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Editorial

EDITORIAL

Overdiagnosis in the Age of Digital Cancer Screening

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In 2000, the US FDA approved digital mammography technology. Studies suggested the new technology was equivalent to older film technology in detecting cancer. There was also limited evidence that digital imaging might be more specific, meaning that it would reduce the number of callbacks for positive findings. Many also believed that the newer "improved" digital technology might find more disease and lead to fewer interval cancers (cancers diagnosed between scheduled screenings).

Today, digital mammography is dominant. In a meta-analysis of 24 published studies comparing outcomes with digital and film mammography, Farber and colleagues pose the question, "Does this new technology lead to improved health outcomes?" They find the shift to digital mammography translates into higher cancer detection rates and higher recall rates but not a reduction in interval cancers (1).

It is human nature to think that new technology is better, and many experts thought digital mammography would lead to improved health outcomes. Sometimes the truth is different from what the experts think. These findings demonstrate the importance of postmarketing assessment and keeping an open mind. They also show the varying biology of breast cancer.

The concept of cancer screening involves finding a tumor early so that it can be removed before it can grow, metastasize, and kill. If screening is effective, a cohort undergoing regular screening should result in an increase in the diagnosis of localized tumors, a decrease in tumors diagnosed between scheduled screenings, and a decline in the incidence of cancers diagnosed at late stage. Each of these 3 steps is an increasingly stronger surrogate endpoint for the real purpose of screening: preventing death.

How can there be a higher cancer detection rate without a decline in interval cancers? This can happen when the new screening technology finds tumors of no threat to the patient that are not discovered by the old technology. The screening term for this is "overdiagnosis."

Overdiagnosis is something that looks like cancer but does not behave like cancer. Overdiagnosis is accepted in prostate cancer, thyroid cancer, and renal cancer. There has been substantial debate about the existence of overdiagnosis in breast cancer. Some say that overdiagnosis does not exist. Others estimate it to be one-half of all screen-detected breast cancers (2). This meta-analysis does not allow for a precise estimation of its prevalence but suggests that as much as 11% of cancers found through digital mammography are overdiagnosis. It is likely that film mammography finds some overdiagnosis. Film mammography was introduced in the 1970s. The US breast cancer age-adjusted incidence rate increased more than 30% from 1975 to 2000, whereas the incidence of advanced breast cancer at diagnosis was stable for all 25 years (3).

It is easier to understand and accept overdiagnosis if one looks at the history of pathology. The histologic definition of cancer came out of the fledgling profession of pathology in the mid-19th century. The pathologist Rudolf Virchow made important contributions to the development of the biopsy and the histologic description of adenocarcinoma. His original biopsies were taken at the autopsy of cancer patients. With the advances in medical imaging and stereotactic biopsy technology, radiologists can now routinely find and biopsy 3- to 5-mm localized breast lesions. Pathologists then note whether these biopsies have the characteristics of cancer as defined in the mid-1800s. Some of these small lesions are not destined to grow, spread, and kill. Some may even regress.

We already accept that there are varying biologic behaviors of breast cancers. Genomic tests are used to predict faster growing cancers requiring aggressive therapy vs slower growing tumors needing less aggressive therapy (4). Length bias is the screening concept that slower growing tumors are less aggressive and easier to find in regular screening. Faster-growing tumors are harder to find and more aggressive. Overdiagnosis is an extreme form of length bias.

Length bias and overdiagnosis are among the reasons why prospective randomized trials are necessary to prove that cancer screening reduces risk of death. Improvement in a survival statistic is a poor surrogate of progress because it can be dramatically affected by the inclusion of just a few persons with a cancer that will not kill.

Farber and colleagues show that improved imaging is linked to increased overdiagnosis. Mammographic imaging defines

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tissue structure. Digital mammography is an attempt to better image the breast structure compared with film mammography. Tomosynthesis or 3-dimensional mammography is an attempt to even better image the breast structure. This study justifies concerns that overdiagnosis could be an even greater problem with tomography. It justifies the National Cancer Institute's Tomosynthesis Mammographic Imaging Screening Trial, which compares the efficacy of 2-dimensional and 3-dimensional mammography.

Farber and colleagues demonstrate the diversity in the biologic behavior of breast cancers and help define the limitations of structural imaging. The findings in no way suggest that digital mammography is not worthwhile. Indeed, it is justified by easier storage and handling of images. There is also a potential for computer-assisted diagnostics. It is noted that digital mammography has lower per-test radiation exposure than film mammography. The higher recall rate and associated added tests do open the question whether this claim is valid for all women.

The true measure of the value of effective screening at a population level is a reduction in cancer death rates and in receipt of unnecessary treatment. The emphasis in screening should not be on finding more cancer but finding more cancer that matters, meaning finding the cancers that need treatment because they are clinically significant. Further breast cancer screening research might focus on modalities such as molecular breast imaging, which is a nuclear medicine test that provides structural and functional information or assay of blood for circulating DNA fragments consistent with aggressive breast cancer.

Going forward, we will find better ways to distinguish the diagnosed cancers that need to be treated from the cancers that need to be watched. Genomic profiling will likely determine the breast cancers (both invasive and noninvasive) that will be observed as initial therapy.

Note

Conflicts of interest: The authors have no conflicts of interest to disclose.

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