Developing Technologies for Early Detection of Breast Cancer: A Public Workshop Summary

By Laura Newman for the Committee on the Early Detection of Breast Cancer, National Cancer Policy Board, National Research Council

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A Public Workshop Summary

Written by Laura Newman, M.A. Medical Writer

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Willing is not enough; we must do."
—Goethe

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While the individuals listed above provided many constructive comments and suggestions, responsibility for the final content of the report rests solely with the author and the Institute of Medicine.

Developing Technologies for Early Detection of Breast Cancer: A Public Workshop Summary

BACKGROUND

In November 1999, the Institute of Medicine, in consultation with the Commission on Life Sciences, the Commission on Physical Sciences, Mathematics, and Applications, and the Board on Science, Technology and Economic Policy launched a one year study on technologies for early detection of breast cancer. The committee was asked to examine technologies under development for early breast cancer detection, and to scrutinize the process of medical technology development, adoption, and dissemination. The committee is gathering information on these topics for its report in a number of ways, including two public workshops that bring in outside expertise. The first workshop on "Developing Technologies for Early Breast Cancer Detection" was held in Washington DC in February 2000. The content of the presentations at the workshop is summarized here. A second workshop, which will focus on the process of technology development and adoption, will be held in Washington, DC on June 19–20. A formal report on these topics, including conclusions and recommendations, will be prepared by the committee upon completion of the one-year study.

INTRODUCTION

The goal of early breast cancer detection is to identify cancers at a more curable stage and thus improve disease-specific mortality and improve other important clinical outcomes. The breast cancer detection technologies discussed at the workshop may have the potential to enhance breast cancer detection. Right now, these emerging technologies show promise primarily as adjuncts to existing standard detection techniques, but with further development, some technologies may perhaps eventually replace current early detection modalities. The goal of this workshop was to examine a diverse sampling of some of the emerging technologies—there are many other novel technologies on the horizon that could not be covered in the limited time frame of the conference.

The workshop presenters described how far along the technologies are in development and their potential strengths and weaknesses. They also addressed real-world considerations, such as cost considerations and current reimbursement. Despite the promise of many of these modalities, adopting these technologies would raise new questions, namely the potential for both benefit and harm, appropriate case selection, and cost/benefit tradeoffs.

In particular, workshop participants were quick to point out that improved methods for early detection of breast cancer bring new challenges as well as opportunities for intervention. If the information generated by new technologies cannot be acted upon appropriately to improve survival, then women are not likely to benefit from the technological advances. Furthermore, as technologies become better and better at finding very small, early lesions such as carcinoma in

situ, treatment decisions can be difficult to make because so little is known about the malignant potential of these premalignant cells. As a result, some women may face the diagnosis of breast cancer and the subsequent therapy for a lesion that may never have become a lethal, metastatic cancer. These issues are revisited frequently in the workshop summary.

Advances in Traditional Imaging Technologies

Full-Field Digital Mammography*

Digital mammography consists of a dedicated electronic detector system that captures and displays the x-ray signals on a computer rather than film. Full-field digital mammography (FFDM) offers new capabilities not provided by conventional film-screen mammography, according to Carl D'Orsi, who described the current status of development of diagnostic full-field digital mammography. Unlike film-screen mammography, full-field digital mammography offers an infinite ability to manipulate contrast and brightness with one exposure. Many investigators in this field consider such flexibility as a critical advance in helping to reduce false negatives, which are most likely to occur when imaging dense breast tissue. Without the ability to adjust contrast and brightness, dense tissue can obscure precancerous and cancerous lesions.

Digital mammography separates the process of image acquisition from that of image display. The detector responds to x-ray exposure and then sends an electronic signal for each pixel to a computer where it is digitized, processed, and stored. Because the signal for each pixel is digitally stored, the same image can be manipulated to show different brightness and contrast combinations, allowing radiologists to more easily see through denser tissues.

Digital mammography examinations can be displayed in either hardcopy (laser-printed film) or on screen (using a Cathode Ray Tube (CRT) monitor). With hard copy display, spatial resolution and gray scale range are comparable to standard film screen mammography. However, laser-printed film is costly, involving significant costs for printing, development, personnel, supplies, and printing more than one version of the mammogram.

With screen display (also known as softcopy), digital mammography can be used for computer-aided diagnosis, using algorithms similar to those available for reading film screen mammography. A potential advantage of softcopy display over conventional film-screen mammography is that it permits adjustment of magnification, brightness, and contrast after the mammography examination, thus enabling a more detailed examination of questionable areas without necessarily requiring additional imaging.

Other potential benefits are its ease of image retrieval and transmission; ability to work in tandem with computer aided detection, and digital tomosynthesis, a process whereby digitized images of the breast taken at different angles are used to reconstruct a three-dimensional image or hologram of the breast. Studies on the feasibility of satellite transmission of digital mammography, or telemammography, are also currently underway.

A major limitation, however, is that spatial resolution and luminance range—even with the most advanced CRT technology—is significantly lower than conventional film screen mammography. The speakers suggested that reading softcopy off a CRT display ultimately will prove unattractive to users. Instead, they envision using a technology that involves liquid crystal displays similar to those on laptops because they are likely to provide better image quality. However, an

*Based on presentations by Carl D'Orsi and Etta Pisano.

evaluation of the usefulness of soft copy display system such as very high resolution CRTs and active matrix screens has not been reported.

If the technology is to pass muster, questions concerning the optimum spatial resolution must be resolved. A major unknown is whether increased contrast resolution can compensate for a lower spatial resolution. Pisano believes it will, but only if the image is displayed well. Further, she says that much of the power of digital mammography lies in its ability to distinguish between cancerous tissue and background dense breast tissue. "It is likely that subtle lesions can be seen on digital mammography much more easily," including diffuse calcifications, she believes.

A multicenter trial supported by the U.S. Army Breast Cancer Research and Materiel Command is currently evaluating full-field digital mammography against film-screen mammography in a population of over 7,000 women age 40 and older (principal investigator Ed Hendrick, Ph.D., Northwestern University). Preliminary results based on 4,945 screening exams show that digital mammography performs no better than standard film screen mammography in detecting malignant lesions, but has so far led to fewer recalls than conventional mammography in a screening population. Sensitivity was 58.3% for digital mammography compared with 63.8% for screen-film mammography (the difference was not statistically significant). Positive predictive value (the proportion of recalled exams that led to a diagnosis of cancer) was 3.7% with digital mammography, compared with 3.3% with screen film mammography. Positive biopsy rate with digital mammography appeared to be higher with digital mammography than conventional mammography (30% vs. 19.8%), but this difference was not statistically significant. Digital mammography's lower recall rate (11.5%) compared to screen-film mammography's (13.9%) was statistically significant ($p<0.001$). If projected to U.S. women receiving screening mammograms (5 million), this could amount to 50,000 fewer women recalled for follow-up procedures.

Digital mammography has yet to reach its full potential, according to results from this trial. D'Orsi cautioned that the study described above is not yet completed and may have insufficient statistical power to detect a difference in sensitivity. The Department of Defense will not be supporting further patient accrual to this trial. However, further studies are underway. The American College of Radiology Imaging Network (ACRIN) trial of digital mammography will be especially important in answering many unresolved issues. Thus, the presenters urged the committee not to "throw the baby out with the bath water," not to prejudge digital mammography's effectiveness, and adopt a wait-and-see approach in evaluating it.

Currently, at least four manufacturers have digital mammography machines with differing spatial resolutions: both Fuji and General Electric machines have a resolution of 100 microns, Fischer's machine is 54 microns; and Trex's digital mammography machine can obtain a 41-micron resolution. In January 2000, the Food and Drug Administration approved the first digital mammography machine, General Electric's Senographe 2000 D digital mammography machine. However, it was approved for use only with hardcopy display, which eliminates the opportunity for enhanced softcopy manipulation and computer aided detection. Studies are currently underway to obtain FDA approval for softcopy interpretation. However, another consideration is that prior films taken with standard film screen mammography cannot be imported easily into digitized formats for serial comparisons, posing a problem not uncommon in adopting new technologies.

Cost may be another significant barrier. The GE digital mammography machine costs approximately $450,000 per unit. Thus, purchasing the machines will entail significant up-front costs. Current reimbursement for mammography also makes digital mammography an unappealing investment for radiologists, according to D'Orsi and Pisano. Both presenters said that

mammography reimbursement has remained unchanged over the last 10 years and that mammography facilities are having a difficult time meeting their expenses. They also suggested that radiologists in training are pursuing other more lucrative areas of radiology, a trend that could erode access to mammography.

Although the price could drop with broad use, insurers are likely to take a hard look at whether the machine offers added value. Responding to the mammographers' reimbursement concerns, a managed care representative said that many physicians have a “cottage industry mentality” that should be abandoned. In medicine, he offered, providers need to learn how to do more for less or insurers will redirect their patients to providers who can offer more value for less money. He noted that technologies are unlikely to be attractive to insurers unless they can improve upon existing technology, demonstrate cost-effectiveness, save lives, or show improvements in important clinical endpoints. Thus, if digital mammography cannot show superior performance in early detection by improving the sensitivity and specificity, insurers won't find it attractive in replacing conventional film screen mammography. However, if it can be better exploited to permit tomosynthesis (3-D imaging), digital subtraction mammography with x-ray-based contrast agents, computer-aided detection, multimodality imaging, or telemammography, it might offer added value over existing film-screen mammography.

Computer-Aided Detection*

Computer-aided detection (CAD) systems for screening mammography consist of sophisticated computer programs that are designed for recognizing features of breast cancer, that is, microcalcifications and masses. They are intended to help radiologists identify suspicious areas that may otherwise be overlooked. CAD software works similarly to a spellchecker, according to Ronald A. Castellino, M.D., and has the potential to increase the detection of cancer.

The interpretation of screening mammograms is particularly challenging, since a large number of cases are viewed to detect a small number of cancers (3–10 cancers per 1,000 women screened), which are often manifest by subtle alterations superimposed upon the complex radiographic structure of the breast. As a result, some cancers are missed. Studies show that a significant number of cancers (as many as 30–65%) can be visualized on prior mammograms in retrospective review. Double reading of mammograms by two radiologists can improve the detection rate of cancer (which yields a 4–15% increase in cancers detected), but is expensive and time consuming. The goal of CAD is to improve detection rates in a more efficient and cost-effective manner.

Dr. Castellino summarized the results of a large clinical trial (subsequently published in Radiology, May 2000) consisting of all breast cancer cases diagnosed at 13 clinical sites by screening mammography (1,083, Current mammograms) over a two year period, and the most recent available prior screening exam (427, Prior mammograms). The CAD system correctly marked 99% of the 406 microcalcification cases and 75% of the 677 mass cases, or 84% of the 1,083 Current mammograms. Subsequent algorithm improvements marked 86% of the mass cases. The original radiologist's sensitivity for screening mammography was determined to be 79% (21% false negative rate). The CAD system correctly marked 77% of these cases.

The sensitivity and specificity of CAD in a general screening population, however, has not yet been defined. Further research is needed to resolve these issues.

*Based on a presentation by Ronald A. Castellino.

Initially, there was some concern that CAD might result in a higher recall rate for suspicious lesions. However, according to Castellino, data on recall rates at five clinical sites before (23,682 cases) and after (14,817 cases) the installation of a CAD system showed no increase the recall rate (overall preinstallation recall rate 8.3% vs. postinstallation recall rate 7.6%) for any individual radiologist or for the group overall.

Further studies of CAD with digital mammography also are underway. Several CAD systems are being developed by a number of companies and are being tested on populations around the world.

Magnetic Resonance Imaging

Magnetic resonance imaging is the creation of images from signals generated by the excitation (the gain and loss of energy) of elements such as the hydrogen of water in tissue in a magnetic field. The signals have characteristics which are reflective of the types of tissues (e.g., fat, muscle, fibrotic tissue, edema, etc). The method has no hazards from magnetic field effects and does not use ionizing radiation. Breast magnetic resonance (MR) imaging was first attempted in the 1980s, but early results were disappointing. Subsequently, intravenous contrast agents were used with MR in the late 1980s, offering a clear advance: in general, malignant tumors showed intense uptake of contrast, while surrounding normal tissue did not enhance. Following this discovery, MR has been studied as an emerging, but as yet unproven technology for breast cancer detection. Recently, a number of investigators in this field have demonstrated the potential of breast MRI, but it is currently confined to experimental protocols. Improvements in specificity, and optimal acquisition protocols, examination and interpretation standards remain as ongoing areas of investigation.

MRI Screening in High-Risk Women*

Contrast-enhanced magnetic resonance imaging is currently under active investigation for several applications, notably for imaging dense breast tissue in younger women; surveillance of high-risk women; presurgical planning and surgical guidance; evaluation of recurrence and drugtherapy monitoring; and for imaging elastography.

Contrast-enhanced magnetic resonance breast imaging requires an intravenous injection of Gadolinium chelate contrast agent and a dedicated breast coil. The technique is often performed one of two ways: (1) by using high-resolution three-dimensional magnetic resonance imaging capable of rendering the details of lesion morphology with a resolution of 300 microns, or (2) using high-speed, lower resolution (~1mm), two-dimensional magnetic resonance imaging, to collect multiple images to track the kinetics of uptake and washout of contrast media in tumors. These are currently the best achievable resolutions on a very limited number of MR scanners. The three-dimensional technique takes approximately 4–7 minutes to collect detailed images of both breasts, while the two-dimensional technique requires 5–20 seconds per image section.

Recent studies have shown that contrast-enhanced magnetic resonance imaging confers a greater than 90% sensitivity in detecting lesions, according to Donald Plewes, but the specificity can be lower, ranging between 60% and 90%, depending on the patient population and interpretation technique used.

*Based on a presentation by Donald B. Plewes, Ph.D.

In the trial taking place at Dr. Plewes's institution, 200 women are undergoing four different detection strategies: mammography, clinical breast examination, ultrasound, and magnetic resonance imaging, to determine the relative sensitivity of each method. In addition, clinical trials are underway in other countries throughout the world. In the US, a study is being conducted under the aegis of the International Consortium on Breast Magnetic Resonance Imaging, the National Cancer Institute, and the National Institutes of Health's Office of Women's Health. Similar studies in the UK and Europe are also underway or being planned. According to Dr. Plewes, within the next three years, approximately 5,000 high-risk women will have been scanned with MRI.

MR Spectroscopy*

Magnetic resonance spectroscopy uses MR to measure the biochemical composition of tissues. It is under active investigation as an adjunct to mammography and other accepted imaging techniques. According to Mitchell Schnall, M.D., MR spectroscopy research is in the early stages of development but research with human subjects is underway.

MR spectroscopy is being explored to help characterize human breast tissue. According to recent studies, MR spectroscopy has successfully characterized breast lesions of 1 centimeter or more. Dr. Schnall believes that the technique has the potential to offer much more precise information about the signature of tumors. For example, in an investigational setting, researchers are looking at the chemical constituents, such as choline content, of cancerous tissue. One hypothesis generated from animal studies suggests that the more choline found in breast tissue, the more likely that it is cancerous. However, the technology is not yet far enough advanced for clinical use. There are many challenges that must be overcome if it is to prove beneficial as an adjunct to other detection techniques. For example, the sensitivity and specificity of MR spectroscopy need to be improved for small lesions.

At present, the International Consortium on Breast Magnetic Resonance Imaging, the National Cancer Institute, and National Institutes of Health are supporting research aimed at standardizing lesion characterization.

MR spectroscopy is costly and it will be very important to determine its place among the emerging breast cancer detection modalities. Head-to-head trials of alternative detection techniques may answer unresolved questions about how the technology could be optimally used. Such studies would also help determine its use as an adjunct to existing technologies.

MR Imaging of Angiogenesis*

Imaging of tumor angiogenesis, or new blood vessel formation, using magnetic resonance imaging also shows promise for detection of breast cancer lesions.. Using dynamic contrast technology and kinetic analysis, scientists are able to derive quantitative parameters, which correlate to the histopathology of angiogenesis. State-of-the-art MR scanners can be used to image angiogenesis.

There are several potential advantages of this emerging technology, according to Michael Knopp, M.D. With further study, Knopp hopes that MR imaging of angiogenesis might permit more precise depiction of how tumors evolve at the molecular level. Another potential advantage

*Based on a presentation by Mitchell Schnall, M.D.
*Based on a presentation by Michael Knopp, M.D.

is that angiogenesis studies provide a noninvasive assessment of tumor biology. The clinical utility of this method has not yet been demonstrated, but in the future, the technique could establish itself in the setting of predicting response to and in monitoring therapy. In high-risk populations and patients with highly aggressive tumors, this modality might prove particularly beneficial, according to Knopp. It has the potential to aid in surveillance and in developing more targeted therapies that are not currently available, he says.

Important drawbacks must be overcome if the technology is to pass muster. Current research shows that the technology is not yet able to detect very small tumors and won't work unless angiogenesis is induced or revascularization occurs.

Scientists have recently learned that contrast agents that work well in MR angiography also have the potential for imaging angiogenesis. Gadolinium chelates are the contrast agents most commonly used today, but newer compounds are available in Europe, and are entering the FDA pipeline in the US. Examples include the supraparamagnetic compounds NC100150 (Clariscan (Tradename), Nycomed-Amersham, Oslo) and SHU 555 (Resovist (Tradename), Schering, Berlin). These compounds are in various stages of clinical trials relevant for angiogenesis imaging. New classes of Gd-chelates that exhibit some reversible protein interactions are also being developed, such as Gd-BOPTA (Multihance (Tradename), Bracco SpA, Milan), which was the first available agent and has weak interaction, and MS-325 (Angiomark (Tradename), EPIX Medical, Cambridge), which is a complex Gd-agent with strong interaction. Other examples of agents with potential for tumor imaging include Gadomer 17 (Schering, Berlin) and B-22956/1 (Bracco SpA, Milan).

Recent research shows that MR coupled with new contrast agents can detect angiogenesis induced by factors such as VEGF (vascular endothelial growth factor) and FGF (fibroblast growth factor). Accuracy is above 90% in most cases, with a 95% sensitivity or higher in patients with invasive ductal cancers, 90% or greater for lobular cancers. However, in noninvasive cancers, its sensitivity(about 50%) is low.

If the technique is to be used effectively, good case selection must be established. The National Cancer Institute is supporting research on the pharmacokinetics and standardization of the nomenclature for MR imaging of angiogenesis.

Ultrasound*

Ultrasound waves are high frequency sound waves that reflect at boundaries between tissues of different acoustic properties. The depth of these boundaries is proportional to the time intervals of reflection arrivals. Thus, ultrasound can map an image of tissue boundaries. Ultrasound can also provide information about blood flow by mapping the amount of acoustic frequency shift as a function of position in tissue, the Doppler effect. Within the category of non-ionizing radiation imaging techniques, ultrasound has been the most widely used. Traditionally used as an adjunct to mammography in the identification of cysts and in guiding aspiration and biopsy, improvements in ultrasound technology may expand the role of ultrasound in the differentiation of benign and malignant breast lesions and selection of patients for biopsy, according to Christopher Merritt, M.D. Ultrasound has also been shown, in limited studies, to hold promise as a method for early detection of cancers in women with dense breast tissue, which is often problematic with conventional film-screen mammography.

*Based on a presentation by Christopher Merritt, M.D.

Among the recent technological advances showing potential in expanding the capability of ultrasound are methods for improving image quality through use of high frequency transducers with improved spatial and contrast resolution and by reducing noise through compound imaging. Enhanced detection of tumor vascularity through use of echo enhancing contrast agents and improved Doppler techniques, three-dimensional imaging, and novel approaches such as elastography may further expand the role of breast ultrasound in the near future.

A limitation of conventional ultrasound has been its poor ability to detect small calcifications in the breast (microcalcifications). Usually identifiable with mammography, these tiny calcifications range from 50 to several hundred microns in diameter and may be an important early indication of breast cancer. Contributing to the difficulty of identifying small calcifications with ultrasound is a phenomenon called "speckle" that arises from the interaction of the ultrasound field with tissue. In the breast speckle may produce small bright echoes within tissue that have an appearance quite similar to small calcification, making detection of true calcifications difficult. Speckle and other forms of noise also degrade the definition and characterization of very small breast cysts and solid masses.

Conventional ultrasound generates images using a beam that strikes tissues from a single direction. Recent developments have made it possible to generate an ultrasound image using several beams that strike the tissue from several angles. This technique, called compound imaging, significantly reduces speckle in images of the breast and improves the contrast and definition of small breast masses. Limitations of compounding include a reduction in the display of shadowing and enhancement from some masses.

The detection of tumor blood supply may be important both in the early diagnosis of cancer and in the differentiation of benign and malignant masses. Assessment of tumor vascularity may also be important in predicting the biological activity of tumors and in monitoring response to treatment. Doppler ultrasound permits the identification of blood flow within some breast masses, but has limited sensitivity. Ultrasound contrast agents *might* substantially improve the ability of Doppler ultrasound to evaluate tumor blood supply, particularly when coupled with new signal processing methods such as harmonic and pulse inversion contrast imaging. Several contrast agents are now in the pipeline and are undergoing clinical trial.

Innovations in three-dimensional ultrasound imaging are also proceeding rapidly. Three-dimensional ultrasound permits the examination of a volume of tissue, rather than a single slice. Researchers at the University of Michigan have developed innovative techniques for registration of images from 3-D data sets, permitting more accurate measurement of tumor volume and comparison of changes in the size of masses over time.

In contrast to fetal and gynecological ultrasound, where 3-D methods have received considerable attention, 3-D scan of the breast is in an early stage of development. In the breast, 3-D imaging deserves evaluation for early breast cancer detection as in serial studies, according to Merritt. Coupled with contrast agents, 3-D Doppler imaging may provide more detailed assessment of tumor vascularity than is currently possible. However, additional research in the use of ultrasound contrast agents and three-dimensional ultrasound imaging is needed to fully define the contributions of these methods to detection, diagnosis, and assessment of treatment response.

A novel use of ultrasound in the breast currently under development is elastography. Elastography uses information from the ultrasound signal to produce an image displaying the elastic properties of breast tissue. Like palpation, elastography is able to detect and display differences in tissue stiffness. Since most cancers are hard in comparison to the tissues that surround them, elastography provides a high contrast image, in some cases revealing features that may not be

visible with conventional ultrasound or mammography. Investigators in the field are optimistic that elastography may improve upon conventional ultrasound's specificity and sensitivity, but further study is needed.

According to Dr. Merritt, clinical trials that allow head-to-head comparisons of these innovative technologies with conventional screening techniques are needed, particularly in settings where conventional methods are limited, such as in high-risk young women with dense breast tissue and for detection of multifocal disease in women with dense breasts. Ultrasound should also be investigated aggressively as an adjunct to mammography among patients with suspicious breast lesions, he says.

Looking further into the future, it is possible to envision other new approaches to cancer treatment aided by ultrasound technology. High intensity focused ultrasound (HIFU) is currently under investigation as a noninvasive method for the tumor ablation that may lead to nonsurgical options for treatment of breast cancers in some patients, and ultrasonic destruction of microbubbles carrying chemotherapeutic or gene therapy products is an intriguing possibility that could substantially increase the dose of the agent delivered to the area of the tumor with minimal systemic toxicity. However, the clinical utility of these novel methods has not yet been determined.

Functional Imaging*

Traditional early cancer detection technologies use an anatomical imaging approach, but a new era in medical oncology that focuses on imaging of molecular markers is under active development. Bench researchers suggest that it has the potential to identify the molecular changes in breast cancer much earlier than with conventional anatomical imaging techniques, but this potential is still far from being realized.

Imaging Molecular Markers*

Scintimammography uses radioactive tracers that are taken up more readily by breast tumors compared to normal breast tissues to produce an image of a tumor. This is a relatively new technology that some clinicians may use as an adjunct to standard x-ray mammography to help localize tumors, to distinguish malignant and benign lesions, and to identify lymph node metastases. Studies indicate that the overall sensitivity of scintimammography ranges from 75 percent to 94 percent, and the specificity ranges from 80 percent to 89 percent. However, one limitation of scintimammography is its resolution, which is between .8 and 1 cm. As a result, the scans cannot detect tumors smaller than 1 cm. Developments in positron tomography and compact, special purpose devices may improve detection capabilities.

In the future, it may be possible to advance this technology by combining it with a molecular biology approach. Scientists are examining specific molecules that define cancer and the transformed cancer cell. Using radiopharmaceuticals in conjunction with nuclear medicine imaging techniques such as positron emission tomography (PET), and single photon emission computed tomography (SPECT), they are just beginning to examine those molecules in living tissues.

David Piwnica-Worms, M.D., suggested that if scientists can identify early markers of tumor aggressiveness —depending on receptor and enzyme levels, for example—they may be able to establish biochemical maps that could help individualize treatments. Currently, this technology is

*Based on a presentation by David Piwnica-Worms, M.D, Ph.D.

in the laboratory, but with continued research, he believes it might be sufficiently developed to enter the clinic within the next five to ten years.

One example of this type of molecular imaging research has focused on the imaging of multidrug resistance. Piwnica-Worms and other investigators are actively studying the fundamental mechanisms of radiopharmaceuticals and multidrug resistance. The radiopharmaceutical 99m-Tc-sestamibi is selectively taken up by tumor cells compared to normal cells. Recent research in the laboratories of Silvana Del Vecchio, Ph.D. (Naples, Italy), Piwnica-Worms, and others suggests that the radiopharmaceutical is pumped out of cells just like the chemotherapeutic agent adriamycin. Piwnica-Worms demonstrated in humans that excretion of 99m-Tc-sestamibi is mediated by P glycoprotein function. Del Vecchio subsequently carried out the pilot clinical research that correlated very rapid 99m-Tc-sestamibi washout rates with treatment failure. This process can be imaged with 99m-Tc-sestamibi using SPECT.

Previous research suggests that approximately 25% of patients with stage I breast cancer overexpress P-glycoprotein and are at increased risk for failing conventional chemotherapy. Preliminary scintigraphic research has shown that patients who fail breast cancer chemotherapy clear the radiopharmaceutical 99m-Tc-sestamibi three times faster if they overexpress the multidrug resistance P glycoprotein (MDR1).

Piwnica-Worms suggested that these MDR imaging trials might permit molecular characterization of breast tumors and aid in early detection. Novel interventions, yet to be fully developed and proven effective, could then be combined with molecular detection to improve treatment. For example, researchers are now beginning to test P-glycoprotein inhibitors in phase II/III clinical trials. Such inhibitors may increase the efficacy of chemotherapy regimens in women who overexpress MDR.

This is a burgeoning area of research and studies with other molecular markers are actively underway. Work with other contrast agents and PET imaging is also under active investigation (e.g., labeled endothelial growth factor and labeled steroids).

If molecular imaging ultimately proves to aid in prognostic stratification and more targeted molecular therapies become widely available, health outcomes might improve, while subsets of women could be spared iatrogenic morbidity, and costs could be reduced. However, much more bench research and clinical trials are necessary to prove efficacy and effectiveness before this technology enters the clinic.

Imaging Gene Expression by MR*

Another emerging imaging technique uses “smart” magnetic resonance contrast agents to reveal biochemical and physiological information, such as gene expression and other physiological processes in the form of a 3D-MR image. This approach is similar to some of the radiopharmaceutical techniques described above, but in this case, the technology uses gadolinium contrast agents within a molecular shell. Specific biochemical processes open the protective shell, allowing hydrogen nuclei to interact with the gadolinium, which changes the MRI signal.. This work is under active study in the laboratory of Thomas Meade, Ph.D., at Caltech. He sees its development as a fundamental key to a future in which we can detect cancer and other disease processes much earlier than shown with conventional anatomical imaging techniques.

*Based on a presentation by Thomas Meade, Ph.D.

Imaging gene expression that can be correlated to disease states is in the very early stages of development and is being pursued commercially by a company founded by Dr. Meade known as Metaprobe (Pasadena, CA). With further development, Meade says the novel imaging technique could track cell growth and behavior in breast and other cancers, including imaging of intracellular protein communication, apoptosis (or programmed cell death), and angiogenesis. With more precise imaging of cancer cell biology and function, the goal is to intervene earlier in the cascade of breast cancer progression, hopefully resulting in better clinical outcomes. If the technology proves to better stratify cancers early on, he says it may permit better targeting of therapies. However, so far, all research has been conducted on animals and testing in humans in clinical trials is still a long way off. Thus, little is known about the technology's sensitivity, specificity, toxicity, and prognostic value.

Optical Scanning*

Optical scanning uses non-ionizing radiation and a variety of contrast agents to produce an image of the breast. Potential advantages of the technology include speed, comfort, noninvasiveness, and easy access to the breast. Optical scanning is able to penetrate deeply into the breast and do so without using ionizing radiation. To take an optical scan of the breast, an image pad is simply placed over the breast. An image can be taken in less than 30 seconds without breast compression. Using a near-infrared light probe and novel contrast agents, the technology has the potential to show the key molecular and enzymatic events involved in cancer development and progression. Optical contrast agents (termed “molecular beacons”) fluoresce (or light up) after cleavage with specific enzymes. Optical scanning images can also be digitized, thus allowing image manipulation and serial studies. Hurdles that must be overcome before this technology reaches the clinic relate to accuracy and resolution, which are not yet optimized.

The technique is actively under investigation for a variety of cancers, including breast and prostate cancer, and in the assessment of lymph node metastases, according to Britton Chance, Ph.D., a pioneer in the field who spoke on behalf of the seven other laboratories and industries developing breast imaging optical devices. With optical scanning, he says, it may be possible to obtain a coherent image of enzymatic and molecular processes, offering depiction of abnormal cells before conventional anatomic imaging would be able to detect them. Dr. Chance said that the technique is very inexpensive and simple to use, especially in comparison to many other imaging modalities.

Proponents of the technique hope that with further research, it may become possible to use optical scanning to enhance cost effectiveness of early detection and treatment. In the future, optical scans might prove capable of enhancing the sensitivity and specificity of other detection techniques, and thus might help reduce unnecessary biopsies. The technique has already been shown to be relatively unaffected by the problem of dense breast tissue, a limitation of mammography.

Biological Detection

The recognition that breast cancers of the same stage progress with widely varying rates underlies much research into biological detection. Current staging techniques are considered relatively imprecise in predicting prognosis. The goal of biological research is to classify tumors

*Based on a presentation by Britton Chance, Ph.D.

based on their molecular biology rather than their morphology as is currently done. If this goal can be achieved, then this new knowledge could potentially be used to develop new methods for earlier detection and also better stratifying cancers. However, biological analysis is most likely to be used as an adjunct to imaging technologies once a lesion has been located based on its morphology. In some cases, the techniques might also be used to identify women who need further evaluation in addition to the usual screening mammography, which is unable to detect certain breast tumors.

Biology of Early Breast Cancer*

Understanding the molecular biology of premalignant breast disease and early breast cancer is in its infancy and is relatively uncharted terrain, according to D. Craig Allred, M.D. “We are a long way off from a major paradigm shift in how we treat patients with these lesions and translating knowledge about their biology from the bench to the bedside,” he observes. However, in pursuing research on the molecular biology of premalignant disease and early breast cancer, it may become possible to prevent or delay more advanced invasive breast cancer.

Conventional imaging techniques offer relatively imprecise estimates of those premalignant lesions most likely to progress to invasive breast cancer (IBC) or those IBC's most likely to metastasize. Tremendous biological variability exists in these lesions and the ways in which they grow and spread. Identifying the molecules associated with invasive breast cancer could open the door to developing more targeted prevention strategies and could potentially aid in stratifying an individual's risk for invasive breast cancer and response to therapy.

As Allred described, pathologists have long understood that breast lesions exist on a histological continuum. Cells in the stem cell compartment, the normal terminal duct lobular units, begin to undergo a hyperplastic proliferative response, the first phase in the continuum. However, in conceptualizing breast cancer in terms of a linear process carries with it an oversimplification of the development of breast cancer.

Just in the past decade, there has been an explosion in research on the biological determinants of breast cancer. Scientists are investigating breast cancer biology in studies examining the growth of premalignant lesions, the estrogen receptor, other growth factors, and genetics, for example. Immunohistochemistry on tissue sections is a technology that can show tumor marker expression in cells, and along with histological grading systems, can partially convey the morphological and biological heterogeneity of lesions. So far, the most thoroughly studied molecules are the estrogen receptor, HER-2/neu, and p53.

Both apoptosis and proliferation are under hormonal regulation in normal breast epithelial cells. Preliminary studies suggest that average rates of growth are higher and apoptosis is lower in premalignant cells compared to normal cells, which may be important in the development and progression of premalignant disease.

In studying the genetics of breast cancer, loss of heterozygosity (LOH) is an intriguing area of research, according to Allred. LOH occurs when one copy of a gene is deleted from a cell's genome. The remaining copy is often mutated. The studies are based on DNA isolated from archival tissue samples that are microdissected, allowing independent examination of lesions. They are incubated with primers for different microsatellite markers, PCR-amplified, and separated on a gel. There have been at least thirty studies that have found significant rates of loss of heterozy

*Based on a presentation by Craig Allred, M.D.

gosity at dozens of genetic loci in premalignant disease and early breast cancer. However, the contribution of these genetic alterations to the initiation or progression of breast cancer is largely unknown.

One impediment to moving ahead in our understanding of early breast cancer is that researchers have been largely restricted to working with small archival tissue samples from premalignant breast tissue, which means that scientists have been limited to doing correlative studies. Such studies do not provide information on mechanisms, and there is a lack of animal models or cell lines to address these mechanistic questions.

Microarray Analysis*

DNA chips, or cDNA microarray analysis, holds promise for pinpointing which genes are differentially expressed in cancer compared to normal tissue, according to Stefanie Jeffrey, M.D. Microarrays display thousands of DNA dots on a single slide. Each dot represents an individual gene, and as many as 24,000 dots make up a gene chip. The microarray technology enables researchers to look at thousands of genes at once and obtain a tumor "signature." Scientists working in this field believe that the technology will eventually be able to differentiate tumors that are aggressive from those that might lie dormant. In the future, it may also be able to determine how a given tumor will respond to systemic therapy, but currently, applications of the technology are in very early stages of investigation.

The technology first emerged in the mid-1990s. Early pioneers include Patrick Brown, Ph.D., and David Botstein, Ph.D., from Stanford University School of Medicine. They have been using microarrays to study a variety of cancers. Jeffrey is using the technology to study breast cancer. She is now studying late-stage breast tumors (generally greater than 2 cm), using frozen breast tumor tissue. As of now, Jeffrey says that her group has been making microarrays with 23,000 genes. With the microarrays, it is possible to analyze tumors for expression of specific gene markers, such as HER-2/neu and ER. It may also be possible to identify new genes involved in breast cancer progression. Once genes are identified, researchers can conduct verification studies using a variety of techniques to see whether it is important in cancer.

So far, Jeffrey's lab has been able to develop a cluster scheme that groups together tumors that are similar in gene expression. To further develop this technology, Jeffrey believes that examining normal breast tissue, as well as earlier stage cancers, is important. Currently, she is looking at RNA that is harvested from core needle biopsies. Another approach uses a technique known as laser capture microdissection to collect cells. The technique permits examination of small clusters of cells, and can be used to collect pure samples of endothelial cells, stromal cells, as well as epithelial cells, which cannot be done with other techniques. The high costs associated with DNA chips and banking sufficient tissue for study are potential barriers to moving this research forward. The need for better "bioinformatics" was also raised as an issue that must be reconciled to allow further technology assessment.

Another unrelated technique that Jeffrey and others are using involves NASA-type "smart probes," which differentiate tumor from benign tissue. These minimally invasive probes identify physiologic properties of tumors, such as optical reflectance, intratumor O2 measurements, electric potential differences, and laser doppler bloodflow of tumor vascularity. Other ways to potentially exploit the technology include measuring temperature changes, drug levels, and serial

*Based on a presentation by Stefanie Jeffrey, M.D.

changes within a tumor. With this technology, it is may be possible to show very small physiological differences within a breast tumor and at its margin. Jeffrey noted that she has been testing the smart probe technology in only in rats so far..

Nipple Aspiration of Fluids and Cells*

Nipple aspiration is another early breast cancer detection modality under investigation. Nipple aspiration uses breast massage and a modified breast pump to aspirate fluid and cells for determining a cytological diagnosis. It can also facilitate measurement of protein markers such as growth factors and tumor-specific antigens, which are likely to be more concentrated in the breast fluid than in serum. However, to date, analyses such as these have not demonstrated the sensitivity necessary to accurately predict the presence of breast cancer, and thus further research will be required to develop the technology.

According to Edward Sauter, M.D., the technique could serve as an adjunct to mammography and other conventional imaging studies. He suggests that it might be particularly useful for detection of breast cancer in young women with dense breasts or women who have undergone radiation for breast cancer, both of which are not as easily monitored by mammography. Potential strengths of this evolving technology are that it can be done inexpensively by trained nurses and there are no age limits in using it. Proponents of the technique say it is noninvasive, painless, and nontoxic.

Early studies of the technology have stymied development because initial data showed a poor yield of cells and low sensitivity and specificity. According to Dr. Sauter, there is a learning curve in performing the technique. After performing approximately 30 to 40 cases, nurses become proficient at aspirating fluid successfully.

Culturing Breast Cells†

According to Jean Latimer, Ph.D., bench researchers are also developing novel ways of culturing the specific cells that develop into breast cancer, the mammary epithelial cells. These cells make up the three-dimensional plumbing system for milk in the breast. Latimer reported that her laboratory has developed a cell culture system that is able to maintain viable primary human mammary epithelial cultures from breast reduction mammoplasty surgeries for at least three months in a laboratory incubator. These normal cultures grow and differentiate into three-dimensional structures similar to those seen in the breast, she says. Progressive duct formation and branching are manifested in these cultures, as well as the organization of lobules (epithelial structures at the ends of ducts, which are necessary for milk production).

In addition, Latimer's laboratory is also obtaining and studying fresh cells taken from malignant breast tissues. The tumor primary cultures generally do not form the same complex architectures seen in the nonmalignant cultures, but manifest more independent cell behavior, depending on the stage of the tumor, she says.

Understanding the cellular communication factors in the normal breast is essential to producing and maintaining organotypic in vitro models, according to Latimer. Knowing how these factors lead to the differentiation of epithelial architecture and the corresponding cascades of gene expression may be important for determining the pathway leading to breast cancer.

*Based on a presentation by Edward Sauter, M.D.
†Based on a presentation by Jean Latimer, Ph.D.

In addition, Latimer indicated that her laboratory has extended the life-span of these primary cultures to develop 70 immortalized cell lines from nonmalignant breast epithelium as well as tumors from stage 0 (Ductal Ccarcinoma In Situ) to stage IV. Every primary culture is now being extended for the production of an immortal cell line. All of these cell lines are available to the scientific community and primary cultures are available upon request through a material transfer agreement or collaboration.

With further research, the technology shows promise in stratifying tumor cell aggressiveness and possibly in predicting metastatic potential, says Latimer. At present, tumor aggressiveness varies widely within a given stage. For example, although some 75% to 80% of stage I breast cancers can be cured with lumpectomy, 15% to 20% will recur, despite surgery. If the more aggressive tumors can be distinguished from those that are slow-growing or less likely to metastasize, women with less aggressive tumors could eventually be spared the morbidity of high-cost therapies that also compromise their quality of life, while not enhancing clinical outcomes. At the same time, in better identifying more lethal, aggressive tumors, researchers might be better able to deliver systemic therapy earlier on, optimizing outcomes.

This technology is in a very early stage of development. Using time-lapse digital movies of the live cells taken from tumors, it is possible to capture living cell movements and cell-to-cell interactions. So far, the time-lapse live cell videos have revealed markedly different behavior and cell-to-cell interaction in tumor cells compared with normal cells, according to Latimer. Normal cells retain contact with each other and form three-dimensional structures. Breast tumor cells often behave quite differently, with the cultures containing a high proportion of rapidly moving, independent cells, which do not retain contact with each other. Significant variability among similarly staged tumors has been documented in these time-lapse digital movies. At present, Latimer is prospectively following patients whose tumors have been captured in movies to determine whether more aggressive tumors demonstrate more aggressive behavior in culture. Results of this ongoing investigation will dictate the chemical utility.

WORKSHOP SPEAKERS

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