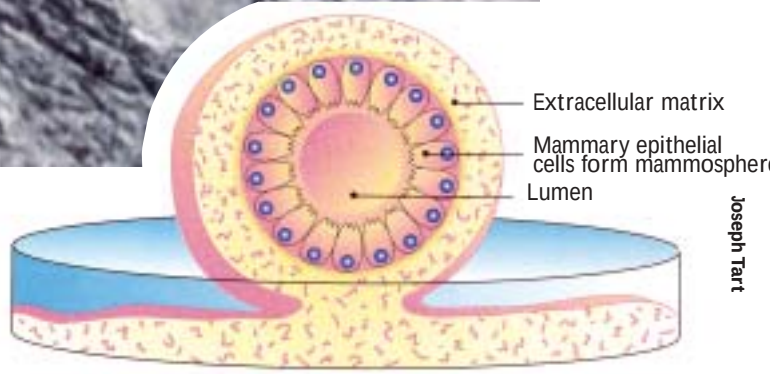
The Role of Carcinogens in Breast Cancer

Biochemical studies show lifestyle and environmental links

By Susan McGinley

Photograph at left shows microscopic view of mammary gland tissue reconstructed in the laboratory. The diagram below is a cross-section of the spheres shown in the photograph. These spheres are the milk-producing structures of the mammary gland. The development of this structure in human breasts may protect against onset of breast cancer. (Reproduced with permission from Environmental Health Perspectives, *Volume 102, Number 10, October 1994, p. 847.)*



Mammary epithelial cells secrete milk containing desired proteins into the lumen of the mammosphere. (Reproduced with permission from Environmental Health Perspectives, *Volume 102, Number 8, October 1994, p. 644.)*

Breast cancer ranks second among cancer deaths in women, with more than 40,000 deaths occurring out of an estimated 182,800 cases in the United States in 2000. Of those, about 2,400 cases were in Arizona, with 600 deaths. Breast cancer is considered such a serious threat to national health that the United States Department of Defense initiated a full-scale research program ten years ago to investigate causes and treatments. At the University of Arizona, interdisciplinary research programs in the College of Agriculture and Life Sciences (CALS), Arizona Cancer and Health Sciences Centers, and other departments are underway to find out more about breast cancer and aid in its prevention and treatment.

Some of the risk factors that may contribute to the development of breast cancer include age, family and personal history of breast cancer, menstrual periods that started early in life, late menopause, no childbirth, alcohol consumption, recent use of oral contraceptives or postmenopausal estrogens, and inherited gene changes. Yet contrary to popular belief, more than 80% of breast cancers are *not* linked to family history or to mutations in breast cancer susceptibility genes. Research shows that environmental factors, including diet, also may play a part, but this connection is less well understood.

To fill in the gaps in this area, faculty and graduate student researchers in the CALS Department of Nutritional Sciences are researching environmental and dietary influences on breast and colon cancer development. Donato Romagnolo, director of the Laboratory of Mammary Gland Biology, is an associate professor of nutritional biochemistry and biology and a faculty of the Cancer Biology and Genetics Interdisciplinary Programs. He is also a member of the Arizona Cancer and Southwest Environmental Health Sciences Centers.

His team is focusing on the biochemical processes that take place in animal and human mammary glands upon exposure to environmental carcinogens, and on how these substances suppress the action of genes in the breast that normally protect against cancer — the BRCA-1 (BR=breast CA=cancer) and BRCA-2 genes. Their work connects information learned from studying the mechanisms in animal mammary glands with the same functions in human breast tissue. They are also looking at the links between high fat intake and the development of excess bile acids in the colon that lead to colon cancer. This re-

search is funded in part by the Arizona Disease Control Research Commission and the National Institutes of Health.

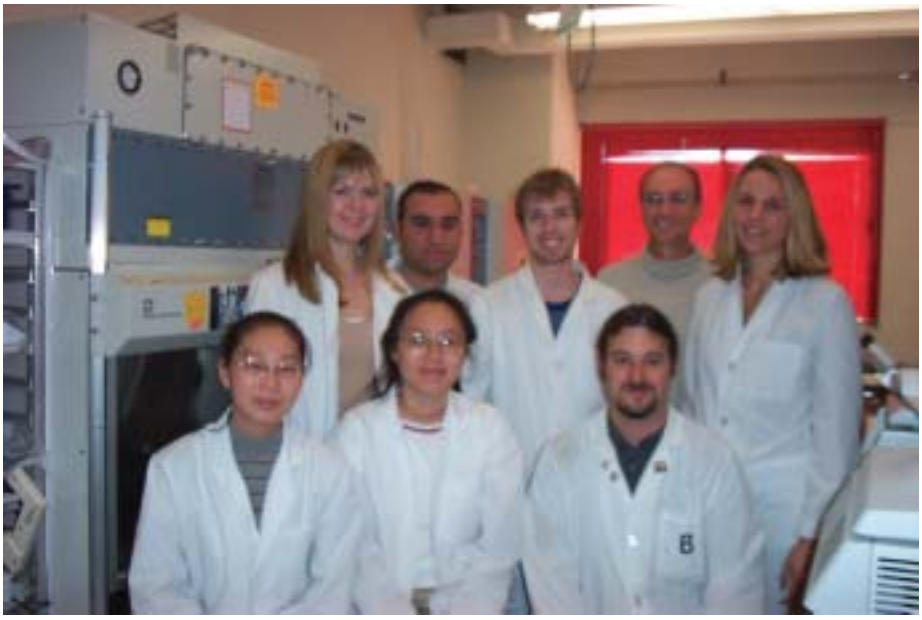
What the researchers find is that powerful carcinogenic substances such as polycyclic aromatic hydrocarbons (PAHs), found in foods (charbroiled meat), coal tar, tobacco smoke and industrial pollution may repress endocrine functions necessary for maintaining normal levels of the BRCA-1 protein in breast epithelial cells. Because BRCA-1 is involved in DNA repair, loss of the BRCA-1 protein may allow DNA damage to accumulate, stimulating the onset of sporadic breast cancer. As women are exposed over time to PAHs, their susceptibility to mammary tumor growth may increase, says Brandon Jeffy a cancer biology Ph.D. candidate working in Romagnolo's laboratory.

The researchers use tissue culture, molecular biology techniques, genomics and other biochemical methods to study changes in the expression of key genes in cells exposed to PAHs. To better understand the effects of these environmental carcinogens, they use cell culture systems to reconstruct mammary tissue in the laboratory. These mammary cells differentiate into alveolar structures capable of producing milk proteins and offer a model system to study the role of nutrients and hormones in this process and biochemical pathways involved in growth and breast cancer, says Wenjing Liu, a nutritional sciences Ph.D. student.

These studies include an analysis of the potential protective effects of conjugated linoleic acid (CLA), a fatty acid present in ruminant milk, against proliferation of breast and colon cancer cells. Results from the Mammary Gland Biology Laboratory show that CLA prevents the proliferation of cancer cells by regulating specific genes involved in cell cycle progression, thus leading to cell cycle arrest and cell death.

Identified in 1990 and sequenced in 1994, the BRCA-1 gene is induced in cells exposed to DNA damaging agents as well as estrogen. The BRCA-1 is a tissue-specific gene associated with breast, ovarian, and possibly colon cancer. One of BRCA-1 functions is to repair DNA double-strand breaks. Romagnolo and his team are studying the ways estrogen and DNA damaging agents regulate BRCA-1 and how p53, the most well-known and studied tumor-suppressor gene, represses BRCA-1 production.

"One function of p53 is to regulate cell cycle division. It stalls the cell, causing it to stop dividing," says Jennifer Ku, a second-year cancer biology graduate student. "Because p53 is the guardian of the genome, it can direct the cell to arrest and allow time for DNA repair. If the damage is too severe, p53 will commit the cell to a suicide program, which prevents division of damaged cells.



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Laboratory of Mammary Gland Biology faculty and students (back row, from left) Jill Hager, Sherif Morgan, Michael Kemp, Donato Romagnolo, Stephanie Degner; (front row from left) Wenjing Liu, Jennifer Ku, Brandon Jeffy.

"We're looking at how p53 may alter the regulation of BRCA-1" say Jill Hager and Sherif Morgan, who hold research staff positions in the laboratory.

Others in the laboratory are studying the relationship between fat intake and bile acid production and how bile acids can enhance the susceptibility to dietary carcinogens. This work has been undertaken in collaboration with Claire Payne and Harris Bernstein in the Department of Microbiology and Immunology and with scientists from the Southwest Environmental Health Sciences Center.

"We're looking at how bile acids and PAHs influence the expression of BRCA-1 in colon cancer," says Michael Kemp, registered dietitian and Nutritional Sciences Ph.D. student. "We are interested in understanding how ingestion of chemicals present in grilled meat and other foods can affect health." The team has shown that cells of colonic origin exposed to PAHs and the bile acid deoxycholate contain reduced levels of BRCA-1. Bile acids are present at higher levels in the colon of people who eat a high fat diet. These findings establish a potential link between stimulation of bile acids secretion and intake of carcinogens in the progression of colon cancer.

"Diet is the most important avenue of exposure to chemical agents, which may modulate people's susceptibility to developing various types of cancer," Romagnolo says. "Diet is not simply an assorted combination of foods we ingest to satisfy our nutrient requirements, but can also be a vehicle for many chemical agents that may promote toxicity and cancer." For example, overcooking of foods generates mutagens, which in dietary epidemiology studies have been linked to increased risk of breast and colon cancer in humans.

"Of course, susceptibility to dietary mutagens as well as other food carcinogens may depend on what your individual genetic makeup is and on your levels of protective and detoxifying enzymes," adds Stephanie Degner, Ph.D. student in nutritional sciences, who recently joined the laboratory.

Research projects undertaken in the Mammary Gland Biology Laboratory bridge the gap between traditional nutritional and biomedical sciences, according to Romagnolo.

"We want to find out how diet and environmental chemicals contribute to cancer development," Romagnolo says. "Once we find out the mechanisms involved, then we can design preventive and therapeutic dietary intervention strategies."

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