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Foyer

Sponsored by the PHS Office on Women's Health and the National Cancer Institute in collaboration with the Congressional Caucus for Women's Issues

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New Frontiers in Breast Cancer Imaging and Early Detection

From Missiles to Mammograms
A Capitol Hill Briefing

Planning Committee

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Last year, numerous provisions initially introduced as part of WHEA were enacted as part of legislation to reauthorize the National Institutes of Health. These provisions include: permanently authorizing the Office of Research on Women's Health at NIH, codifying NIH's policy regarding the inclusion of women and minorities in research, and authorizing additional money for research on breast and ovarian cancer, contraception and infertility, and osteoporosis.

The Women's Health Equity Act of 1993 continues to focus on unmet needs in women's health research, medical education, and meeting women's needs for health care services.

Family and Medical Leave: The Family and Medical Leave Act (FMLA) became the first legislation passed by the 103rd Congress and signed into law. Under the new law, employers are required to provide their workers with up to 12 weeks of job-protected unpaid leave each year to care for a newborn or newly-adopted child, for a seriously ill immediate family member, or in cases of the worker's own serious illness. First introduced in 1985 by Caucus Co-Chair Rep. Patricia Schroeder, the Caucus has been involved in the FMLA from its inception.

Civil Rights: During the 102nd Congress, the Caucus worked along with a broad coalition of women's and civil rights advocates for the passage of the Civil Rights Act of 1991, legislation that expands remedies available to victims of job discrimination and overturns several Supreme Court decisions that made it more difficult for women and minorities to prove cases of employment discrimination. The Caucus will focus attention on the Equal Remedies Act (H.R. 224), legislation that will lift the cap on damages included in the 1991 Civil Rights Act. In addition, the Caucus will also work to redress the recent U.S. Supreme Court rulings. The Caucus has also continued its commitment to equality for women through active support for the Equal Rights Amendment.

Family Planning: The Caucus has been a committed defender of family planning programs, both here and abroad. The Caucus has worked as part of a broad coalition seeking to overturn the family planning "gag rule," regulations issued in 1988 that prohibited federally-funded family planning clinics from providing abortion information or referrals. One of the first acts of the Clinton Presidency was to overturn this regulation. In addition, the House of Representatives recently passed legislation to reauthorize the Title X family planning program, and to require that Title X recipients inform pregnant women about *all* their options for dealing with an unwanted pregnancy.

Violence Against Women Act: The Caucus has committed itself to curbing the rising tide of violence against women. The Violence Against Women Act (VAWA) is designed specifically to address the needs of sexual assault and domestic violence victims. The passage of VAWA during the first session of the 103rd Congress was the culmination of the work of the Caucus over several years. During the second session of the 103rd, the Caucus will work to ensure the final passage of the most comprehensive version of VAWA.

Gender Equity in Education Act: The Caucus's longstanding commitment to ensuring educational equity for the first time developed into its third omnibus legislative package—the Gender Equity in Education Act. This package of nine bills focuses primarily on reforming elementary and secondary education to provide for teacher training, dropout prevention for pregnant and parenting teens, sexual harassment prevention, and other initiatives designed to improve the quality of education for all the nation's children. In addition, the package will address continuing inequities in college athletics programs. Caucus members will work to have gender inequities in education addressed when Congress considers the reauthorization of the Elementary and Secondary Education Act (ESEA) this year.

Foreword

For American women, breast cancer is a dreaded and devastating disease. It is the most commonly diagnosed cancer and the second leading cause of cancer death in women. In 1993 alone, there were approximately 182,000 new breast cancer diagnoses and 46,000 deaths. In fact, over her lifetime, one in eight American women is affected by breast cancer.

Although we cannot prevent breast cancer, we can detect it early. Early detection and diagnosis is a woman's best hope for cure. Through the use of conventional mammography and clinical breast examination, breast cancer deaths among women over 50 can be reduced by 30 percent.

The Public Health Service's Office on Women's Health and the National Cancer Institute (NCI) within the U.S. Department of Health and Human Services (DHHS) are co-sponsoring, in collaboration with the Congressional Caucus for Women's Issues, this Capitol Hill Briefing to examine and discuss breast cancer detection technologies currently under exploration, such as digital mammography, magnetic resonance imaging (MRI), positron emission tomography (PET), ultrasound, and computer-assisted diagnosis, and to explore the potential application of other imaging technologies, such as those used by the defense, space, and computer graphics industries, to the early detection of this disease. It is our hope that this briefing will facilitate collaborations among those in government, academia, and industry who are involved in the imaging field to increase our ability to detect breast cancer and also highlight opportunities for telemedicine on the "information superhighway."

Most importantly, we hope this meeting will demonstrate how our national investment in defense and other imaging fields, such as those used to detect missiles and satellites, can be applied to save the lives of American women.

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What is Breast Cancer?

Breast cancer occurs when breast cells become abnormal and divide without control or order. Cancer cells do not necessarily reproduce faster than normal cells; their growth is the result of a failure to respond to normal signals to stop reproducing. The specific cellular events that trigger the transformation of a normal cell into a cancerous one are still not fully understood, but the process seems to involve a complex interplay of heredity and environment. While certain risk factors for breast cancer have been identified, aging is the major risk factor for breast cancer. From 1973 to 1991, the incidence of breast cancer in the United States rose 24 percent. Only two decades ago, 1 in 20 women in this country developed breast cancer during her lifetime. The rate is now 1 in 8. The death rate has also increased, by 2 percent.

Unlike abnormal growths, cancer is able to metastasize—to break off from the primary tumor, travel through the bloodstream or lymph system, and grow in other parts of the body. In recent years, researchers have discovered two important facts about metastasized cancer. These facts have been crucial in the development of early detection strategies for breast cancer.

First, approximately 50 percent of women diagnosed with breast cancer will die of metastatic disease. The likelihood of a breast cancer metastasizing is related to the size of the primary tumor. Small tumors (less than 1 cm) have a 20 percent or less chance of leading to metastasis. So, early detection is critically important.

Second, invasive breast cancer is believed to be preceded by several characteristics, one of which is angiogenesis—the development of new blood vessels to support the tumor's growth. When enough breast cancer cells in the tumor have angiogenic activity, the tumor grows quickly and provides more avenues for the spread of cancer cells through these new blood vessels. Recent studies have shown a direct relationship between the chance of metastasis and the extent of new blood vessel development in the primary breast tumor. This highlights the importance of new strategies that focus on imaging blood vessels, which are being actively studied.

National Cancer Institute

The mission of the National Cancer Institute (NCI) is to find the means to prevent death and suffering from cancer, to cure cancer or palliate it once diagnosed, and, as its first priority, to prevent its occurrence. NCI, the largest of the seventeen Institutes comprising the National Institutes of Health (NIH), plans, conducts, supports and coordinates a national program of research. In addition to basic and clinical research, the foundation of the program, NCI focuses on cancer prevention and control, demonstration and education programs, and education and training in the fundamental sciences and clinical disciplines. Other programs address health information dissemination regarding the cause, prevention, detection, diagnosis and treatment of cancer, rehabilitation from cancer, and the continuing care of cancer patients and their families. Special programs of research and outreach are supported to advance knowledge about and improve the health of women, minorities, the medically underserved, and aging populations.

Breast cancer research is a major priority for the NCI. With 183,000 cases and 46,000 deaths, annually, breast cancer is the most frequent cancer diagnosed among women. The NCI breast cancer research program extends from the most basic research including that to identify the genetic factors involved, through prevention and all phases of research to information dissemination.

Finding new methods to improve the early detection and diagnosis of breast cancer is a particularly important focus. The effort centers on five national research initiatives:

National Digital Mammography Development Group

An international, multi-institutional, multi-disciplinary collaboration of academic centers, industry and NCI to develop and validate digital mammographic systems. The program consists of five major components:

- digital mammographic imaging system prototype development;
- image processing for improved visualization;
- computer-aided diagnosis for enhanced image interpretation;
- telemammography, or image transmission, as the means to bring radiologic expertise to underserved and rural areas; and
- clinical comparison of advanced technologies with conventional studies.

Joint NCI and NASA Federal Technology Transfer Program in Digital Mammography

More than twenty five multi-disciplinary consortia of investigators from radiologic, space and military communities were formed to advance digital mammography through transfer of digital technologies originally developed for space and military applications.

vance the health of women through the avenues of research, education, and service delivery. This position is also intended to heighten health care professional, scientific and public awareness of critical issues affecting the health of women.

The Office also promotes a PHS regional women's health agenda by assisting the PHS regional women's health coordinators in establishing a framework within women's health issues can be addressed in communities across the nation; by supporting the development and implementation of women's health policies, programs, and initiatives and by coordinating the systematic sharing of information among the PHS regions. The OWH is concerned with developing and disseminating information on women's health, research advances, services, and related issues to the general public, governmental organizations, consumer groups, healthcare professionals, and the academic and scientific communities. Another critical area of emphasis for OWH is the recruitment, retention and promotion of women in the health professions and in scientific careers.

Among the Office's accomplishments has been the development and publication of a document that details a national strategy for improving women's health, the *PHS Action Plan for Women's Health*, a comprehensive, nationwide assessment of the priority health concerns confronting women. The OWH monitors implementation of the *PHS Action Plan for Women's Health*, which involves an ongoing, bi-annual assessment of the progress made towards achieving the Plan's goals, and facilitates collaborative women's health activities between federal, state, and local governments and communities. Breast cancer is a major priority for the office.

New initiatives underway include: implementation of the National Breast Cancer Action Plan, a major public/private partnership to eradicate the threat of breast cancer from the lives of American women; revitalization of the PHS Coordinating Committee on Women's Health Issues; development of a women's health curriculum for health care professional training programs; promotion and development of minority women's health programs; development of an information clearinghouse on women's health; promotion and coordination of violence prevention activities for women; a public/private initiative on eating disorders; a national conference on women's health issues; initiatives to promote healthy behaviors in young women; and continued implementation of the *PHS Action Plan for Women's Health*.

Through the activities and programs of the PHS Office on Women's Health, progress should be made in advancing the health of women in this decade and beyond.

Early Detection and Breast Imaging

While we are currently exploring ways to prevent breast cancer, a successful prognosis today depends on early detection, on finding cancers when they are small and before they have developed the ability to metastasize. Many thousands of lives depend on this success: when a cancer is found and treated early, a woman has more treatment choices and a greatly improved chance of recovery.

Currently, there are three principal ways breast cancer can be detected: (1) through a conventional x-ray mammogram, which can find a tumor that is too small to feel; (2) through a breast exam by a trained health professional; or (3) by the woman herself.

The use of technology to produce, in effect, a picture of the breast is termed "imaging." Mammography is one of several imaging methods.

Imaging has several roles in breast cancer, among them:

- Finding unexpected abnormalities (screening) in the general population. Cancers found by screening imaging have a greater chance for cure and can usually be treated without mastectomy.
- Determining which abnormalities are cancer (diagnosis), and their extent (staging). Information about stage of disease is used to select appropriate treatment options.
- Guiding biopsies of tumors that cannot be felt. Image-guided needle biopsies can replace many surgeries, reduce cost, eliminate scarring, and be more accurate.

Mammography represents the current standard in breast imaging. It is a technique that uses x-rays to create an image of the internal structure of the breast on film. In recent years, advances have refined the procedure and reduced the radiation dose involved to miniscule levels. During mammography, a woman undresses to the waist and stands in front of the mammography equipment, where her breast is slowly pressed between two plastic plates for less than a minute. This "flattening" technique gives a clear picture of the breast with the least amount of radiation. Typically, two x-rays are taken of each breast; more may be needed to produce good images of the entire breast or areas of special concern.

Today's mammograms provide better images with better safety than ever before (see Fig. 1). And they work: a regular program of mammography has been shown to reduce breast cancer mortality by 30 percent or more in women age 50 and over. Despite these successes, however, the technology has limitations. It tends to miss cancers in younger women, because they are more likely to have dense breasts that hide tumors. About 40 percent of women in the general population have dense breasts. Mammography also has problems distinguishing malignant from benign tumors, with the result that many biopsies are done for benign conditions.

These limitations create a place for new technologies that can detect breast cancer earlier, eliminate unnecessary biopsies, and provide more information about the extent of cancer. Research on a number of these technologies is being actively pursued at multiple academic and scientific centers. One of the key issues being considered is how advances in the new technologies might affect actual clinical practice. For example, it may be that certain new imaging technologies might not be appropriate in screening for breast cancer, but could prove effective as diagnostic aids if they replace less accurate tests, or surgery.

The results of studies will provide answers about which new approaches offer true improvement in the detection, diagnosis, and treatment of breast cancer. The studies will also ensure that new technologies are firmly supported by scientific evidence before they take their place alongside existing, well-established methods. The following sections of this brochure describe some of the current research on breast cancer imaging technologies as well as offer a glimpse at several "new frontiers," in which technologies from other fields outside of medicine such as those used in the defense, space, and computer industries are being applied to breast cancer imaging. Some of the technologies described are in use today; others are more distant visions. All are being pursued in the hopes of reducing the threat of breast cancer from the lives of American women.

FIGURE 1. EVOLUTION OF MAMMOGRAPHY

A. General-purpose x-ray equipment was used for this 1939 mammogram. Details were limited, and the radiation dose was high.

B. This 1992 screening image, taken with dedicated mammography equipment, provides excellent detail of breast tissue. The arrow points to a tiny, dart-shaped mass, which biopsy found to be a cancer that had not spread to the lymph nodes.

photos courtesy of Lawrence Bassett, M.D.

Office on Women's Health
U.S. Public Health Service
U.S. Department of Health and Human Services

MISSION

To improve and protect the health of women through policy, research, regulation, prevention, education, and services by advancing and coordinating a comprehensive women's health agenda across the agencies, offices and regions of the United States Public Health Services (PHS) and the Department of Health and Human Services (DHHS), with other governmental organizations and with the private sector.

The Public Health Services' Office on Women's Health (OWH), established in 1991 within the Department of Health and Human Services, coordinates and stimulates programs and activities across the agencies of the PHS including the National Institutes of Health, Centers for Disease Control and Prevention, Agency for Health Care Policy and Research, Food and Drug Administration, Health Resources and Services Administration, Indian Health Service and the Substance Abuse and Mental Health Services Administration. The office also advises the Assistant Secretary for Health and the Surgeon General on scientific, medical, legal, ethical, and policy issues relating to women's health issues. The OWH serves as a catalyst for women's health programs, initiatives and policies across the agencies, offices, and regions of the PHS, providing the structure throughout PHS for addressing the crosscutting women's health issues that require the combined resources, blending of programs and activities administered by the respective PHS agencies and offices.

The goals of the office include:

1) To stimulate the development and implementation of effective women's health policies and programs;

2) To foster access to a full range of health care services for women of all ages and all socioeconomic, cultural and educational backgrounds;

3) To promote comprehensive, integrated, and culturally appropriate health promotion/disease prevention diagnostic and treatment programs for women;

4) To support public and professional education, training and information dissemination on women's health issues;

5) To promote the appointment of women to Departmental, national and international leadership positions which impact the health and well being of women.

In 1994, a new senior level position, Deputy Assistant Secretary for Health (Women's Health) was established within the Department of Health and Human Services, to provide leadership and to give greater emphasis to women's health issues across the agencies of the Public Health Service. This position is designed to redress the inequities in the health care system and in the conduct of research that has put the health of American women at risk and to adin standardizing and improving the MR imaging technology and supplying MR-guided biopsy equipment will have a direct and immediate impact on the quality and outcome of this national study.Ongoing collaborations of government and industry, in partnership with the medical profession for development of new imaging technologies, hold out a promise for a brighter tomorrow, a tomorrow in which the toll of breast cancer for all women will be substantially lessened.

CURRENT RESEARCH AND EXPLORATION

Digital Mammography

During the past two decades, mammography practice and interpretation have improved dramatically through advances in film and x-ray technology and education of physicians, other health care professionals, and patients. Despite these advances, mammography still has considerable room for improvement. Digital mammography—in which visual information is generated, displayed, enhanced, stored, and

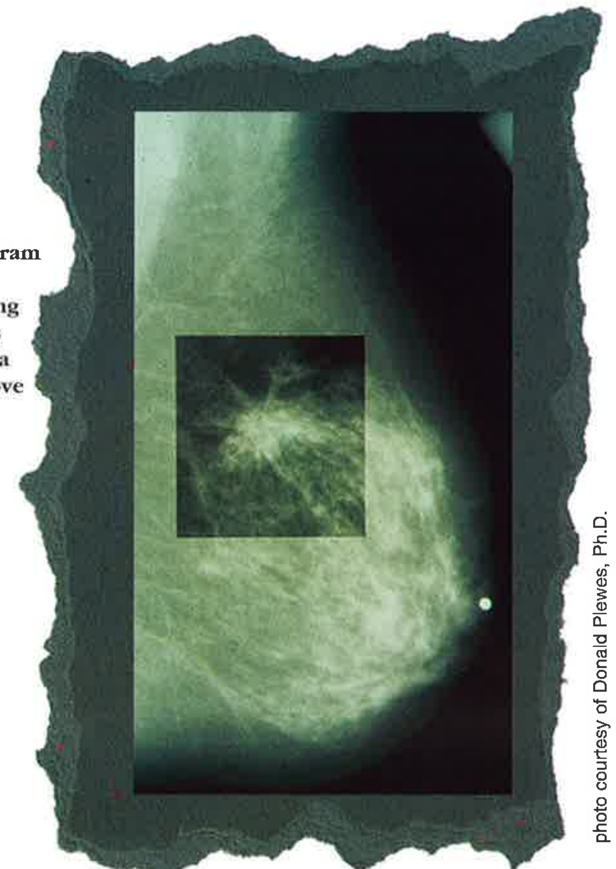


photo courtesy of Donald Plewes, Ph.D.

FIGURE 2. Digitized mammogram where a region of interest surrounding a breast cancer has been enhanced by a computer to improve visualization.

transmitted by computers—offers hope of major improvements in the early detection of breast cancer.

Processing of digital images can improve visualization of the extent of breast cancer (see Fig. 2), especially for women with dense breasts, for whom screening mammography today is often inadequate. For all women, digital mammography offers the prospect of better physician/radiologist consultation and coordination by allowing rapid transmission of images to major medical centers through digital information networks (telemammography). This feature will be of particular value for women in more isolated communities, who will have access to experts nationwide through telemammography.

Advances in digital mammography are the focus of the National Digital Mammography Development Group, a research consortium of five academic and one industrial laboratory formed by the National Cancer Institute and co-funded by industry. The consortium is working to develop alternative technologies for digital mammography hardware, image processing, telemammography, and computer-aided detection and diagnosis. Its ultimate aim is to determine the impact of digital techniques for women with breast cancer through a series of clinical evaluations in major university hospital centers.

Bridging the Gap Between Research and Marketing: Public/Private Partnerships and Policy Implications

Before new technologies for breast imaging can be brought to market, they must move through several stages, from the new idea to research and development, clinical evaluation, and approval by the Food and Drug Administration and Health Care Financing Administration and, finally, to manufacture of a marketable device. This process usually takes 5 to 10 years. However, coordinated efforts of government, industry, and the academic community may facilitate bridging the gap between research and marketing of promising new technologies. Indeed, NCI collaboration with industry and the academic community facilitated development of full-field digital mammography.

Large clinical trials, which may need to image thousands of women, are required to demonstrate the clinical role, if any, for a promising newly developed technology. Government funding is traditionally needed to support technology evaluation, although in many cases, only medical industry can supply commercially unavailable equipment required for successful completion of such projects.

The importance of collaborations between government and industry is clearly illustrated in the NCI initiative devoted to centrally coordinated evaluation of breast MRI in multiple academic centers. Industry's role

Defense Imaging Technologies

The technology of imaging is advancing at a rapid rate, rivaling that of information processing. Driven by surveillance and target recognition missions, the defense community has invested tremendous sums in research and development (R&D) of imaging systems. The resulting technology has found other applications in transportation, environmental monitoring, crime prevention, remote sensing, personal security, civil space programs, and biological science (see Fig. 11).

Historically, adoption of medical applications of new imaging methods has been slow, for several reasons. The obstacles to adopting new technologies include rigorous Food and Drug Administration procedures, limited funds for developing prototypes and models and conducting field tests, and radical deviations from conventional procedures required by the new technology. Recent industry-government technology efforts, however, may herald a change in this historical trend. Research and development programs are ongoing to improve the hardware and software needed to generate, process, analyze, store, and transmit the data used in imaging.

In some cases, the military state of the art is more than a decade ahead of medical applications. An aggressive program to further catalyze cooperative efforts between defense R&D investigators and the breast-imaging community is urgently needed if the Nation is to take advantage of this dual-use technology.

FIGURE 11.
Advanced sensors on board the satellite CLEMENTINE produce a detailed image of the lunar surface from a distance of 300 miles. Similar sensors may be used for digital mammography.

photo courtesy of Dwight Duston, Ph.D.

Computer-Aided Diagnosis

In computer-aided diagnosis (CAD), a specially programmed computer completely searches a mammogram for questionable areas that may contain cancer and flags them for the radiologist for further examination (see Fig. 3). The radiologist uses this computerized analysis as a tool in detecting lesions. These computer programs also may help the radiologist decide whether lesions are cancerous. In this way, CAD serves as an expert "second opinion" or interpreter.

CAD generally works in three steps: 1) possible abnormalities are enhanced visually through image processing techniques and comparison of images of both breasts (or comparison of images of the same breast taken at different times); 2) abnormal regions are isolated from the rest of the image; and 3) various features of the abnormal region, such as size and shape, are used to identify normal, benign and cancerous regions.

In observer studies conducted in simulated environments, CAD has been shown to improve radiologists' ability either to detect breast abnormalities or to distinguish benign from cancerous lesions. Research studies indicate that a computer can identify approximately half of the lesions that a radiologist overlooked. CAD is still at an early stage of development. However, large-scale testing of CAD in a clinical setting are expected to start this year.

photo courtesy of Robert Schmidt, M.D.

FIGURE 3.
An example of a small breast cancer (*arrow*) missed by a radiologist but detected by a computer.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is the creation of images from signals generated by the excitation—the gain and loss of energy–of nuclear particles in a magnetic field. Although breast MRI is still being studied, it shows particular promise in detecting and staging cancers in dense breasts, where mammography is not as effective.

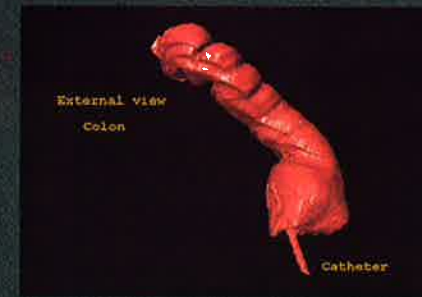
Currently, breast MRI is performed with conventional whole-body MRI units that have been specially adapted. A contrast dye injected into the blood stream gives additional information about blood supply to tissues. This takes advantage of a key characteristic of malignant breast tumors, which is that when they grow beyond a certain volume, they require an increased blood supply. MRI can help to identify breast cancers smaller in size than was previously possible. MRI is done both before and after infusion of the contrast medium (see Fig. 4). Currently, breast MRI takes 35–40 minutes to complete.

At the current stage of development, MRI using pre- and post-contrast scanning, has promise for breast cancer detection and diagnosis. MRI is capable of detecting most cancers, including some not detectable by clinical breast examination or mammography. However, with current techniques, breast MRI does not detect cancers that lack supplemental blood supplies (nonvascular cancers), and it cannot always distinguish vascular benign from vascular cancerous growths. Current results indicate that breast MRI is unique in its ability to define tumor extent, which is important for treatment selection.

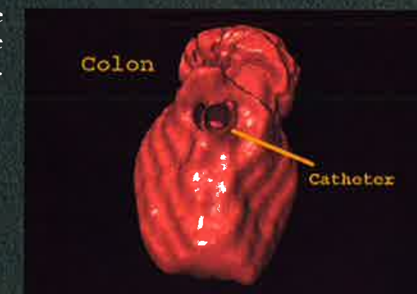
Technological needs include computer-aided display and diagnosis, MRI-compatible biopsy equipment, and development of optimal, cost-effective approaches to generation of breast images. While breast MRI is expensive today, development of dedicated breast MRI units may permit major cost reductions.

There are several potential applications of breast MRI that may increase our ability to detect the disease: assisting in diagnosis for women with hard-to-interpret mammograms and possible cancer; clarifying how much breast tissue is involved to aid in treatment planning for women with known cancer; evaluating response to treatment (reevaluating cancer stage) after chemotherapy; and detecting recurrent cancer in the breast after breast-conserving therapy.

FIGURE 10.
VIRTUAL COLONOSCOPY



A. External view of the colon, with catheter inserted into rectum.



B. Approaching the colon in a "down the tube" view.

C. Inside the rectum, looking toward the junction of the upper part of the rectum and adjoining portion of the sigmoid colon.

D. A 3-cm cancer in the cecum, the pouch that forms the beginning of the large intestine.

photos courtesy of David Vining, M.D.

Cancer Detection Using Interactive Computer Graphics

The results of interactive computer graphics, already being applied to the detection of colon cancer, may suggest intriguing possibilities for wider adaptation to screening and diagnosis of breast cancer.

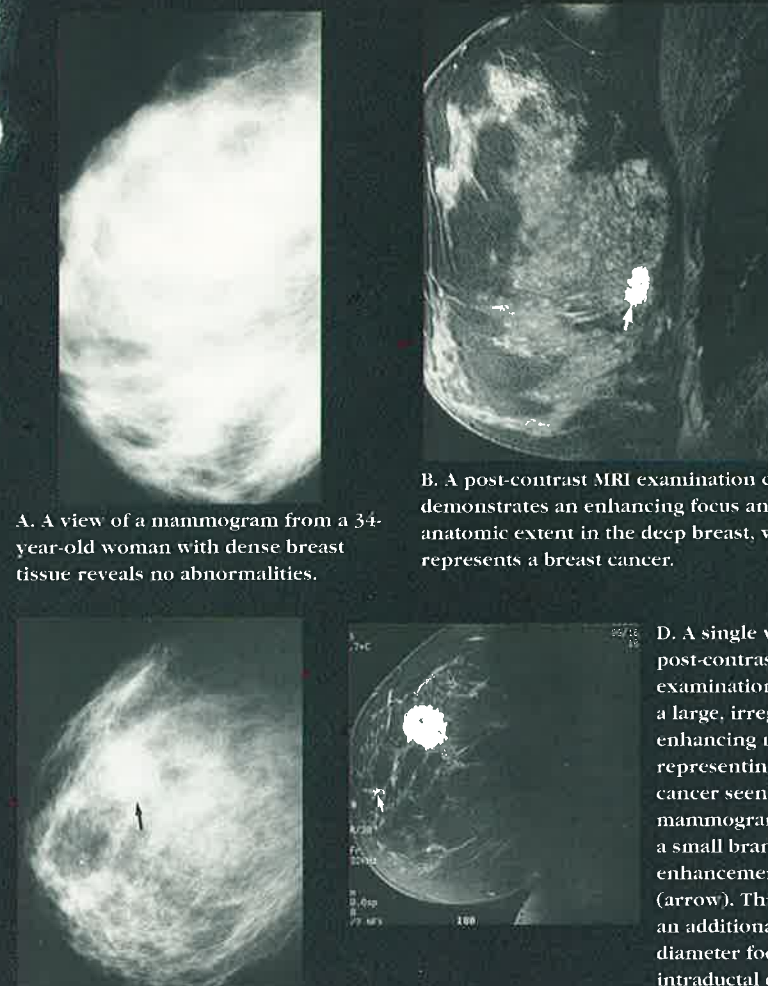
It is thought that most colon cancers develop from preexisting polyps, and that removal of these polyps can prevent the development or spread of cancer and thus reduce the high mortality from this disease. Conventional screening examinations for colorectal cancer—barium enema and colonoscopy—involve a certain degree of discomfort and inconvenience; for this reason, most people avoid them. "Virtual colonoscopy," the application of interactive three-dimensional (3-D) computer graphics to this problem, offers an easier way to examine the colon. The technique involves inflating the patient's colon with air, performing a 30-second spiral-shaped (helical) computed tomography scan of the abdomen, and constructing a 3-D simulation of the colon visualization. With "virtual colonoscopy," a physician can literally closely examine the colon on a computer workstation to search for polyps and suspicious masses (see Fig. 10).

From a patient's perspective, the advantages of "virtual colonoscopy" are substantial: it is considerably cheaper than traditional colonoscopy ($500 vs. $2,000), requires less radiation than a barium enema, and reduces the examination time dramatically (30 seconds vs. 20 minutes for a barium enema and most of a day for colonoscopy).

"Virtual colonoscopy" is an example of computer graphics that was originally developed by the entertainment industry for movie special effects that is now being tested for its usefulness in enhancing visualization of cancer.

Clinical tests are needed to compare MRI to mammography and ultrasound for effectiveness in staging and detection. The NCI program "Multicenter Clinical Evaluation of Breast MRI" is expected to facilitate clinical validation of this technology.

FIGURE 4. MRI SCANS



A. A view of a mammogram from a 34-year-old woman with dense breast tissue reveals no abnormalities.

B. A post-contrast MRI examination clearly demonstrates an enhancing focus and its anatomic extent in the deep breast, which represents a breast cancer.

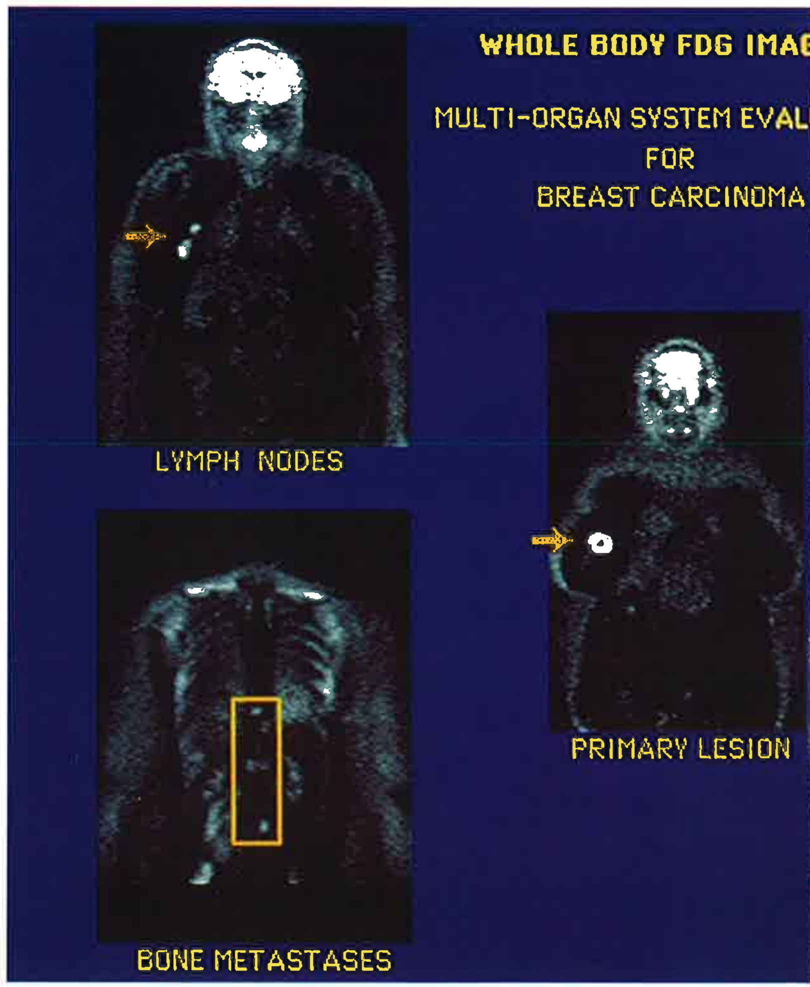
C. A mammographic view demonstrates a focal area of increased density that was later shown to be cancer (arrow).

D. A single view from a post-contrast MRI examination demonstrates a large, irregularly shaped enhancing mass representing the same cancer seen in the mammogram. In addition, a small branched focus of enhancement is also seen (arrow). This represents an additional 1.5 mm diameter focus of intraductal cancer missed by mammogram.

photos courtesy of Mitchell Schnall, M.D., Ph.D.

Nuclear Medicine

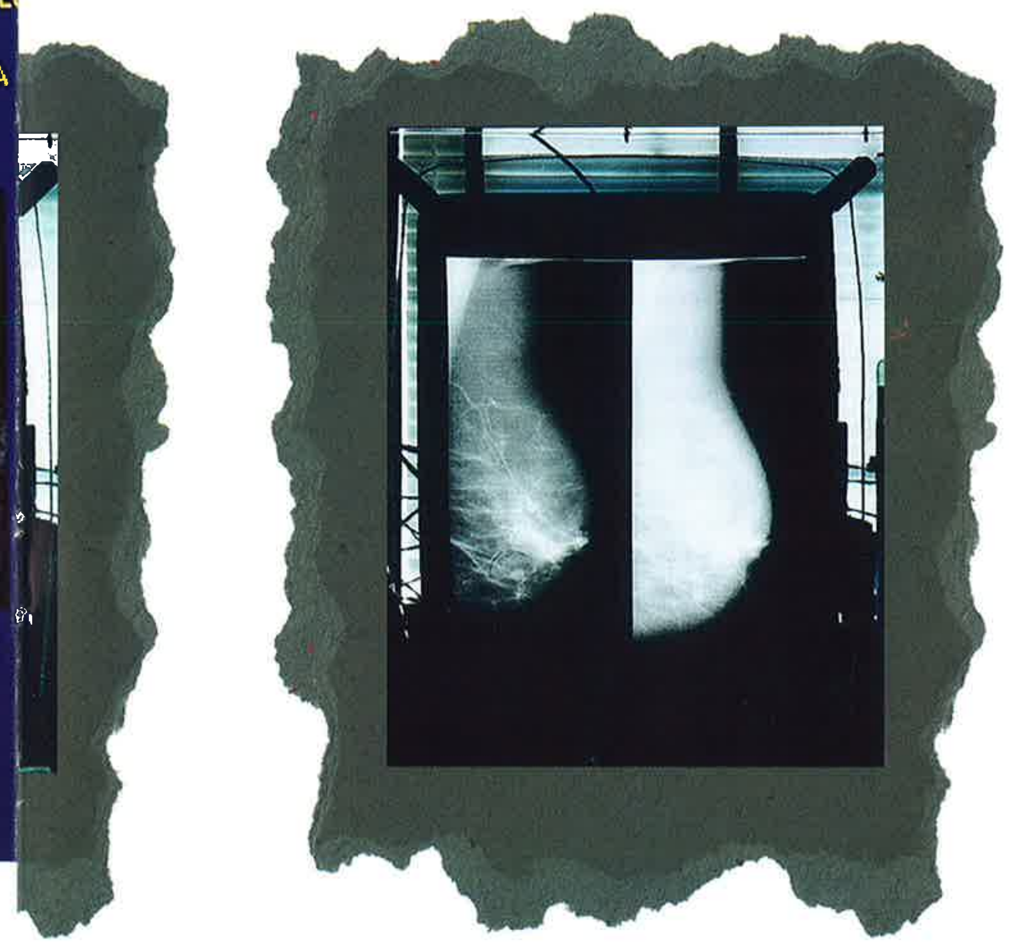
Nuclear medicine imaging techniques include positron-emission tomography (PET) and single photon emission computer tomography (SPECT), which produce images of biochemical and physiological processes in the body.



meet such imaging needs. Film has high resolution, is convenient to handle, and can be displayed easily; however, it cannot be disseminated easily, processed to allow for detection of change, or fused with other imaging techniques. As a result, both the intelligence and the medical communities are moving from "hard copy" (film) to "soft copy" (digital images).

The intelligence community has developed several approaches that may be applicable to early detection of breast cancer: neural nets (or networks), modeled after human brain cells (neurons), to search for cancer cells by examining the context in which they appear; image-processing tools that align mammograms and magnetic resonance scans, to alert the radiologist to changes that may have occurred over time; and new tools, to allow the physician to visualize—or actually feel immersed in—the information. For a successful transition from film to digital images, it is necessary to have displays with very high resolution, high brightness, and uniform resolution. At the moment, displays with two of these attributes are available. In response, the National Information Display Laboratory has been developing a monochrome cathode-ray tube display that features all three essential attributes (see Fig. 9). This display offers excellent potential for radiological as well as intelligence applications.

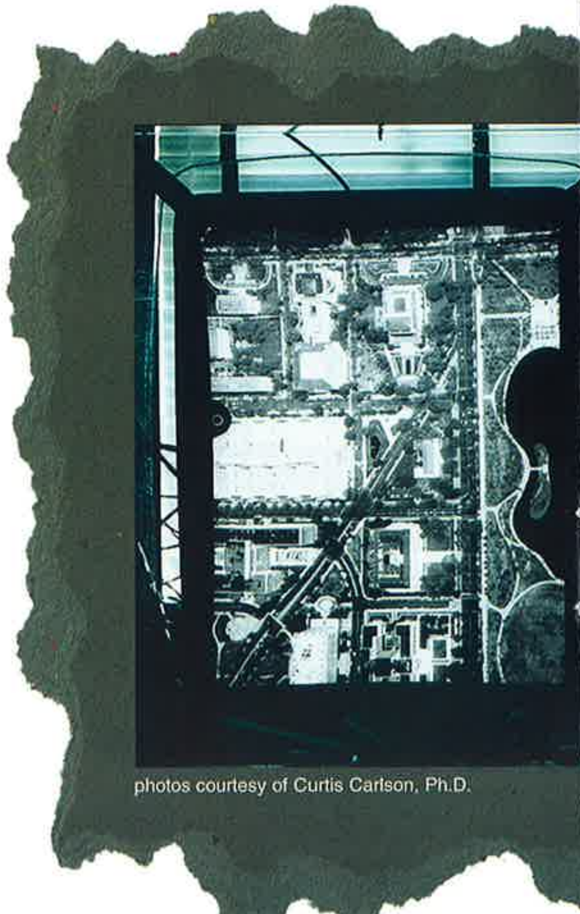
FIGURE 9.
Prototype high-performance display, showing a breast x-ray image (*right*) and an overhead surveillance image for military target interpretation (*left*).



Transferring Technologies from the Intelligence Community to the Medical Community

The medical and intelligence communities share some challenging information processing, display, and image transmission needs. For example, radiologists and intelligence image analysts both must look for subtle changes while rapidly scanning a large number of high-resolution images. Incorrect analyses—a missed cancer or a missed military target—can have profound consequences.

Historically, film has been the medium to

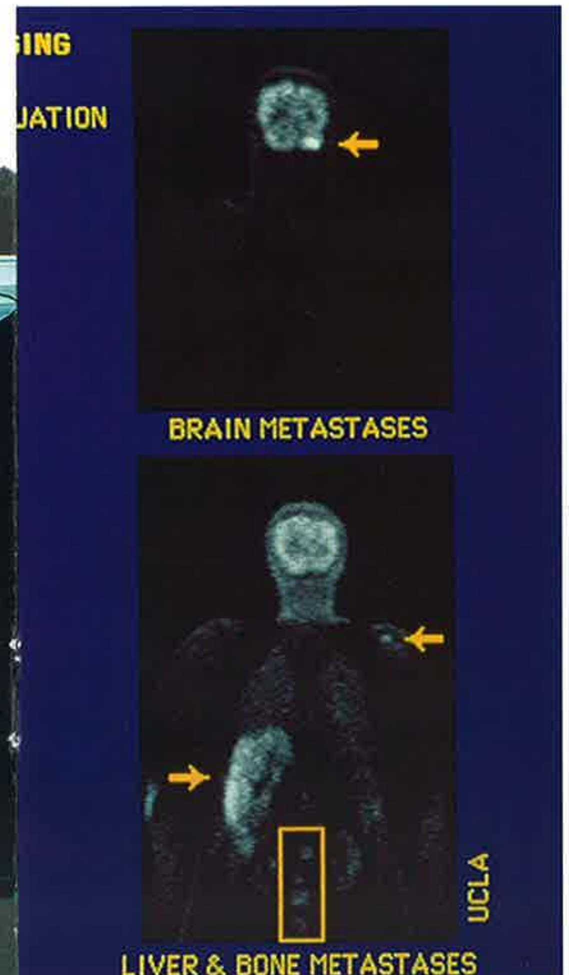


photos courtesy of Curtis Carlson, Ph.D.

PET scans use an agent called fluorodeoxyglucose (FDG) to indicate sites of cancer in the breast and areas where the disease has spread. Like other cancers, breast cancer has a high glucose metabolic rate, which makes it possible for FDG to produce images of glucose metabolism. Different imaging agents are used with SPECT.

Fine-detail imaging with PET is not as good as with mammography or magnetic resonance imaging: however, the biochemical images PET provides can indicate cancer even when other imaging techniques show no structural abnormality. Research suggests that PET-FDG scans in breast cancer will probably be most helpful in staging the disease—determining whether it has spread to lymph nodes or other sites. Whole-body PET scans can be used to search for metastasis to any organ (see Fig. 5). SPECT scans also can be valuable in search for metastases.

Although other imaging methods are more appropriate to breast cancer screening and detection on a large scale, in the future, metabolic imaging methods may help guide treatment of breast cancer, because treatment-induced biochemical changes in tumors should occur before the tumors change in size.



slide courtesy of Randall Hawkins, M.D., Ph.D.

FIGURE 5.
Whole-body PET scans with glucose analog FDG. In the center is a primary breast cancer; the other images show metastatic disease elsewhere in the body.

Ultrasound

Breast ultrasound, unlike other innovative imaging techniques, already has an established role in diagnosis and management of breast disease. High-resolution, hand-held breast ultrasound is used to identify whether masses found on mammography or clinical examination are benign cysts or solid (potentially malignant) lesions. It is also used to guide procedures such as aspiration of cysts and needle biopsy. Because approximately 50 percent of well-circumscribed masses are benign cysts, reliable ultrasound recognition of their fluid-filled nature is cost effective in avoiding unnecessary surgical procedures to rule out cancer (see fig. 6).

Ultrasound is not currently used to screen for breast cancer because it often misses microcalcifications, which are important in diagnosing cancer. It is, however, used for:

1) Characterization of masses as fluid filled or solid, where mammographic diagnosis is uncertain.

2) Guidance of procedures such as aspiration of cysts and biopsies.

FIGURE 6A: SIMPLE CYST
Four criteria are fulfilled to be able to diagnose this palpable mass (*curved arrow*) as a fluid-filled benign cyst. The walls are smooth, the shape is oval, no "echoes" (small white dots of sound) are seen within it, and the acoustic beam travels easily through it leaving a bright white column behind. Pectoral muscle bundles (*arrow*) are at the bottom of the image.

For orientation: the skin is at the top of the image and the cyst is approximately 1.5 cm deep. Pectoral muscle (*arrows*) is at the bottom of the image.

photos courtesy of Ellen Mendelson, M.D.

Firms in the defense and medical research fields have joined together to apply automatic recognition technology used to detect tanks and other military targets to enhance mammographic screening for potential cancers. The concept is based on combining an optical processor and a neural network (computational elements modeled after living brain cells). When searching for military vehicles that are camouflaged by trees or foliage, the system correctly identified 99 percent of the targets with a false-positive rate (identification of nontarget objects) of less than 5 percent. Originally designed for the Department of Defense, this system is now being developed for computer-aided analysis of mammograms (see Fig. 8).

The optical processor extracts characteristic features of the target (in this case the breast) and passes them to the neural network for evaluation. This process is similar to the way radiologists work: they use their optical systems (eyes) to notice features on mammograms, which are then passed to their neural networks (brain cells) to determine if a lesion is present. Optical processing technology has one significant advantage: speed. Current optical processing allows for 1,000 comparisons between a mammogram and lesion characteristics per second; in a few years, the rate will increase to 10,000 comparisons per second. The best digital computers can produce fewer than 100 correlations per second. The tremendous speed of this technology gives feedback to radiologists and patients in a much faster time frame. The next step is to test this technology in a clinical setting.

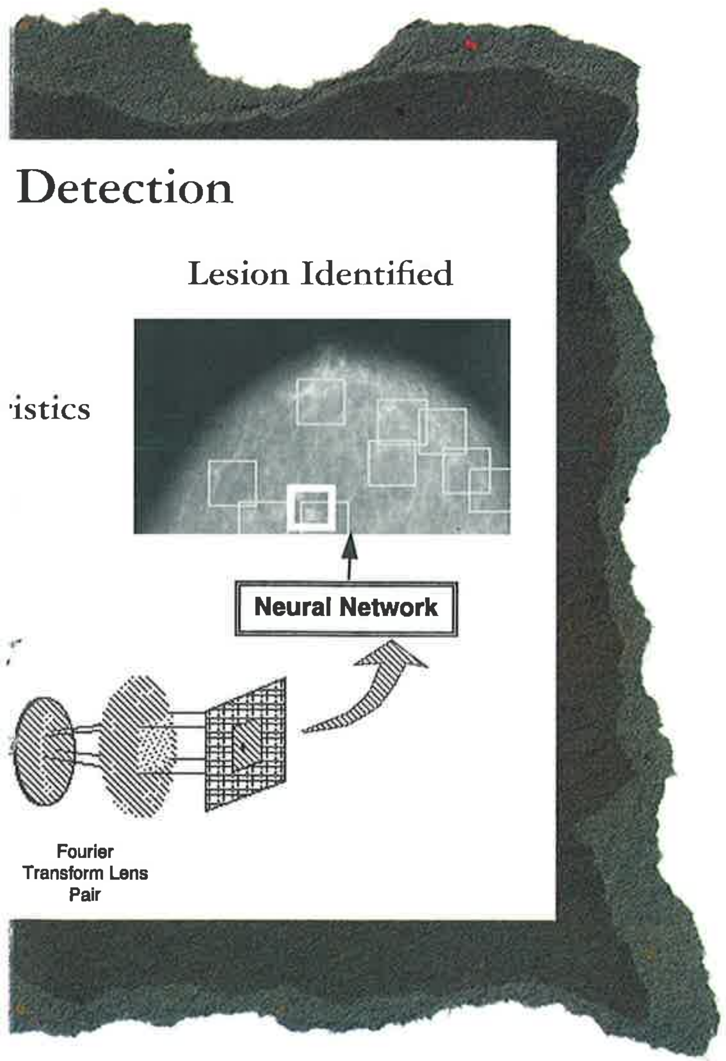
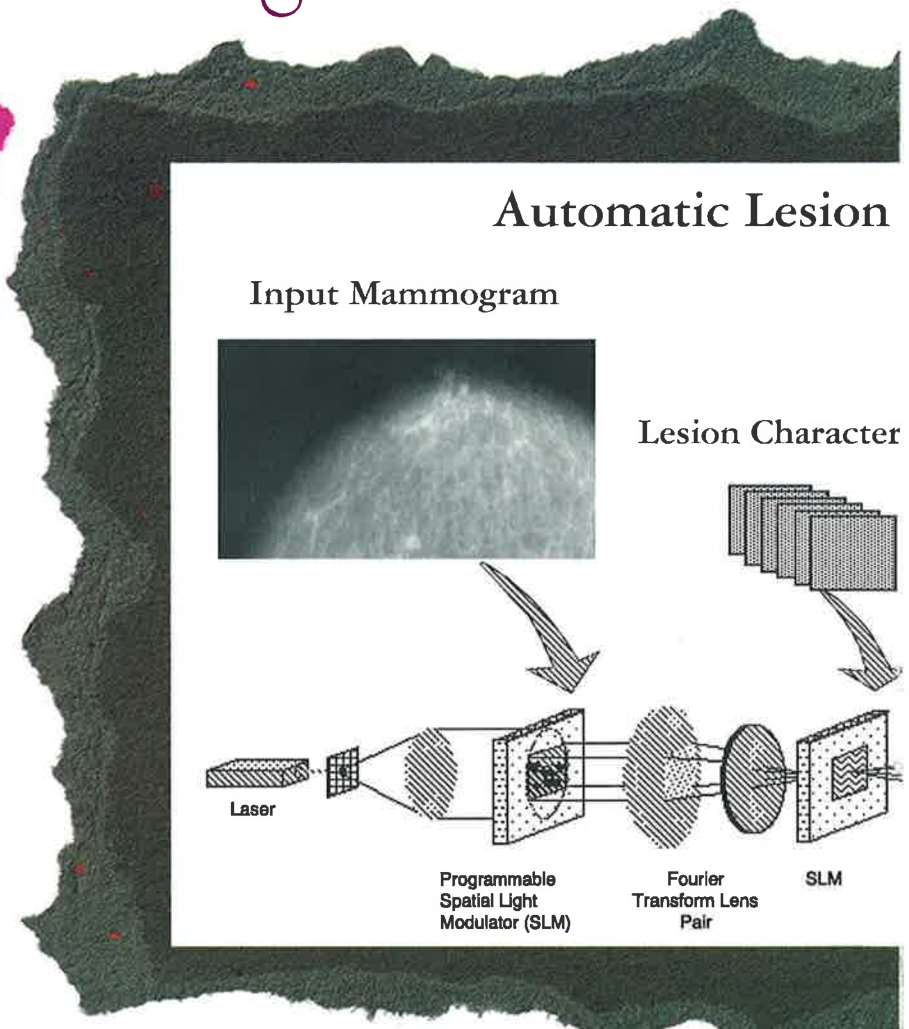


FIGURE 8.
Automatic lesion detection.

Optical Targeting: From Missiles to Mammograms



graphic courtesy of E. Michael Henry, Ph.D.

3) First imaging of palpable masses in women who are under age 30, pregnant, or lactating.

4) Evaluation of an asymmetrical density shown on a mammogram where the cause is suspected to be an underlying mass.

5) Confirmation and better imaging of an abnormality spotted on a mammogram.

Sonographic evaluation of breast lesions after administration of enhancing contrast agents is being studied. The agents may help highlight areas of cancer angiogenesis described earlier. Also under investigation are other features that can help identify cancers, such as tissue compressibility and elasticity (tumors tend to have less elasticity than normal tissue); three-dimensional ultrasound; and computer-aided diagnosis to facilitate interpretation.

Technical advances in breast ultrasound, coupled with the limitations of mammography, raise an important question: whether it is now reasonable to consider using ultrasound to screen for cancer in women with dense breasts, particularly high-risk women, in whom cancers are often obscured by fibroglandular tissue, which is found in a high percentage of women.

FIGURE 6C: BREAST CANCER
Irregular mass with indistinct margins (*arrows*) and a fuzzy rim around it. One of many typical appearances of breast cancer. With fine needle or core biopsy sampling under direct ultrasound visualization the diagnosis can be made. Pectoral muscle (*arrows*) is at the bottom of the image.

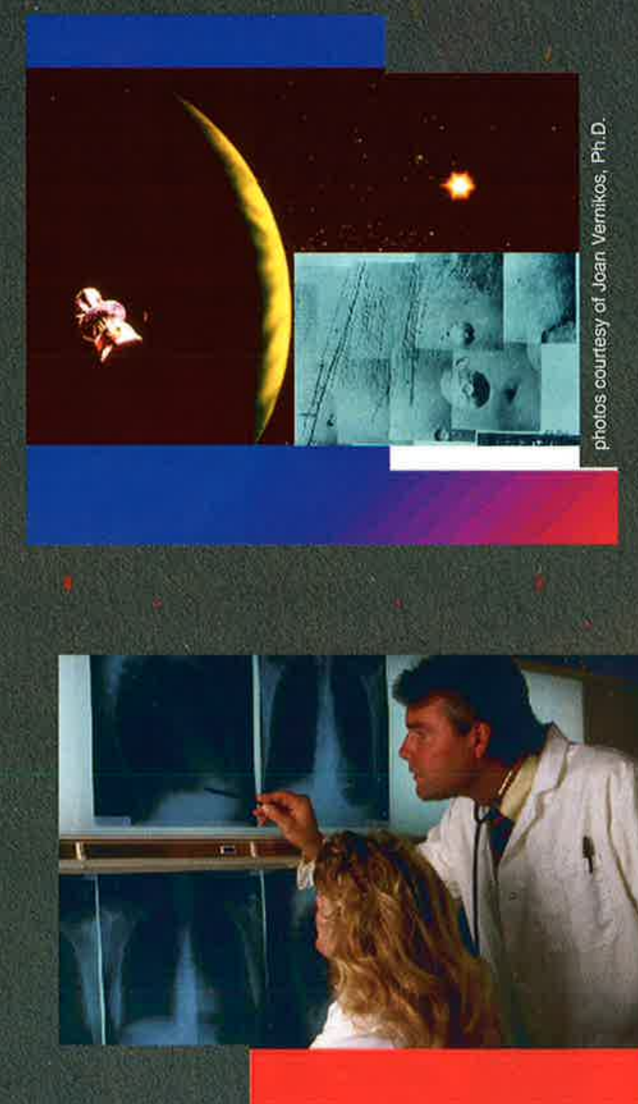
FIGURE 6B: COMPLEX CYST
Looking very similar is a fluid-filled mass except that it contains a nodule (*arrow*) against one wall. Although rare, this was a small cancer that was easily seen within the fluid-containing mass. The mass was removed and the patient has done well since.

Digital Imaging: Space Technology Supporting Women's Health

Scientists and engineers of the National Aeronautics and Space Administration (NASA) develop advanced imaging devices and innovative image processing tools to meet the requirements of space exploration and earth remote-sensing applications. Over the years, these developments have been applied to medical diagnostic imaging (see Fig. 7), including a charge-coupled device (CCD) detector developed for the Hubble Space Telescope that is now used in a digital mammography-guided needle biopsy system for diagnosis of breast cancer.

For the past 3 years, NASA has worked with the NCI to apply the latest in advanced imaging technologies to the development of digital mammography systems. This initiative investigated 43 different aerospace and defense imaging and image-processing technologies with the potential to improve image quality and enhance recognition of features and diagnosis of breast cancer. Now NASA and NCI are jointly supporting three research projects that should, in the next 1 to 2 years, yield new high-resolution, high-contrast digital detectors, which are expected to find smaller breast cancers.

In recent years, scientists and other experts from a variety of fields have come together to discuss ways in which advances in imaging technologies in non-medical fields can be applied to the early detection of breast cancer. They have found that there are a number of ways in which investments in the space, defense, and intelligence industries can be used to save the lives of women. The PHS Office on Women's Health and the NCI are fostering initiatives to facilitate collaboration among these experts to develop new imaging technologies for breast cancer detection.



photos courtesy of Joan Vernikos, Ph.D.

FIGURE 7. Space Technology Applied to Diagnostic Imaging