Point: The *New England Journal of Medicine* Article Suggesting Overdiagnosis From Mammography Screening Is Scientifically Incorrect and Should Be Withdrawn

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The publication of the recent *New England Journal of Medicine* (*NEJM*) article [1] on the effectiveness of mammographic screening raises two major issues that I will try to address. The first is the lack of scientific rigor in the paper itself. The second is why a highly respected journal would publish such a flawed analysis.

It should be clearly stated that mammography does not cause "overdiagnosis" or "overtreatment." Pathologists cannot distinguish cancers that will be lethal from those that do not require treatment, and oncologists cannot determine who will be cured without systemic treatment and who will be "overtreated." Palpable cancers are routinely "overtreated." Thirty percent of women treated by mastectomy alone in the 1940s were alive 30 years later. Because there is still no way of identifying women with similar cancers today, all now receive systemic therapy. None of these women benefit from this therapy, and so are all "overtreated."

Unfortunately, approximately 40,000 women still die each year from breast cancer. Almost all receive systemic therapy that does not save them. Would opponents of screening argue to stop all treatment, sacrificing those who actually benefit? Women should not be denied access to screening and its potential to save lives simply because all of medicine (not just breast cancer treatment) is inexact.

There is nearly universal agreement (including the US Preventive Services Task Force and the American College of Physicians) that the most rigorous studies of breast cancer screening prove that its use reduces the death rate from breast cancer for women beginning at the age of 40 years. The *NEJM* paper [1] is just one in a series of methodologically flawed attempts to reduce access to mammography screening. If, as one of the authors has written, thousands of breast cancers would have regressed and disappeared had they not been found by screening [2], why is there not one credible report in the literature of an invasive breast cancer disappearing on its own without therapy?

It is not oncologists, but rather analysts, who have no experience in caring for women with breast cancer, who argue that screening can be stopped because the new therapies are all that is needed. I am not aware of a single responsible oncology group that has called for a cessation of screening. Oncologists know that therapy saves lives when cancers are found earlier.

The Paper's Lack of Scientific Rigor

The authors of the *NEJM* paper [1] argue that mammographic screening is leading to massive overdiagnosis. The paper is fundamentally flawed. Reliable science is based on direct measures of individual patients and their outcomes. This paper has no individual patient data. The entire argument is based on assumptions and estimates. It is specious to blame mammography when these authors have absolutely no idea which women actually underwent mammography and which cancers were actually detected by mammography.

In addition, they provide no cogent reason for grouping women with ductal carcinoma in situ (DCIS) and women with small invasive cancers and analyzing them together. It is well known that the diagnosis and treatment of DCIS is highly controversial. Efforts have been under way for decades to try to find a reasonable approach to these lesions. This is nothing new and not worthy of publication. The detection of small invasive cancers, however, is fundamental to saving lives. The combination of DCIS with these lesions only dilutes the results for small invasive cancers.

The authors compared national registry estimates of incidence with the incidence they "guesstimated" would have occurred had there not been any screening. Their contention is based on their estimated rate had there been no screening during the period from 1976 to 1978. This 3-year period is insufficient to establish a real trend, and the data are influenced by the screening triggered by Happy Rockefeller's and Betty Ford's cancers. The authors, incorrectly, decided that the incidence of breast cancer would have increased by only 0.25% each year had there been no screening, completely ignoring more than 40 years

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of data showing that from 1940 to 1980, the incidence of invasive breast cancer actually increased by 1% per year—4 times their estimate [3]. The authors estimated that many more cancers were diagnosed in 2008 than would have occurred in the absence of screening and that the excess must represent overdiagnosis. In fact, by greatly underestimating the background increase in invasive cancers, they drastically overestimated the amount of overdiagnosis. The actual long-term data, before any screening, show that in 1940, 60 per 100,000 women were diagnosed with invasive breast cancer. This had increased to approximately 100 per 100,000 by 1980. Had this rate continued (and there is no reason to expect that it would not), the expected incidence of invasive cancers, in the absence of screening, would have been approximately 132 per 100,000 by 2008. In fact, the rate of invasive cancers in 2008, according to the Surveillance, Epidemiology and End Results program, was 128 per 100,000. The more accurate numbers show that the authors are simply incorrect. Not only was there no overdiagnosis, but because the observed rate was actually lower than the expected rate, it is possible that the removal of DCIS over the preceding years resulted in fewer subsequent invasive cancers.

The authors' insistence that screening is ineffective unless the rate of advanced cancers is lowered is also incorrect. Although screening has been shown to lower the rate of advanced cancers, this is not required. Women die from breast cancers diagnosed at all stages. Finding cancers at smaller sizes within stages saves lives [4]. Regardless, the authors also underestimate the decline in advanced cancers. If we accept their highly questionable use of the rate of advanced cancers among women aged <40 years, then the rate increased by 20% (from 5 per 100,000 to 6 per 100,000) over the time period. The rate for older women would have increased from 100 per 100,000 in 1975 to at least 120 per 100,000 by 2008. Instead, it dropped to 94 per 100,000, a decline of 26 per 100,000, not the 8 per 100,000 suggested by the authors.

Using scientifically unsupportable methodology and incorrect assumptions and estimates, Bleyer and Welch [1] are simply incorrect. The issues surrounding DCIS are nothing new. Using their approach, with better estimates, there is no overdiagnosis of invasive breast cancer, and the paper should be withdrawn.

The *NEJM*'s Publication Bias Against Mammography

The *NEJM* is one of the world's most highly respected medical journals. However, a review of papers published in the *NEJM* suggests a major publication bias against mammography. From 1992 to 2012, the *NEJM* published 14 papers dealing with mammography. Not one of these supported screening for women aged 40 to 49 years, and the *NEJM* has never published a paper articulating strong support for screening. Without knowledge of all of the papers submitted and rejected, it is not possible to prove this bias, but I personally submitted 3 papers to the *NEJM* that were turned down and, ultimately, published elsewhere. All 3 show that using the age of 50 years as a threshold is not supported by biology or science [5-7]. Had they been published in the *NEJM*, the continued use of the age of 50 years, as if it represents a legitimate threshold, may well have stopped. In 2010, the *NEJM* refused to publish my paper [7] raising scientific concerns about the US Preventive Services Task Force's 2009 guidelines and, instead, published a paper arguing that radiologists' concerns were due to greed [8]. The journal has published other methodologically flawed material. The authors of a 2010 article claimed that screening women in Norway had very little effect on mortality [9]. The paper was completely specious, reporting only 2.2 years of follow-up, given that the benefit from screening is not expected to begin to appear until 5 to 7 years after it is initiated. In November 2012, the *NEJM* published an attack on the American Cancer Society, criticizing a 1970s advertisement and suggesting that advocacy groups mislead women [10], ignoring the fact that one of the authors is the editor of the *Journal of the National Cancer Institute*. Is it not, ultimately, misleading to call your journal the *Journal of the National Cancer Institute* when it has "no affiliation with the National Cancer Institute"?

I believe that there is an undisclosed bias at the *NEJM* against publishing positive articles about mammographic screening, particularly for women aged 40 to 49 years, and this recent paper is a reflection of that bias. In my opinion, there has been a similar publication bias at *JAMA* and the *Annals of Internal Medicine*. When the American College of Physicians agreed with the ACR that screening women beginning at age 40 saves lives, the *Annals* refused to publish the combined declaration.

Virtually every responsible group agrees that the science shows that mammographic screening saves lives. As with all medical interventions, everyone deserves accurate information about risks and benefits so that they can make informed decisions, but the use of nonscience to discourage participation in a potentially lifesaving test is unconscionable. No responsible expert has ever suggested that mammography is the ultimate answer to breast cancer. Probably at its best, it can reduce the death rate by 40% to 50%. Clearly, a universal cure or safe prevention is needed, but neither is on the horizon. Until these are discovered, thousands of lives can be saved by mammographic screening.

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