With breast cancer incidence rates showing no signs of abating, advances in risk stratification and increasing awareness of cancer control, there is interest in expanding the breast imaging arsenal. Mammography is still the standard of care, and a recent meta-analysis of seven large studies supports its value as a screening tool. There is, however, clear need for improved sensitivity and specificity. Imaging of function, metabolism and molecular activity in breast tissue is of potential benefit in addressing these issues. In this article we provide an overview of the current methods of imaging in breast cancer, including mammography, ultrasound, digital mammography, magnetic resonance, positron emission tomography and magnetic resonance spectroscopy. Screening and surveillance should, ideally, be tailored to an individual’s cancer risk and breast tissue. Current evidence questions the recent move toward magnetic resonance imaging as a single or multimodality strategy for breast cancer screening. In a high-risk group, the cost effectiveness of technical innovations may be justified.

Key words: breast cancer, imaging, screening

Introduction

Breast cancer is the most common cancer, and is the second leading cause of cancer-related mortality of women in our society. Thus, prevention and screening have become important health issues. Statistics indicate that one in nine women will develop breast cancer during her lifetime [1, 2]. In general, cancer control is essential for any high prevalence disease, progressive at all its stages, and where timely treatment and earlier detection can alter its natural course [3]. It has been demonstrated that screening and detection in preclinical and premetastatic stages affect treatment decisions and outcome [4]. Eight randomized trials enrolling 500,000 women in Sweden, Scotland, Canada and New York led to the NIH consensus on mammographic screening guidelines in 1997. These studies support the ability of mammography screening to improve outcome in breast cancer. Up to a 30% decrease in breast cancer mortality in the screened population has been demonstrated [5–8]. Smaller tumors and earlier stage disease, detected by mammogram, have improved prognosis and afforded more treatment options. Evidence supporting the usefulness of mammography in this setting is strongest for women between 50 and 69 years old; however, recommendations from expert groups vary with regard to screening women in their 40s.

The Cochrane report in 2000 challenged the efficacy of screening mammograms. Olsen and Gotzsche [9] reviewed the data, and concluded that only three of the eight randomized trials were of sufficient quality to determine the efficacy of mammography as a screening tool, and that the combined results of these three trials showed no benefit. Although the investigators defended their trials, and many criticisms were answered, the news reignited a debate in the USA over the value of this technique. Overall, the independent reviews concluded that mammography is effective, especially for women 50 years old or more. After reconsidering the issue in 2001, the US Preventive Services Task Force has continued to recommend regular mammograms beginning at age 40 years [10, 11].

Although mammography remains the gold standard, it is not an ideal screening tool. Even when performed optimally, the sensitivity is between 69% and 90% [11–17]. Radiation risk and diminished sensitivity in radiographically dense breasts represent the most significant disadvantages of the technique, thus limiting its usefulness in high-risk younger women. Other clinical areas in which mammography is of restricted use include: detection of lobular cancer; detection of ductal carcinoma in situ (DCIS) without associated calcifications; work-up of a cancer of unknown primary presenting as an axillary mass (these are usually small high-grade lesions lodged in dense breast tissue); multifocal cancer; and characterization of locally advanced cancer [18]. Moreover, its usefulness may be diminished in a breast that has been subjected to prior radiation therapy.
Over the last decade there has been progress in our understanding of risk factors for breast cancer. Female breast cancer is a complex multifactorial disease, the etiology of which involves a strong interplay between environmental and genetic factors. Family history is a known risk factor. Although high penetrance cancer genes, \textit{BRCA1} and \textit{BRCA2}, have been identified, these account for only 5–10\% of cases [19, 20]. The remaining cases are generally considered sporadic, although this group may include cancers resulting from low penetrance genes. Non-genetic risk factors are also important in the etiology of sporadic cases, and may influence the penetrance of breast cancer-predisposing genes. Warner et al. [21] have shown that the presence of mammographic densities, in and of themselves, increases the risk of developing breast cancer, compared with their absence. Several models have been developed to assess the interactive effect of multiple risk factors on the overall patient risk, such as Claus, Gail, BRCAPRO and Couch [22–26]. These models rely on epidemiological, statistical, hormonal and reported family history data, to varying extents.

More successful breast cancer screening requires increased sensitivity and specificity, and should, ideally, be tailored to the individual’s cancer risk.

In this review we discuss the current evidence for the value of modern imaging techniques as well as multimodality imaging approaches to high-risk screening.

\textbf{Improved mammography}

\textbf{Digital mammography}

Digital mammography uses an electronic system to record an image of the breast that can be stored on a computer instead of on hardcopy films. Image-processing algorithms allow manipulation of fine differences in image contrast. As a result, subtle differences, even in dense tissue, can be appreciated [27]. A number of digital mammography technologies are under evaluation. Potential advantages include improvements in image contrast, post facto manipulation of the image (avoiding the need for repeat exposures due to technical problems), elimination of the problem of lost films, reduction in film library maintenance costs and the ability to transmit the images over long distances (telemammography). Early experience has shown that digital mammography reduces the number of patients recalled for additional views, reduces the number of false-positive breast biopsy results and can potentially enable detection of breast cancer at an earlier stage [28, 29]. Lewin et al. [30] prospectively compared full-field digital mammography (FFDM) with screen-film mammography (SFM) for cancer detection in 4945 women aged 40 years or older. Although the difference in cancer detection was not significant, FFDM had a significantly lower recall rate than SFM. Similar results were reported in another series of 6736 examinations by the same author [28]. In a third study, digital mammography had equivalent diagnostic accuracy compared with SFM, and higher sensitivity and reliability in characterization of microcalcifications [29]. Challenges and potential problems for digital mammography include: a need to prove equivalence in detection and diagnosis with conventional mammography; the high cost of digital mammography equipment; and cumbersome workstation technology.

Computer-aided detection and diagnosis (CAD) uses analysis by a computer program to assist the physician in identifying abnormal findings on mammograms, and in making a determination of benign versus malignant calcifications and masses. Several studies suggest that this technology can reduce the incidence of missed cancers and improve the positive predictive value for biopsies. CAD can be performed after digitization of hardcopy films, but is best suited to digitally acquired, softcopy images. Although digital mammography holds promise for improved diagnostic accuracy, image display is not currently ideal [30]. Clinical softcopy workstations are unwieldy to use, and image processing has not yet been optimized for each machine or for each clinical task. In addition, the cost-effectiveness and accuracy of the technology warrant careful study before digital mammography becomes widely disseminated and potentially replaces SFM [31].

A multicenter study enrolling 50 000 women across the USA and Canada is ongoing (ACRIN), and the results should give valuable information about sensitivity, specificity and cost effectiveness [32].

\textbf{New image acquisition technology}

\textbf{Ultrasound}

The addition of ultrasound to mammography can improve the overall sensitivity of conventional breast imaging [33]. Ultrasound is an excellent method for differentiating solid from cystic breast lesions, and can also be used in a limited fashion to characterize solid masses. It is particularly useful in aiding the characterization of lesions found on screening mamograms in women with dense breasts [34, 35]. It is not, however, recommended as a primary screening method, because of a variable false-negative rate (ranging from 0.3\% to 47\%), the operator-dependent nature of efficacy and the low cancer-to-biopsy yield for women with a dense breast.

\textbf{Magnetic resonance imaging}

Magnetic resonance imaging (MRI) is a modern breast imaging technique that is gaining popularity.

First experiences with MRI in breast cancer detection date to the 1980s, and were disappointing. Use of intrinsic tissue contrast based on T1- and T2-weighted sequences and spatial resolution was not shown to be helpful for the detection and diagnosis of breast cancer [36–38]. Recent advances with the use of supercoils have resulted in an increase in sensitivity and specificity [39–41]. The most widely used contrast agents are chelates of gadolinium, a lanthanide with three unpaired electrons, which has a very strong magnetic field.

Breast MRI has been shown to be capable of detecting early breast cancer, with sensitivities in the range of 95–100\%, i.e. a low false-negative rate [42, 43]. Enhancement
of the lesion reflects local tissue changes in blood flow, capillary permeability and extracellular volume. These changes are thought to be characteristic of angiogenesis, a hallmark of cancer, thus revealing detailed information about the anatomic location of structural abnormalities.

The reported specificity of MRI, however, is low, ranging from 37% to 97% [40, 41, 44, 45]. Benign fibroadenomas and fibrocystic disease, in large part, account for this, which can mean unnecessary biopsies and undue anxiety for patients [46]. Other issues causing problems with specificity include different interpretation strategies and criteria, patient- and tumor-related factors that influence interpretation, lack of a standardized MRI contrast technique, and the absence of a unifying definition of what constitutes clinically important enhancement [46–48]. With breast cancer incidence showing no signs of abating, and increasing numbers of women being screened for breast cancer every year, there is a clear need for effort to transform MRI into a valid screening tool. From its origins, primarily as a means of evaluating implant integrity, advances in its application are rendering the MRI a sophisticated bioimaging tool that provides additional data about function. Detailed spatial resolution, excellent sensitivity and the recent ability to perform MRI-guided biopsies, are the strengths of this modality. Specificity is the primary challenge. Barriers to MRI usefulness in the staging and diagnosis of breast cancer are being resolved through merging technologies.

Staging

Several studies have demonstrated the potential of MRI for greater sensitivity than mammography [44, 46, 48–50].

Of particular promise is its usefulness in the detection of multicentric disease and in mapping the extent of tumor in newly diagnosed patients. We have learned from six randomized clinical trials that for women with stage I and stage II disease that the choice of local therapy does not affect survival [51–56]. Whether or not an individual patient can undergo breast-conserving surgery depends on the size of the mass, particularly in relation to the size of the breast, the presence of multifocal disease, involvement of the nipple and ability to obtain clear excision margins. Clearly, we must focus on tools that guarantee minimum intervention, while still allowing the full extent of disease to be appreciated.

Harms et al. [50] reported that MRI detected additional cancers, not seen at mammography, in 11 of 30 patients. Imaging findings were correlated with serially sectioned pathological specimens in 30 breast samples. This study was the first careful MRI–pathology correlation to clearly establish that MRI can detect mammographically occult breast cancer.

A study by Orel and Schnall [46] followed, in which 34% of patients were found to have additional cancers not visible on mammography, and 20% had unsuspected multifocal disease that altered the surgical approach.

One of the potential impacts of MRI is the ability to detect, particularly in the dense breast, low-density processes such as DCIS (especially those lesions not associated with microcalcifications) and to determine, before surgery, the extent of DCIS that may be incompletely represented by amorphous or pleomorphic calcifications [57]. Since mammographic determination of DCIS relies heavily on detection of calcifications, this technique tends to favor detection of high-grade DCIS [18].

Even optimally performed conventional imaging is less likely to determine the extent of low-grade or non-comedo DCIS, where calcifications may underrepresent the extent of disease. It may be that the biology of this lesion, characterized by poor vascularization, results in variable contrast enhancement as the DCIS develops and grows along the lumen of the duct [42, 58, 59]. MRI incorporation of vascular perfusion information may aid in the detection of DCIS that does have increased vascularization [29, 59, 60]. It is a technique that potentially offers a non-invasive alternative to ductograms in the work-up of a clinically suspicious nipple discharge. These are often associated with occult DCIS undetected by mammogram [61]. Gilles et al. [58] investigated early enhancement in 36 women with DCIS; angiogenesis in the stromal surrounding ducts was shown to be correlated with early enhancement in 34 patients with DCIS, but was not seen in two with comedo-type.

Boetes et al. [12] compared the accuracy of MRI with mammography and ultrasonography for assessing the extent of breast tumors, and found MRI to be the most accurate of the three preoperative imaging modalities in determining size and number of malignant lesions in the breast.

Similar results have been reported by other investigators [62]. In a study by Kramer et al. [63], the multicentric extent of disease was determined with highest sensitivity (89%) by MRI, compared with clinical palpation (47%), mammography (67%) and ultrasound (79%). It was, however, the least specific, and specificity is a particular issue in radiodense breasts when breast-conserving therapy is planned. The importance of the increase in sensitivity with MRI is also apparent when evaluating chest wall and nipple involvement preoperatively [12, 64, 65].

The role of MRI in the examination of patients after excisional biopsy but before re-excision was investigated by Orel and Schnall [66] in 47 patients. The authors concluded that MRI has a high positive predictive value for residual tumor after excisional biopsy (92%). In this series, detecting mammographically and clinically occult multifocal disease, or extensive residual tumor, weighted the decision toward mastectomy rather than re-excision in four out of 14 patients. False-negatives resulting from post-surgical changes, and false-positives due to enhancement of granulation tissue and benign breast tissue, however, remain limitations in this study.

Axillary adenopathy of unknown primary

Breast cancer can, although rarely (<5% of cases), present as an axillary mass without an obvious primary [67]. The ability of mammography to detect a primary in the breast, and to define its extent in these patients, has been notoriously poor. The reported incidence of finding an occult primary lesion ranges from 0% to 56% [68]. The traditional treatment
approach for this group of patients has been mastectomy and axillary node dissection [69, 70]. This ‘blind mastectomy’ for a presumptive diagnosis of breast cancer, which may or may not be confirmed at pathology, remains controversial [69]. Articles supporting the use of breast conservation therapy in these patients show no survival difference between those who undergo mastectomy and those who undergo irradiation of the breast without surgery [69, 70]. There is limited information about the outcome of treatment with definitive radiation, as an alternative to mastectomy, and concern remains over the inability to control extensive loco-regional occult tumor with whole-breast irradiation [69, 70].

Although the numbers are small, there are a few studies that suggest a role for MRI in identifying a primary breast cancer in patients with isolated axillary metastases at presentation. In one study of 12 patients, MRI identified a primary breast cancer in nine [71]. Similarly, Orel et al. [72] reported finding a breast primary on MRI in 19 (86%) of 22 patients. In this setting, MRI may provide clinically valuable information that cannot be obtained by conventional imaging, and could affect patient care.

**Challenge: how do we make MRI a clinically relevant screening tool?**

**Screening at high risk**

Despite the endorsement of mammographic screening for high-risk women, no evidence to date has shown that routine use of this modality reduces cancer mortality in BRCA1 and BRCA2 carriers. Most hereditary breast cancers occur in young, premenopausal women, when the sensitivity of the mammography is most limited by dense breast tissue [73, 74].

While the evidence for use of the mammogram as a screening tool in women <50 years old remains controversial, the facts that age decreases the combination of increase in breast tissue density, there is relatively greater sensitivity of breast tissue and there is an extremely low frequency of breast cancer in women under 40 years have made this technique of limited documented diagnostic accuracy [75, 76].

A further consideration is the potentially harmful effect of radiation exposure on genes associated with increased risk of breast cancer [77].

Current recommended surveillance for high-risk women includes semi-annual clinical breast examination and annual mammography beginning between the ages of 25 and 35 years, although the effectiveness of these screening techniques in mutation carriers has not been established [78]. MRI use as a screening tool specifically in young women at high risk is attractive due to its high sensitivity, which is not affected by the presence of dense breast tissue. In a retrospective comparative study of 196 women at high risk for hereditary cancer by genetics or family history, Warner et al. [79] found that MRI increased detection of small cancers, compared with the combination of mammography, clinical breast examination and ultrasound. Six invasive cancers were discovered, in contrast to three detected by ultrasound and only two identified by mammogram. These results are similar to those of Kuhl et al. [80], who, in their study of high-risk women, reported an MRI sensitivity of 100%, compared with mammography or ultrasonography alone (33% and 33%, respectively), and 44% when combined. In this study, specificity was also higher for MRI (64%), compared with 30% for mammography and 12% for ultrasound.

In a study that lends support to this approach, Stoutjesdijk et al. [81] found MRI to be more accurate than mammography in the annual surveillance of a cohort of 179 women with hereditary risk of breast cancer. Thirteen cancers were detected by MRI, seven of which had been missed by mammograms.

A notable retrospective study by Liberman et al. [82] at the Memorial Sloan-Kettering Cancer Center looked at MRI diagnosis of ‘probably benign’ interpretations given to 24% of 367 women at high risk with normal mammograms within the previous 2 years. Seven to 10% were found to be malignant. This is significantly higher than the 0.2–2% frequencies of malignancy reported in studies of non-palpable, mammographically detected ‘probably benign’ lesions. Of the MRI-detected malignant group, more than half were DCIS and more than half were detected by MRI only. The nature of this imaging technique, which enhances with increased blood flow, as well as the nature of this population, may combine to result in the increase in the frequency of cancers found [83, 84]. There are currently ongoing trials investigating the potential move of MRI to a clinically relevant screening tool in such high-risk populations. Although the final results are not yet available, during the annual meeting of the American Society of Clinical Oncology in Chicago in 2003, mid-term results were presented. Several investigators addressed the value of MRI for the early detection of breast cancer in women at high risk because of a family or personal history. Kuhl et al. reported results of the first 5 years (1996–2001) of a prospective clinical trial in Germany. In this study, a total of 462 women with proven or suspected hereditary breast cancer participated in a standardized screening protocol including clinical breast examination, two-view mammography (from age 30 years onward), high resolution breast ultrasound and MRI. A total of 51 breast cancers were identified in 45 patients. MRI offered by far the highest sensitivity for diagnosing familial breast cancer, and had the lowest rate of unnecessary biopsies. In fact, sensitivity for MRI was 96.1%, compared with only 42.8% for mammography and 47% ultrasound. Specificity, again, was the issue. Rates for MRI, mammography and ultrasound were found to be 95.1%, 94.3% and 88.3%, respectively. Negative predictive values were 99.7% for MRI, 95.1% for mammography and 96.9% for ultrasound. Based on these results, and considering the increased radiosensitivity of breast parenchyma in gene carriers, the principal investigator suggested that MRI replace mammography for screening for familial cancer [85].

The second abstract reported the first results of the Dutch MRI screening study, a non-randomized, prospective, multicenter study that compared the value of different screening modalities in women with high familial or genetic cumulative
lifetime risk [86]. This study included 1848 women from November 1999 to August 2002. Thirty tumors were detected, including six DCIS. The authors also concluded that the sensitivity of MRI is higher than that of mammography, but the specificity lower. Robson et al. described the outcomes of breast MRI screening in 53 women with documented BRCA mutations. Sensitivity and specificity were 100% and 81%, respectively.

Overall, breast MRI screening in women with BRCA mutations appears to be sensitive, and may detect mammographically occult disease. Specificity in the clinical setting, however, is suboptimal, resulting in a significant number of false-positive results. Further investigations are required to improve specificity, and to investigate the psychological and economic impact of this screening modality in mutation carriers.

**Challenge: approach to MRI suspicious lesions**

**MRI-guided biopsy**

We have seen that MRI is increasingly being used in breast cancer diagnosis, and is particularly valuable in searching for a breast primary when evaluating women with metastatic carcinoma in the axillary lymph nodes, improving surgical planning in women with a biopsy-proven breast cancer, and in screening very high-risk women [87–89]. Problems result when suspicious lesions found on MRI cannot be visualized with mammography or ultrasonography [90]. Because of specificity limitations with this technique, MRI-based guidance systems are needed for needle biopsy or localization of the lesion before surgery. Fischer et al. [91] reported rates of MRI-guided intervention of ~3–5% in all patients undergoing MRI mammography. Closed magnet systems and breast immobilization devices have been developed; however, problems have been recognized with needle artifacts, tissue shifts and rapid equalization of contrast with surrounding tissue. Nevertheless, at present closed magnet systems remain the most widely used, for reasons of both cost and image quality, and because limited experience exists with interventions using open magnets. Recently, percutaneous vacuum biopsy of enhancing breast lesions has become possible under MRI guidance [92, 93]. This new system may permit accurate and safe access to lesions in any location in breast, with immediate confirmation of complete excision by visualization of the cavity. Thus, reliable histological evaluation of lesions smaller than 10 mm may be possible with this approach [94, 95].

**Magnetic resonance spectroscopy**

Proton magnetic resonance spectroscopy (H-MRS) of the breast has been proposed as an adjunct to MRI to improve specificity. While the contrast-enhanced MRI generates an anatomic image of the tumor directly, spectroscopy generates a complimentary biochemical image. Alterations in metabolic processes of tumors are probably associated with enhanced cell membrane synthesis, cellular growth and nutrient availability, as well as cell signaling and lipid hydrolysis. Specifically, an association has been observed between transformation and an increase in phosphomonoesters (PMEs) detected in the $^{31}$P MRS spectrum, as well as an increase in choline-containing metabolites detected in the $^1$H spectrum [96, 97]. Several *in vivo* studies have investigated the use of MRS in differentiating benign and malignant lesions. In a comprehensive review, Negendank et al. [98] concluded that malignant lesions have high phospholipid metabolites and more alkaline cellular pH. In line with results obtained in model systems, a review of nine different P MRS studies *in vivo* demonstrated greater PME and phosphodiesterase signals in proliferating breast tumors [99].

More recently, H-MRS studies performed *in vivo* have also demonstrated an increase in choline metabolites [100, 101]. Metabolites were detected in 70–80% of breast carcinomas, whereas only 14–18% of benign tumors demonstrated detectable choline peaks.

In a review by Katz-Brull et al. of the five studies of breast H-MRS performed in four independent centers around the world to date, the combined analysis of the data from a total of 153 tumors demonstrated sensitivity and specificity as high as 92% in distinguishing malignant from benign tumors using the choline signal. Of special interest, in a subgroup of 20 younger women the sensitivity and specificity of the method approached 100% [102]. Although the technical limitations are challenging, the excellent diagnostic performance of breast H-MRS in young patients makes MRI/MRS a promising candidate for screening this particularly important population. The technical demands of MRS, however, preclude its routine use in breast MRI examination at this time.

**Positron emission tomography**

Positron emission tomography (PET) is a unique form of diagnostic imaging that can detect biologic changes *in vivo* using radiolabeled tracers. Fluorine-18 fluorodeoxyglucose ($^{18}$F-FDG) is used most commonly, and closely mimics endogenous molecules [103, 104]. Tumor cells have increased glucose metabolism owing to enhanced expression of glucose transporters and hexokinase. The addition of $^{18}$F-FDG PET to the imaging armamentarium can therefore provide metabolic information complementary and additive to the morphologic imaging data, thereby increasing sensitivity and specificity in evaluating potential disease sites.

In a small study to identify the value of PET imaging in conjunction with MRI, nine of 10 patients were found to have locoregional metastases in axillary nodes or chest wall when PET scanning was added. Axillary and supraclavicular MRI alone identified four of the nine. MRI was, however, useful in pinpointing the location suggested by the PET image [105]. Another group of researchers addressed differentiation of tumor recurrence from scar tissue due to surgery or radiation. They used computed tomography to localize PET findings, and found the PET scan valuable in identifying active lesions [106]. A recent article by Wahl [107] gives an overview of the current status of PET imaging in breast cancer. Some tumors demonstrate avid $^{18}$F-FDG uptake, while others, such as invasive
lobular cancer, seem to be ametabolic. Of note, metastatic disease from these cancers does demonstrate $^{18}$F-FDG uptake.

Lobular cancer can be difficult to detect with any imaging modality. It is one of the most frequently missed cancers by both mammogram and ultrasound. This probably results from its diffuse pattern of growth, in which small cells form columns infiltrating the breast. Discrete masses, especially in small lesions, are generally absent [108]. Although experienced radiologists may be able to utilize the enhancement patterns on MRI to help identify the presence of lobular carcinomas, the inherent sparse vascularity of these lesions make this diagnosis radiographically difficult [21, 109–111]. PET scanning may be useful in these cases.

The exact role of PET scanning for imaging management of patients with known or suspected breast cancer is still evolving. For assessing primary lesions, it is sometimes possible with PET to detect cancers that are occult by standard methods, and this may have some use in the high-risk population. It must be remembered, however, that in dense breasts, background $^{18}$F-FDG uptake is often higher than in women with fatty breasts, making identification of lesions <1 cm in size improbable with the current technology. Overall, the evidence thus far does not favor use of $^{18}$F-FDG PET as a means of distinguishing which lesions require biopsy [112].

Investigators at the New York University Cancer Institute are currently conducting a study to determine whether a fusion technique of MRI and $^{18}$F-FDG PET can increase the specificity of the breast MRI for diagnosis and staging of breast lesions in women at high risk for breast cancer.

Conclusions

There is increasing interest in the development of imaging tests to screen for breast cancer, especially in high-risk groups where conventional technology falls short. Mammography has been the technique most extensively studied. The problems that have been encountered in demonstrating screening efficacy with this technique foreshadow the complexities of issues with newer screening tests. Although mammography remains the standard of care for breast cancer screening and diagnosis (with biopsy), evidence is accumulating that new imaging technologies are becoming important in breast cancer research and management. Ultrasonography is also limited in resolution, and its diagnostic application is as an adjunct to mammography. MRI, currently the next most widely used adjunct imaging modality, has been demonstrated to have efficacy in local staging, in evaluating extent of disease and, more importantly, in using architectural enhancement to differentiate benign from malignant lesions [113, 114]. The most exciting application of this modality is, perhaps, for screening and early detection in high-risk populations.

Modern imaging modalities are beginning to focus on biochemical and physiological alterations specific to tumors. MRS, together with improved localization techniques, generates metabolically linked images that may enable better distinguishing between tumor and normal tissue. $^{18}$F-FDG PET has already gained acceptance in staging, management of recurrence and monitoring of response to therapy. It is likely that, as our understanding of functional and molecular characteristics of tumors improves, a multimodal imaging approach will evolve, enhancing diagnostic accuracy and lowering the current threshold for detection, thus minimizing the troublesome false-negative rate.

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