SEMINARS IN BREAST DISEASE

Breast MRI Screening for High-Risk Patients

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Although mammography can reduce breast cancer mortality rates in screened populations, its modest sensitivity, especially in younger women with strong family histories for breast cancer, has prompted the introduction of breast magnetic resonance imaging (MRI) for high-risk screening. Seven prospective screening trials for high-risk patients in which MRI has been added to mammography indicate the sensitivity of MRI to be twice that of mammography alone. The specificity of MRI is lower than mammography in most, but not all studies; however, the specificity of MRI improves to a level comparable to mammography in screenings subsequent to the initial prevalence screen. Although the target populations in breast MRI screening studies have been identified by genetic and familial risks, the superior sensitivity of MRI has been demonstrated at all levels of elevated risk, raising the possibility that MRI screening could benefit women with risk factors other than a positive family history. The published studies on breast MRI screening are reviewed herein, along with new screening guidelines that are currently shaping practice patterns.
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After many years of controversy, it is now generally accepted that mammography reduces breast cancer mortality in screened populations,[1] and that this benefit is, partly or largely, responsible for the decline in breast cancer mortality seen outside the confines of clinical trials in countries where mammography is a standard screening practice.[2] Effective screening at specific intervals for any type of cancer is based on: (1) the natural history of the disease and its interruption, taking into account epidemiologic concerns, such as selection bias, overdiagnosis bias, lead-time bias, and length-time bias; and (2) the sensitivity of the screening tool. After an effective tool has been identified, there is the additional challenge of population compliance. Disease prevalence and incidence, along with specificity of the tool, are more pertinent to the socioeconomic realities of screening rather than effectiveness as defined by a reduction in mortality. Although great enthusiasm exists among health care professionals and the public for cancer screening,[3] it is not always clear that screening strategies for earlier diagnosis alter outcomes, an issue that still surrounds lung cancer screening today.[4] In the evolution of breast cancer screening, while the historic mammography trials were underway, the Fisher theory of breast cancer biology was revolutionizing local management of the disease.[5] The Fisher theory de-emphasized variations in local control since systemic disease dictated outcome early in the biologic life of the tumor. A corollary of this theory, unstated because its tenets were first proposed in the premammographic era,[6] would have been that early diagnosis should have little or no impact on a cancer that has already established its tumor–host relationship, thus diminishing the importance of sojourn time. Yet, despite the widespread adoption of the Fisher theory, achieved primarily through the success of the NSABP B-04[7] and B-06[8] trials, the screening mammography trials (grounded more in Halstedian theory) were likewise successful,[9] helping to merge theories of breast cancer biology into the "spectrum theory,"[10] often called the "Hellman theory." As currently conceptualized by the spectrum theory, the natural history of breast cancer allows a vulnerability to early detection in many, but not all, malignant tumors.

With natural history generating less controversy today, we are still left with potential epidemiologic biases; however, given the endpoint of mortality reduction achieved through the prospective, randomized trials with mammographic screening, these biases are minimized, if not negated.[11] Thus, the success of the mammography screening trials was much more than a victory for radiograph technology; instead, the trials were a victory for the early detection of breast cancer as a general

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principle, opening doors for further improvement. The remaining variables, then, are *compliance* at the population level and *sensitivity* of the screening tool at the individual level. Compliance with screening mammography has been heavily promoted in selected countries with efforts underway to expand access worldwide. As for improving sensitivity of the screening tool, in this case mammography, technologic developments to date have had limited impact.

Sensitivity of Screening Mammography Variously Defined

Although the landmark prospective trials in screening mammography have been scrutinized to an extraordinary degree with regard to mortality reduction, little attention has been paid to the sensitivity of mammography in the detection of cancer in these same clinical trials. Yet, in a review of sensitivity and estimations of sojourn times,[12] the sensitivity of mammography in these trials ranged from 39% in the Health Insurance Plan (HIP) study to 92% in the age 70 to 74 subset of the Swedish Two-County study. Most sensitivity determinations, though, were in the range of 60% to 66%, with Malmo at 61% overall, Edinburgh 63%, Canadian National Breast Cancer Screening Study (CNBSS-1, ages 40-49) 61%, and CNBSS-2 (ages 50-59) 66%.[12] Despite these relatively low values, a sensitivity level that often appears in the disclaimers of radiology reports, and is regularly reported by the mainstream media, is that mammography can find "90% of breast cancers in women who have no symptoms of the disease."[13] Even the American Cancer Society offers the position statement that "mammography will detect about 80% to 90%" of asymptomatic cancers,[14] although the origin of this sensitivity level is not referenced. Although 90% sensitivity may be the case for subsets of women based on age or low-density mammograms, the source of this number as erroneously applied to all screening mammograms is difficult to trace, perhaps reflecting omission of the word "palpable" from early studies of sensitivity. However, almost two decades ago, it was recognized that mammographic sensitivity was "approximately 50%" in the HIP study and "approximately 70%" in the Breast Cancer Detection Demontration Project (BCDDP).[15]

Although mammography outcome data are monitored more than any other radiologic study, with performance benchmarks well defined,[16] the critical data reflective of mammographic sensitivity are not routinely monitored due to the inherent tracking challenges. Therefore, the sensitivity rate at one's own facility is usually unknown, and this has translated to a paucity of published data on the subject.

Because the historical screening trials employed what is now considered outmoded technology, the question arises as to the impact of technologic improvements in mammography. Although many advances are being studied, including contrast-enhanced mammography[17] and tomosynthesis,[18] the gradual improvement over the years in film screen mammography and the introduction of digital mammography has not yielded impressive gains in sensitivity. The Digital Mammographic Imaging Screening Trial (DMIST) coordinated by the American College of Radiology Imaging Network (ACRIN) was focused on a comparison of digital versus film screen; however, the overall sensitivity as defined by 12-month follow-up revealed 70% sensitivity with digital and 66% for film screen,[19] comparable to the sensitivities in the historical trials. When the definition of sensitivity was extended to the unconventional duration of 15 months, there was no difference between the technologies, with both digital and film screen showing a remarkably low 41% sensitivity.

Trying to define false-negatives in a meaningful fashion is a difficult task with nonpalpable tumors. Traditionally, the method used to measure false-negative rates was through long-term follow-up, wherein the miss rate correlates with duration chosen, as noted in the DMIST study above. However, in studies using long-term follow-up, so-called false-negatives are actually a mix of: (1) true interval cancers that may not have been detectable on the prior screen by any means, (2) radiologic misinterpretations, (3) cancers with subtle mammographic changes not meeting biopsy threshold, and (4) mammographic failures due to dense breast tissue. From such a mix, it is difficult to sort out true mammographic failures.

Although overall density is implicated as the primary culprit in false-negativity, the more exact issue is the density level immediately adjacent to the tumor borders. A malignancy that develops within an island of patchy density will be equally occult on radiograph as a tumor developing in a mammographic "white out," at least until the former becomes large enough to interface with adipose tissue. When this anatomic limitation is added to the problem of diffuse histology as seen in lobular cancers, the implementation of a physiologic component to screening seems warranted.[20]

Given these difficulties in accurately defining false-negatives through long-term follow-up, attention has focused recently on the more accurate approach of simultaneous adjunct imaging, primarily ultrasound and MRI. Although ultrasound has improved the sensitivity for cancer detection in women with dense breasts, defining tumors of similar size and stage as mammography,[21] there has been some hesitation to endorse its routine use given its performance in the multimodality studies to be noted below in which all three common methods of breast imaging have been employed.

Breast MRI can be conceptualized as improving sensitivity through two means: (1) as with ultrasound, MRI helps to identify the cancers that are currently being missed through conventional mammography, and (2) MRI uniquely lowers the threshold of detection and thus re-defines sojourn times, the preclinical, but screen-detectable, phase of a tumor. In the first instance, that of more *reliable detection*, one should be able to predict improved survival (with either ultrasound or MRI) since many of these tumors are missed on mammography simply because of anatomic issues, not inherent biology. However, in the second instance, a hypothesized survival benefit of *earlier detection* is more tenuous given length-time bias, although there seems to be little reason to abandon spectrum theory, which so nicely explains the success of the mammography screening trials.

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