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Overdiagnosis in Breast Cancer Screening: Time to Tackle an Underappreciated Harm

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The earlier that cancer is found, the better. This underlying tenet of cancer screening has saved many lives. However, studies are beginning to challenge the certainty that finding cancer early is always better. One stark example was the practice of screening infants for neuroblastoma. After the introduction of a simple urine test in Japan led to nationwide screening, the incidence of neuroblastoma approximately doubled, whereas that of mortality and late-stage disease remained unaffected. Widespread urine testing of infants was subsequently abandoned (1). The excess cases of cancer found on screening were examples of over-diagnosis, defined as occurring when "a condition is diagnosed that would otherwise not go on to cause symptoms or death" (2). Overdiagnosis need not imply that a given screening effort is ineffective or ill-advised. Indeed, overdiagnosis has been documented in effective screening programs for several types of cancer, including breast cancer.

Pathologically diagnosed breast cancer is heterogeneous; whereas some tumors grow rapidly, others grow slowly, and still others may never grow. Tumors that grow slowly or not at all can lead to overdiagnosis. Unfortunately, mammography screening programs cannot distinguish between fatal and harmless breast cancer. Breast cancer overdiagnosis can only harm the affected woman. Whereas other harms of breast cancer screening, such as pain from compression of the breasts during examination or anxiety due to false-positive results, are transitory, the impact of a cancer diagnosis lasts a lifetime.

Reported estimates of breast cancer overdiagnosis range from 0% to 54%, highlighting the complexity of this topic (3– 8). Long-term follow-up of women in randomized trials provide some estimates. For example, in the Malmö randomized, controlled trial (3), the total number of diagnosed invasive breast cancer remained higher in the screened group than in the control group after 15 years of follow-up, a persistent excess of 115 cases. A spike in breast cancer incidence would be expected early in the screening group, but the number of cases in the control group should "catch up" over time if no overdiagnosis occurred. Population-level cancer registries offer another approach, tracking the incidence of breast

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cancer before and after screening is introduced. However, changes other than the introduction of screening might influence breast cancer incidence. Estimates of overdiagnosis tend to be higher when studies use a denominator that is restricted to only screening-detected cancer (because overdiagnosis can occur only in this subset), include ductal carcinoma in situ cases as well as invasive cancer, involve shorter follow-up, or include control groups that have little or no access to screening.

Kalager and colleagues' study (9) in this issue adds valuable data by presenting a population-based trial that describes the incidence of invasive breast cancer in Norway; the authors took advantage of the fact that breast cancer screening was gradually introduced in different geographic areas of the country between 1996 and 2005. Staggered introduction enabled comparison of both concurrent and historical trends in breast cancer incidence and allowed comparison of regions with and without mammography screening. The study included 39 888 patients with invasive breast cancer, of whom almost 8000 were diagnosed after the introduction of routine screening. Overall, Kalager and colleagues estimated that 15% to 25% of the cases diagnosed in the screening areas represented overdiagnosis (9). Their estimates varied depending on the length of follow-up and were calculated from a denominator that included all cases of cancer, not just those detected by screening.

Strengths of the study include the high attendance rate (77%) of women in the screening program and the reported low rate of mammography in areas where the screening program had not yet been introduced. However, because the study was not a randomized trial, women in the various regions may have differed in ways other than breast cancer screening; the authors point out that different regions of Norway varied in breast cancer incidence rates and temporal trends. The study is also limited in that the follow-up after introduction of screening in some areas may not have been long enough to allow stable estimates of the degree of overdiagnosis.

Two factors suggest that estimates of overdiagnosis from Norway may not generalize to the United States. First, U.S. radiologists are more likely than their European counterparts to report abnormalities found on mammograms (10, 11). Second, U.S. women often start annual mammography screening at age 40 years, whereas Norwegian women start biennial screening at age 50 years. Given more frequent screening over a longer time, overdiagnosis probably occurs more often in the United States than in Norway.

Instead of focusing on the exact extent of overdiagnosis, it is time to agree that any amount of overdiagnosis is serious and to start dealing with this issue now. Ultimately, better tools are needed to reliably identify which breast cancer will be fatal without treatment and which can be safely observed over time without intervention, but we cannot wait for these tools to be developed. Mammographers, especially those in the United States, could help by considering changes in the threshold for calling a mammographic feature abnormal. Evaluating strategies for observing change in some lesions over time instead of recommending an immediate biopsy has been suggested (10, 12, 13). This may be a tough sell for women with anxiety as a result of the "watch-and-wait" approach, as well as for radiologists who do not want to miss any sign of disease and fear malpractice lawsuits. Nevertheless, unless serious efforts are made to reduce the frequency of overdiagnosis, the

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problem will probably increase as newer imaging modalities, such as breast magnetic resonance imaging, are introduced.

Finally, we have an ethical responsibility to alert women to this phenomenon. Most patient-education aids do not even mention overdiagnosis (14), and most women are not aware of its possibility (15). Effective communication about overdiagnosis of breast cancer will require great care—and evaluation to determine how best to do it; otherwise, women may become fearful or angry. Just because communicating with patients will be difficult does not mean that we should not tackle this problem. Informed women deserve no less when deciding about breast cancer screening.

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