Mammography and Beyond: Developing Technologies for the Early Detection of Breast Cancer: A Non-Technical Summary

Margie Patlak, Sharyl J. Nass, I. Craig Henderson, and Joyce C. Lashof, Editors, Committee on the Early Detection of Breast Cancer, National Cancer Policy Board, Commission on Life Sciences, National Research Council

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Mammography and Beyond: Developing Technologies for the Early Detection of Breast Cancer

A Non-Technical Summary

COMMITTEE ON THE EARLY DETECTION OF BREAST CANCER

Margie Patlak, Sharyl J. Nass, I. Craig Henderson, and Joyce C. Lashof, *Editors*

National Cancer Policy Board
INSTITUTE OF MEDICINE
and
COMMISSION ON LIFE SCIENCES
NATIONAL RESEARCH COUNCIL

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ABOUT THIS PUBLICATION

The Institute of Medicine report *Mammography and Beyond: Developing Technologies for the Early Detection of Breast Cancer* evaluates the scientific evidence regarding the use of technologies for breast cancer screening and diagnosis, and examines the process by which new technologies are developed, assessed, and adopted into clinical practice. It contains a comprehensive list of references, and makes recommendations for further research, for improving the technology development process, and for making optimal use of the technologies currently available for breast cancer detection.

The intent of this publication, which is derived exclusively from that report, is to make the information contained in the original report more accessible to women who are concerned about public policies regarding early breast cancer detection. In this publication, the Institute seeks to provide a short, easily understood version of that information to women.

Joyce C. Lashof
Chair
Committee on Technologies for the Early Detection of Breast Cancer

I. Craig Henderson
Vice Chair
Committee on Technologies for the Early Detection of Breast Cancer

Sharyl J. Nass
Study Director

Mammography and Beyond

A SUMMARY OF A STUDY BY THE INSTITUTE OF MEDICINE

X-ray mammography screening is the current mainstay for early breast cancer detection. It has been proven to detect breast cancer at an earlier stage and to reduce the number of women dying from the disease. However, it has a number of limitations.

These current limitations in early breast cancer detection technology are driving a surge of new technological developments, from modifications of x-ray mammography such as computer programs that can indicate suspicious areas, to newer methods of detection such as magnetic resonance imaging (MRI) or biochemical tests on breast fluids. To explore the merits and drawbacks of these new breast cancer detection techniques, the Institute of Medicine of the National Academy of Sciences convened a committee of experts. During its year of operation, the committee examined the peer-reviewed literature, consulted with other experts in the field, and held two public workshops.

In addition to identifying promising new technologies for early detection, the committee explored potential barriers that might prevent the development of new detection methods and their common usage. Such barriers could include lack of funding from agencies that support research and lack of investment in the commercial sector; complicated, inconsistent, or unpredictable federal regulations; inadequate insurance reimbursement; and limited access to or unacceptability of breast cancer detection technology for women and their doctors. Based on the findings of their study, the committee prepared a report entitled *Mammography and Beyond: Developing Technology for Early Detection of Breast Cancer,* which was published in the spring of 2001. This is a non-technical summary of that report.

The committee concluded that a great deal of work remains to be done, particularly in the field of cancer markers (the study of biological characteristics, or markers, associated with cancer). This area holds promise, however, for improving the accuracy of breast cancer screening, diagnosis, and prognosis. The committee noted that improved imaging technologies that allow doctors to detect

breast abnormalities at an earlier, pre-invasive stage may lead to more overtreatment of women unless the imaging procedures are coupled with molecular marker technology that can determine which abnormalities are likely to spread aggressively and become life-threatening.

The committee provided several suggestions for improving the process of developing new technologies, including government support for the discovery and development of markers associated with breast cancer or breast cancer precursors, more consistent FDA regulations regarding approval of cancer detection devices, and a coordinated approval and coverage assessment scheme for screening tests.

The committee also made several recommendations intended to optimize the use and benefit of the proven technologies that are currently available. Those recommendations include expanding the breast cancer screening program of the Centers for Disease Control and Prevention (CDC) for women without health insurance, studying reimbursement rates for x-ray mammography to determine whether they adequately cover the total costs of providing the procedure, and determining whether there is a current or impending shortage of radiologists trained in breast imaging.

The rationale for these recommendations is summarized in this report.

INTRODUCTION

Breast cancer takes a tremendous toll on women in the United States. Next to skin cancer, breast cancer is the most common cancer in women, and the second leading cause of cancer death in women in the United States (lung cancer is the leading cause of cancer death). Each year invasive breast cancer is diagnosed in 180,000 women, and more than 40,000 women die from this disease. Until research uncovers a way to prevent breast cancer, or to cure all women with the disease regardless of when their tumors are found, the best hope for reducing its toll is early detection when tumors are small and local. Treatment in the early stages is more likely to be effective. Researchers hope that early detection of breast cancer by screening could eventually be as effective in saving lives as the Papanicolau (Pap) smear used for cervical cancer screening (Figure 1).

The current mainstays for breast cancer detection are regular physical exams by women themselves and their doctors, and annual or biannual x-ray mammogram screening. Monthly breast self-exams by women and regular physical exams of the breast by their doctors are aimed at finding any unusual lumps. Such physical exams, when performed carefully, can detect tumors at a smaller size than they would otherwise be found. But research showing that mammography can reduce the number of women dying from breast cancer is

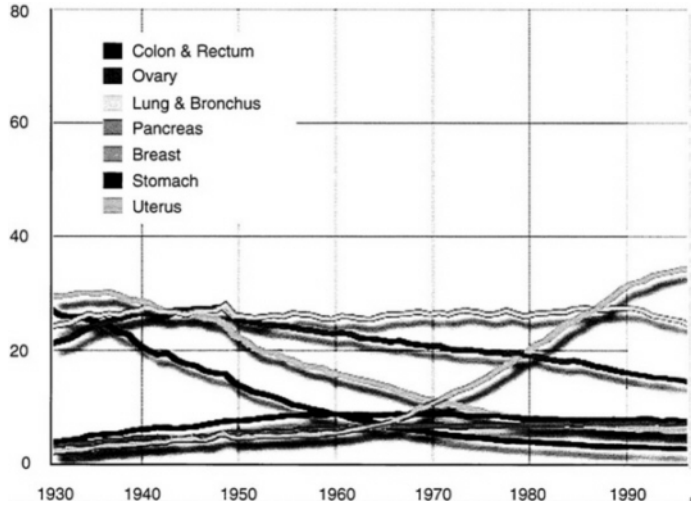

FIGURE 1 Age adjusted cancer death rates, females by site, 1930-1996. Per 100,000, age-adjusted to the 1970 US standard population. Uterus cancer death rates are for uterine cervix and uterine corpus combined. Note: Due to changes in ICD coding, numerator information has changed over time. Rates for cancers of the uterus, ovary, lung & bronchus, and colon & rectum are affected by these coding changes. SOURCE: US Mortality Public Use Data Tapes 1960-1996, US Mortality Volumes 1930-1959, National Center for Health Statistics, Centers for Disease Control and Prevention, 1999; American Cancer Society, Surveillance Research.

much stronger than research for physical breast exams.

With x-ray mammography screening, radiologists examine two x-rays taken of each breast from different angles (mammograms) for abnormalities associated with malignant tumors (Figure 2). Research reveals that regular mammography screening, when coupled with appropriate treatment, can detect cancer at an earlier stage and reduce the number of women dying from breast cancer.

But mammography is not perfect. Studies have shown that routine mammography screening can reduce the number of deaths from breast cancer by about 25–30% among women between the ages of 50 and 70. A lesser benefit was seen among women aged 40–49. Screening mammography cannot eliminate all deaths from breast cancer because it does not detect all cancers, including some that are detected by physical exam. As many as 15% percent of breast cancers may be missed by mammography screening. Some tumors may also develop too quickly to be identified at the most treatable stage using the standard screening intervals.

In addition, it is technically difficult to consistently produce mammograms

of high quality, and interpretation is subjective and can be variable among radiologists. Mammograms are particularly difficult to interpret in women with dense breast tissue, which is especially common in young women. The dense tissue interferes with identification of abnormalities associated with tumors, leading to a higher rate of false test results (both positive and negative) in these women. These difficulties associated with dense tissue are especially problematic for women who wish to begin screening at a younger age because their family history or genetic test results suggest they are at high risk of developing breast cancer.

Mammogram screening also frequently gives inconclusive results, often requiring additional invasive, expensive, and discomforting follow-up procedures, such as surgical biopsies, in which a suspicious area of the breast is removed and examined by a pathologist. As many as three-quarters of such biopsies are negative, that is, they do not reveal the presence of a malignant tumor.

Another limitation of mammography is that the methods for classifying the abnormalities it detects are based on the appearance of the tissue structure (Figure 3). The ability to determine the lethal potential of breast abnormalities by using this method is crude at best. Because the basic understanding of the biology of breast cancer is not yet complete, some of the breast abnormalities mammography can detect may not be aggressive malignancies requiring intensive treatment, but rather pre-malignant or non-invasive conditions that will not progress to life-threatening disease. Because of this uncertainty, doctors tend to be cautious, treating all such questionable abnormalities as cancers. As a result, some women may be unnecessarily treated for cancer and affected by the psychological distress associated with cancer diagnosis.

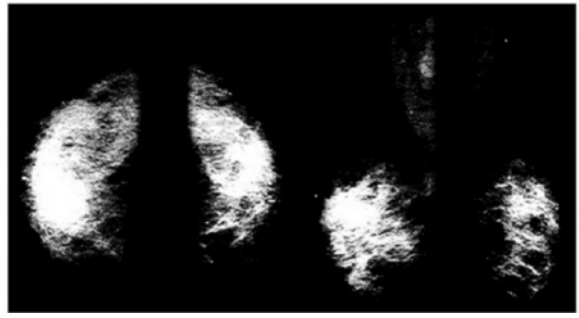

FIGURE 2 An example of conventional x-ray film mammography. SOURCE: Miraluma Educational CD-ROM, Dupont Radiopharmaceutical Division, The DuPont Merck Pharmaceutical Company.

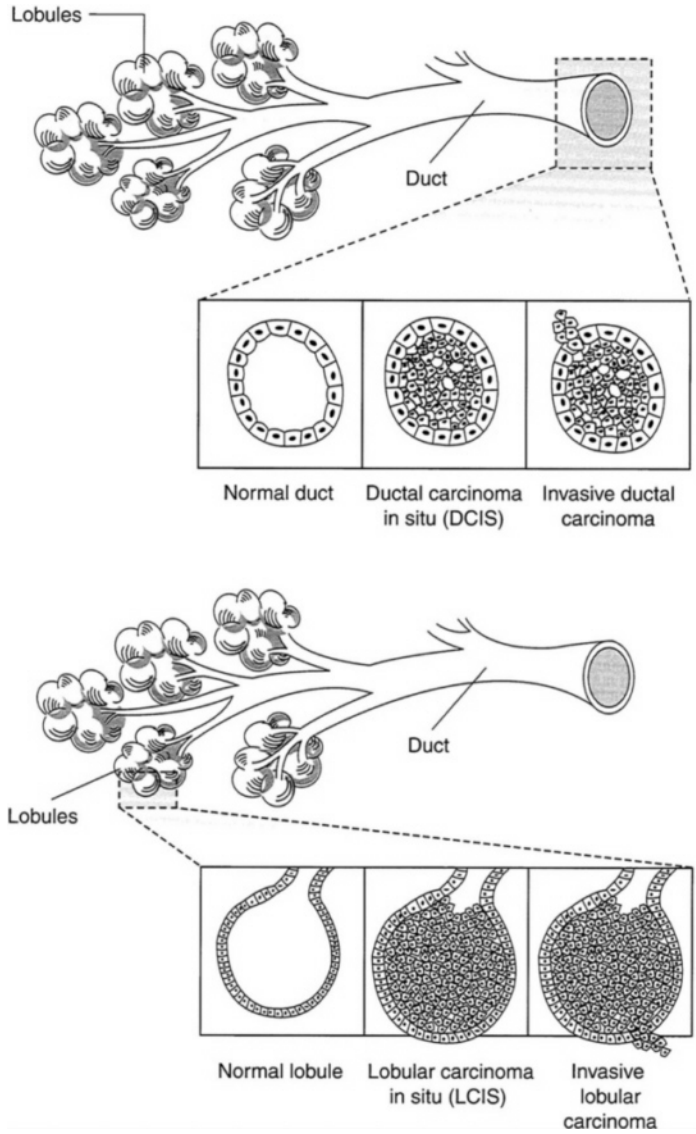

FIGURE 3 Schematic representation of ductal (a) and lobular (b) carcinoma of the Breast (adapted from Love, 1995, p. 220).

THEORY AND PRINCIPLES OF CANCER SCREENING AND DIAGNOSIS

Screening tests are performed on people who have no physical signs of the disease being tested for. The goal of cancer screening is to detect tumors at an early enough stage so that they will be curable when treated. It is important to keep in mind, however, that even if a screening device is effective at detecting small tumors, it may not detect them early enough to make a difference in reducing the number of cancer deaths. For example, chest x-ray screening for lung cancer did not decrease the number of lung cancer deaths among the people screened for the disease, even though tumors identified by screening were smaller than those found in the absence of screening. By the time lung tumors were detectable on an x-ray, they usually had already advanced to a stage that was incurable by spreading beyond the lung.

According to guidelines established by the World Health Organization, screening should be used only if it provides a net benefit to those screened. For example, a test should reduce the number of deaths from a particular condition without excessively harming people without the condition. But it can be difficult to assess the real benefit of any cancer screening technology or program.

It is often assumed that any improved survival time observed among people who undergo a particular screening program is beneficial, but this may not actually be true (Figure 4). For example, a woman who dies two years after she finds a lump in her breast may not necessarily have survived longer if she had undergone mammogram screening two years earlier. Some aggressive cancer cells can spread beyond the breast even when the tumor is relatively small and undetectable. Similarly, it is impossible to know whether a woman who survives four years after her cancer is detected with mammography has truly gained an extension of her life. It may be that she has simply been aware of her diagnosis for a longer period of time. Because of this phenomenon of "lead-time bias," measuring the length of survival after diagnosis is not a valid way of assessing the effectiveness of a screening test.

Screening tests done on a regular basis are also more likely to detect a disproportionate number of people with slow-growing tumors, a phenomenon known as "length bias." This is because a cancer that takes many years to reach a size that can be felt on a breast exam is more likely be detected as a smaller tumor by regular mammography screening than one that grows to the same size in a much shorter period of time. If an aggressive, fast-growing tumor is more likely to become life-threatening than a slow-growing tumor, then many women whose tumors were identified through a screening program will inherently have

a more favorable outcome following treatment. Consequently, a higher survival rate among women whose tumors are detected by breast cancer screening may not actually result from the screening itself. That is, the tumors may have responded well to treatment even if they weren't detected until they grew large enough to be felt on a breast exam.

Additional difficulties encountered in assessing breast cancer screening programs include selection bias and overdiagnosis. Selection bias assumes that women who are at higher risk for breast cancer will be more likely to participate

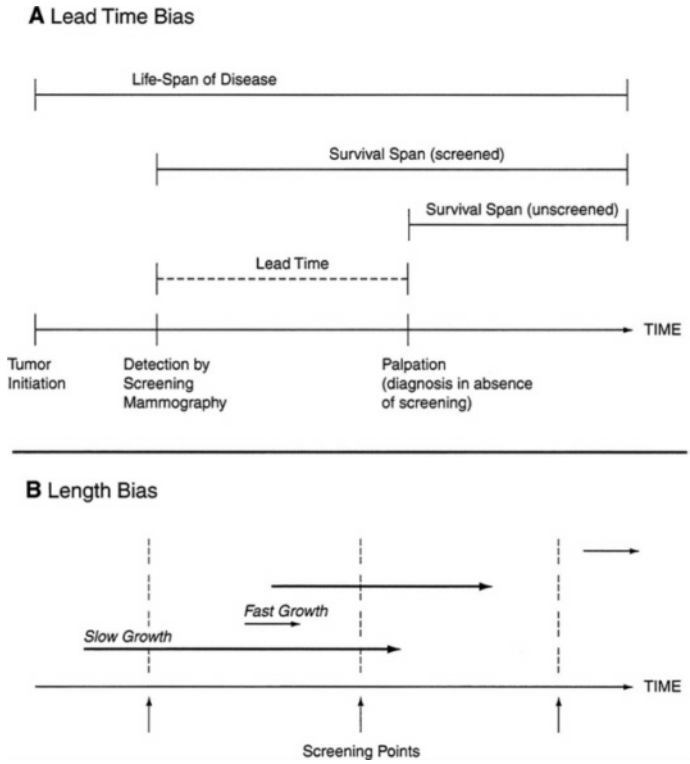

FIGURE 4 Lead-time (A) and length (B) bias. In part B, the length of the arrows represents the time required for the tumor to reach a palpable size. For a more detailed description of lead-time and length bias, see the accompanying text in the summary.

in breast cancer screening studies and will comply more with the recommended guidelines for the screening. Since such screening may be more beneficial and cost-effective in high-risk populations than in the general population, a selection bias may result in overestimating the value of using a screening program for the general population.

"Overdiagnosis" results from labeling some abnormalities as cancer or pre-cancer when in fact these abnormalities may never have progressed to a life-threatening disease if left undetected and untreated. In such cases, some of the "cures" following early detection may not be real. In addition, overdiagnosis prompts some patients to undergo expensive, uncomfortable, and potentially damaging treatments that may not be necessary.

The best way to counter some of these problems inherent in assessing the value of cancer screening techniques is to conduct large studies in which participants are randomly selected to receive a screening test. Researchers then need to study these participants over a long enough period of time to determine whether the screening test reduces the number of deaths from breast cancer. Such studies may require hundreds of thousands of women and take 10 to 15 years to complete. (For example, over the course of nearly 20 years, approximately 500,000 women participated in 8 studies to assess the benefits of mammography screening, among which about 2,500 deaths from breast cancer occurred.) Because of the extensive costs and time involved, researchers have yet to conduct the large, randomized screening studies required to assess the value of using new breast cancer screening technologies.

Once a breast abnormality has been detected by screening mammography or physical exam, the abnormality must be diagnosed as benign or malignant using additional imaging techniques and/or biopsy and microscopic examination of the tissue. Many new breast cancer detection technologies are being studied as diagnostic tools, often as an addition to diagnostic mammography, in the hopes of avoiding unnecessary biopsy of benign abnormalities.

The assessment of diagnostic technologies differs from that of screening technologies. Diagnostic studies primarily involve an evaluation of a test's accuracy in determining which women with a suspicious breast abnormality have cancer and which do not. Such studies do not examine differences in clinical endpoints such as death from breast cancer. Consequently, studies to evaluate diagnostic technologies are usually much smaller, shorter in duration, and less expensive.

BREAST CANCER DETECTION TECHNOLOGIES IN DEVELOPMENT

To the extent that it was possible, the committee evaluated the apparent strengths and weaknesses of the new breast cancer detection technologies. However, the experimental evidence available for most new breast cancer detection technologies was not strong enough to support definitive conclusions about their ultimate clinical value and use, as discussed below. None of the newer technologies have been studied to the same extent as conventional mammography.

Advances in breast cancer detection technology include improvements to current techniques, new ways to image the breast, and new detection strategies aimed at finding distinctive "molecular signatures" of a pre-malignant or malignant breast tumor. The Food and Drug Administration (FDA) has approved some of these new techniques for clinical use, but many are in earlier stages of development and have not been used outside a research setting.

Digital Mammography

In an attempt to improve x-ray mammography, several companies have developed digital mammography devices. Unlike film mammography devices that produce an x-ray image of the breast directly on photographic film, digital

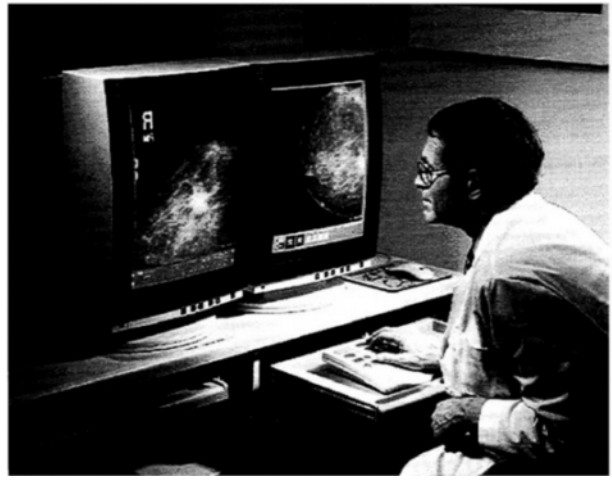

FIGURE 5 Examples of Full-Field Digital Mammography of the breast. SOURCE: General Electric Medical Systems

mammography devices (which still require breast compression) capture the x-ray image digitally (Figure 5). An array of detectors creates a digitized image that can be viewed and manipulated on a computer screen. In theory, this could enable better detection of tumors obscured by the dense breast tissue frequently seen in younger women. The ability to enlarge or adjust the contrast of questionable areas without requiring new x-ray exposure may facilitate the detection of lesions that have been missed by film mammography. The technology could also improve screening mammography by allowing electronic storage, retrieval, and transmission of mammograms. However, one important limitation of digital mammograms is that the images are not as finely detailed as film mammograms.

Although digital mammography has been promoted as a major technical improvement over conventional mammography, preliminary studies have not yet confirmed a significant improvement in the accurate detection of breast cancers. More studies need to be done to assess its accuracy. One digital mammography machine has been approved by the FDA based on a small study of accuracy. Several other digital mammography units await FDA review and approval. To date, no studies have shown that digital mammography is more accurate or effective in reducing breast cancer deaths than film mammography.

Computer-Aided Detection (CAD)

Digital mammograms also make the use of computer-aided detection (CAD) systems easier. These systems use sophisticated computer programs to recognize patterns in images that might suggest a malignancy. If such patterns are detected, the CAD system notifies the radiologist, who can then examine the suspicious area more carefully. CAD can be used directly on digital mammograms or on conventional mammogram films that have been converted to a digital format.

Several studies suggest CAD can improve a radiologist's ability to detect and classify breast abnormalities on mammograms. One study suggested that CAD could have diminished the number of breast cancers missed in film mammography screening by nearly three-quarters. Other studies indicate that the addition of CAD to mammogram screening does not significantly boost the number of abnormalities inaccurately identified as potential tumors (false positives). More extensive studies must be done, however, to ensure that CAD does not lead to more false positive or negative results, and to define more clearly the value and appropriate use of this technology. The FDA recently approved one CAD detection system for breast cancer screening.

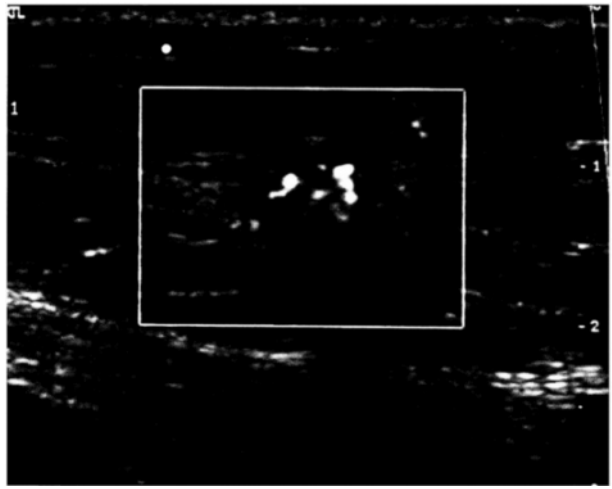

FIGURE 6 An example of an ultrasound image of the breast. SOURCE: Janet Baum, Director, Breast Imaging, Beth Israel Deaconess Medical Center, Boston, Massachusetts.

Ultrasound Imaging

X-ray mammograms are frequently followed by ultrasound imaging (Figure 6) to determine whether a mass that appeared on a mammogram is solid tissue or a harmless cyst containing fluid. Ultrasound imaging devices emit high-frequency sound waves, which penetrate the body. When these waves bounce off the boundaries between tissues in the body, they generate distinctive echoes that a computer uses to generate an image known as a sonogram. Because a fluid-filled cyst has a different "sound signature" than a solid mass, radiologists can reliably use ultrasound to detect cysts, which are commonly found in breasts.

Ultrasound imaging of the breast may also help radiologists evaluate some lumps that can be felt (palpable lesions) but are difficult to see on a mammogram, especially in women with dense breasts. One study of women with palpable lesions suggested that ultrasound was very accurate at diagnosing non-malignant abnormalities and could have eliminated the need for more than half the biopsies that were done. Other studies suggest that ultrasound may also be able to characterize non-palpable solid lesions as benign or malignant. Additional research suggests that ultrasound combined with x-ray mammography might improve the accuracy of breast cancer screening and also enable the detection of early-stage tumors in women with dense breasts. Further study is needed to assess the usefulness of ultrasound as a screening method

used along with mammography.

Although ultrasound may be useful as an addition to mammography, it has limitations for breast cancer detection when used alone. Ultrasound often cannot detect small tumors (less than 5 mm or about one-quarter inch) and abnormalities (microcalcifications) linked to certain types of breast cancers. Recent improvements in ultrasound technology have the potential to overcome some of these limitations and to expand its usefulness in breast cancer detection. But their ultimate usefulness in breast cancer detection cannot be predicted at this stage of development.

Magnetic Resonance Imaging (MRI)

Physicians have been using MRI for a wide variety of medical applications since it was FDA-approved for body imaging in 1985. MRI, generally considered to be a safe procedure, generates an image by measuring the responses of tissue components to a magnetic field. Specialized MRI systems, designed for breast imaging (Figure 7) and approved by the FDA, show promise as a detection method to be used with mammography, especially for dense breasts.

Studies suggest that although MRI is highly sensitive at detecting tissue abnormalities that indicate cancer, it is sometimes unable to distinguish malignancies from other harmless tissue abnormalities in the breast. Also, like ultrasound, it cannot detect microcalcifications. Despite this limitation, an MRI

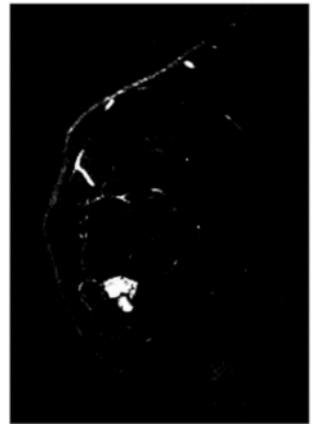

FIGURE 7 Example of a magnetic resonance image of the breast. SOURCE: Drs. D. Plewes and R. Shumak of Sunnybrook and Women's College Health Centre, University of Toronto.

could potentially detect the presence of a breast cancer in a patient whose mammogram, sonogram, and physical exam are not definitive.

Another possible use for MRI is to detect recurrent breast cancer in breasts previously subjected to lumpectomies, because unlike mammography, MRIs are usually not limited by scarring that can occur after surgery. Also, MRI can detect tumors in women with breast implants or dense breasts, both of which can interfere with interpretation of x-ray mammograms. Consequently, MRI may prove useful in the screening of high-risk young women (based on genetic testing or strong family history), who tend to have dense breasts. Preliminary results are encouraging in this regard, but further studies are needed to define the usefulness of MRI breast cancer screening in this population.

Other Imaging Technologies Under Development for Breast Cancer Detection

Several other imaging systems have been developed for breast cancer detection. These systems include some that use radioactive compounds that concentrate in cancerous tissue to image breast cancer, such as scintimammography and positron emission tomography (PET). Others aim to identify cancerous tissue by analyzing temperature, optical, electrical, or elastic properties. Many of these systems are being developed as additions to film mammography, but studies have yet to demonstrate definitively their usefulness for this purpose. Because no single imaging device can accurately detect all types of breast abnormalities in all kinds of breast tissue (for example, in dense as well as fatty breasts, or in breasts with implants or significant scarring), the committee noted that ideal breast cancer detection may ultimately require the use of multiple imaging techniques. In summary, after reviewing all the evidence to date, the committee concluded that despite its limitations, x-ray mammography is currently the only imaging technology that has been adequately studied and is suitable for breast cancer screening in the general population.

The Potential of Molecular-Based Detection

Knowledge about the genetic basis of cancer has grown dramatically over the past two decades. Scientists now believe that cancer develops in an individual only after a number of steps have occurred. These steps involve a series of genetic changes that trigger cells to make too much or too little of a protein, or to make a malfunctioning protein. The result of these changes is that normal breast cells grow uncontrollably into malignant tumors.

By inheriting a changed gene that can foster breast cancer, some women are born with one of the steps on the path to cancer already taken. Researchers are

beginning to uncover some of these inherited genetic changes linked to a high risk of developing breast cancer, including changes in the BRCA1 and BRCA2 genes. But only about 10 percent of breast cancer cases stem from inherited susceptibility. Most breast cancers arise from genetic changes that occur during a person's lifetime.

Researchers are currently trying to detect markers of such genetic damage. Newly developed methods for growing breast cells in culture and new automated systems for screening large numbers of genes or proteins in cells should aid this endeavor.

Currently, abnormalities detected with mammography are crudely classified as malignant or benign based on their structural appearance under the microscope, and not by what genetic changes they may have. If reliable markers of breast cancer progression can be identified, tests for such markers may play a role in determining whether doctors should treat the pre-malignant abnormalities and early-stage lesions that are now so commonly identified by screening mammography.

Many of these abnormalities may not progress to life-threatening disease. The discovery and development of molecular markers for breast cancer, consequently, might help reduce the “overtreatment” of harmless abnormalities. They might also be able to identify women who should undergo more frequent screening or consider prophylactic treatment (for example, mastectomy or tamoxifen), or those who might benefit from newer imaging technologies. If and when these molecular markers prove useful for diagnosing or predicting the aggressiveness of breast cancers, researchers could then also examine their usefulness in breast cancer screening.

There are many ways that gene or protein screens could be used for breast cancer detection. Researchers are trying to develop specialized imaging systems that can use “smart” contrast agents to reveal telltale genes that may be activated in cancerous breast tissue, or other biochemical markers of early breast cancer. Such systems might eventually be used in breast cancer screening, but their development is too preliminary at this point to assess their usefulness for this purpose.

Other researchers are trying to develop screening tests for tumor markers or tumor cells in breast fluid or blood serum. Breast fluid can be obtained from women who are not pregnant or breast-feeding with the aid of breast massage and a modified breast pump. In addition, researchers have recently developed a device that is inserted into the nipple and uses salt water to flush breast duct cells out of some of the breast ducts (a process known as ductal lavage). The FDA recently approved this device for breast fluid removal. More studies need to be done to

assess the usefulness of this device in breast cancer screening or diagnosis.

For example, pathologists could examine cells taken from breast fluid for any abnormalities that might indicate breast cancer. Measurement of genetic or protein markers of breast cancer in such fluids is also being considered. The tests developed for breast fluid so far are not sensitive enough for breast cancer screening, and it is not clear how to intervene if abnormalities are found.

Researchers are now exploring a number of potential markers of breast cancer in blood, including proteins made by genes linked to cancer (oncogenes), growth factors, antibodies associated with tumors, and markers of blood vessel development, which is common in tumors. Researchers are also developing tests to detect the tumor cells themselves in blood. Although some of these markers and tests are sometimes used to monitor breast cancer progression, they are currently not sensitive enough to be useful for breast cancer screening.

In summary, the committee felt that studying the basic biology of breast cancer in order to develop molecular markers of breast cancer should be a high priority because molecular markers show promise for breast cancer screening, diagnosis, and prognosis. But these molecular markers require much more study and development before their usefulness in breast cancer detection can be evaluated.

BARRIERS TO THE DEVELOPMENT OF BREAST CANCER DETECTION TECHNOLOGY

The process of developing new technologies for breast cancer detection is quite complex, and several hurdles must be overcome to bring budding technologies to fruition. For example, sponsors of new technologies must have adequate resources for gathering the evidence necessary for FDA approval and for obtaining medical insurance coverage. Acceptance and use of the new technology by women and their doctors is also essential.

Research Resources

Once a new strategy for detecting cancer has been developed, a great deal of research is required to refine and test it. The complex nature of biomedical research requires enormous financial investments to undertake such testing and refinement.

Traditionally, private companies and other investors have played a major role in developing medical technology. More recently, resources are also being provided through newly developed government programs aimed at translating research findings into practical clinical applications. Other resources are shared

through collaborations between industry, academia, and government agencies, such as the National Cancer Institute (NCI), the U.S. Army, NASA, and others. For example, some of these agencies joined forces to adapt defense technologies used in missile and target recognition for breast cancer detection. This collaboration also assisted in the development of the current commercially available CAD software for mammography. Other government agencies that fund research on breast cancer detection include the Department of Defense and the National Institute of Standards and Technology.

As noted previously, a major goal of breast cancer research is to identify molecular changes in the various breast cancer stages and precursors. Such markers could help doctors determine which abnormalities detected in screening are likely to become life-threatening and thus require treatment. The committee noted that this was an important area of research and recommended that the government continue to fund the development of breast cancer markers, as well as research aimed at determining the appropriate clinical use of such markers. The committee noted that such research should focus on use of markers in screening as well as diagnosis and treatment of breast cancer.

Two important resources for this research avenue are automated genetic or protein testing devices, and specimen banks, which collect pre-cancerous as well as cancerous breast tissues, breast fluid, and blood serum. By using these devices to analyze breast specimens, researchers hope to pinpoint differences in biochemistry or gene activity that could serve as molecular red flags for all types of breast tissue, ranging from normal to malignant.

But most breast specimen banks, which are run by academic, government, and/or private institutions, are inadequately supplied and staffed. Additional problems for researchers using the specimen banks may include issues related to informed consent, privacy, and patents.

Women who donate tissue or blood samples to a specimen bank usually sign a general consent form to allow future unspecified research, but occasionally some research projects on the specimens are not approved because the donors did not specifically consent to the given research project.

Some genetic research that is conducted on patient specimens could potentially indicate the donor's inherent genetic susceptibility to breast or other cancers. Some women choose not to donate specimens because they are concerned that the genetic information gathered from studies will not be kept private and could lead to discrimination by health insurers or others. The NCI recently proposed methods for protecting the identity of specimen donors, although these methods have not been put into place by all specimen banks.

Some specimen banks require a share of any profits from technologies that

stem from research conducted on their samples. Companies that operate automated genetic or protein analytical devices may also claim patent rights on future products based on discoveries made using their technology. Such profit sharing and limitations on patent rights can be a financial disincentive for researchers conducting studies on molecular markers of breast cancer. In addition, the patents on the specific gene sequences used in some automatic genetic testing devices raise the price of such technology too high for many investigators.

Recognizing these problems, the committee recommended that breast cancer specimen banks be expanded and that researcher access to their samples be improved. They suggested that these specimen banks be a funding priority of the government and that the NCI devise and enforce strategies to make it easier to use patient samples in specimen banks. More specifically, the committee recommended that funding for specimen banks include support for the costs incurred by sharing specimen samples with collaborators, and that government-funded specimen banks not place excessive restrictions on the use of the specimen with regard to potential future patent rights. The committee also recommended that health care professionals and patient advocacy groups educate women about the importance of building specimen banks and encourage women to provide consent for research on specimen samples. However, stronger laws should also be passed at the national level to prevent genetic discrimination and to ensure the protection of patients who donate specimens for biomedical research.

In addition, the committee recommended that the government provide funding for the purchase and operation of automated technologies for the study and assessment of genetic and protein markers. Noting that the ability to draw conclusions from such research depends on innovative computerized data analysis techniques that are often lacking, the committee also recommended that the government fund the development of new approaches for analyzing large amounts of biological data.

FDA Regulations

In order for a medical device to be put into widespread clinical use, its manufacturer must provide the data needed for the Food and Drug Administration (FDA) to assess its safety and effectiveness. If the FDA determines that the device meets the appropriate standards, it approves the device for specific uses, such as breast cancer screening or diagnosis.

The FDA was originally established to evaluate the safety and effectiveness of drugs and other therapeutics. Since medical devices came under its domain in

1976, the FDA has reviewed relatively few cancer screening technologies. This relative lack of precedent, combined with the complexity involved in assessing the safety and effectiveness of screening or diagnostic devices as opposed to a drug, has caused some difficulties in FDA's evaluation of new breast cancer detection devices, the committee noted. Drug treatments directly generate clear-cut endpoints that can be measured, such as the ability to reduce illness or to cause various side effects. In contrast, screening and diagnostic tests generate information, which is subject to interpretation and has only an indirect effect (mediated by subsequent therapy) on a person's health.

Depending on the nature of the medical device, FDA may require companies to show that it is equivalent to devices currently in use, or they may require more involved studies designed to show the safety and effectiveness of the device. The effectiveness of these devices is generally determined by their ability to accurately detect breast tumors. Such accuracy depends on two factors. One factor is sensitivity, or the ability to detect all tumors present. The other factor is specificity, which is the ability to rule out cancer in people who do not have a tumor.

Accuracy comparisons between two detection devices can be very difficult, however, because of the inherent variability of technologies like mammography. Mammograms can be quite difficult to interpret. Moreover, the recommendations of radiologists can vary depending on their level of experience and their tendency to order invasive biopsy procedures as a follow-up to moderately suspicious findings. As a result, different radiologists can interpret the same mammograms differently. Furthermore, subtle differences in the placement of the breast during the different testing procedures can alter the resulting images and how those images are interpreted. Such variability can obscure the differences between breast cancer detection devices.

In fact, accuracy comparisons were found to be meaningless when companies tried to show the equivalence of their new digital mammography devices to conventional film mammography devices. This led to a long and costly approval process, during which the FDA changed its requirements several times. For breast MRI, in contrast, the FDA only required companies to show that the breast coil used in the imaging was equivalent to MRI devices used to image other parts of the body. Little consideration was given to the accuracy of interpreting the images generated by the breast coil.

In order to reduce some of these difficulties in the future, the committee recommended that the FDA generate more consistent and clearly stated criteria for the approval of screening and diagnostic devices and tests, and thus speed the process. Given the complexity of assessing new technologies, the committee

also suggested that FDA improve the external advisory panels that make recommendations to the FDA by including more experts in biostatistics, technology assessment, and epidemiology. For "next generation devices," which have a technical adaptation to improve a device already in use, the committee recommended that advantages in addition to accuracy, such as patient comfort or ease of data acquisition and storage, be considered in the approval process. The committee also recommended a more coordinated approach for assessing new technologies when making decisions about both FDA approval and insurance coverage, as will be described in more detail in the next section.

Insurance Coverage

FDA approval is only the first hurdle that new technologies face once they have been developed. Although both the public and physicians commonly perceive that FDA approval means technologies "work" and should be reimbursed, health care coverage decisions are rarely that simple. FDA approval does not mean that a new device is better than its predecessor, or that it is useful for applications that have not been evaluated. For example, once devices have been FDA-approved for diagnostic tests and are thus available to general clinicians, health care providers may opt to use them for screening purposes, even though they have not been tested for that purpose (good diagnostic tests are not necessarily good screening tests). Ideally, breast screening devices would be deemed effective if they reduced the number of deaths from breast cancer. But FDA approval for screening technologies generally does not require such studies, which are very large and last for many years.

FDA approval simply allows the device to be sold. Ultimately, though, coverage decisions by insurers are likely to determine whether the technology becomes widely used. Developers of new technologies face a major challenge in seeking coverage and reimbursement. Insurers are increasingly basing their coverage and reimbursement rates on evidence of whether a procedure reduces illness or prolongs life. If such improved "patient outcomes" cannot be shown, then coverage may be legitimately denied and/or reimbursement may be low. For example, the additional costs of new technologies such as computer-assisted detection and digital mammography, which have not yet been definitively proven to improve patient outcome or detection accuracy, are currently not reimbursed.

However, technology development is often a process that continues after a given device enters the clinic. Most technologies that ultimately achieve widespread use go through successive stages of development, variation, and appraisal of actual experience in the market, as clinicians using new devices

provide valuable feedback to manufacturers. Thus, assessment at early stages of development may not recognize the full potential of a new medical device. Because of this conundrum, the concept of "conditional coverage" has been explored as a potential way to allow new medical technologies to enter the market before making a final and definitive yes/no decision about coverage. Conditional coverage refers to limited, temporary coverage under specified conditions to allow for collection of data that can be used in determining the value of a technology and for setting a definitive coverage policy

The committee advocated a more coordinated approach than the current system for testing new screening technologies. They propose that FDA approval and insurance coverage decisions for new screening tests should depend on evidence of improved patient outcome from clinical trials. These studies should be designed, approved, and conducted with input and support from FDA, NCI, the Healthcare Financing Administration (HCFA, which oversees Medicare), private insurers, and breast cancer advocacy groups. The committee suggested that if a new device already approved for breast cancer diagnosis shows promise for accurate screening, an "investigational device exemption" (which allows the device to be used in clinical trials for FDA approval) should be granted for this use. Conditional coverage should then be provided within the context of approved clinical trials. Trial data should be reviewed at appropriate intervals, and the results would determine whether FDA grants the device approval for screening, and also whether coverage is extended to general use (outside of clinical trials).

This coordinated assessment approach would help prevent new technologies approved only for diagnosis from being widely adopted as screening tools before their effectiveness for screening is proven. At the same time, support by NCI and medical insurers would make it easier for technology sponsors to conduct the clinical studies needed to assess whether a new breast cancer screening technology reduces breast cancer deaths. For example, health insurers would cover the costs of performing tests in approved clinical studies, and the NCI and the technology manufacturers would share the other costs involved with the studies. Participation by private insurers would be particularly important for assessing new technologies intended for use in younger women who are not yet eligible for Medicare coverage. While this expense may initially seem burdensome to private insurers, the cost of providing tests within a clinical trial would be much less than the costs associated with broad adoption by the public (and the associated pressure to provide coverage) in the absence of experimental evidence for improved clinical outcome.

The committee also recommended that NCI create a permanent system for

testing the effectiveness of new technologies for early cancer detection. The committee noted that the NCI's Breast Cancer Surveillance Consortium or the American College of Radiology Imaging Network, with their extensive databases, tissue samples and other resources, may provide a useful model or platform for such an undertaking.

Dissemination

Once a new technology receives FDA approval and insurers agree to reimburse the costs associated with its use, adoption of this technology will ultimately depend on whether consumers and their health care providers fred it acceptable, necessary, affordable, and accessible. Experience with x-ray film mammography screening suggests that these factors can be important barriers to a new technology being used by the public. Only 69 percent of women 50 years old and over reported having a recent mammogram in 1998 (figure 8 and figure 9). In addition, not all women who receive mammograms do so at the recommended intervals. One study indicated that only about a quarter of women are screened at the intervals appropriate for their age.

A number of factors that hinder mammography screening are likely to also play a role in limiting the adoption of new breast cancer screening technologies. The most important factor is whether a woman's doctor recommends mammography screening, even though a physician referral is not needed for a screening exam. A significant fraction of women between the ages of 50 and 75 do not receive recommendations for such screening from their doctors.

A number of scientific and professional organizations provide guidelines for breast cancer screening, but these guidelines lack consistency as to when to begin screening, how often to screen, and when to discontinue screening. The guidelines have also changed over time as the results of new studies on screening mammography were published.

There currently is no universal consensus on the value of screening for women under 50 or over 70. The committee noted the lack of studies on whether screening mammography benefits women over the age of 70, despite the fact that breast cancer is most prevalent among women in this age group. The committee recommended that the NCI, through the American College of Radiology Imaging Network or the Breast Cancer Surveillance Consortium, sponsor a large clinical study to define more accurately the benefits and risks of screening mammography in women over the age of 70.

The committee also recommended that NCI sponsor large randomized clinical studies every 10–15 years to reassess the benefits of screening techniques. These studies would compare two technologies in current use, and

assess how each reduces the number of breast cancer deaths among the women who undergo the screening. This would address the continually evolving nature of breast cancer screening and treatment and detect any changes in benefits that would affect screening recommendations.

A lack of health insurance that reimburses the costs of mammography clearly hinders this form of screening. To overcome this barrier, the 1990 Breast and Cervical Cancer Mortality Prevention Act mandated the establishment of the National Breast and Cervical Cancer Early Detection Program. This program, which is run by the Centers for Disease Control and Prevention (CDC), targets women who lack health insurance, with a focus on encouraging screening at recommended intervals. Approximately 60 percent of the budget is allocated for screening services, with the remaining 40 percent devoted to education and

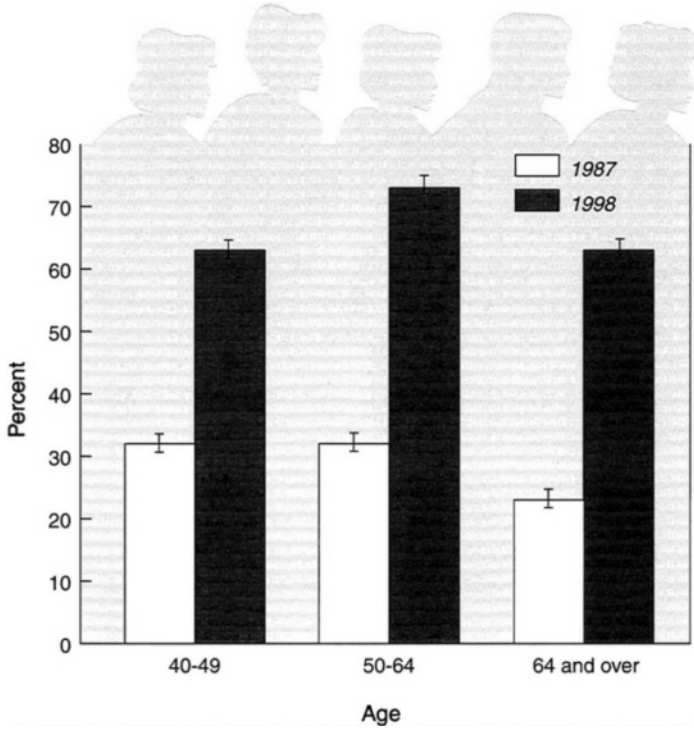

FIGURE 8 Use of mammography by women 40 years of age and over, 1987 and 1998. The percent of women having a mammogram within the last two years. SOURCE: U.S. Department of Health and Human Services, 2000. (www.cdc.gov/nchs/products/pubs/jubd/hus/hus.htm). Data are based on the National Vital Statistics System, National Center for Health Statistics.

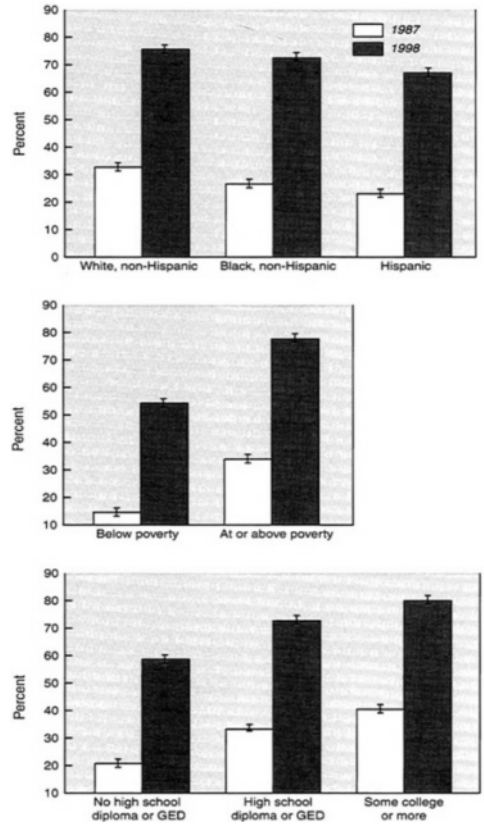

FIGURE 9 Use of mammography by women aged 50 to 64, according to various attributes (1987, 1998). Percent of women having a mammogram in the last two years. SOURCE: U.S. Department of Health and Human Services, 2000. (www.cdc.gov/nchs/products/pubs/jubd/hus/hus.htm). Data are based on the National Vital Statistics System, National Center for Health Statistics.

outreach. Currently, only 12–15% of eligible women are served by the program, largely because of a lack of adequate resources. The committee recommended that the CDC screening program be expanded to reach more eligible women.

The services available through the program include mammography and such follow-up diagnostic procedures as ultrasound, fine needle aspiration, and breast biopsy. (One or more of these procedures may be needed if a mammogram shows a suspicious finding.) Federal legislation recently provided funding through Medicaid for treatment of cancers detected through the program. But Medicaid funds are provided by both federal and state governments. (A certain amount of federal Medicaid dollars is allocated for each

Medicaid dollar spent by a state government for the program.) The committee urged states to provide Medicaid funds for treatment of cancers diagnosed through this early cancer detection program.

Another possible barrier to mammography screening is that the capacity of screening facilities may not be keeping pace with the increasing demand for mammography services. Because our nation's population is aging, the number of women eligible for screening in this country is increasing each year. A recent survey of the Society of Breast Imaging indicated that waiting times for screening appointments have been increasing over the last two years.

There are anecdotal reports that low reimbursement rates for x-ray mammography may have prompted some facilities to close or decrease their volume of breast cancer screening. Radiologists have argued that the reimbursement for mammography is too low for the time, effort, and interpretive skill it requires compared to other imaging procedures. In addition, the Mammography Quality Standards Act (MQSA), which was enacted in 1994, may boost the cost of providing mammography services. MQSA requires all mammography facilities to meet minimum quality standards for equipment and health care professionals, and requires extensive records to show they meet such standards. Since its inception, the quality of mammograms has improved. But this regulation, which is unique to mammography, also increases costs to facilities, and MQSA does not require reimbursement levels to cover those costs.

The committee recommended that the Heath Care Financing Administration (HCFA) analyze the current Medicare and Medicaid reimbursement rates for x-ray mammography. This analysis should include a comparison with other radiological procedures to determine whether they adequately cover the total costs of providing the x-ray mammography.

Concerns have also been raised about a possible shortage of radiologists and technologists trained in mammography, although to date these claims have not been substantiated with careful studies. The number of mammography training fellowships for radiologists has decreased by about one-quarter over the last five years. Radiologists may be deterred from specializing in mammography by the relatively low reimbursement for mammography, combined with the rising number of malpractice suits linked to breast cancer screening, although these connections have not been documented. The committee recommended that the Health Resources and Services Administration (HRSA) analyze trends in specialty training for breast cancer screening among radiologists and technologists, as well as try to pinpoint the factors affecting decisions to enter or remain in the field. If trends suggest there will be a shortage of trained experts, HSRA should seek input from professional societies such as the American

College of Radiology and the Society of Breast Imaging in making recommendations to reverse the trend.

Other factors that might prevent women from undergoing screening mammography include intolerance of the discomfort associated with the screening test, fear of what could be found, disabilities that make screening facilities inaccessible, language and cultural barriers for immigrant women, and inconvenience due to a lack of nearby screening facilities. A lack of education as to the benefits of undergoing mammograms on a regular basis can also be an impediment to such screening.

Lessons learned from the adoption and dissemination of mammography may be useful as new technologies become available. However, because mammography filled a breast cancer detection void, the adoption process for new technologies is likely to be quite different. New breast cancer detection technologies will not be adopted unless they can provide added value to technologies currently in use. If they can, then such new technologies might enable breast cancer detection to be more tailored to an individual woman's needs. For example, MRI might be used to screen young women who have a high risk of developing breast cancer and also have dense breast tissue that makes it difficult to interpret x-ray mammograms. However, the adoption of such new technologies will also make developing guidelines for breast cancer screening and diagnosis more complex.

SUMMARY

The committee determined that an ideal screening tool for breast cancer detection should be:

- linked to low health risks stemming from its use;
- sensitive enough to detect nearly all breast cancers, yet specific enough to rarely falsely indicate the presence of tumors;
- able to detect breast cancer at a curable stage;
- able to distinguish life-threatening abnormalities from those not likely to cause harm;
- non-invasive and simple to perform;
- easy to interpret objectively and consistently; and
- cost-effective, widely available and acceptable to women.

The ideal breast cancer screening tool has not yet been developed. Conventional x-ray mammography is the current mainstay for early breast cancer detection, and has been proven to reduce the number of women dying

from the disease. However, it has a number of limitations, including fostering overtreatment of some breast abnormalities likely to be harmless, and an inability to detect all breast cancers in all types of breast tissue (that is, in dense or scarred tissue). A number of technical improvements have been made to x-ray mammography, but studies have not been undertaken to determine whether these changes have reduced the number of deaths from breast cancer.

Researchers are also developing additional imaging tools and other means for detecting breast cancers. These new technologies have the potential for improving breast cancer screening and diagnosis, but it appears that no major steps forward have yet been taken in this area. All of the technologies being developed for breast cancer detection have different strengths and limitations. Many of these new technologies may first be introduced as additions to mammography to improve its accuracy and reduce the number of unnecessary biopsies.

The pathway from the development of new techniques for detecting breast cancer to their mainstream use in clinics is long, arduous, and costly. Also, the end results of such research and development are unpredictable, making it a financially risky undertaking. A number of challenges must be met along this development pathway. Researchers must secure access to research resources and funding, meet the standards for FDA regulation and insurance coverage (including conducting expensive clinical trials to show that a new device is effective), and gain the acceptance of patients and their health care providers.

After studying these issues in depth, the IOM committee has made a number of recommendations that aim to improve the development and adoption process for new technologies. They have also put forth a series of recommendations that aim to make the most of the technologies currently available for breast cancer detection, as described in this report.

The committee cautioned that we should temper our eagerness to embrace new technologies by keeping in mind the ultimate goal: to reduce the toll of breast cancer in our society. Technologies that enable detection of breast abnormalities at an even earlier stage than what is currently possible may or may not meet that goal. It is essential to understand what is being detected and how to intervene appropriately. Concerted efforts to improve our understanding of the biology of breast cancer, coupled with improved technologies for screening and diagnosis, could help overcome some of the present limitations of breast cancer detection, ultimately reducing the burden of breast cancer in this country.

GLOSSARY

Bias: a process at any stage of inference tending to produce results that depart systematically from the true values.

Biopsy: excision of a small piece of tissue for diagnostic examination; can be done surgically or with needles.

***BRCA1*:** a gene located on the short arm of chromosome 17; when this gene is mutated, a woman is at greater risk of developing breast or ovarian cancer, or both, than women who do not have the mutation.

***BRCA2*:** a gene located on chromosome 13; a germ-line mutation in this gene is associated with increased risk of breast cancer.

Breast self-examination: monthly physical examination of the breasts with the intent of finding lumps that could be an early indication of cancer.

Cell culture: the growth of cells in vitro for experimental purposes.

Clinical breast examination: a physical examination of the breasts, performed by a doctor. or nurse, with the intent of finding lumps that could be an early indication of cancer.

Clinical outcome: the end result of a medical intervention, e.g., survival or improved health.

Clinical trial: a formal study carried out according to a prospectively defined protocol that is intended to discover or verify the safety and effectiveness of procedures or interventions in humans. The term may refer to a controlled or uncontrolled trial.

Computer-aided detection: use of sophisticated computer programs designed to recognize patterns in images.

Contrast agent: a substance that enhances the image produced by medical diagnostic equipment such as ultrasound, X ray, magnetic resonance imaging, or nuclear medicine or and imaging-sensitive substance that is ingested or injected intravenously to enhance or increase contrast between anatomical structures.

Cost-effectiveness analysis: methods for comparing the economic efficiencies of different therapies or programs that produce health.

Detection: finding disease. Early detection means that the disease is found at an early stage, before it has grown large or spread to other sites.

Diagnosis: confirmation of a specific diseaseusually by imaging procedures and from the use of laboratory findings.

Diagnostic mammography: X-ray-based breast imaging undertaken for the purpose of diagnosing an abnormality discovered by physical exam or screening mammography.

Digital mammography: see *full-field digital mammography.*

DNA: abbreviation for deoxyribonucleic acid. DNA holds genetic information for cell growth, division, and function.

Duct: a hollow passage for gland secretions. In the breast, a passage through which milk passes from the lobule (which makes the milk) to the nipple.

Ductal carcinoma in situ: a lesion in which there is proliferation of abnormal cells within the ducts of the breast, but no visible evidence of invasion into the duct walls or surrounding tissues; sometimes referred to as “precancer” or “preinvasive cancer.”

Ductal lavage: a procedure in which a small catheter is inserted into the nipple and the breast ducts are flushed with fluid to collect breast cells.

Effectiveness: the extent to which a specific test or intervention, when used under *ordinary* circumstances, does what it is intended to do.

Epidemiology: science concerned with defining and explaining the interrelationships of factors that determine disease frequency and distribution.

False-negative result: a test result that indicates that the abnormality or disease being investigated is not present when in fact it is.

False-positive result: a test result that indicates that the abnormality or disease being investigated is present when in fact it is not.

Fine-needle aspiration: a procedure by which a thin needle is used to draw up (aspirate) samples for examination under a microscope.

Full-field digital mammography: similar to conventional mammography (film-screen mammography) except that a dedicated electronic detector system is used to computerize and display the X-ray information.

Gene: a functional unit of heredity that occupies a specific place or locus on a chromosome.

Invasive cancer: cancers capable of growing beyond their site of origin and invading neighboring tissue.

Invasive ductal carcinoma: a cancer that starts in the ducts of the breast and then breaks through the duct wall, where it invades the surrounding tissue; it is the most common type of breast cancer and accounts for about 80 percent of breast malignancies.

Invasive lobular carcinoma: a cancer that starts in the milk-producing glands (lobules) of the breast and then breaks through the lobule walls to involve the surrounding tissue; accounts for about 15 percent of invasive breast cancers.

Lead-time bias: the assumption that identifying and treating tumors at an earlier point in the progression of the disease will necessarily alter the rate of progression and the eventual outcome.

Length bias: the assumption that screening tests are more likely to identify slowly growing tumors than those with a fast growth rate.

Lobular carcinoma in situ: abnormal cells within a breast lobule that have not invaded surrounding tissue; can serve as a marker of future cancer risk.

Magnetic resonance imaging: method by which images are created by recording signals generated from the excitation (the gain and loss of energy) of elements such as the hydrogen of water in tissue in a magnetic field.

Malignant: a tumor that has the potential to become lethal through destructive growth or by having the ability to invade surrounding tissue and metastasize.

Mammogram: X-ray image of the breast.

Mammography: technique for imaging breast tissues with X rays.

Medicaid: jointly funded federal-state health insurance program for certain low-income and needy people. It covers approximately 36 million individuals including children; aged, blind, and/or disabled people; and people who are eligible to receive federally assisted income maintenance payments.

Medicare: a program that provides health insurance to people age 65 and over, those who have permanent kidney failure, and people with certain disabilities.

Microcalcifications: tiny calcium deposits within the breast, singly or in clusters; often found by mammography. They may be a sign of cancer.

Molecular markers: changes in cells, at the molecular level, that are indicative of cancer or malignant potential.

Mortality: the death rate; ratio of number of deaths to a given population.

Overdiagnosis: labeling an abnormality as cancer when it in fact is not likely to become a lethal cancer.

Palpable tumor: a tumor that can be felt during a physical examination.

Positron emission tomography: use of radioactive tracers such as labeled glucose to identify regions in the body with altered metabolic activity.

Premalignant: changes in cells that may, but that do not always, become cancer. Also called "precancer."

Prognosis: prediction of the course and end of disease and the estimate of chance for recovery.

Prophylactic bilateral mastectomy: surgical removal of both breasts with the intent of reducing the risk of developing breast cancer later in life.

Randomization: a method that uses chance to assign participants to comparison groups in a trial by using a random-numbers table or a computer-generated random sequence. Random allocation implies that each individual being entered into a trial has the same chance of receiving each of the possible interventions.

Risk: a quantitative measure of the probability of developing or dying from a particular disease such as cancer.

Scintimammography: use of radioactive tracers to produce an image of the breast.

Screen-film mammography: conventional mammography in which the X rays are recorded on film.

Screening: systematic testing of an asymptomatic population to determine the presence of a particular disease or certain risk factors known to be associated with the disease.

Screening mammography: X-ray-based breast imaging in an asymptomatic population with the goal of detecting breast tumors at an early stage.

Sensitivity: a measure of how often a test correctly identifies women with breast cancer.

Specificity: a measure of how often a test correctly identifies a woman as not having breast cancer.

Specimen bank: stored patient tissue samples that are used for biomedical research (also tumor or tissue banks).

Tomography: any of several techniques for making X-ray pictures of a predetermined plane section of a solid object by blurring out the images of other planes.

Tumor marker: any substance or characteristic that indicates the presence of a malignancy.

Ultrasound: use of inaudible, high-frequency sound waves to create an image of the body.

COMMITTEE ON TECHNOLOGIES FOR THE EARLY DETECTION OF BREAST CANCER

JOYCE C. LASHOF, M.D., FACP, *CHAIR,* Professor Emerita, School of Public Health, University of California at Berkeley, Berkeley, CA

I. CRAIG HENDERSON, M.D., *VICE CHAIR,* Adjunct Professor of Medicine, University of California at San Francisco, San Francisco, CA

D. CRAIG ALLRED, M.D., Professor of Pathology, Baylor College of Medicine, Houston, TX

WADE M. AUBRY, M.D., Vice President, The Lewin Group, Associate Clinical Professor of Medicine, University of California at San Francisco, San Francisco, CA

JANET K. BAUM, M.D., FACR, Associate Professor of Radiology, Harvard Medical School, Director, Breast Imaging, Beth Israel Deaconess Medical Center, Boston, MA

SUZANNE W. FLETCHER, M.D., M.Sc., Professor of Ambulatory Care and Prevention, Harvard School of Medicine, Harvard Pilgrim Health Care, Professor of Epidemiology, Harvard School of Public Health, Boston, MA

MARTHE R. GOLD, M.D., M.P.H., Chair, Department of Community; Health and Social Medicine, City University of New York Medical School, New York, NY

LEON GORDIS, M.D., D.P.H., Professor of Epidemiology, Johns Hopkins School of Public Health & Hygiene, Baltimore, MD

DANIEL F. HAYES, M.D., Clinical Director, Breast Cancer Program, Lombardi Cancer Center, Georgetown University Medical Center, Washington, DC

CAROLINA HINESTROSA, M.A., Cofounder and Executive Director, Nueva Vida, Silver Spring, MD

JEAN J. LATIMER, Ph.D., Investigator, Magee-Womens Research Institute, Assistant Professor, Department. of Obstetrics, Gynecology, and Reproductive Sciences, University of Pittsburgh, Pittsburgh, PA

RICHARD R. NELSON, Ph.D., George Blumenthal Professor, School of International and Public Affairs, Columbia University, New York, NY

KENNETH OFFIT, M.D., M.P.H., Chief, Clinical Genetics Service, Department of Human Genetics, Memorial Sloan-Kettering Cancer Center, New York, NY

FAINA SHTERN, M.D., Director, Office of Research Affairs, Department of Radiology, Beth Israel-Deaconess Medical Center, Harvard Medical School, Boston, MA

MICHAEL W. VANNIER, M.D., Professor and Head, Department of Radiology, University of Iowa College of Medicine, Iowa City, Iowa

DEREK VAN AMERONGEN, M.D., M.S., FACOG, Chief Medical Officer, Humana/Choice Care, Cincinnati, OH

LIAISON FOR THE NATIONAL CANCER POLICY BOARD

ROBERT DAY, M.D., M.P.H., Ph.D., Emeritus President and Director, Fred Hutchinson Cancer Research Center, Seattle, WA

CONSULTANTS

LARRY NORTON, M.D., Chief, Solid Tumors, Memorial Sloan-Kettering, New York, NY

BARRON LERNER, M.D., Ph.D, Assistant Professor of Medicine and Public Health (in the Center for the Study of Society and Medicine), Columbia University, New York, NY

IOM Staff

IOM STAFF

SHARYL NASS, Ph.D., Study Director

ROBERT COOK-DEEGAN, M.D., Director, National Cancer Policy Board (through August 2000)

ROGER HERDMAN, M.D., Director, National Cancer Policy Board (from September 2000)

CARMIE CHAN, Research Assistant (through August 2000)

MARYJOY BALLANTYNE, Research Assistant (from August 2000)

BIANCA TAYLOR, Project Assistant

JOHN KUCEWICZ, Intern

KEVIN COLLINS, Intern

ELLEN JOHNSON, Administrative Assistant (through June 2000)

NICCI DOWN, Administrative Assistant (from August 2000)

GARY WALKER, Financial Associate (through September 2000)

JENNIFER CANGCO, Financial Associate (from September 2000)