



Breast Cancer Screening Update and Evaluation of the High-Risk Patient

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Introduction

Breast cancer is the most common noncutaneous malignancy in women and accounts for 30 percent of the new cancer cases in American women. Approximately 180,000 new cases of invasive breast cancer are diagnosed each year, with 62,000 new cases of in situ breast cancer, mainly ductal carcinoma-*in-situ* (DCIS) also diagnosed annually. (American Cancer Society, 2007)

Approximately 40,000 American women die of this disease annually. Between 11 and 13 percent of US women (one out of eight or nine) will develop breast cancer if they live to age 85. Breast cancer is the second-most common cause of cancer death in women. Lung cancer is the most common cause of cancer mortality in women.

The keys to surviving breast cancer are early detection and treatment. Survival rates depend on the stage at which the cancer is detected. The five-year relative survival rate for

Stages 0 and 1 are near 100 percent. The survival rate decreases with more advanced stages. The survival rate for Stage 4 has a relative five-year survival rate of 20 percent.

While the incidence of breast cancer diagnosis has increased, the survival has improved dramatically in the last few decades. In the 1940s, the five-year survival rate for early-stage localized, node negative disease was 72 percent. Today, the survival rate has improved to 97 percent for the same stage disease.¹ The decline in mortality from breast cancer in the face of rising incidence rates is testimony to the success of interventional strategies in the form of screening and adjuvant systemic therapy.

Breast cancer is a very heterogeneous disease that requires the coordination of a multidisciplinary team for optimal treatment and outcomes. This team includes a breast radiologist, pathologist, breast surgeon, medical oncologist, radiation oncologist, plastic surgeon and genetic counselor.

Evaluation of the tumor size, any multifocality or multicentricity, the surgical margins, histologic grade, exam of the sentinel node, immunohistochemical and gene-based assays are all critical to decision-making and treatment.²

Breast cancer is a unique disease that has sufficient prevalence in the population to make it feasible to screen that population. It also has a preclinical stage prior to the progression of micrometastases and “phenotypic drift,” during which the disease can be detected by screening. Phenotypic drift is the natural evolution of the more aggressive cells in a heterogeneous tumor to be the dominant histologic type.

Randomized Clinical Trials

There are three cornerstones of any breast cancer screening program that lead to early detection. They are annual mammography, a yearly clinical breast exam and a monthly breast self-exam. The efficacy of screening mammography has been studied extensively. The current U.S. recommendations for screening mammography are based on evidence gathered in seven randomized controlled trials performed between 1963 and 1988 and several meta-analyses.³⁻¹⁰ These studies showed that screening mammography in women aged 40 years and older reduced cancer deaths by 29 to 45 percent.

In evaluating the results of the screening mammography trials, a few potential biases should be considered. One potential bias is lead-time bias, which refers to the interval between disease detection and the usual manifestations of the disease. The estimated lead time in cancer detection with mammography is 18 plus or minus six months. Another potential bias is length time bias, which refers to differences in the rate of growth of tumors. It is thought that interval cancers, those that present clinically during the interval between regularly scheduled screening mammograms, are the fastest-growing cancers and have a worse prognosis than cancers detected on regularly scheduled annual mammograms. The ability to discriminate between the less aggressive and the more aggressive disease is an important area of breast cancer research.¹¹ There is also the possibility of self-selection bias in clinical trials, which refers to the fact that patients who volunteer for studies tend to have better health awareness than the general population. The optimal method to screen for breast cancer is constantly being re-evaluated. Until there are further breakthroughs in research and treatment, mammography remains the only proven screening technique to decrease breast cancer deaths in the general population.

Risk Factors

There are a number of established risk factors for breast cancer. The first and most obvious is being female. Just 1 percent of breast cancer is diagnosed in males.

Age is the next most important risk factor, with a steadily

increasing risk as a woman ages. A woman in her 70s is three times more likely to develop breast cancer than a woman in her 40s.

A family history of breast cancer, particularly in a first-degree relative (mother, sister, daughter) is an important risk factor. If the relative had a premenopausal breast cancer or bilateral breast cancer, the risk increases even further. A family history of ovarian cancer and any history of breast cancer in a male relative also increase risk of an inherited mutation. Approximately 5 to 10 percent of breast cancer cases result from inherited mutations in breast cancer susceptibility genes BRCA1 and BRCA2. It is very important to identify these individuals as some families have as high as an 80 percent lifetime risk. Affected individuals have unique primary prevention and screening needs which will be detailed later.

Hormonal factors can increase a woman's risk of breast cancer. These include early menarche (before age 12), late menopause (after age 55), late age of first full term pregnancy (after age 35), nulliparity and hormone replacement therapy.

Mammographic density has been shown to be a powerful predictor of breast cancer risk. A woman with greater than 75 percent density on a mammogram has a five times greater risk of developing breast cancer than a woman with a fatty replaced parenchymal pattern.

Proliferative breast disease found on a prior biopsy is a risk factor. This includes atypical ductal hyperplasia (ADH), atypical lobular hyperplasia (ALH) and lobular carcinoma in situ (LCIS).

Irradiation of the breast region at an early age can increase risk of breast cancer by as much as 35 percent. This is usually for treatment of a cancer such as Hodgkin's disease.

Personal history of malignancy increases the risk of a subsequent breast cancer. In addition to a personal history of breast cancer, the other cancers that can increase breast cancer risk include a history of endometrial, ovarian or colon cancer.

While these factors can increase a patient's individual risk, approximately 75 percent of new breast cancer patients have no more risk than being a woman over 40 years of age.

Certification

In 1987, the American College of Radiology developed the Mammography Accreditation Program. This was incorporated into the 1992 Mammography Quality Standard Act (MQSA) and became mandatory through FDA regulation in 1994. The MQSA is a law that provides minimum training, interpretation and reporting standards and regulates all of the aspects which contribute to image quality and patient dose. All facilities in the United States are required to be MQSA-certified prior to providing

mammographic services and must continue to pass a yearly inspection.

When Should Patients be Screened?

Annual screening mammography should begin at age 40. This recommendation is supported by major medical organizations, including the American Cancer Society, the National Cancer Institute, American College of Radiology (ACR), American College of Obstetricians and Gynecologists (ACOG) and the American Medical Association.¹²

In November 2009, the *Annals of Internal Medicine* published an article on screening mammography by the U.S. Preventive Services Task Force (USPSTF). They recommended screening women every other year from age 50 to 74 and recommended against breast self-exam and also questioned the usefulness of clinical breast exam. This created much furor among patient and advocacy groups. The task force was criticized for not having breast cancer or breast screening experts in its membership.

Soon after the article was published, the U.S. Secretary of the Department of Health and Human Services, Katherine Sebelius, issued a news release stating that "They (USPSTF) do not set federal policy... and I would be very surprised if any private insurance company changed its mammography coverage decisions... There is a great need for more evidence, more research and more scientific innovation... My message to women is simple. Mammograms have always been an important life-saving tool in the fight against breast cancer and they still are today. Keep doing what you have been doing for years..."

The American Cancer Society has reaffirmed its position that breast cancer screening should be annual and start at age 40. This position is supported and endorsed by numerous additional medical groups including ACOG, ACR and the Society of Breast Imaging (SBI). One in every 69 women develop breast cancer in their 40s.

There is no established upper age limit to the beneficial use of screening mammography, because the age at which a woman would cease to benefit from screening mammography varies depending on the individual's overall health. The decision as to when to stop routine mammography should be made on an individual basis by each woman and her physician. As long as a woman is in reasonably good health and would be a candidate for treatment, she should continue to be screened with mammography.¹³

If a patient has a first-degree relative who has had breast cancer, screening should begin 10 years earlier than the age at which that relative was diagnosed or at 25, or whichever is older. For example, if the patient's mother was diagnosed at age 40, the daughter should begin screening at age 30.¹³ Patients who have received high-dose chest radiation

(mantle therapy) should begin mammographic screening eight years after her radiation treatment or at 25 years, or whichever is older.¹³

Any patient with symptoms such as palpable mass, skin changes or pain is not a candidate for screening mammography and should have a diagnostic mammogram ordered where the breast radiologist can tailor the set of images to the particular patient's symptoms. This may involve getting a detailed history of the patient's symptoms and occasionally also using ultrasound to further evaluate any findings.

Technique

Mammography currently remains the only imaging modality that is recommended for routine screening for breast cancer in the general population because it has proven to decrease the death rate from breast cancer. A screening mammogram includes a craniocaudal and mediolateral oblique view of each breast. The technologist positions the patient to project as much of the tissue as possible on the images. Compression of the breast tissue to tolerance is obtained to eliminate motion artifact, separate the glandular densities, decrease scatter irradiation and even out the overall density of the breast. The quality of these images is of utmost importance for accurate interpretation.

The radiologist makes an assessment of the relative density of the breast using a quartile system., i.e. "almost entirely fat," 0 to 25 percent glandular density; "scattered glandular density," 25 to 50 percent glandular density; "heterogeneously dense," 50 to 75 percent dense; and "extremely dense," greater than 75 percent dense.

All mammograms are reported using the Breast Imaging-Reporting and Data System (BI-RADS). BI-RADS is a mammographic terminology which standardizes lexicon and facilitates reporting of the interpretation, communication, recommendations and outcome monitoring. This system uses category numbers of zero through six with each linked to a clear assessment and recommendation.

Findings

The most common mammographic findings of breast cancer include a mass or suspicious calcifications. There are many modifiers which the radiologist uses to separate the majority of masses and calcifications that are benign from the few that are indeterminate and need further workup. While there are many exceptions to the rule, malignant masses frequently have irregular shape, indistinct or spiculated margins and high radiographic density. Malignant calcifications can be found alone or in association with masses. Malignant calcifications are usually grouped or clustered, pleomorphic (varying in size and shape), fine, linear and branching. There are additional indirect signs that may indicate that a patient has breast cancer and these include evolving density, architectural

distortion and asymmetric density.

Once the diagnosis of breast cancer is obtained by biopsy, it is then important for the diagnostic mammographer to precisely establish “extent of disease,” since this determines the next step in treatment, whether lumpectomy, mastectomy or neoadjuvant chemotherapy, and assures complete removal of all disease. Extent of disease is determined by assembling imaging information (from mammography, ultrasound and MRI) and comparing this with all biopsy information. Multicentric disease is found in 30 to 40 percent of all breast cancer cases. MRI is the most sensitive imaging modality to determine extent of disease.

Full Field Digital Mammography

Full field digital mammography (FFDM) units have replaced screen/film mammography (SFM) in greater than 60 percent of the mammography facilities in the U.S. This percentage continues to increase. Digital mammography has a higher contrast resolution and higher signal-to-noise ratio and a lower radiation dose.

In a film-screen system, the film functions as the detector, storage and display device. With digital systems, these tasks are separated allowing for optimization of each function. Full field digital also allows for rapid throughput and electronic transmission of the image. There also is reduced cost of archiving. The final image can be manipulated to enhance interpretation with functions such as magnification, windowing and level adjustments and edge enhancement.¹⁴ Breast radiologists find these features to be very helpful in interpretation, despite that evaluating a digital mammogram takes considerably more time than for an analog mammogram.

The Digital Mammography in Screening Trial (DMIST) demonstrated that digital mammography was superior to film-screen mammography in detection of breast cancer in certain subgroups, which included women under age 49, women with dense breast tissue and pre- and perimenopausal women.¹⁵ A number of additional studies have been published comparing FFDM and SFM in large population-based screening trials. FFDM finds more cases of both invasive carcinoma and DCIS with similar positive predictive value and slightly increased recall rate. The most recently published trial in October 2009 was a review of 188,823 screening mammograms. It showed that FFDM found 21 percent more cancers than SFM.¹⁶ The Oslo II study revealed an even higher percent of additional cancers detected when comparing FFDM with SFM.¹⁷

There are a number of additional techniques amenable to digital mammography that are being investigated at this time. These techniques include tomosynthesis and dual energy mammography. Tomosynthesis is a cross-sectional technique which minimizes the effect of overlapping structures in the breast and should facilitate cancer

detection. Clinical trials are underway to establish efficacy of tomosynthesis and define its role in future practice.

Computer-Aided Detection

Computer-aided detection (CAD) is becoming commonplace in U.S. screening programs. Mammographic CAD has proven to improve the rate of cancer detection in screening populations. In the case of screen-film mammography, the images are digitized and then subjected to a computer-based analysis. In the case of digital mammography CAD analysis is included in the display algorithm. The prompts, which are designed to detect calcifications, masses or asymmetry, are projected on the images with a keystroke. CAD offers the interpreter and ultimately the patient the advantage of increased sensitivity to detection of suspicious abnormalities.¹⁸ Studies indicate that readers using CAD detect 19.5 percent more cancers than without CAD.¹⁹ Detection is not diagnosis, and, therefore, it is still up to the interpreter to determine if a finding rises to the level of a suspicious lesion that would require additional evaluation.

Core Needle Biopsy

When a patient is screened and mammographic abnormalities are detected, the patient is called back and a diagnostic workup is performed frequently using special mammographic techniques such as magnification mammography or focal spot compression images. Ultrasound may also be used depending on the specific type of abnormality. If the lesion is still suspicious after the diagnostic evaluation, a core biopsy is frequently performed. A core biopsy is a tissue-sampling procedure guided by stereotactic technique in the case of calcifications or ultrasound if the lesion is a mass and visible with ultrasonic imaging.

In a recent multispecialty consensus conference² published in the *Journal of the American College of Surgery*, Silverstein, et al. stated that “percutaneous needle biopsy has demonstrated accuracy and is the optimal initial tissue-acquisition procedure for image-detected breast abnormalities. The use of percutaneous biopsy for diagnosis significantly reduces the overall cost of treatment and potential disfigurement of patients with breast lesions... In spite of the fact that there are few patients for whom needle biopsy is technically not feasible, an alarming 35 percent of initial diagnostic breast biopsies in the United States are still done using open surgical techniques. It was the Panel’s unanimous opinion that percutaneous needle biopsy represents ‘best practice’ and should be the new ‘gold standard’ for initial diagnosis. It should essentially replace open biopsy in this role.”

Core needle biopsy uses multiple devices. These range from 14G to 7G in size. Some of these devices have vacuum-assist and are superior in obtaining ample tissue for histologic analysis.

Ultrasound

Ultrasound should always be used as an adjunct and never as a primary screening tool. Results of ultrasound studies vary widely depending on the operator. There are at present no data to support whole-breast ultrasonic screening to decrease breast cancer death rates. A study by the American College of Radiology Imaging Network, ACRIN Study 6666, is underway to investigate this issue.

The goal of diagnostic breast ultrasonography should be to make the overall imaging assessment more specific, helping to guide further care. In the setting of a suspicious lesion, the ipsilateral breast should be scanned sufficiently to determine the extent of the index lesion and to assess for any satellite or synchronous lesions. Ultrasonography of the ipsilateral axilla should be performed for all suspicious or biopsy-proven invasive lesions to assess for morphologically abnormal nodes. If an abnormal node is detected, confirmation of malignant involvement by ultrasound-guided core biopsy will allow the surgeon to proceed directly to axillary dissection rather than sentinel node biopsy. Radiologic marker placement at the time of ultrasound-guided axillary node biopsy may facilitate subsequent confirmation of proper node recovery.²

Medical Audit

Under MQSA, all practices must strive to have 100 percent follow-up of all screened patients and any subsequent biopsy and staging information. Each individual interpreter receives this information based on their cases. Each screening center also makes a combined report based on the accumulated data yearly. The Department of Health and Human Services has published desirable goals for the medical audit of screening outcomes. These include a less than 10 percent recall rate, sensitivity of greater than 85 percent and specificity of greater than 90 percent. The number of screen-detected cancers varies from two to 10 per 1,000 patients screened. This is usually six to 10 per 1,000 in those who have never been screened before and is usually two to four per 1,000 in those with yearly follow-up screening. Greater than 50 percent of cancers detected by screening should be either Stage 0 or Stage 1. Greater than 75 percent of screen-detected invasive cancers should have negative nodes. Greater than 30 percent of screen-detected cancers should be "minimal" cancers, i.e. less than 1 cm in diameter.²⁰ These numbers should be obtainable with adequate experience of the interpreter and attention to all the details of imaging and diagnosis. Bassett at the University of California, Los Angeles published in the American Journal of Radiology that biopsy of palpable masses yielded a positive predictive value (PPV) for primary breast malignancy 34 percent of the time, and biopsy of mammographically detected abnormalities revealed malignancy in 31 percent of cases.

The American College of Radiology launched a national mammographic database in October 2009. This is intended to be an aid to medical auditing where a practice will submit their data and have their outcomes analyzed and fed back in a meaningful way and thus create a large enough cumulative data warehouse from which to compare one's practice and eventually to strengthen any weakness.

High-Risk Patients

Mammography alone is not adequate for surveillance of high-risk patients. Patients who have multiple family members with breast cancer may have an inherited high risk of developing breast cancer. High-risk clinics evaluate the actual level of risk in these patients and provide specialized services, such as genetic counseling/testing, risk reduction and screening breast MRI.

There have been tremendous advances in the field of genetics that allow for these patients to be tested for genetic predisposition. Potential high-risk patients are referred to a genetic counselor for risk assessment and possible genetic testing. If this testing proves to be positive, these patients then can pursue various risk reduction strategies and/or begin high-risk surveillance. Advances in MRI technology allow for rapid simultaneous bilateral acquisition of high-resolution cross-sectional images of the breast.

Hereditary breast and ovarian cancer syndrome is associated with mutations of the BRCA1 and BRCA2 genes and is the most common form of inherited predisposition to breast cancer. Approximately 80 percent of cases of inherited breast cancer are due to mutations in either the BRCA1 gene (chromosome 17q12-21) or the BRCA2 gene (chromosome 13q12). Fifty percent of patients with the BRCA1 gene develop breast cancer by the time they reach 50 years old. Some of the 20 percent of inherited breast cancers not associated with mutations in BRCA1 or BRCA2 are associated with other genes, such as PTEN (Cowden disease), TP53 (Li-Fraumeni syndrome), STK11/LKB1 (Peutz-Jeghers syndrome), CDH1 (hereditary diffuse gastric carcinoma), and ATM (ataxia-telangiectasia). However, there are probably other susceptibility genes that have not yet been identified since BRCA1-2 and these other genes do not account for all cases of familial breast cancer.

Genetic Counseling

Genetic counseling has become very important to educate patients, their families and other health care providers about the role of genes in the development and transmission of cancer. Patients are referred for genetic counseling when they are suspected of having a hereditary cancer syndrome. (Figure 1) The genetic counselor performs a formal risk assessment based on the patient's personal and family history. They use various risk assessment models including the Gail, Claus or BRCAPRO models to determine relative

risk of developing breast cancer and whether to do genetic testing based on this information. They discuss the benefits, risks, limitations and possible results of genetic testing and any recommended cancer screening and risk reduction strategies. We have found this to provide psychosocial support to patients and their families throughout the genetic counseling and testing process. Genetic testing provides patients with information about themselves and their families that may affect their medical care and health. On the federal level, the Health Insurance Portability and Accountability Act (HIPAA) prohibits group health insurance plans from using genetic information as a basis for denying, canceling or limiting eligibility for coverage or increasing an individual's premium and also prohibits the use of genetic information as a pre-existing condition. Most states have enacted similar laws that prohibit the use of genetic information in decision-making regarding health insurance coverage, eligibility or employment.¹⁴

Risk Reduction

Breast cancer risk reduction strategies in those found to be at documented high risk include chemoprevention with selective estrogen receptor modulators such as tamoxifen or raloxifene, prophylactic mastectomy and prophylactic oophorectomy. A recent international study documented that prophylactic oophorectomy is generally accepted by women and their physicians. However, only a minority of women with BRCA1 or 2 mutation opt for prophylactic mastectomy or take tamoxifen for the prevention of hereditary breast cancer. Approximately one-half of these women at high risk for breast cancer rely on screening alone.²¹

Screening Breast MRI

Screening breast MRI has proven to be a powerful adjunct to mammography in patients with a BRCA mutation.²² The benefit of breast MRI is that it has markedly increased cancer detection compared to mammography with significantly more of these cancers being detected prior to nodal metastasis, i.e. MRI detects breast cancer at early stages. The invasive breast cancers detected by MRI had a node

positive rate of seven percent compared to a node positive rate of 28 percent for those invasive cancers diagnosed by mammography. The call back rate for breast MRI screening compares favorably with mammography at 10 percent (range eight to 17 percent) The positive predictive value for biopsies is slightly higher for MRI than mammography at 43 percent (range 17 to 89 percent).²³

Screening MRI in high risk patients detects both mammographically and clinically occult breast cancers. Adding MRI to mammography gives an additional cancer yield of eight to 67 (mean=30) in 1,000 high-risk women screened. The consistent finding of numerous studies at numerous institutions of high-risk patients is that MRI has the highest sensitivity and cancer yield of any of our screening tools. The sensitivity of MRI in these studies ranges from 71 percent to 100 percent. The sensitivity of mammography at diagnosing cancers in these same patients is measured as only 13 percent to 40 percent.²⁴ One study by Lehman compared cancer yield of mammography, MRI and ultrasound in high-risk women. This revealed that mammography found only one-third as many cancers as MRI and that ultrasound was not useful to screen high-risk women. The PPV for biopsies performed as a result of MRI was 43 percent. This compares favorably with biopsies performed for palpable masses (34 percent) and for mammographically detected lesions (31 percent).

Patients with a sufficiently high risk undergo yearly mammograms and breast MRI. A number of international clinical trials support the use of yearly MRI and mammography to screen patients at high risk of developing breast cancer.²⁵⁻³⁰ The American Cancer Society has recently recommended that high risk patients pursue breast MRI due to its high sensitivity and proven ability to detect small curable cancers not seen on mammography.³¹ An expert panel endorsed the ACS guidelines regarding screening MRI.

Appropriate candidates include:

1. Women with a lifetime breast cancer risk or 20 percent or higher based on predictive models. This usually means those with two or more first-degree relatives with diagnosed breast cancer (mother, sisters or daughter);
2. Those with BRCA1 or 2 mutations or those having a first-degree relative with a BRCA 1 or 2 mutation who have not yet been tested themselves;
3. Those who have had radiation therapy to the chest between ages 10 and 30; and/or
4. Women with Li-Fraumeni, Cowden or Bannayan-Riley-Ruvalcaba syndromes and their first-degree relatives.

The ACS recommends that patients with less than 15 percent lifetime risk of breast cancer not be screened with MRI. They do, however, recommend further study on the group of patients with between 15 percent and 20 percent lifetime risk. This group includes women with a personal

Figure 1. Genetic Counseling Referral of Patients at High Risk of Hereditary Breast Cancer

Indications for Referral for Cancer Risk and Genetic Evaluation

Any personal and/or family history of:

- Breast cancer diagnosed <50;
- Breast cancer in 2 or more close relatives;
- Bilateral breast cancer;
- Male breast cancer;
- Breast & ovarian cancer in the same woman or in close relatives;
- Ovarian cancer at any age; and/or
- Ashkenazi Jewish with breast or ovarian cancer at any age.

history of invasive breast cancer or DCIS, previous diagnosis of ADH, ALH or LCIS and women with mammographically dense breasts. A recent consensus panel² states that “the commonly used predictive models may not reliably identify all women at high risk. Many women who have significant risk may fail to meet the ACS threshold for screening. In the Panel’s view, screening MRI may be appropriate” for women with a 15 percent and 20 percent lifetime risk. (Figure 2)

MRI uses magnetic fields along with radiofrequency transmitters and receivers to produce cross-sectional images. These images can be reconstructed in 3-D (sagittal, axial and coronal planes), particularly when high-field strength (3 Tesla) magnets are used. One advantage is that no ionizing radiation is used with MRI.

For cancer detection protocols, a paramagnetic contrast agent containing gadolinium is injected to evaluate enhancement. The patient lies prone on a padded table that contains the specialized imaging receivers, or coils. Scans are acquired rapidly, but image reconstruction and post-processing continue after the patient has left the scanner. Post-processing usually utilizes computer aided detection software to aid in interpretation. Pre and post-contrast images can be subtracted to emphasize enhancement. Breast MRI is interpreted in comparison with the mammogram. A complete breast MRI with CAD contains thousands of images.

Contraindications to MRI include implant expanders, cardiac pacemakers, neurostimulator devices, extreme claustrophobia and morbid obesity.

The sensitivity of MRI is high, and, therefore, a negative MRI is highly reassuring that there is no cancer in that patient. High sensitivity, however, means that there is a moderate false-positive rate and decreased specificity. Experts recommend that breast MRI only be done where MRI-guided core biopsy is also available.² Future improvements are expected with advanced pulse-sequences and incorporation of diffusion-weighted MR potentially being added to present protocols at 3 Tesla.³²

Remaining Challenges

Research is being done on many fronts to find “the cure.” Promising areas of cellular biology research include the PI3K enzyme, which is a central player in the pathway that controls cell growth and survival.

“Epigenetics” looks at how certain genes are used in the cell and how genes get turned on and off. There is also research into the molecular diversity of breast cancer and to define these various subtypes. The hope of these three promising areas of research is to find specific drugs to control each of these cell processes and disease subtypes. This in turn could improve the screening and treatment paradigm to discrimi-

Figure 2. Risk Information

The American Cancer Society recommendations are as follows:

- Women at high risk, greater than 20 percent lifetime risk, should get an annual MRI and mammogram.
- Women at moderate risk, 15 percent to 20 percent lifetime risk, should visit with their physician about an MRI in addition to their annual mammogram.

Women at high risk include those who:

- Have a known BRCA1 or BRCA2 gene mutation;
- Have a first-degree relative (parent, brother, sister or child) with a BRCA1 or BRCA 2 gene mutation, and have not had genetic testing themselves;
- Have a lifetime risk of breast cancer of 20 percent or greater, according to risk assessment tools that are based mainly on family history;
- Had radiation therapy to the chest when they were between the ages of 10 and 30; and/or
- Have Li-Fraumeni syndrome, Cowden syndrome or Bannayan-Riley-Ruvalcaba syndrome, or have one of these syndrome in first-degree relatives.

Women at moderately increased risk include those who:

- Have a lifetime risk of breast cancer of 15 percent to 20 percent, according to risk assessment tools that are based mainly on family history;
- Have a personal history of breast cancer, ductal carcinoma in situ (DCIS), lobular carcinoma in situ (LCIS), atypical ductal hyperplasia (ADH) or atypical lobular hyperplasia (ALH); and/or
- Have extremely dense breasts or unevenly dense breasts when viewed by mammograms.

nate minimal-risk disease from high-risk disease and therefore reduce treatment burden for patients and society.¹¹

The American Cancer Society has released data showing that the breast cancer mortality rate decreased by 2.2 percent per year between 1990 and 2004.³³ However, in African American women, the breast cancer death rate declined by only 1.6 percent per year and remained unchanged among Asian American and Native Americans. Reasons for the differences in mortality rates remain unclear.

Many challenges remain in order to realize the maximal benefit from earlier detection. There is a concerning decrease in the usage of screening mammography. Nearly one-third of American women are not undergoing mammographic screening at appropriate intervals. Thirty percent of American women who are 40 and older have had no mammograms in the last two years. Most women who are not having routine mammograms are not receiving a recommendation for mammography from their physician, among other reasons.³⁴ We must continue to communicate to our patients the importance of routine screening mammography and offer our high-risk patients genetic referral, risk reduction and breast MRI when appropriate.

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