Dr. Daniel Kopans Review of:

"Effect of Implementation of the Mass Breast Cancer Screening Programme in Older Women in the Netherlands; Population Based Study"

The publication of the 25 Year Follow-up of the Canadian National Breast Screening Study in the British Medical Journal (BMJ), despite indisputable evidence that it was a compromised trial whose results are unreliable, was evidence of failed peer review at the BMJ. The paper by Glas et al "Effect of Implementation of the Mass Breast Cancer Screening Programme in Older Women in the Netherlands" in the BMJ is, unfortunately, another example of that failure. Peer reviewers failed to understand the fundamentals.

There first error is the assumption that if the rate of advanced cancers is not reduced, then screening has little effect. This was shown years ago to be untrue. Screening can reduce deaths by reducing the size of cancers within stages. Ignoring this fundamental fact there are other problems with this analysis.

The authors adopted the faulty method that was used by Bleyer and Welch in their New England Journal of Medicine article in which they too, incorrectly claimed massive overdiagnosis of breast cancer, as well as incorrectly claiming a failure to reduce the rate of advanced cancers.

Bleyer A, Welch HG. Effect of Three Decades of Screening Mammography on Breast-Cancer Incidence. N Engl J Med 2012 :1999-2005.

Both the Bleyer and Welch article and the article by Glas et al rely on estimating what the number of cancers would be each year (incidence) had there not been any breast cancer screening. Based on these guesses, they both concluded that there were many more cancers diagnosed in the screening period than they "guesstimated" would have occurred without screening. They concluded that the difference was cancers that would have never become clinically significant and were "overdiagnosed" because of screening. In addition, because they claimed to see little decline in the number of invasive cancers with the introduction of screening they concluded that the number of advanced cancers had not been decreased by very much based on screening.

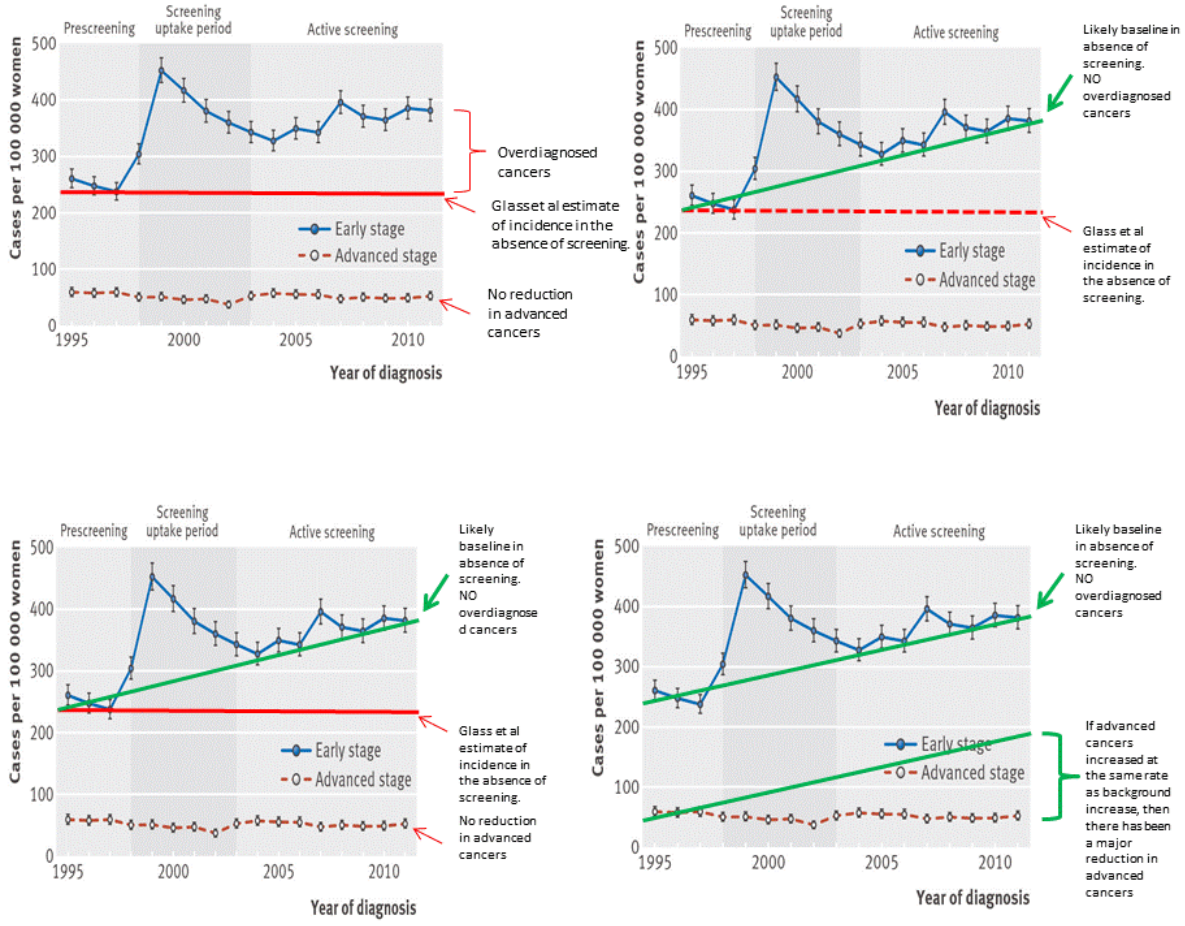
Bleyer admitted that their estimates were based on "best guesses". They chose the most unstable portion of the U.S. data 1976-1978 to determine what the yearly change in incidence of breast cancer was prior to the start of screening in the mid 1980's. This period was, perhaps the worst one they could have chosen since it was soon after many women underwent ad hoc screening due to the diagnosis of breast cancer in the wives of the President and Vice President of the U.S. in 1974. Had they used actual data going back to 1940, and not "guesses" it can be shown that there was no overdiagnosis:

Kopans DB. Arguments Against Mammography Screening Continue to be Based on Faulty Science. The Oncologist 2014;19:107–112

Bleyer and Welch also grossly underestimated the reduction in advanced cancers.

Helvie MA, Chang JT, Hendrick RE, Banerjee M. Reduction in late-stage breast cancer incidence in the mammography era: Implications for overdiagnosis of invasive cancer. Cancer. 2014 May 19. doi: 0.1002/cncr.28784. [Epub ahead of print] PubMed PMID: 24840597.

The single graph in the Glas et al paper showing breast cancer incidence over time provides most of the information needed to understand their errors. They assumed that the so-called "prescreening period" as from 1995-1997 to establish the baseline incidence before there was any screening. They assumed that this was, essentially a flat line - namely there was no increase in breast cancer incidence prior to the start of screening. They ultimately compared the number of cancers detected years later in 2011 with the number that they guessed would have been diagnosed had there not been any screening by extrapolating this baseline and concluded that the difference were cancers that would have never become clinically evident, were non-lethal, and, hence, "overdiagnosed". The argument is completely reliant on their guess as to what the incidence would have been had there not been any screening in the Netherlands.



In fact, one has to wonder why the incidence from 1995-1997 was not actually flat, but was actually declining. The authors make no mention of this phenomenon. It is critical to know. One possible reason is that, just as in the U.S., perhaps there was a period in the early 1990's in the Netherlands when women were screened on their own. If some women had been screened in the early 1990's, on their own, this would have caused a bump due to prevalence

cancers as is apparent in 1995. If they stopped being screened than there would have been a drop in incidence because cancers had been found early. The authors do not provide any data on how much screening was occurring prior to the national program. Does this explain the numbers from 1995-1998? Regardless, the "pre-screening" numbers are completely insufficient to predict what the incidence would have been had the screening program not begun. The authors assumed that the incidence would have increased very little. In other words, in the absence of screening there would have been the same number of cancers diagnosed in 2011 as in 1996. They concluded that since there were many more than what they guessed should have been, the difference between what they guessed and the real numbers must be cancers that would have never become clinically evident and were ovediagnosed.

The entire argument revolves around what the authors "guessed" the incidence would have been had there not been any screening. In the U.S. the incidence of invasive breast increased steadily going back to 1940 (decades before mammography was even available) at 1% per year right into the 1980's when screening began in the U.S. I would suspect that the incidence of breast cancer had been increasing steadily in the Netherlands as well for many years prior to the dates used in this paper. The short "prescreening period" almost certainly cannot be used to estimate what the incidence of breast cancer would have been in 2011 had there not been any screening.

There is, in fact, data in this paper that strongly suggest that the incidence of invasive breast cancer had been increasing fairly rapidly in the Netherlands independent of screening. In a well attended screening program, once screening is established and the "prevalence" cancers (prevalence peak) have been removed ("Screening Uptake Period") the annual incidence should return toward the baseline from before screening. We would expect to find cancers at the same annual rate as before screening, but at a smaller size (It will not go completely back due to leadtime, but will approximate the prescreening incidence). If the prescreening incidence was increasing on its own, once a new steady state is reached with screening, the incidence will return to its prescreening increase that is independent of screening. The prevalence peak is clearly seen in their graph. It increases from 1997-1998 and then comes back down until 2004. It then begins to increase again during a period when the authors claim women were being screened regularly. Beginning in 2004, the incidence has now returned to the slope that it was likely following prior to the start of screening. This would mean that instead of a line parallel to the x axis used by the authors, the baseline, in the absence of screening, was likely increasing with the slope seen by the rates from 2005-2011. The real incidence numbers in 2011 are likely close to or the same as the extrapolated numbers and this would mean there was little if any overdiagnosis.

Furthermore, if the baseline (incidence in the absence of screening) was increasing steadily with a slope "x", then the number of advanced cancers would be expected to increase with a slope "x" as well. Given that these numbers appear constant or even down somewhat, instead of increasing, this would mean, contrary to the authors, that there has been a major reduction in advanced cancers.

In fact, contrary to their assertions, if the proper extrapolations are used, there may well be profound benefit among these women. Before potentially lifesaving interventions are withdrawn to save money, analyses should be based on the scientific evidence and not "guesses", particularly when those guesses are likely incorrect.

Daniel B. Kopans, M.D.
Professor of Radiology, Harvard Medical School
Senior Radiologist, Breast Imaging Division
Department of Radiology, Massachusetts General Hospital
Avon Comprehensive Breast Evaluation Center