Reviewer’s report

Title: Comparative benefit from small tumour size and adjuvant chemotherapy: clues for explaining breast cancer mortality decline

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Reviewer: Karsten Juhl Jørgensen

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This study aims to shed a bit of light on, arguably, the most difficult subject in breast cancer screening: differentiating between the contributions of screening and adjuvant therapy, respectively, to the large reductions in breast cancer mortality rates that we have seen across the Western world in the past 20-30 years. The authors use data from an RCT on CMF-adjuvant treatment and compare survival and total mortality in treated versus non-treated women for various tumor sizes. The analysis hinges on two central assumptions which seem to be taken for granted and not considered as possible limitations to the design, although they may be wrong.

1: Screening reduces the rate of late stage breast cancers (those >2cm). This may seem obvious, but to my knowledge it has never been shown. In their Discussion, the authors refer to a couple of papers (25, 26), but these do not show the rates of late stage tumour, they show percentages. Less recognized at the time of the trials, overdiagnosis of small tumors may substantially affect such percentages, seemingly lowering them, even if the rate of large tumors were constant. Interestingly, one of the papers (25) highlights that the Canadian trial, which showed no effect on breast cancer mortality, had smaller (1.6cm) average size tumors in the intervention group than the Two-County trial (2.2 cm), which showed a large effect.

Autier and colleagues have looked at rates of breast cancers > 2cm at detection in several countries and found no reduction (Arch Int Med), even though many of the countries had introduced breast screening. Norway introduced screening in a staggered fashion and Kalager and colleagues showed that rates of tumours >2cm had dropped 24% in both screened and non-screened regions (Ann Int Med).

The reason screening may not reduce the rate of breast cancers >2cm is that there is a link between size at detection and aggressiveness/fast growth. Tumors detected clinically when >2 cm may have reached this size without prior detection simply because they grow fast. Fast growing tumors are particularly difficult to catch with screening, as slow growth increases the time available for screen-detection (length bias). This relates to the second assumption in this paper, which may also be wrong:

2: If a tumor is detected when small rather than large due to screening, it will attain the same prognosis as clinically detected small tumors. The link between size at detection and the fundamental biology of the individual tumor also
challenge this assumption. If a tumor that is aggressive and fast growing also tends to form metastases early on (at a smaller size than what screening can detect), detecting this tumor earlier with screening may not make any difference to the prognosis of the patient. The metastases have already formed, in which case only systemic treatment can help.

Our comparatively poor knowledge of tumor biology (no-one knows exactly at what tumor size micro-metastases are formed) is the reason that this assumption cannot be made without caveats. It is why the US Preventive Services Task Force noted that, as the mechanism of effect for breast screening has not been proven, this places extra high demands on the quality of the randomized trials. Indeed, it is a main reason for doing RCT’s of breast screening in the first place.

The authors need to discuss their fundamental assumptions in much greater detail.

Like the authors, I believe improved treatment has played a much larger role than screening in the observed reductions. Central points supporting this assessment could be mentioned in the manuscript, e.g. that reductions in breast cancer mortality have been almost twice as large in European women >50 years who have never been invited to screening as in the screened age range (Autier BMJ 2010) and that comparisons of reductions in screened ages between countries have shown no correlation with the introduction of breast screening – all reductions began in the early 90’s with the introduction of adjuvant therapy, regardless of the introduction of screening, which happened 10-15 years apart between countries. Comparisons between screened and non-screened areas in Norway (Kalager NEJM 2010) and Denmark (Jørgensen BMJ 2010) have also shown that reductions have been similarly large in screened and non-screened areas. The size of these reductions are compatible with effects predicted in RCT’s of adjuvant therapy. In other words, adjuvant therapy has visibly and markedly impacted population statistics on breast cancer mortality. Breast screening has not.

Karsten Juhl Jørgensen

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**

I have no conflicts of interest