Review of Breast Screening Guidelines and Disease Management for the Primary Care Physician

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Abstract

The aim of this review article is twofold: 1) to review the United States Preventive Services Task Force recommendations for breast cancer screening, issued in 2009, which were updated in final form in January 2016, and present the evidence-based criticisms of those guidelines, and, 2) to identify the most common breast complaints encountered by primary care physicians and review evidence-based strategies for management. These complaints include the red, "inflamed" breast, nipple discharge, and the palpable concern. Finally, the controversial issue of dense breast legislation, currently passed in 28 states, is presented in the context of the impact of the New Jersey law on one of the largest Breast Centers in the state.

Introduction

Primary care providers such as internists and gynecologists are tasked with ensuring their adult female patients undergo screening mammography. Current breast screening recommendations issued by the United States Preventitive Services Task Force (USPSTF) are at odds with those from many other organizations. Moreover, new breast density laws, currently passed in 28 states, have impacted screening protocols and standards of care in those states. In addition to making sure breast screening occurs according to up-to-date guidelines, internists and gynecologists are usually the first clinicians to identify breast problems and must be familiar with proper management and imaging strategies.

The aim of this article is twofold: 1) to review the USPSTF recommendations for breast cancer screening issued in 2009, and updated in final form in January 2016 and present the evidence-based criticisms of those guidelines, and 2) to identify the most common breast complaints encountered by internists or gynecologists and review evidence-based strategies for management. Finally, the topical issue of "dense breast" legislation is discussed in the context of the impact of the law passed in New Jersey on one of the largest Breast Centers in the state.

Screening for Breast Cancer

In January of 2016, the USPSTF issued its final recommendations for breast cancer screening.[i] Every other year mammography was recommended for women aged 50-74 (B recommendation). Women aged 40-49 were advised to discuss screening mammography with their physicians to determine if the benefits outweighed the harms (C recommendation). Harms were identified as radiation exposure, pain from the procedure, false positive studies, resulting in additional imaging and anxiety as well as "over-diagnosis" of malignancies that would not impact life

expectancy but which would entail treatments, such as surgery, radiation, and chemotherapy.

The USPSTF in 2009 also recommended *against* teaching breast self-examination (BSE) as a cancer screening strategy (D recommendation), and concluded that evidence was insufficient to assess the additional benefits and harms of clinical breast examination (CBE) beyond screening mammography in women age 40 years or older (I Statement).[ii]

The USPSTF recommendations met with widespread criticism by specialists in the breast imaging community. Daniel Kopans, MD, renown professor of Radiology at Harvard Medical School and a senior radiologist in the Department of Radiology, Breast Imaging section of Massachusetts General Hospital, cited fallacies in the USPSTF arguments and the data they used to reach their conclusions.[iii] He points out that the 30% reduction in death rates from breast cancer since 1990 to the present is largely attributable to mammography screening, not improved therapies, supported by population studies in the Netherlands and Sweden. *These data included women aged 40-49.* Benefit of screening mammography in breast cancer death reduction for women aged 40-49 was demonstrated unequivocally in multiple trials. The USPSTF acknowledged that screening reduces cancer mortality in every age group, but since the incidence of cancer is lower in the 40-49 year age group, the number of cancers detected in this age group is fewer. The USPSTF minimized the importance of breast cancer among women in their 40s, apparently unaware that over 40% of life-years lost to breast cancer are among women diagnosed in their 40's.

According to Kopans, studies performed in the 1990's artificially dichotomized patients by using the age of 50 years as an arbitrary threshold. The large

jump in cancer incidence after age 50 was spurious; in actuality there is a gradual increase with increasing age. None of the parameters of screening (recall rates, biopsy recommendation rates, and cancer detection rates) change abruptly at the age of 50, or at any other age. Age of 50 years is a not a biologically valid threshold, but an arbitrary threshold attributable to the grouping of patient data into artificial subgroups.

The USPSTF claimed that even if breast cancers were diagnosed at a later stage (which would result from biennial rather than annual screening), "breast cancer treatments have improved, and as treatment improves, the advantage of earlier detection decreases." This position requires ignoring the advantages of detecting cancer at an earlier stage when treatment would require less radical surgery or oncologic treatment.

With no scientific justification, the USPSTF advised that only high-risk women in their 40's should participate in mammographic screening, ignoring the fact that the randomized controlled trials did not stratify by risk. There is no scientific evidence proving that screening only high-risk women 40-49 will save any lives. The USPSTF chose to ignore the fact that the vast majority (75%–90%) of women who are diagnosed with breast cancer each year are not at high risk.

The American College of Radiology (ACR) and Society of Breast Imaging (SBI) continue to recommend that annual screening mammography starts at age 40. 10 percent of women whose mammograms are coded as BI-RAD 0, or inconclusive, simply require additional mammogram images and/or an ultrasound for clarification. Only 1 to 2 percent of women have a needle biopsy as a result of a screening mammogram. Short-term anxiety from test results is a minor inconvenience compared to the reduction in breast cancer

deaths with thousands of lives saved each year by mammography screening.[iv]

Diagnostic Dilemmas

1. The red, "inflamed" breast

The differential diagnosis of the inflamed breast is short and includes infectious mastitis, non-puerperal mastitis, and inflammatory breast cancer.

Infectious mastitis is usually secondary to oral nipple contact, and therefore most frequently associated with lactation, but may develop in sexually active women. The offending organism is usually *Staphylococcus aureus*, but other bacteria may be causative.[v] Patients present with breast pain, redness and possible systemic complaints, including fever.

The World Health Organization review of mastitis recommends that initial treatment should include continuous milk expression with breast-feeding or pumping, warm soaks, and better infant positioning for improved suckling for 24 hours before antibiotics are started.[vi] There are few randomized clinical trials addressing the management of mastitis, including the use of antibiotics. Given the paucity of evidence-based research, the Academy of Breastfeeding Medicine has based recommendations on expert consensus, and concurs with the WHO recommendations to initiate basic first measures for 24 hours before starting antibiotics. However, if a patient appears toxic, antibiotics are recommended immediately. Antibiotics include dicloxacillin, or cephalexin, (or clindamycin for B lactam hypersensitivity). If there is no clinical improvement on antibiotics within 2-3 days, imaging is suggested to determine if there is an underlying abscess.

Non-peurperal mastitis occurs in the non-breast feeding patient and clinically mimics lactational mastitis. Less common than lactational mastitis, it was first described by Zuska in 1951.[vii] In the normal

breast, squamous epithelium is present in the lactiferous ducts 1-2 mm deep to the nipple and abruptly changes to cuboidal or columnar epithelial bilayer. In this disease, squamous metaplasia arises in the central retroareolar ducts, producing keratin plugs which lead to duct obstruction, and rupture, with inflammation, and possible secondary infection.[viii] For first episodes, treatment consists of the same antibiotics as lactational mastitis, since initial infections are often due to *S. aureus*. Also similar to lactational mastitis, if no improvement occurs, imaging is required to exclude an abscess, which may require drainage. However, unlike the abscesses seen in lactational mastitis which are mostly peripheral, non-peurperal abscesses are subareolar and may fistualize to the periareolar skin. This entity is more likely to recur than lactational mastitis due to the underlying metaplasia, with repeated duct plugging and stasis. Recurrent episodes are more likely to contain mixed flora, including anaerobes and may require multiple percutaneous drainages or surgery.[ix]

Inflammatory breast cancer is a highly aggressive form of breast cancer, accounting for approximately 1% of female breast cancers in the United States, at a somewhat younger median age compared to all breast cancers (51 v. 66).[x] These patients also present with the appearance of an inflamed breast, with redness, and swelling but there is no true inflammation. The breast is edematous due to tumor infiltration of the dermal lymphatics, resulting in pitting of the skin similar to the skin of an orange, termed p'eau d'orange. Onset of symptoms is slower, on the order of weeks to months rather than days. Since its presentation may resemble infectious mastitis, these patients are often initially treated with antibiotics, but, of course, are non-responsive, and so should be referred for imaging. This disease is secondary to an

aggressive local breast cancer that rapidly invades the dermal lymphatics and spreads to ipsilateral nodes. The primary breast lesion may not be clinically evident due to breast swelling and skin thickening, nor may be evident on imaging. Mammography demonstrates increased breast density, skin thickening and adenopathy. Diagnosis is usually made by core biopsy of the underlying breast lesion if found, or axillary nodes and/or skin punch biopsy to prove dermal lymphatic involvement.

2. The palpable breast abnormality

Palpable concerns include lumps, or focal areas of thickening, and may be found by the patient or by clinical breast exam. Since there is broad overlap between the palpable findings for benign and malignant lesions, imaging is usually required and should be performed prior to any sampling procedure including aspiration since diagnostic aspirations or biopsies can cause bleeding which may confuse the imaging appearance of benign or malignant lesions. Cysts, which are quite common breast lesions, cannot reliably be distinguished from solid breast masses by palpation. Imaging prescriptions should always indicate the site of concern with a drawing showing the quadrant and distance from nipple since the patient may not be able to locate the lesion for the radiologist. The breast radiologist is obliged to palpate the lesion in the ultrasound suite to assure the palpable concern is correctly imaged.

Although older literature advocated diagnostic mammography as a necessary first imaging study for women over 40, a recent article showed that if the patient has had a normal mammogram within the recent 12 months, only a diagnostic ultrasound is required to evaluate a palpable concern.[xi]

In this study, 618 lumps were evaluated in 612 women. Approximately half of the women (304) had no imaging

findings, half (314) had positive imaging findings (on mammogram, ultrasound, or both modalities). 234 had an ultrasound finding only; three had a mammographic finding only and 77 had findings on both mammogram and ultrasound.

In the 311 patients with sonographic findings, most (almost 75%) were categorized as benign or likely benign, mostly cysts (129). 80 lesions were classified as BI-RADS 4 or 5, requiring biopsy; 48 malignancies were diagnosed. 10 of the 48 cancers were not visible mammographically, but were seen sonographically.

So, in the setting of a palpable concern, ultrasound is indispensible in identifying normal tissue as well as benign or probably benign lesions and can eliminate the need for biopsy in 87% of patients. Almost 20% of the cancers were not seen on mammogram.

Although most palpable concerns are benign, it must be emphasized that these concerns cannot be dismissed or followed clinically. Breast cancer is frequently discovered by palpation, either by patient self-exam, accidental discovery or clinical breast exam. In the National Health Interview Survey (NHIS), conducted between 1980 and 2003, 57% of breast cancer patients reported that their cancers were discovered by palpation, not by imaging.[xii] More recent data reflects the increased utilization of screening mammography as well as improvements in mammographic technology (now mostly digital). A recent review of how breast cancers were detected in a large New Jersey Breast Center showed that nearly one-third of breast cancers diagnosed by imaging performed on site (excluding referrals by outside imaging) were detected by palpation.[xiii]

3. Nipple discharge

Suspicious nipple discharge is almost always localized to a solitary duct and can be serous (clear) or bloody. Green discharge is usually due to fibrocystic disease. Multiple ducts manifesting discharge almost always indicates a benign process.

Bloody nipple discharge (BND) has the highest risk of malignancy, albeit low. Standard imaging evaluation must include both diagnostic mammography and ultrasound, which may identify the underlying causative lesion. However, the management of patients with negative combined imaging has been controversial, with central duct excision (CDE) recommended in the surgical literature.

In a recent review of 200 patients presenting with this complaint, patients who had BND but negative mammogram and ultrasound were analyzed.[xiv] 115 patients went to CDE and 85 patients underwent preoperative MRI prior to CDE. The incidence of malignancy in the two groups was 7% and 9.4% respectively, with a combined incidence of 8%. MRI was able to correctly identify 7 out of 8 cancers correctly but missed one case of clinically apparent Paget's disease of the nipple, which was surgically biopsied. The most common benign etiologies for nipple discharge included: papilloma, periductal inflammation, duct ectasia/hyperplasia, and fibrocystic disease. Many patients had more than one benign pathologic diagnosis.

There is valid concern that false-positive MRIs result in unnecessary biopsies. In the preoperative MRI group, indeterminate/suspicious findings prompted additional core biopsies in just 5 patients (5.9%). In the preoperative MRI group, additional sites of malignancy were detected far from the nipple in two patients, which would not have been found by CDE. In addition, three occult contralateral malignancies (all DCIS) were detected by

MRI in patients without malignancy on the side of the BND (incidence: 3.5%).

In view of the low incidence of malignancy in the setting of BND, the high sensitivity of MRI in detecting breast cancer, the low incidence of false positive studies, the yield of contralateral breast cancer, and the incidence of multifocal malignancy far from the nipple which would not have been diagnosed by CDE, the authors urged MRI in patients with BND and negative conventional imaging. MRI allowed identification of any relevant causative lesion and was preferable to blind CDE in this setting.

Topical Controversy: Dense Breasts

There are four categories of breast composition as determined mammographically as per the ACR's BI-RADS: fatty, scattered fibroglandular, heterogeneously dense, or extremely dense.[xv] These discrete categories belie the fact that in actuality, breast density is a continuum. For those mammograms that lie on the cusp between categories, assignment to a category is somewhat subjective, with considerable inter-observer variability. Approximately half of all mammograms depict dense breasts. It is accepted dogma that dense breast tissue can obscure cancer on mammography. Studies performed over the last few decades have suggested that women with dense breasts on mammogram have a higher risk of breast cancer; however, the underlying biological mechanism has never been clarified. Consider this: breast cancer is correlated with increasing age and obesity, both of which *decrease* breast density. These facts appear contradictory. A recent article about breast density and breast cancer risk addressed this issue.[xvi] The authors found that increasing body adiposity (as measured by the thickness of subcutaneous upper abdominal fat on breast MRI), and increasing age both were statistically associated with breast cancer,

while the breast density (as measured quantitatively on MRI) had no statistical association. The authors acknowledge some flaws in their study, including its retrospective nature, and small sample size (483 patients with cancer and 361 controls), and urge validation of their results on a larger scale.

Legislation related to mandatory breast density notification was first enacted in Connecticut in 2009 and there are now 28 states with similar legislation. The New Jersey law was signed in January 2014 and went into effect May 1, 2014. It included an insurance provision that ensured coverage for additional screening exams including ultrasound and MRI. A recent retrospective review on the impact of NJ breast density law demonstrated a large increase in screening ultrasound and MRI compared to pre-legislation levels.[xvii] There was an increase in the number of breast cancers diagnosed following the implementation of the law compared to pre-legislation diagnoses. Increased screening ultrasound volumes were expected to cause a significant rise in total breast biopsies due to the false positive rate of ultrasound, however, a modest decrease in total breast biopsies occurred. This was attributable to the use of MRI, which relies on non-enhancement as a reliable sign of benignity.[xviii] Increased cancer diagnoses with fewer biopsies (i.e, increased biopsy efficiency) were cited as a positive outcome following implementation of the law. Most cancers were found on screening mammography (235); the average density of mammography in these patients was lower than those whose cancers were found on screening ultrasound (21) or screening MRI (26). Interestingly, the average risk of breast cancer among the three screening modality groups was below 15%, supporting the statistic that most women who develop breast cancer are not high risk. Of the

women whose cancers were found by MRI, either screening or diagnostic, half had undergone recent prior ultrasound, which failed to detect their cancers. MRI had the highest efficiency for cancer diagnosis (13 cancers per 1,000 women screened) compared to mammography (4.2 cancers per 1,000 women screened) and ultrasound (1.8 cancers per 1,000 women screened).

To summarize the key points regarding breast density: a) breast density is not quantitatively measured effectively by 2D mammography, b) breast density is a continuum, and, c) assigning a BI-RADS density category is sometimes subjective, with inter-observer variability. The association between breast density and breast cancer risk requires more definitive study. Clearly, however, mammographic accuracy is limited by increased breast density. MRI is the most efficient means to both diagnose and exclude breast cancer.

Conclusion

40% of life-years lost to breast cancer are due to deaths of women in their 40's. The American College of Radiology and the Society of Breast Imaging continue to support *annual* mammographic screening for women *beginning at age 40* based on sound evidence.

The differential diagnosis of the red, "inflamed" breast includes lactational mastitis, non-peurperal mastitis and inflammatory breast cancer. If antibiotics do not result in clinical improvement in the first few days of therapy, imaging is appropriate to detect an abscess in the first two conditions, and a malignancy in the last.

Palpable concerns, although frequently benign, cannot be followed or dismissed and must be evaluated by ultrasound, and mammography if there has been no recent mammogram (within a year). In a recent review, approximately one-third of cancers presented with palpable concerns.

Bloody nipple discharge is most frequently benign, but combined imaging with mammography and ultrasound is a necessary first step. If conventional imaging is unrevealing, breast MRI is suggested to detect occult malignancy rather than blind central duct excision.

Dense breasts can mask malignancy. 28 states have passed breast density legislation. The impact of such legislation in New Jersey, which included an insurance provision, was a large increase in ultrasound studies, and a modest increase in MRI exams. Although breast biopsy volume was expected to soar, increased access to MRI permitted work-up of indeterminate sonographic lesions. Non-enhancement on MRI confirms benignity of indeterminate sonographic lesions, obviating core biopsy. More breast cancers were diagnosed following implementation of the legislation, with fewer total core biopsies. MRI was by far the most efficient modality to both exclude and diagnose breast cancer.

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