Will Early Detection for Breast Cancer Ever Work?
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The fundamental challenge for those who advocate for screening and early detection of breast cancer is that breast cancer is not a single disease. It is a collection of heterogeneous diseases, ranging from those that grow slowly and pose little risk, to diseases with the potential for metastatic spread, even at a very early stage.

To understand how to refocus early-detection efforts in breast cancer, it is important to examine the trends in cancer incidence since the introduction of widespread screening mammography. Routine screening mammography in the US has produced an increase in the detection of early-stage disease, particularly in situ (stage 0) and early-stage (stage 1) cancers. Despite the considerable increase in the detection of ductal carcinoma in situ (DCIS), there has not been a proportional concomitant decline in the incidence of early-stage invasive cancers, which is what one would expect if DCIS were an obligate precursor to invasive breast cancer. Similarly, the overall incidence rates of stage 2 and 3 cancers have shown only a small decline over the last 20 years, despite the overall significant increase in the detection of in situ and early-stage cancer. This finding suggests a bias toward the detection of indolent rather than aggressive cancers (1, 2). This trend is particularly worrisome because the goal of screening is to prevent lethal, progressive disease by detecting cancer at an earlier, more treatable stage, or by detecting precursor lesions that can be removed before they develop into lethal invasive cancers. Yet epidemiologic data suggest that screening has substantially contributed to an increase in the detection of early-stage disease that may have little chance of progressing or becoming lethal over the course of a person’s lifetime.

The original notion behind screening, based on the excellent survival rate for stage 1 cancers, was that targeting removal at an early stage would prevent death. What we have learned is that cancer is not homogeneous and that the early-stage cancers may represent just a different pathway or tumor type than the more aggressive tumors. The facts have led us to a new hypothesis. Some cancers progress slowly or not at all. These kinds of tumors are largely hormone driven, and the outcomes for these tumors are excellent regardless of when they are detected, especially given the setting of modern adjuvant endocrine therapy. Women who develop these kinds of tumors will not benefit from screening and will likely be subjected to overtreatment. Others will develop tumors that will grow at a moderate pace; these tumors are likely to be those for which early detection is likely to be most helpful. Still other women will develop cancers that arise quickly and either present as a large mass between screens or still pose a lethal threat even when small. Screening will not hold the key to the cure for women with these kinds of tumors. The key to improving survival for these women is to focus on how to develop and effectively tailor treatments at the time of diagnosis, or to understand ahead of time who is at risk for what type of disease (3). This new understanding of how tumors behave should lead us to a new framework that allows us to focus on developing subtype-specific screening, prevention, and treatment strategies.

The concern about the possible overdiagnosis and overtreatment that may be caused by mammography screening is not universal. Some feel that the benefits of mammography outweigh these possible risks for all women. For example, the American Cancer Society (4) and the American College of Obstetricians and Gynecologists (5) recommend yearly exams starting at age 40 years, with no specified age at which to stop screening. However, as we come to better understand the biology of breast cancer and are better able to predict who will be at risk for which kind of cancer, we will begin to see a shift in policy that better reflects biology and affords us ample opportunity to improve on our current practice.

What Can Improve the Value of Early Detection?

1. THE ABILITY TO DISTINGUISH CONSEQUENTIAL TUMORS FROM INCONSEQUENTIAL TUMORS, ONCE DETECTED

Clearly, diagnostic screening tools are needed for distinguishing between the cancers that, once resected, pose a lethal threat to women and cancers that do not, in order to reduce overtreatment and associated morbidity for low-risk disease. Several tissue-based tools are now available to estimate the overall prognosis of breast cancer at diagnosis (6) and/or to predict out-

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come with adjuvant hormonal treatment alone (7) as a means to evaluate the potential chemotherapy benefit. As these tools become routinely integrated into practice, we need to provide feedback to the screening community so that we can learn whether there are imaging characteristics that can identify these patients prior to biopsy.

2. THE ABILITY TO AVOID BIOPSY AND INTERVENTION IN THE SETTING OF LOW-RISK LESIONS (FALSE POSITIVES ARE MINIMIZED)

It is critical to avoid “harm” in the effort to find consequential disease. For example, there is significant international variation in recall rates and biopsies of mammographic abnormalities (8). Most lesions that turn out to be benign are pursued because of the risk of non–high-grade DCIS. Such lesions should not be targets of screening. Working together to focus screening efforts on what will make a material difference is critical to the overall success of an early-detection program. The goal of screening should not be to work up and define every abnormality but to focus on evaluating the lesions with a high likelihood of being consequential cancers.

Mammography is controversial for women in their 40s. That is due in part to the lower sensitivity and specificity in women from 40 to 49 years of age (9, 10), which contributes to the higher recall rates and false-positive rates in younger women. Screening in women between 40 and 49 years of age has been shown to be substantially less cost-effective than screening in women from 50 to 75 years of age. Such screening leads to a higher cost per quality-adjusted life-year in younger women. These numbers highlight the importance that the recall rates and rates of false positives be low for an effective early-detection program. The net gain from screening can easily be outweighed by the additional burden of false positives, especially if indolent lesions are the largest fraction of what is being detected (11).

3. IMPROVE THE DETECTION AND DIAGNOSIS OF AGGRESSIVE CANCERS THROUGH RISK-BASED SCREENING STRATEGIES

One can envision screening strategies that are less biased towards indolent cancers than our current screening mammography practice. The biology of cancers presenting at stage 2 or 3 is different from that of screen-detected cancers (12). Interval cancers, for example, which present between regular screening intervals, have higher growth fractions and worse outcomes (13). Such results suggest that they arise quickly and have a more invasive phenotype.

One approach to improving early detection is to target screening to women who are most likely to benefit (and those who are least likely to be overdiagnosed). Screening based on an individual’s risk is a feasible approach and should be explored. We should harness existing and emerging models about family history, environmental exposures, genetic variation, and breast density to identify who is at risk for what kind of tumor. These models can then be tested prospectively to determine not just whether to screen but also how often to screen and how to tailor prevention interventions.

4. BE COGNIZANT OF THE COST-EFFECTIVENESS OF SCREENING AND PAY ATTENTION TO STRATEGIES THAT LOWER COST AND IMPROVE EFFICACY OF BOTH SCREENING AND PREVENTION

The current cost of screening women in the US is in the range of $8 billion to $10 billion. Given the very modest benefits, we need to be more thoughtful about how resources are deployed for early detection. A large driver of cost is our policy of annual rather than biennial screening (Thorsen CEM, Eklund M, Ozanne E, Esserman LJ). The number of screening breast biopsies performed in the United States in 2010; 98th American College of Surgeons Clinical Congress; Chicago, IL; 2012 Sep 30–Oct 4). On the basis of modeling, we hypothesize that an initial screen (e.g., a combination of data from questionnaires, single-nucleotide polymorphisms, and breast density) will be much more cost-effective, because it could enable decisions about whether screening ever should be done in very low–risk patients and about the optimal frequency of screening based on the tumor type for which a woman is at risk. Simply screening every person every year regardless of risk poses a serious burden on society, with only limited benefit.

One particularly challenging problem is the fact that some of the most aggressive tumors arise in younger women, who are not the current target of screening. The best strategy would be to identify women 30 to 50 years of age who are at substantial risk and screen only those women. We already use this strategy for a very small segment of the population, those with inherited mutations in the BRCA1 (breast cancer 1, early onset) and BRCA2 (breast cancer 2, early onset) genes. If we were to find a much more common marker for susceptibility, it would be important for the marker-based test to be inexpensive so it can be paired with a marker for short-term risk. Within this framework, the sensitivity and specificity of the combination of markers would need to be high, but each individual marker could perform with high sensitivity and lower specificity.

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2 Human genes: BRCA1, breast cancer 1, early onset; BRCA2, breast cancer 2, early onset.
specificity. The end point is to be able to combine the power of markers and imaging.

5. USE DETECTION TO DRIVE PREVENTION
The optimal intervention is to use the information from susceptibility and short-term risk screening tools to identify targeted interventions for preventing breast cancer (14). Screening is early detection, not prevention; however, biomarkers that are associated with the development of specific types of cancer have the potential to completely change our approach through the use of an initial “screen” to drive prevention (15). If successful, this strategy would make early detection more likely to be successful. Another, related strategy is to try to develop treatment strategies that are more effective and less invasive, even for aggressive cancers, if they are detected at a very early time. Such strategies should be designed to address our better understanding of the complex factors that control whether a tumor progresses and becomes lethal (see Figure 1).

Conclusion
Early-detection strategies must evolve to fit the heterogeneous nature of breast cancer and the heterogeneity among the women at risk. Indeed, we are learning to tailor treatment to biology, and we need to do the same for screening and prevention. This goal will require us to improve the science of risk assessment and develop clinical strategies for risk-based screening and prevention.

What will it take to implement this change in clinical practice? It will take education of primary-care physicians, allied health professionals, and the population at large. The first-line health professionals will need to understand the issues surrounding breast cancer screening and opportunities for improving it by tailoring its application on the basis of risk. Likely to be necessary for leading the way would be one or more large demonstration projects in which the primary-care physicians and specialists approach screening in an integrated manner. Ultimately, the primary-care and allied professionals will be responsible for translating the screening criteria and guidelines to women on the basis of individual risk factors.

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