

## UNMC researchers: Estrogen derivative may initiate certain cancers

by Vicky Cerino, UNMC public affairs

UNMC researchers are part of a team that studied simple urine samples and found that certain estrogen derivatives can react with DNA to cause damage that may initiate breast, prostate and other cancers.

These findings -- which are published in the Dec. 20 issue of the International Journal of Cancer -- could result in better assessment of cancer risk and prevention, the researchers said. The team published similar findings in the journal The Prostate in 2006.

"We have a novel approach to cancer. We know the initiating step," said Ercole Cavalieri, D.Sc., a professor at the UNMC Eppley Cancer Center. "We think prevention of cancer can be solved by eliminating this initiating step."

The team's findings were confirmed in a second, larger study and presented at a recent gathering of international scientists and physicians in San Antonio.

The study involves researchers at UNMC, Mayo Clinic and the Italian National Cancer Institute. The majority of the study was funded by a U.S. Army Breast Cancer Research Program Center of Excellence Award.

Estrogens can initiate cancer when natural mechanisms of protection do not work properly in the body, allowing estrogen metabolites to react with DNA.

"If these protections are insufficient, due to genetic, lifestyle or environmental influences, we think cancer can result," Dr. Cavalieri said. "Now that we have the basic knowledge about this unifying mechanism of cancer initiation, we have a greater sense of urgency to assess people at risk and, at the same time, begin studies of prevention by using specific natural compounds."

The screening test developed by the researchers analyzes estrogen metabolite profiles in humans and can simultaneously associate the profile with one's risk of getting breast cancer. It involves testing a one-ounce sample of urine using a sophisticated method called tandem mass spectrometry, which analyzes about 40 estrogen-related compounds, including estrogen-DNA adducts formed by a chemical reaction of estrogen metabolites and DNA.

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Researchers analyzed estrogen-DNA adducts from 46 women with normal risk for breast cancer, 12 women at high risk of developing breast cancer, and 17 women diagnosed with breast cancer.

They found women at high risk of breast cancer and the women with breast cancer had significantly higher levels of the estrogen-DNA adducts in their urine samples, while the women with normal risk for breast cancer had low levels of the DNA adducts in their urine.

Nilesh Gaikwad, Ph.D., a UNMC researcher who developed the methodology for the screening tool, said the simple, non-invasive test could easily be applied in the clinical setting.

"We have found the first step that starts a cell down the road to becoming a cancer cell," said UNMC research collaborator Eleanor Rogan, Ph.D. "By preventing this first step from happening, we think we can stop the development of breast or prostate

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cancer. The combination of an early detection test for cancer risk with administration of preventing agents should enable us to significantly reduce the number of women and men that develop breast or prostate cancer."

The results are exciting because they show women at high risk of breast cancer can be identified by the level of adducts in a urine sample, researchers said.

"Similarly, initial studies in men have shown that healthy men have relatively low levels of estrogen-DNA adducts in their urine samples, but men with prostate cancer have much higher levels of the estrogen-DNA adducts in their samples," Dr. Cavalieri said.

Researchers can use these estrogen-DNA adducts as a measure of cancer risk, he said.

"In addition," Dr. Cavalieri said, "we have begun to establish how effective natural compounds may be at preventing cancer by determining their ability to reduce the levels of these adducts in urine."

Dr. Cavalieri also said accumulating evidence suggests that specific metabolites of estrogens, if abundantly formed, can become cancer-initiating agents by reacting with DNA and generating mutations leading to cancer.

DNA is composed of four bases called adenine, guanine, cytosine and thymine.

He said estrogen metabolites react predominantly with the first two DNA bases, adenine and guanine, to form estrogen-DNA adducts.

The resulting damage generated by the reaction can give rise to mutations that eventually initiate cancer. The important estrogen-DNA adducts spontaneously fall out of the DNA, leaving behind gaps that generate the cancer-initiating mutations. The estrogen-DNA adducts eventually make their way out of cells and are excreted in urine.

"This finding identifies a new biomarker in the urine, which appears to correlate with a women's risk of developing breast cancer," said Kenneth Cowan, M.D., Ph.D., director of the UNMC Eppley Cancer Center. "While these studies need to be confirmed in a prospective study in a larger group of patients, this could become an important screening assay for women and could lead to new therapies to prevent breast cancer."

Dr. Cavalieri said one of the major obstacles in cancer research is related to the concept that cancer is a problem of 200 diseases -- a viewpoint that has impeded researchers from looking at the origin of cancers because the search would be prohibitively complex.

While the expression of various cancers coincides with the concept of 200 diseases, some scientists consider there to be a common origin for many prevalent types of cancer. There is widespread agreement in the scientific community that cancer is triggered by genetic mutations in critical genes, he said.

"The article is the best example of translational research. They have generated a unified concept of carcinogenesis and obtained a practical marker detectable in the urine of breast cancer patients," said Jose Russo, M.D., senior member, at the Fox Chase Cancer Center in Philadelphia. "This article provides the adequate setting to explore this concept further by laying the basis to prepare a set of prospective clinical trials testing the preventive effects of the agents or mixtures of agents that can intercept the initiation event in breast or other cancers."

The work represents a paradigm shift in detection of cancer risk in humans and provides the earliest possible rational marker for prevention strategies and regimens, said David Longfellow, Ph.D., president and chief executive officer of the Toxicology Forum -- an international, nonprofit organization devoted to conducting open dialogues about problems in toxicology.

"This work conveys a very exciting message -- that breast and prostate cancer risk can be identified years before the development of a tumor and suggests that natural preventive agents may be effectively used to prevent the initiation step in cancer," Dr. Longfellow said. "Although this is a single manuscript, it is based on an extensive body of work in animal models and humans that consistently supports these findings and is complemented by collaboration with many international cancer scientists."

