Perspective

More misinformation on breast cancer screening

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Provenance: This is a Guest Perspective commissioned by the Section Editor Rong Tang (Surgical Oncology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA).

Comment on: Welch HG, Prorok PC, O'Malley AJ, *et al*. Breast-Cancer Tumor Size, Overdiagnosis, and Mammography Screening Effectiveness. N Engl J Med 2016;375:1438-1447.

Abstract: Unfortunately, a great deal of misinformation has accumulated in the breast cancer screening literature that is based on flawed analyses in an effort to reduce access to screening. Quite remarkably, much of this has come from publications in previously highly respected medical journals. In several papers the intervention (mammography screening) is faulted yet the analyses provided no data on who participated in mammography screening, and which cancers were detected by mammography screening. It is remarkable that a highly respected journal can fault an intervention with no data on the intervention. Claims of massive over diagnosis of invasive breast cancer due to breast cancer screening have been made using "guesses" that have no scientific basis. No one has ever seen a mammographically detected, invasive breast cancer, disappear on its own, yet analysts have claimed that this occurs thousands of times each year. In fact, the" miraculous" resolution, without intervention, of a handful of breast cancers have all been palpable cancers, yet there is no suggestion to stop treating palpable cancers. A review of several publications in the New England Journal of Medicine shows some of the flaws in these analyses. There is clearly a problem with peer review that is allowing scientifically unsupportable material, which is misleading women and their physicians, to be published in prestigious journals.

Keywords: Mammography; breast; breast cancer; screening

Submitted Nov 05, 2016. Accepted for publication Nov 25, 2016.
doi: 10.21037/gs.2016.12.15
View this article at: http://dx.doi.org/10.21037/gs.2016.12.15

There are now three papers denigrating the value of mammography screening that should have never passed peer review, but have been published in the prestigious *New England Journal of Medicine* (*NEJM*) (1-3). The papers falsely claimed that mammography has had little effect on breast cancer in the U.S. while also falsely claiming that mammography screening was leading to massive "overdiagnosis" of breast cancers that would have regressed or disappeared had they not been detected by screening. They are all based on scientifically unsupportable estimates as to what the incidence of breast cancer would have been had screening not begun in the United States in the mid 1980's.

All three papers were based, not on direct patient data, but rather on analyses of the Surveillance, Epidemiology and End Results (SEER) databases of the National Cancer Institute which (incredibly) do not contain information on how breast cancers are detected. All three of these papers faulted mammography screening, yet none of the papers had any information on which women had mammograms and which cancers were detected by mammography. It is hard to understand how papers could pass peer review that attacked an intervention when the papers provided no data on who had the intervention and which cancers were detected by the intervention.

The first and third articles (1,3) claimed that there were tens of thousands of breast cancers each year that would have regressed or disappeared had they not been detected by screening ("overdiagnosed"). It is difficult to understand

this conclusion since they had no idea which cancers were found by mammography and they ignored the fact that no one has ever seen a mammographically detected invasive breast cancer disappear on its own without any treatment. You would think that with tens of thousands each year someone would have seen some cases. One of the authors, in a previous paper, suggested that there are reports of this happening (4), but, in fact, the few reports of such a phenomenon have all been palpable cancers (yet they are not arguing to ignore palpable cancers). In several of the few reported cases the primary lesion supposedly disappeared, but the women still died from their cancers. These cases are so uncommon and so unlikely that they fit the category of miraculous events rather than the common occurrences suggested by the authors.

The first of the three articles was published in 2012 (1) in which it was claimed that in 2008 alone there 70,000 of cases of breast cancer that would have disappeared on their own had they not been found by mammography. This paper relied on what the authors considered their "best guess" as to what the incidence of breast cancer would have been in 2008 had screening not begun in the mid `1980's. Their conclusions relied on their claim that the underlying breast cancer incidence would have only increased by 0.25% per year had there been no screening. Although this extrapolation had no scientific support, they, nevertheless, used this "Annual Percentage Change" (APC) and projected it out to 2008 claiming that, in the absence of screening, there would have been far fewer cancers diagnosed in 2008 than were actually found. Using this faulty extrapolation they were allowed to claim that there were tens of thousands of cancers in 2008 alone that would have regressed or disappeared had they not been detected by mammography. The *NEJM* refused to publish a letter from more than 40 experts in breast cancer care calling for the paper to be withdrawn due to its faulty science. At least three papers were published, subsequently, that have shown that *NEJM* analysis was scientifically flawed and its conclusions not supported (5-7).

More recently one of the authors of the above paper published a second analysis in the *NEJM* claiming that, since there had been little decline in the rate of women presenting with metastatic breast cancers, since the start of the SEER database in 1974, this (falsely) indicated that mammography screening had had little impact (2). This too was based on the same argument that the underlying incidence of invasive cancers (had there not been any screening) had not been increasing over the period from 1975–2010. In fact, if the correct extrapolation of the APC from invasive cancers had been used (see below) it shows that the rate of women with metastatic cancers has declined dramatically in the U.S. (6) consistent with the earlier detection of breast cancers by screening. It also explains the major decline in the annual breast cancer death rate, previously unchanged for 50 years, that is now down by more than 35% since 1990 (soon after the start of screening).

The most recent article in the *NEJM* (3) is simply more misinformation. The entire argument from these authors rests on a similar "guess" as in the two other papers. As the authors stated "*We started with the assumption that the underlying probability that clinically meaningful breast cancer would develop was stable, an assumption we believe was warranted given the stable incidence of metastatic breast cancer for more than three decades, despite spanning the era of increasing prevalence of screening-mediated breast cancer.*"

Using SEER data they, once again, estimated what they thought the incidence of breast cancer would have been had screening not begun in the mid 1980's. As noted above, in the first paper, it was claimed that the APC for the incidence of breast cancer, based on SEER data from 1976–1978, was 0.25% per year. In this current paper, looking at the same data (and one of the same authors), they now guessed that the APC was "0.0%" contradicting the "guess" in the first paper. Using this new guess their thesis relies on the false belief that the incidence of breast cancer in 2012 would have been the same as it was in 1977 had there not been any screening. Since the actual incidence in 2012 was higher than this faulty "guess", they concluded that the excess cancers were fakes and had been "overdiagnosed".

Not only was one of the authors allowed to change his estimate from the first paper in which he claimed an APC of 0.25% to claiming in the third paper that the APC was 0.0%, but both estimates are incorrect. The first "guesstimate" was based on the incidence rates from 1976–1978 while the second was based on the period 1975–1979. Had the authors understood the data they would have realized that these years in the SEER database are the least reliable with regard to the underlying (prescreening) breast cancer incidence. It is no secret that, in 1974, the wives of the President and the Vice President of the U.S. were diagnosed with breast cancer. Highly publicized, these were followed by a short "burst" of "ad hoc" breast cancer screening that can be seen reflected in the graph in this most recent paper in their Figure 1. The authors provide no explanation as to why the incidence of breast cancer in 1975 starts high, declines until about 1978, when

it starts back up again. They clearly do not understand the fundamental epidemiology which provides the reason for this pattern. The ad hoc screening in 1974 and 1975 resulted in a small prevalence "bump" in 1975. Had they understood basic epidemiology, they would have known that the first time women are screened the cancers expected to be detected in that year are found, but screening also finds the cancers that could have been detected (but would have been overlooked). Added to these are the cancers that are found 1, 2, or 3 years earlier (leadtime) by screening (the reason for screening). This is why there is a "bump" in "incidence" with the first (prevalence) screen, and this is what is evident in the SEER database in 1975. What the authors also ignored is when screening stops (as it did after the short burst of ad hoc screening) there is a "compensatory" decline in cancer incidence because cancers that would have been clinically evident from next year and the year after, had already been found earlier by screening. This means that the "incidence" will drop below the "baseline" after screening has stopped (8). This is also a completely expected phenomenon and has been used to calculate how much earlier screening can detect cancers before they become palpable (9) (leadtime). Once leadtime has been exceeded, then the annual incidence returns to the baseline as cancers are once again discovered when they become palpable. This is basic epidemiology. Consequently, the period used by the authors [1975–1979], immediately after the short burst of screening in 1974 and 1975 (during the compensatory decline), is completely unreliable for establishing a baseline for incidence in the prescreening period.

Contrary to their assumptions, and fundamental to these three papers, is the fact that the incidence of invasive breast cancer had not been increasing slowly at 0.25% prior to the start of screening, and it had certainly not been completely stable (APC=0.0%) as suggested in the most recent paper. In fact decades of data show that it had been increasing fairly steadily with an APC of 1–1.3% per year dating back to at least 1940 long before there was any screening. Data from the Connecticut Tumor Registry (10), which is the oldest in the Country, highly regarded, and now part of the SEER program, have shown that for decades, prior to the start of screening, the incidence of invasive breast cancer had been increasing steadily. Papers that have evaluated breast cancer incidence, prior to the start of the SEER database in 1974, have relied on the data from the Connecticut Tumor Registry (11-14). In fact, in this most recent paper, the SEER data from 1978–1982 (after the prevalence bump and compensatory decline described above, but still in the prescreening era as agreed by the authors), show that the baseline once again returned toward a 1% per year increase.

If the authors were to repeat their analysis using the actual data that show that the baseline incidence had been increasing at an APC of at least 1% per year for decades, their results would show that there has been a major benefit from mammography screening. Had they used the scientifically supported extrapolation of the baseline, and not the most unreliable portion of the SEER data, they would have shown that, not only is there no overdiagnosis of invasive cancers, but there were actually fewer invasive cancers in 2012 than would have been expected had there been no screening. It makes complete sense that the incidence was lower since everyone agrees that mammography screening has led to the removal of DCIS lesions over the many years. Removing some DCIS should reduce the development of invasive cancers and this is exactly what their data suggest had they used the proper underlying APC and the increasing baseline of invasive cancers in the absence of screening.

As in the second *NEJM* paper described above, the authors in this third paper also, incorrectly, concluded that there has been only a small reduction in the rate of metastatic disease over the same time period. They used circular reasoning by using this to reinforce their faulty idea that the baseline incidence of breast cancer had been stable. If, as the data show, the baseline incidence of invasive cancers was increasing at 1–1.3% per year, and had screening not had any effect, then the rate of women with metastatic disease should also have increased in parallel with the rate of total invasive cancers. Since, as they point out, the actual rate of metastatic disease has decreased, then using appropriate numbers for the baseline in the absence of screening, and contrary to the authors' assertion, the material in this paper shows a major decline in women with metastatic disease. As they point out, this parallels the major increase in the detection of small invasive cancers. These data clearly explain the more than 35% decline in annual breast cancer deaths that has occurred since 1990. If actual data are used, and not the unsupportable "guesstimates" used by the authors, this is very strong evidence that screening has had a major impact on breast cancer deaths and women should be urged to participate in annual screening.

The authors also tried to denigrate the impact of screening by claiming that most of the decline in deaths is due to improvements in therapy. They did this by comparing the "case fatality" rates between two periods

1975–1979 and 2008–2012. Their approach is misleading. They grouped cancers within large size ranges when it is clear that the individual size of a cancer is directly related to cure. A 2-cm cancer is likely to have a better case fatality rate than a 2.9-cm cancer, but they were counted together. This is also true for 1.0 cm cancer *vs.* 1.9 cm cancer, etc. They should repeat the analysis using actual sizes and not size ranges. Since screening reduces the size of cancers within stage, and this can reduce deaths as well (15), it is likely that screening will show a much larger impact than claimed by the authors.

Although much less common, men are diagnosed with breast cancers that respond to therapy in the same way as in females. However, if you look at the death rate from breast cancer for men starting in 1990, it actually increased while the death rate for women began to decline. The death rate for men finally came back down to 1990 levels, but has remained stable while the rate for women has continued to fall. The difference is that women are being screened and their cancers are found at smaller more curable sizes.

Therapy has improved, but it is clear that screening is the major reason that deaths from breast cancers have declined. Numerous observational studies have shown that the death rate for women who participate in screening has declined dramatically relative to women who do not participate in screening (16-31) despite having access to the same therapies.

The final piece of evidence comes from a study of women in the two largest Harvard teaching hospitals who died from breast cancer. Despite having access to the most advanced therapies, more than 70% of the women who died in these hospitals were among the 20% of women who were not participating in screening (32).

It is time for the medical journals to improve their peer review and stop publishing scientifically unsupportable material to reduce access to screening. Screening is not the ultimate answer to breast cancer, but until a universal cure is devised, or there is a safe way to prevent breast cancers, the most lives are saved by annual screening starting at the age of 40 (33,34).

Acknowledgements

None.

Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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Cite this article as: Kopans DB. More misinformation on breast cancer screening. Gland Surg 2017;6(1):125-129. doi: 10.21037/gs.2016.12.15

