrosomes. These, in turn, lead to abnormal numbers of chromosomes in the daughter cells - a condition called aneuploidy.

Sen, Czerniak and others, showed that the AURKA gene is overexpressed and numerous in human bladder cancer and in 2004 reported that it destabilizes and inhibits the cancer-fighting gene p53.

Building on this work, the team analyzed 15 paired samples of bladder cancer and nearby urothelium for AURKA overexpression. Higher levels of expression were associated with high-grade, late-stage tumors with abnormal numbers of chromosomes. Next, they analyzed 11 bladder cancer lines and found a tight correlation between high levels of AURKA expression and multiple copies of chromosomes.

Finally, they forced AURKA overexpression in a urothelial cell line and found that greater gene activity was associated with a four-fold increase in the number of cells with more than three centrosomes, a two-fold increase in cells with multiple copies of chromosomes 3, 7 and 17, and a four-fold increase in the percentage of cells with abnormal chromosomal counts.

Source: University of Texas M. D. Anderson Cancer Center