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Review Article

Implications of Overdiagnosis: Impact on Screening Mammography Practices

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Abstract

This review article explores the issue of overdiagnosis in screening mammography. Overdiagnosis is the screen detection of a breast cancer, histologically confirmed, that might not otherwise become clinically apparent during the lifetime of the patient. While screening mammography is an imperfect tool, it remains the best tool we have to diagnose breast cancer early, before a patient is symptomatic and at a time when chances of survival and options for treatment are most favorable. In 2015, an estimated 231,840 new cases of breast cancer (excluding ductal carcinoma in situ) will be diagnosed in the United States, and some 40,290 women will die. Despite these data, screening mammography for women ages 40–69 has contributed to a substantial reduction in breast cancer mortality, and organized screening programs have led to a shift from late-stage diagnosis to early-stage detection. Current estimates of overdiagnosis in screening mammography vary widely, from 0% to upwards of 30% of diagnosed cancers. This range reflects the fact that measuring overdiagnosis is not a straightforward calculation, but usually one based on different sets of assumptions and often biased by methodological flaws. The recent development of tomosynthesis, which creates high-resolution, three-dimensional images, has increased breast cancer detection while reducing false recalls. Because the greatest harm of overdiagnosis is overtreatment, the key goal should not be less diagnosis but better treatment decision tools. (*Population Health Management* 2015;18:S3–S11)

Introduction

Screening mammography is an imperfect tool. Yet it is the best tool we now have to diagnose breast cancer early, before a patient is symptomatic and at a time when chances of survival and options for treatment are most favorable.

But can we make screening mammography better? In particular, can we resolve the complex issue of overdiagnosis? If so, then medical professionals, provider organizations, government advisory panels, and patients alike could take action based on a shared understanding of screening mammography's overwhelming benefits and sometimes unavoidable harms.

In 2015, an estimated 231,840 new cases of breast cancer (excluding ductal carcinoma in situ, or DCIS) among women will be diagnosed in the United States, and some 40,290 women will die.[1] Breast cancer is the second leading cause of death in women, exceeded only by lung cancer. Yet these grim statistics don't tell the whole story. Beginning around 1989, breast cancer mortality rates in the United States began markedly declining by about 2% per year[2] — the first time in 50 years that the death rate fell, with larger declines in women younger than 50. Today, 35% fewer women die each year from breast cancer than would have died had the 1989 death rate remained unchanged. These declines are attributable to early detection through screening and improved treatment.[3]

Despite this encouraging picture, some medical professionals and numerous media outlets have spotlighted the issue of overdiagnosis in screening mammography, at times with charged rhetoric. ''[W]hen directed toward the general U.S. population, the most prominent effect of screening mammography is overdiagnosis,'' concluded one study.[4] Declared another: ''The best method we have to reduce the risk of breast cancer is to stop the screening program.''[5] The issue of overdiagnosis is not confined to screening mammography, of course. It is also a central concern in screening for prostate and lung cancers, hypertension, diabetes, and genomic testing. In some cases, advances in screening and

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the quest for ever-increasing quantities of information have led to net harm — not in the form of overdiagnosis but of overtreatment.

Even so, the overdiagnosis debate seems to have eclipsed screening mammography's genuine achievements. The paradox of screening mammography, note Hendrick and Helvie, is that it is one of the most thoroughly evaluated medical interventions — and one of the few that demonstrates statistically significant mortality benefits, even when broken down into subgroups never intended in original randomized controlled trials.[6] In this article, we summarize current research around this complicated issue and offer a path forward that could resolve many of the unanswered questions and unchallenged assumptions swirling in today's conversation.

Benefits of Mammography Screening

Solid evidence from both randomized controlled trials (RCTs) and observational studies demonstrates that screening mammography for women ages 40–69 contributes to a substantial reduction in mortality from breast cancer.[7] A meta-analysis of eight randomized trials showed a 14–32% mortality reduction among women invited to be screened compared with women who were not invited.[8] A meta-analysis of women participating in organized clinical screening programs showed a 49% mortality reduction.[8] The Cancer Intervention Surveillance Modeling Network (CISNET) models of annual screening starting at age 40 demonstrated a 40% average reduction in breast cancer mortality.[8] And among seven European service screening studies analyzed with incidence-based mortality methods, breast cancer mortality was 38% lower for screened versus nonscreened women.[9]

Organized screening programs have also led to a shift from late-stage to early-stage disease detection — the fundamental goal of screening. In a 2014 analysis based on data from the U.S. Surveillance, Epidemiology, and End Results [SEER] program, Helvie et al. found that, assuming an annual percentage change of 1.3% in incidence, a 37% reduction in later-stage disease was observed in the screening mammography period (2007–2009) compared to the pre-mammography era (1977–1979), with a reciprocal increase in early-stage disease.[8]

Early diagnosis translates into better outcomes. According to SEER data, the 5-year relative survival for women diagnosed with localized disease is 98.6%; for regional disease, 84.9%; and for distant disease, 25.9%.[10] Timely detection of cancer by mammography also leads to a broader range of treatment options, including breast-conserving surgery (lumpectomy vs. mastectomy), the use of less intensive chemotherapy with fewer serious side effects, and in some cases, the option to forego chemotherapy.[11]

The Overdiagnosis Question

In the realm of screening mammography, overdiagnosis is the screen detection of a breast cancer, histologically confirmed, that might not otherwise become clinically apparent during the lifetime of the patient.[12] Some overdiagnosis results from mammographic detection of cancers that would remain asymptomatic throughout a woman's life. Other cases of overdiagnosis occur because, although a tumor is detected early, the woman dies of other causes before symptoms would have developed.[12] Many observers portray overdiagnosis as the most salient potential harm of mammography screening, because a patient may undergo treatment, with its associated morbidity, without enjoying the benefit of life years gained.[13,14]

In the published literature, estimated rates of overdiagnosis in screening mammography vary widely, from 0% to upwards of 30% of diagnosed cases. This almost incomprehensible range partly reflects the fact that estimating the rate of overdiagnosis is not a straightforward calculation, but rather one based on different sets of assumptions and often biased by methodological flaws.

Ductal carcinoma in situ (DCIS) — a noninvasive form of breast cancer that comprises a spectrum of abnormal changes that start in the cells lining the breast ducts[11] — is more likely to be associated with overdiagnosis than invasive cancer. In the premammography era, DCIS was extremely rare, representing fewer than 5% of the annual incidence of breast cancer. Today in the United States, it accounts for 30% of all breast cancers detected at screening and 20% of all newly diagnosed breast cancers (both screen detected and nonscreen detected).[9]

The central question around overdiagnosis of DCIS is: How frequently would screen-detected DCIS become invasive in the absence of screening and over what period of time?[9] DCIS that would have progressed represents invasive cancer prevented — a major benefit of screening. DCIS that would not have progressed represents overdiagnosis and unnecessary treatment — a genuine harm.[15]

Most invasive ductal breast cancers are believed to represent the final step in a sequence from normal tissue, hyperplasia, atypical ductal hyperplasia, DCIS, and invasive ductal carcinoma.[9] While overall survival for DCIS is high when treated, and while some patients may not develop invasive disease until many years after diagnosis, some natural history studies suggest an elevated risk, ranging from 14% to 53% of low-grade DCIS lesions progressing to invasive cancer over 10 years if left untreated.[16] Other estimates are higher. In the UK National Health Service Screening Programme, for example, 60% of cases of DCIS were high grade, 20% intermediate grade, and 20% low grade.[17] According to one estimate, 84% of high-grade DCIS would progress to invasive disease in 5 years, most intermediate-grade DCIS would progress to invasive disease in 10 years, and low-grade DCIS could become invasive in 15 years or longer.[9]

Overdiagnosis of invasive cancer is less likely, largely because these cancers may grow more quickly. Using a new method to estimate tumor growth rate from data on the numbers and sizes of breast cancers detected at screening, Michaelson et al. found that the median volume doubling time for invasive breast cancer is approximately 130 days, meaning that the tumors double in diameter every 390 days.[18] Lending support to the idea that invasive tumors are unlikely to be overdiagnosed is the absence of any documented cases of an invasive cancer regressing without treatment.[3] As any experienced radiologist can attest, even cancers that remain quiescent for years can suddenly spread and become life threatening.

Estimating Overdiagnosis

Overdiagnosis is an epidemiological rather than a pathological concept.[19] There is no way to determine in the pathology lab whether an individual cancer has been overdiagnosed.[9] The frequency of overdiagnosis therefore must

be estimated indirectly, drawing on data from large-scale breast cancer screening programs and population studies.[14]

In a randomized controlled trial, overdiagnosis can be estimated when a sufficiently long period has elapsed from the cessation of screening — that is, when all cancers should have become clinically apparent in both the intervention and control arms.[20] The gold standard study would be a long-term RCT comparing screened and unscreened patients with the same underlying risk factors and representing the same historical period and region, from the onset of screening until death[13] — a study that today would be logistically challenging and ethically dubious.

Because estimates of overdiagnosis range widely, a debate about its magnitude and meaning has arisen in the field and in the media. Recent peer-reviewed medical literature on screening mammography-induced overdiagnosis of breast cancer has jumped nearly 10-fold over the past decade.[21] Yet it's not clear that patients themselves are engaged with the debate. In a qualitative focus group study, Waller et al. found that the concept of overdiagnosis was unfamiliar and confusing to many participants, was regarded as an issue for treatment rather than for deciding whether to participate in screening, and was viewed as less personally relevant than the more troubling possibility of underdiagnosis.[22]

At the high end of overdiagnosis estimates, one of the most contested studies was published in 2012 in *NEJM* by Bleyer and Welch.[23] The authors used SEER data to examine trends from 1976 through 2008 in the incidence of what they termed early-stage (DCIS and localized disease) and late-stage (regional and distant disease) breast cancer among women ages 40 years and older. After excluding transient excess incidence associated with hormone-replacement therapy and adjusting for trends in breast cancer incidence among women younger than 40, they calculated that breast cancer had been overdiagosed in 1.3 million U.S. women over the previous 30 years. According to their estimates, in 2009 more than 70,000 women were overdiagnosed, accounting for 31% of all breast cancers diagnosed. ''Our analysis suggests that whatever the mortality benefit, breast-cancer screening involved a substantial harm of excess detection of additional early-stage cancers that was not matched by a reduction in late-stage cancers,'' the authors concluded.[23] (By contrast, Kopans calculated that the 2009 incidence could be explained entirely by the incidence increase of 1% per year expected in the absence of screening.[24])

Controversial as it was, the *NEJM* report is not the only recent study to arrive at a high estimate of overdiagnosis. In a follow-up to a randomized screening trial initiated in 1980, the Canadian National Breast Screening Study, Miller et al. compared breast cancer incidence and mortality in women ages 40–59 who did or did not undergo mammography screening, for a mean follow-up of 22 years. The authors concluded that, overall, 22% of screen-detected invasive breast cancers were overdiagnosed.[20]

Using SEER data in an ecological study of 16 million women ages 40 years or older, Harding et al. measured breast cancer incidence for the year 2000 and incidence-based breast cancer mortality during the 10-year follow-up. They found that an absolute increase of 10 percentage points in screening was accompanied by 16% more breast cancer diagnoses but no significant change in breast cancer deaths.[25]

Most researchers, however, consider these high-estimate reports to be outliers. One weakness of such trend studies is that, because breast cancer is a chronic disease, reduction in deaths may not be evident until many years after screen detection. The preponderance of scientific evidence suggests far lower rates of overdiagnosis. In a literature review of 13 observational studies reporting 16 estimates of overdiagnosis in seven European countries, including estimates of carcinoma in situ when available, Puliti et al. concluded that the most plausible estimates of overdiagnosis ranged from 1% to 10% (mean = 4.7%).[12]

Drawing on incidence data from two randomized controlled trials of mammographic screening — the Swedish Two-County Trial and the Gothenburg Trial — Duffy et al. ascertained whether the excess incidence of DCIS reported early in each screening trial was balanced by a later deficit in invasive disease. After accounting for the effect of lead time, the authors estimated that less than 5% of cases diagnosed at the prevalence screen, and less than 1% of cases diagnosed at incidence screens, were overdiagnosed. They estimated overall overdiagnosis to be around 1% of all cases diagnosed in the screened populations.[15]

In a separate study, Duffy et al., analyzing the Swedish Two-County Trial and the Breast Screening Programme in England, estimated that in a cohort screened every 3 years for the 20 years from age 50, between 9% and 13% of cases diagnosed had their lives saved, and between 4% and 7% of cases were overdiagnosed. ''Thus,'' the authors wrote, ''the benefits in terms of deaths prevented are around double the harms in terms of overdiagnosis.''[26]

Methodological Flaws

Calculating overdiagnosis can be highly inaccurate if based on misassumptions or flawed methodology. Several well-known statistical biases account for inflated estimates.

Perhaps the biggest challenge is teasing apart excess of incidence due to ''lead time'' from any excess due to overdiagnosis.[12] ''Lead time'' is the period of time by which the diagnosis is brought forward by screening. It shifts both the age of incidence and the calendar year in which a cancer is detected.[7] Detecting cancers earlier means more cancers will be detected, because the underlying incidence of breast cancer rises with age.[27] Yet statistically adjusting for the effect of lead time is one of the most vexing issues in overdiagnosis, because in the modern mammography era, there are few studies with a large enough control population or follow-up period to nullify the effect of lead time; often, researchers make statistical adjustments that shift the time of diagnosis among screen-detected cancers to a later age.[14] One notable exception is the 30-year follow-up in the Swedish Two-County Trial. Here, Yen et al. found that screening did not lead to cumulative increased incidence in the study group compared to the control group that was not offered screening, but rather a temporary increase in incidence because of earlier detection of already existing disease. The authors also found no evidence of overdiagnosis for invasive breast cancer or DCIS.[28]

Another error in estimating overdiagnosis is assuming that the incidence of breast cancer was stable prior to the onset of screening. As noted earlier, in the United States, the incidence of invasive breast cancer had been rising steadily

at just over 1% per year over the decades prior to the start of mammography screening, likely due to changes in diet, lifestyle, and environmental factors.[3,9,27] These temporal trends directly influence calculations of late-stage disease and, therefore, estimates of overdiagnosis. Over 30 years, for instance, a 1% annual increase in incidence compounds over time into an incidence increase of 33%.[8]

''Length bias'' is the concept that screening is more apt to detect slower-growing cancers but miss the faster-growing killer tumors that appear between screens as interval cancers.[9] Slow-growing cancers have better prognoses and are more likely to be detected by screening than clinically without screening. In this sense, overdiagnosis is an extreme form of length bias, because it finds cancers that are so indolent that they never manifest clinically in a woman's lifetime.[21]

Other methodological problems include the use of registry reviews, which compile summary numbers from tumor registries; in these studies, analysts don't know which patients had mammograms nor which cancers were detected by mammography.[3] Also inflating estimates is the categorization of DCIS as early cancer.[14]

Failing to factor in and correct for these biases can yield grossly inaccurate estimations of overdiagnosis. According to Feig, calculations that rigorously account for statistical biases arrive at extremely low rates of overdiagnosis: between 0% and 5% of screen-detected cancers.[9]

Overdiagnosis and Age

Today, the target age range for mammography screening is the subject of conflicting recommendations. In 2009, the United States Preventive Services Task Force (USPSTF) formally recommended biennial screening for women 50–74, noting that for women 40–49, there is moderate certainty that the net benefit of biennial screening is small and that women should consider personal risk before deciding to participate in screening.[29] By contrast, the American Cancer Society (ACS) recommends that women 40 and older have a mammogram every year and should continue to do so for as long as they are in good health.[30] Indeed, studies in Canada and Sweden have shown a 30% mortality reduction from screening women ages 40–49, and 50 years and older.[31] The American College of Radiology likewise recommends annual screening starting at 40 and continuing after age 74, based on life expectancy, willingness to undergo follow-up interventions, and willingness to be treated for breast cancer if diagnosed.[32]

While it is beyond the scope of this article to discuss these conflicting recommendations, age is germane to the issue of overdiagnosis, particularly if concerns about overdiagnosis lead to national guidelines for screening to start at age 50—potentially increasing mortality.

For women under 50, the benefits of mammography screening outweigh the harms of overdiagnosis. Drawing on data from the UK Age trial, a randomized screening trial established in 1991 to determine the effectiveness of annual mammographic screening starting at age 40, Moss et al. found a significant reduction in the risk of breast cancer mortality in the intervention group compared with the control group in the first 10 years. The authors also found no evidence for increased overdiagnosis in that age group.[33]

For older women, the decision to screen is more complicated. ACS guidelines recommend annual screening only if older women have life expectancy of at least 5 years and only if they are in generally good health, with no significant comorbid conditions; thus, there are no data to indicate whether, or at what frequency, screening in older women is or is not supported by ACS guidelines. Because breast cancer incidence rises with age and sensitivity is higher in older women, benefits of screening may be greater for older than for younger women. Screening older women may also spare them the actual risk of more extensive surgery and more chemotherapy.

On the other hand, years of life expectancy saved per cancer detected may be limited and overdiagnosis may be more frequent in older women because of the higher death rate from competing conditions or because older women may not live long enough to suffer the symptoms of breast cancer.[34] Despite this ambiguity, many women 75 and older are being screened in the United States, with one study finding that 62% of women ages 75–79 and 50% of women over 80 received a mammogram in the previous 2 years.[34]

Using three well-established microsimulation models, van Ravesteyn et al. quantified the benefits and harms of mammography screening after age 74, focusing on overdiagnosis of invasive breast cancer and DCIS. The authors found that screening women from ages 50–74 results in 5–32% of screen-detected invasive breast cancers being overdiagnosed (the range reflecting variations among the three models), rising to 14–36% for screening at age 80, and 28–41% for screening at age 90. ''The balance between screening benefits and harms becomes less favorable after age 74 years,'' they concluded. ''At 90 years, harms outweigh benefits, largely as a consequence of overdiagnosis.''[34]

Feinstein et al. addressed the question from a different angle. Today, more than 40% of breast cancers occur in women eligible for Medicare. Survival has improved for women in the Medicare program with stage II breast cancer, and even more so for women with stage III disease. Using the SEER Medicare-linked database, the authors compared changes in costs and survival rates over time among women ages 69–74 diagnosed with stage II or III breast cancer in 1994–1996 or 2004–2006. While median cancer-related costs increased in both groups, adjusted overall 5-year survival improved, from 67.8% to 72.5% for women with stage II disease and from 38.5% to 51.9% for those with stage III disease.[35]

The Harms of Overdiagnosis

Overtreatment — which occurs when such an overdiagnosed tumor is treated, often with surgery or adjuvant therapy — is the main harm of overdiagnosis.[16] This suggests that as the ability to identify lesions of the breast improves, so must the ability to distinguish between lesions that require aggressive treatment and those that don't.

In an apt metaphor, the stepwise, sometimes relentless series of medical procedures that follow an abnormal finding on screening mammography is known as the ''diagnostic cascade.'' It includes imaging with diagnostic mammography or additional views using magnification, spot compression, or new angles; targeted breast ultrasound; and sometimes magnetic resonance imaging (MRI). These results in turn help determine the need for biopsy, which will

reveal if the area of concern is benign, malignant, or something in between, such as a high-risk lesion, which will prompt surgical excision.[2] Even when a cancer diagnosis is ultimately ruled out, the harms of a false positive screening include the economic and emotional costs associated with these interventions.[26]

False-positive results are therefore a key metric in overdiagnosis. Recent evidence from the Breast Cancer Surveillance Consortium suggests that the 10-year cumulative risk of at least one false-positive is 61.3% for women starting screening at ages 40 or 50 years and 49.7% for women ages 66–74 undergoing annual screening.[13] Today, 7.0–9.8% of women undergo unnecessary biopsies after 10 years of annual screening.[13] Brodersen and Siersma found that such false-positive findings on screening mammography can cause psychosocial harm, observing that, ''[T]he degree of change in inner calmness and existential values within the first half-year after final diagnosis were just as great for women with breast cancer as for women receiving false-positive findings.''[36] On the other hand, Feig reports that many investigators have found that the anxiety from screening is relatively mild, short-lived, acceptable to women, and less significant clinically than the anxiety of late-stage breast cancer.[37]

Tomosynthesis: An Improved Screening Technology

The myriad potential harms frequently associated with screening mammography highlight the need for improved imaging technologies. One such technology is tomosynthesis, which the U.S. Food and Drug Administration first approved in 2011 as a modality to be used in combination with full-field digital mammography (FFDM). Also known as digital breast tomosynthesis, or DBT (and sometimes 3D, as distinguished from standard mammography's 2D), this technology acquires low-dose X-ray images from multiple angles during a short scan, reconstructs the images into a series of high-resolution ''slices,'' then displays them individually or in a dynamic three-dimensional ciné mode.[2] DBT reduces the challenges of interpretation due to overlapping structures in breast tissue.[2]

One of the most consistent findings in both retrospective and prospective studies is that DBT both increases breast cancer detection and decreases false recalls. This benefit is most striking in retrospective studies, where absolute false-recall reductions have been reported in the range of 1.6–3.6% and where underlying recall rates for standard digital mammography are relatively high at 8.7–16.2%. This absolute reduction in false-recall rates translates into relative reductions of roughly 15–30%.[38]

In a retrospective analysis of screening performance metrics from 13 academic and nonacademic breast centers, Friedewald et al. found that adding tomosynthesis to digital mammography was associated with an increase in positive predictive value — the likelihood of cancer diagnosis in women called back for additional imaging—from 4.3% to 6.4%, a relative increase of 49%; PPV was also higher for biopsy, from 24.2% to 29.2%. The addition of tomosynthesis was associated with a relative reduction of 15% in the recall rate and a simultaneous relative increase of 29% in the overall cancer detection rate. There was a 41% relative increase in the invasive cancer detection rate, while detection of DCIS was unchanged.[39]

In the Screening with Tomosynthesis OR standard Mammography (STORM) study, a prospective comparative study of asymptomatic women ages 48 and older, Ciatta et al. assessed the effect of integrated FFDM and DBT versus FFDM alone. The authors estimated that conditional recalls (positive integrated FFDM and DBT mammography as a condition to recall) could have reduced false-positive recalls by 17.2% without missing any of the cancers detected in the study population.[40]

And in a large prospective clinical trial, Skaane et al. observed that most additional cancers detected by tomosynthesis were invasive, with a large fraction node-negative: the very types of cancers one wishes to find during screening.[41]

Tomosynthesis also appears to yield cost savings. In a value analysis, Bonafede et al. developed an economic model to estimate system-wide financial impact of FFDM versus FFDM plus DBT within a hypothetical U.S.-managed care plan with one million members. The overall benefit of DBT was calculated at $78.53 per woman screened. Adjusting for a hypothetical $50 incremental cost of DBT examinations, this translated to a $28.53 savings per woman screened and an overall cost savings to the plan of $2.4 million per year. Driving DBT's economic value were lower recall rates and diagnoses at earlier stages.[2]

Lee et al. estimated the clinical effectiveness and cost-effectiveness of biennial screening among U.S. women ages 50–74 with dense breasts, comparing digital mammography alone with digital mammography plus tomosynthesis. The incremental cost per quality-adjusted life year gained by adding tomosynthesis to digital mammography was $53,893—making it cost-effective. The authors concluded that biennial combined digital mammography and tomosynthesis screening for U.S. women ages 50–74 with dense breasts was likely to be cost-effective if priced appropriately (up to $226 for combined exams vs. $139 for digital mammography alone).[42] Both analyses were conducted prior to November 2014, when the Centers for Medicare and Medicaid Services released new codes and reimbursement rates for screening and diagnostic breast tomosynthesis of approximately $56 per exam, or $190 dollars for a combined screening exam.

Despite these advantages, tomosynthesis will not reduce the theoretical risk of overdiagnosis. Though studies of tomosynthesis were not designed to directly evaluate the potential for overdiagnosis, DBT is likely to improve the net screening benefit, because it finds more early-stage invasive cancer while its rate of DCIS detection remains unchanged.[40] For radiologists, pathologists, and breast surgeons, tomosynthesis may present a learning curve, as practitioners sharpen their ability to interpret the architectural distortions seen in 3D images, to distinguish invasive from noninvasive lesions, and to determine the best treatment course. Moreover, published studies on tomosynthesis were not designed to assess benefits in mortality reductions or benefit using a surrogate for effectiveness, such as reduced interval cancer rates.[38] All these issues remain open questions.

Not Less Detection, but More Information

The solution to overdiagnosis is not less diagnosis, but better treatment decision tools and more information about how to discern life-threatening tumors that will need aggressive treatment from non-life-threatening cancers that

can be treated less aggressively.[14,16] Perhaps a more constructive approach is to frame the discussion not in terms of *overdiagnosis* but of *overtreatment*. As Gur and Sumkin note, ''[T]here is no such thing as overdiagnosis, there is only correct, partially correct, or incorrect diagnosis. If abnormal findings are diagnosed correctly, there is only optimally managed, suboptimally managed, mismanaged, and possibly overtreated disease.'' Overtreatment, they add, must be addressed ''by medicine and society as a whole.''[43]

Molecular assays that profile the expression of cancer-related genes may more accurately reflect the biological state of the tumor and offer more relevant information on tumor status than anatomic characteristics, such as lymph node involvement, which do not reveal useful information about the underlying heterogeneity of the tumor.[44] These molecular assays are part of today's information revolution, in which we are rapidly learning how to make sense of massive volumes of data — not only data about populations, but about individuals. How can we best acquire that new information, share it, and deploy it to improve outcomes? And how can we help patients parse this data to make informed choices that fit with their own values and goals?

International RCTs are currently underway to assess how advanced imaging and molecular markers can address these questions. One, the LORIS trial in the United Kingdom, will compare standard surgery with active monitoring and annual mammograms for at least 10 years, to establish whether women with newly diagnosed low-risk DCIS can safely avoid surgery without harm to their well-being (both physical and psychological) and whether those patients who do require surgery can be identified by pathological and radiological means.[45] The TOMMY trial, part of the UK National Health Service Breast Screening Programme, will compare the diagnostic accuracy of tomosynthesis in conjunction with 2D mammography against 2D mammography alone.[46] And in the ECOG-ACRIN E4112 clinical trial, women with newly diagnosed DCIS will have an MRI exam and, based on the results, confer with their physicians about whether to undergo a lumpectomy or a mastectomy. For women who choose to undergo lumpectomy, a separate genotyping test will estimate risk of recurrence over the next 10 years, to help patients and their physicians determine whether radiation therapy is needed. Unlike screening and treatment paradigms of the past, this trial will be guided by advanced imaging, advanced tissue diagnostics, and patient preferences.[47]

Improved imaging will also aid treatment decisions. While digital mammography remains the key tool for population-based screening, breast MRI is becoming more common in community settings. One benefit of MRI is its high sensitivity for identifying clinically occult malignant breast tumors. For high-risk patients, MRI screening detects many cancers that are missed on digital mammography, tomosynthesis, and ultrasound. Compared with mammography, however, breast MRI has a modest specificity that leads to high false-positive rates; it is also more expensive and requires the use of intravenous contrast medium.[48]

Some have suggested that the future lies in risk-based screening, because normal- and low-risk women potentially have lower true-positive recall rates and lower true-positive biopsy rates. The relative benefits of screening diminish when applied to populations without sufficient risk.[16] Yet risk stratification remains problematic, because today 80% of patients diagnosed with breast cancer have no known risk factors, except being female and being older.

A future research agenda might include RCTs that provide more accurate measurement of the frequency of overdiagnosis than is obtainable through trend studies or case-control studies.[9] Although SEER provides detailed information about cancer stage and treatment at the time of diagnosis, therapy completion and long-term outcomes other than death are not accessible. Moreover, SEER also lacks recurrence, radiation, and chemotherapy or hormonal therapy data.[49,50] Though RCTs are lauded as the ''gold standard'' in medical research, they may not be as useful in this case, partly because the results take so long and because the technology is rapidly advancing. One solution may be surrogate endpoints for benefit on which experts can agree.

In the midst of the overdiagnosis debate, we may be losing sight of the fact that underdiagnosis poses the greater harm to patients—though underdiagnosis is equally difficult to measure. Data from the Breast Cancer Surveillance Consortium (BCSC) reflecting performance measures for screening mammography examinations from 2004 to 2008 by age, based on BCSC data through 2009, show that screening mammography sensitivity has much room for improvement, ranging from 86.3% for women ages 65–69 down to 73.4% for women ages 40–44.[51] Another gauge of underdiagnosis is the detection of late-stage cancers. According to 2005–2011 data from the SEER program, 61% of breast cancer cases are localized (confined to the primary site); 32% are regional (spread to regional lymph nodes); 6% are distant (cancer has metastasized); and 2% are unstaged.[10] Because late-stage disease is associated with higher mortality and costly, aggressive treatment, we should embrace new approaches such as breast tomosynthesis, which may reduce the number of late-stage cancers through increased sensitivity and earlier detection and has been shown to substantially improve the sensitivity of screening mammography in dense breasts.[52]

Today, the landscape of screening mammography is filled with new promise and old perils. Pathological examination — the cornerstone of cancer diagnosis — has itself been enhanced by new technologies and the understanding that breast cancer is a heterogeneous disease. The identification of immunohistochemical biomarkers with prognostic and predictive value (such as the estrogen and progesterone receptors, and expression of the Her2/neu, Ki-67, p16, and COX-2 proteins) has opened new avenues for personalized treatment.[52,53] Multiparameter assays such as IHC4, OncotypeDX, and the BCI assays have demonstrated value in assessing the risk of early distant recurrence in women with ER-positive breast cancer who might be spared adjuvant endocrine therapy.[54] Most recently, metabolic profiling of plasma samples and auxiliary lifestyle information has led to the development of so-called biocontours, which may forecast higher risk of breast cancer two-to-five years after the sample is taken, opening the possibility of timely prediction of individual cancer risk and thus more efficient screening.[55] On the other hand, clinical or pathologic markers that can reliably identify the subset of patients with DCIS at greatest risk of developing invasive breast cancers — a crucial population in the overdiagnosis and overtreatment debate — have yet to be identified.[56]

As medical professionals, we must find better ways to communicate the benefits and risks of screening to patients.

We must learn to convey the nuanced message that while detecting a small cancer with mammography could save their lives, screening will also occasionally detect a cancer that may never be life-threatening.[14] And we will need to remember that individualized risk information will be conveyed to *individuals* — people with diverse worldviews and priorities.[13]

We mustn't stop — or reduce or restrict — screening mammography because of the fear that a small percentage of patients will be treated unnecessarily — even as the vast majority are being treated appropriately and lives are being saved. Ultimately, we must ask: How can we make screening mammography — an imperfect tool, but the best one we have now — better? When accompanied by older treatment paradigms that were developed alongside conventional mammography, today's advanced imaging technologies may not necessarily lead to better outcomes. But just as high-quality diagnostic mammography made possible the shift from mastectomy to breast-conserving surgery and radiation for patients with unifocal disease, today's new imaging technologies and precision diagnostics may usher in the next advance in treatment options, tailored to the individual patient's disease profile.[57]

Our goal is to further change the face of this devastating disease, so that some 40,000 women in the United States aren't dying every year of breast cancer. Advanced imaging technology such as tomosynthesis and improved supplementary modalities such as breast MRI and ultrasound will be essential in reaching this goal. These next-generation imaging technologies — abetted by progress in genomic prediction, big data interpretation, professional collaboration, patient–doctor communication, and an openness to doing things differently — will help make an imperfect screening process better.

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