Reviewer’s report

Title: Prognosis of screen-detected breast cancers: results of a population based study

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Reviewer: Laszlo Tabar

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Evaluation of service screening is important and this article set out the goal of presenting the early results of their screening program in Northern Italy. This is an article with results strengthening the findings of other screening programs and confirming the reproducibility of good screening, but there are a few important comments that need to be forwarded to the authors:

1) Background (fourth sentence from the beginning): The statement “Mammography screening was first evaluated in a randomized controlled trial in New York during the 60s”…needs correction, since that RCT included both physical examination and mammography, evaluating the value of “early detection” by using dual modality. It was the Swedish trials that have used only mammography to find out the independent value of a single modality.

2) The last paragraph of the Background gives the impression that the authors are comparing “screen-detected” breast cancers with cancers detected outside screening. Evaluation of the full impact of screening requires the description and analysis of all women “exposed to screening”, i.e. both screen-detected and interval cancer cases combined. In fact, as it turns out later on in the text, the authors have included the interval cases as well in the analysis, but their description is not clear and this flaw keeps coming back in their article. It would be easy to correct it by making it clear already at the end of Background (e.g. by using the term “exposed to screening i.e. screen-detected and interval cancers combined”). Their terminology should be clear and consistent (Top of Table 1 should mention that it is dealing only with invasive cancers, and also, not only screen-detected, but “exposed to screening”, i.e. interval cancers included). Also, please change the tumor size on Table 1., “0-10” to 1-10 mm, since there is no 0 mm invasive carcinoma.

3) I understand that the authors have used the UICC classification and the TNM classification to describe the tumor characteristics, but the authors should be aware of the fact that the so-called T1c category is too broad and they should prepare their future articles taken more modern size descriptions into account, such as 1-9mm, 10-14mm, 15-19mm. Otherwise, the within-same-Stage size-shift cannot be seen well. This is especially valid the size category 20-50mm. Decreasing tumor size from 50 mm to 25 mm (still within the same Stage category) makes a significant difference in the outcome of breast cancer patients, although there is no demonstrable Stage-shift (still Stage II). This inaccuracy of the international classification system is here from the past, from before the screening era, and it is hardly applicable to evaluate modern screening results.

4) Please explain why only 454 “screen-detected” (??)(exposed to screening??) and only 330 in the other group have been followed up when the total number of cases 587 vs 471? What do the authors know about the remaining cases? I could not find any explanation for this discrepancy in the article.

5) Table 3. “Dead”…does this mean breast cancer specific death? Please clarify.

6) One should have corrected for lead time bias, since their explanation does not hold. This is the biggest deficiency of this article. Mentioning the “median age” is not a good excuse, since in this regard the mean age should have been calculated. There is no way of avoiding the correction for lead time bias and the authors may be very surprised when seeing the result. My suggestion is: do not expose an otherwise good material to unnecessary and justified criticism. Rather, please perform the correction.

7) The other deficiency is that there is no adjustment for treatment modalities. Please use multiple
variable regression models, such as Cox regression model. The follow up time is too short to accept the conclusions without all these corrections.

8) Also, their interpretation of length bias sampling requires clarification, since referring to the % of cancer cases lost to f/up does not cover the meaning of LBS.

9) The authors have careful speculation about the “contribution” of chemotherapy to the “falling mortality rates”, but they have no evidence or data supporting this statement. There is sufficient scientific evidence demonstrating that it is the ever-decreasing tumor size that is responsible for the decreasing breast cancer mortality on a population level, but the magnitude of impact of chemotherapy in a given population (i.e. other than in clinical trials) is unknown and it is very likely insignificant. In any case, it seems that a very high rate of their screen-detected cancers received chemotherapy. If they believe in the positive impact of chemotherapy, then they should definitely correct for it before the conclusion is drawn about the beneficial effect of screening.