ENOUGH IS ENOUGH!

Review of:

COMMENT: If a screening trial is compromised from the beginning, no amount of reanalysis will make it more valid. It is well documented by the investigators themselves, as well as by those intimately involved in the Canadian National Breast Screening Study of women ages 40-49 (CNBSS1) that the trial was compromised. It was a trial of screening mammography, yet it employed outdated equipment (at least one second-hand device and some which used tungsten anodes which are known to wash out the important contrast needed for mammography). Scatter reduction grids were not used for a majority of the study and the scatter hid small cancers. Much of the breast tissue was not included on the screening studies because ninety degree lateral images were used and they exclude the axillary tail of the breast. The poor quality of the mammography in the trial was documented in my (and two other radiologists invited by the CNBSS) review.

Kopans DB. The Canadian Screening Program: A Different Perspective. AJR 1990 155:748-749),
Also, their own reference physicist has repeatedly explained that "in my work as reference physicist to the NBSS, [I] identified many concerns regarding the quality of mammography carried out in some of the NBSS screening centers. That quality [in the NBSS] was far below state of the art, even for that time (early 1980's). "

(Yaffe MJ. Correction: Canada Study. Letter to the Editor JNCI 1993;85:94)

They can argue that the nurse examiners were excellent, but one thing is certain - mammography finds cancers too small to feel even when a surgeon knows where to palpate. The poor quality of the mammography is evident by the fact that the cancers in the mammography group were the same size as in the "usual care" group. This means, at the least, that the cancers in the mammography arm which were not found by mammography had to be very large so that when averaged with those small cancers found by mammography, the size would be the same as the control women. This would further support the random allocation imbalance noted below.

The authors failed to point out that the CNBSS1 violated the basic requirements of a randomized, controlled trial. A clinical breast examination was performed on the volunteers before they were assigned to the study or control group. Women with palpable cancers and those with advanced (node positive) cancers were identified to the study coordinators. The coordinators, in turn, assigned the volunteers to one arm or the other on open lists which is another major violation. It would be impossible to prove that they skipped a line to be certain that women with lumps were placed in the mammography arm, but the data support the fact that this happened. The PI of the CNBSS has never allowed independent interviews of the study coordinators with protection from retaliation. Since the women in the "usual care" group had a better than 90% 5 year survival when the 5 year survival for women in Canada at the time was only 75% it is clear that women with advanced cancers were moved from the "usual care" arm and were placed in greater numbers in the screening arm. This unbalanced the trial. This is also the explanation as to why in the first 7 years there was a statistically significant excess of deaths in the screening arm.

and in this latest review of the trial, the excess of cancer deaths persists. This is not because, as the authors imply, early detection leads to early deaths. There is no evidence that this is true. It is obvious that if more women who are destined to die from breast cancer (advanced cancers at the time of allocation) are allocated to the screening arm, more women will die in the group which was allocated the excess advanced cancers. The authors ignore the obvious answer and develop theories that have no scientific basis.

The compromise of CNBSS1 is indisputable. It is inexplicable that journals continue to publish results from this trial. It is completely compromised and its results do not improve with repetitive publications.

SPECIFICALLY:

QUOTE: "In Switzerland, it has been proposed that routine screening mammography be discontinued"

COMMENT: This is misleading. The review was by an ad hoc committee that had no governmental or medical standing. The report has been ignored in Switzerland and screening is expanding.

QUOTE: "Our group has reported that up to 50% of nonpalpable Mammographically-detected invasive breast cancers represent examples of overdiagnosis".

COMMENT: There are no data to support the belief that mammography screening finds invasive cancers that would regress or disappear as suggested by those who claim massive "overdiagnosis". All of the reports making such claims are scientifically flawed.


One paper in the New England Journal of Medicine suggested that there were more than 70,000 cancers in 2008 that would regress on their own if left undetected
It is unclear how a paper can pass peer review that claims that, in a single year, there were 70,000 cancers that would disappear, **when there is not a single credible report of an invasive cancer ever disappearing on its own.** This paper has been shown to be completely flawed and its conclusions not supportable.

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


Informed, scientifically driven peer review has disappeared.

COMMENT: The authors invoke Retsky's observation that in some animal models, metastatic lesions grow more rapidly when the primary lesion is removed. As with many of the arguments made in this paper, the information is incomplete. What they neglect to add is that the phenomenon lasts for a very short period of time, and does not lead to earlier deaths in the animals. They invoke innuendo from incomplete information to make the reader think that removing breast cancers in younger women leads to earlier death. The obvious answer (which the PI's have refused to admit) is that their non-blinded allocation placed more women destined to die in the screening arm. The facts are obvious and well documented. It is stunning that they continue to be ignored.

QUOTE: "In particular, we were interested in the possibility that the number of deaths from breast cancer transiently increases in the immediate aftermath of entering a screening program".

COMMENT: This has never been documented. The authors like to suggest that it has occurred in other trials, but they ignore the fact that in the early years of a trial when there are small numbers of deaths, there is statistical fluctuation. Women don't die at precisely the same time in both groups. One group may have more
deaths than the other by random chance. It takes 5 to 7 years for screening to impact deaths, yet at 7 years the CNBSS had a "statistically significant" excess number of cancer deaths in the screening arm. This is easily explained if more women destined to die are assigned to the screening arm! The obvious and documented explanation is the one that the authors refuse to acknowledge.

QUOTE: "Before randomization, women underwent a physical breast examination..."

COMMENT: This is a fundamental violation of blinded allocation. Even the incomplete review of the allocation process, commissioned to absolve the process, confirms that the study coordinators were informed of the clinical breast examination (CBE) results.


QUOTE: "For the purposes of the present study, we assumed that none of the women assigned to the control arm underwent mammography before age 50".

COMMENT: It has been reported that more than 20% of women in the "usual care" group had mammograms. The PI has argued that they were "diagnostic", but all diagnostic mammography begins with bilateral screening unless the patient has already had a screening study.
Review of:

Commentary: Reflections on screening mammography and the early mammography and the detection of breast cancer, M Baum, MD
Current Oncology- Volume 21, Number 5, October 2014. pp 215-216

QUOTE: "The importance of breast screening programs lies not in their success, but in their failure."
COMMENT: In fact, screening has resulted in a major decline in breast cancer deaths in both the U.S. and other countries.

QUOTE: "Most natural biologic mechanisms are nonlinear or are better described by chaos theory."
COMMENT: Prof. Baum ignores the fact that virtually every study has shown that as breast cancers increase in size the risk of death increases. It is not a random event as he suggests. Prof. Baum is correct that DCIS is problematic, but decades of study have not resolved the problems with dealing with these lesions. He, unfortunately compromises his argument by using an outdated reference from 1980.

QUOTE: "Up to 45% of women with a screen-detected case of ductal carcinoma in situ end up undergoing mastectomy because of the multicentricity of the disease 10"
COMMENT: This is not the reason for mastectomies in 2014.

QUOTE: "In conclusion, then, it can be stated with a great deal of conviction that a large proportion (on the order of 50%) of screen-detected (preclinical) foci of breast cancer are not programmed to progress if left unperturbed."
COMMENT: There are no, scientifically derived data to support this statement. However, I completely support Dr. Baum's quote:

QUOTE: “There’s none so blind as those that will not see.” — Jonathan Swift, Polite Conversation

COMMENT: The data are clear. The CNBSS1 used poor quality mammography that failed to detect small cancers when better mammography would have detected
them. The data are clear that the non-blinded (documented by the investigators themselves) allocation process identified women with lumps and advanced cancers who were then assigned on open lists. This completely compromises the trial and explains the significant excess of deaths in mammography arm of the trial. Perhaps Dr. Baum can explain how the "usual care" women had a greater than 90% 5 year survival. The refusal to understand the facts is what has perpetuated the confusion.
Dr. Narod's allegiance to his "mentor since 1987" is admirable, but does not negate the fundamental facts.

QUOTE: "Most of the criticism from the radiology community focuses on issues of study design (which they claim was inadequate) and on the quality of the mammography (which they also claim was inadequate)."

COMMENT: These are not "claims". They have been documented by the investigators themselves.

QUOTE: "None of the first-generation critics have acknowledged the consistency; instead, they look elsewhere and point out other weaknesses."

COMMENT: This is not true. The concerns with the CNBSS go back to its performance. In the 1980's, Dr. Wendie Logan was their external advisor who heard that the quality of the mammography was poor. Dr. Logan resigned because they would not allow her to see the images. Stephen Feig, M.D. was allowed to see the images that he judged to be poor. Dr. Laszlo Tabar, was brought in and he was astonished at the poor quality. Dr. Feig resigned because the PI would not move to improve the quality. Edward Sickles, M.D. insisted that they perform a blinded review of the image quality or he would resign. Dr. Myron Moskowitz, Dr. Douglas Sanders and I were invited to review their images in a study organized by Dr. Baines of the CNBSS. We showed that the quality was poor to unacceptable for much of the trial

This was confirmed by their own reference physicist. I have never seen any review by radiologists claiming they had excellent mammography in the CNBSS. I am not aware of any of the radiologists in this trial defending the quality of the images. Dr. Narod is confused. The review under discussion is the CNBSS1 study of women ages 40-49, yet he cites

QUOTE: "The most recent NBSS report... counting 2584 cancers in the screening arm and 2609 cancers in the control arm" combines women in the 2 CNBSS trials. "If the screening arm had been enriched for women at “high risk,” that enrichment must have been performed in a peculiar fashion, using only risk factors that have a transient effect."

COMMENT: I have no doubt this was a simple oversight by Dr. Narod and not an effort to obfuscate the issue by citing the COMBINED data from the two separate CNBSS trials. He never mentions the fact that Tarone at the National Cancer Institute showed that there was a statistically significant excess of women with advanced cancers who were allocated to the screening arm in CNBSS1 which is the trial on which he is reporting. Women with palpable axillary lymph nodes are at very high risk (not transient). We have no idea what effect women with breast lumps had on future cancer risk. Dr. Narod certainly knows that women who have had a breast biopsy are at higher risk for breast cancer and that this stems from the fact that they have lumps.

QUOTE: "It follows that the excess of cancers seen in the screening period (years 1–5: 666 vs. 524) was a result of early diagnosis and not from stacking the deck."

COMMENT: As Dr. Narod quotes “A little learning is a dangerous thing. — Alexander Pope, An Essay on Criticism"

COMMENT: It is the excess of cancer deaths in the screening period (years 1-5) that is of concern. Obviously, if you place more women with advanced cancers in the screening arm, then you would expect more deaths in the screening arm which is precisely what occurred!

QUOTE: "Instead, critics now insist that many women with palpable lesions were sent directly to the screening arm by duplicitous research assistants."
COMMENT: As far as I know, this is simply Dr. Narod making it up. I have never heard anyone say that the study coordinators were "duplicitous". No one to my knowledge has ever said that the imbalance was caused on purpose, but it is likely that the coordinators, who probably did not understand the consequences, wanted to be certain that women with very suspicious CBE's got mammograms and, naively, assigned them to the mammography arm. Why has the PI never allowed an independent interview of the coordinators (with protection from retribution)?

QUOTE: "Even if all the women with prevalent cancers had been shunted to the screening arm, the situation could still be remedied by ignoring all cancers found at the first screening round (prevalent cancers) and focusing instead on the incident cancers."

COMMENT: Dr. Narod has suggested this before. If true, then there is no need for blinded allocation in these trials. Simply ignore the first cancers! Really??!! The reason for blinding is that you have no idea what biases can be introduced by not being blinded. You have no idea what effect selection of patients will have downstream. This is basic science!

QUOTE: "Therefore, if we exclude all prevalent cases from the analysis and focus on women with no cancer at study entry, we can re-evaluate the benefit of mammography thereafter."

COMMENT: NO. Perhaps women with lumps, but not obvious cancers in the first year were placed in much higher numbers in the screening arm. This would compromise the results for years after. Sorry Dr. Narod, unblinded allocation is a basic flaw with unpredictable consequences. This is the reason that blinding is so fundamental.

QUOTE: "It is claimed that a certain proportion of the women in the control arm—perhaps as high as 20%—opted for screening off-study, in particular after the screening period was over."

COMMENT: That is not what has raised concern. The concern is that more than 20% of women in the control arm had mammography early on. The PI has argued that these were "diagnostic" mammograms and not screening. Clearly he is uniformed. Diagnostic mammography begins with bilateral **screening** if the patient has not been screened.
Dr. Narod seems confused. He is correct. In the studies where women are "invited" to be screened, they are counted as having been screened even if they refuse (non-compliance). If they die of cancer they are still counted with the screened group. Similarly if a woman assigned to the control arm goes outside the trial and has a mammogram (contamination) that saves her life she is counted with the unscreened controls. Clearly "non-compliance" and "contamination" dilute the benefit from screening in properly performed randomized, controlled trials. These lead to underestimating benefit.

QUOTE: "The second issue raised concerns the quality of the mammography. After all, the NBSS tests were completed 30 years ago using 30-year-old technology. I still wonder how things might have been done differently."

COMMENT: Dr. Narod is not a radiologist. It is not surprising that he does not know how things might have been done differently. The answer is that:
1. The centers should have used modern equipment and not x-ray tubes that made cloudy images
2. The centers should have used scatter reducing grids so that the images were not clouded by scatter obscuring the cancers
3. The centers should have used the mediolateral oblique projection. The straight lateral view that was used misses the axillary tail of the breast where many cancers develop
4. The technologists should have been trained to do modern (for the 1980's) mammograms.
5. The radiologists should have been trained to interpret mammograms
6. When radiologists recommended a biopsy it should have been done. Some surgeons refused.

QUOTE: "In the NBSS, women were randomized on an individual basis after they had attended the study centre".

COMMENT: This sounds good, but is incomplete. The women first had a clinical breast examination (CBE), before allocation, identifying lumps and palpable axillary lymph nodes, and the study coordinators were provided with the findings. This is not allowed in randomized, controlled trials! They were then assigned on open lists, so that the coordinators could place any individual in either arm of the trial. This is another major violation which compromises the integrity of the entire trial.
My concerns are with the poor quality of the mammography in the CNBSS and the major compromise of the allocation process. Dr. Narod's selective comments about the Swedish Two County Trial are only chosen to distract from the facts of the CNBSS.

However,

QUOTE: "The Canadian women were offered 5 mammograms 1 year apart. The Swedish women were offered mammograms every 2 years (ages 40–49) or every 3 years (ages 50–74) for up to 8 years. They underwent fewer screens (Table i). The cancers detected by mammography in Canada were similar in size to those detected in Sweden (Table i)."

COMMENT: So let me understand this defense of the CNBSS. Dr. Narod claims that the cancers in the CNBSS1 (which screened every year), were the same size as in the cancers in the Swedish Two County trial where the screening was every 2-3 years? Unless cancers stop growing, screening every year picks up smaller cancers than every 2 (and certainly 3) years. Dr. Narod is reinforcing the obvious. The mammography in the CNBSS was poor quality and missed small cancers.

QUOTE: "Of the cancers detected in the screening arm of the Canadian trial, 68% were palpable. That fact has been a source of criticism."

COMMENT: Absolutely! Dr. Narod should be criticizing this as well. There is no doubt that quality mammography screening detects the majority of cancers. Dr. Narod is well aware that I developed a guidewire to direct surgeons to the lesions found by mammography (including cancers) because even when surgeons know where the cancer is from the mammogram, they cannot feel the majority of mammographically-detected cancers. The fact that only 32% of the cancers found in the mammography arm were found only by mammography is not because the nurses were so good at CBE (better than surgeons who know where the lesion is??), and it was not because the women were "aware" of their breasts. It was because poor quality mammography does not find small cancers!

QUOTE: "Patrick Borgen has stated that the NBSS is the “worst clinical trial ever done” 5—an extraordinary statement"

COMMENT: I can't say it was the worst, but it is right up there. Once again a trial of mammography screening should use the best technology available, but certainly not the worst as happened in the CNBSS. There are rules for RCT's, and blinded
allocation is fundamental and critical. The CNBSS violated the fundamental rules and the data prove it. This makes it a pretty bad trial. The Edinburgh Trial has been excluded from analyses because there appears to be a socioeconomic imbalance. This pales in comparison to the fundamental violations in the CNBSS.
WHAT IS GOING ON?

If a chemotherapy trial was performed today to test Alkyran (an outdated agent) to treat breast cancer and

All women first underwent a clinical breast examination (CBE) before assigning them to the drug arm or control arm and

If the CBE identified the women with the larger, more advanced cancers before allocation and

If those who allocated the women knew the results of the CBE and

If the assignment to the treatment group or the control group was on open lists so that they could simply skip a line to place the larger cancers in the drug arm and

If a statistically significantly greater number of women with large advanced cancers were allocated to the drug arm and

The trial showed that, not only were there no fewer deaths among the treated women, but there were more deaths and

The investigators concluded that they showed that no form of chemotherapy had any value in treating breast cancer,

*The study would be rejected as completely compromised and it would never be published!*

Why is this acceptable for a treatment trial, but a hopelessly compromised screening trial is held up as a model to guide screening recommendations???

Enough is enough.