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The Swedish randomised controlled trial on mammography screening has been properly designed, conducted and analysed

Autier and colleagues[1] recently published a paper (online 7 July) where they tried to make a systematic review of the Swedish randomised trials on mammography screening and other cancer screening trials concluding that

> the use of unconventional statistical methods in the Swedish trials has led to overestimation of risk reduction in breast cancer death attributable to mammography screening. The constant risk reduction in screening groups was probably due to the trial design that optimized awareness and medical management of women allocated to screening groups.

Autier's re-analysis of the data is biased and the criticism of the design of the Swedish trials on mammography screening is not based on scientific grounds.

Autier and colleagues label the paper a systematic review of cancer trials, but the paper mainly deals with the Swedish trials on mammography screening. The authors state that 'between 1977 and 1996, five randomized trials on mammography screening were conducted in Sweden'. The fact is that the first part of the Malmö Mammography Screening Trial I (MMST I) started to randomise women in October 1976 and the second part of MMST (MMST II) randomised the last birth year cohort in November 1990[2] (Appendix). Further they stated that 'an overview of these trials (the Swedish) published in 2002 reported that two to four rounds . . .'. This is not correct. Women in the Stockholm trials were invited to two rounds, but women in the Göteborg Mammography Screening Trial born in 1923–1932 and 1933–1944 were invited to four and five rounds, respectively[2] (Table 1 and page 910), women in MMST I were invited to six to eight rounds and women in MMST II one to seven rounds[2] (Table 1).

Autier et al. further state that 'breast screening trials were initiated at a time when there was limited experience for designing, conducting and analyzing cancer screening trials'. It is true that there was limited experience of designing, conducting and analysing cancer screening trials, but cancer screening trials do not differ from large clinical trials except from the fact that the risk for contamination due to opportunistic screening is much larger which will result in underestimation of the intervention effect.

The authors describe the follow-up and evaluation model presented in our first report from the overview[3] (Figure 1); however, their Figure 1b is confusing as the intervention period for the control group starts later than in the screening group. This is not correct; e.g. in the Stockholm trial women born day 1 1917–1941 and women born day 11 1917–1941 were randomised to the invited and control group, respectively, on the same day (9 March 1981)[2] (Appendix).

The authors question the evaluation model for including the first screening round of the control group in the intervention period to balance the number of breast cancer cases in the two groups. Duffy and Smith[4] recently showed that this approach resulted in the second best estimate (design 4) of the effect (the ideal is identical screening and observation period (design 1)).

Autier et al. further criticise that cause of death determination in some of the Swedish trials and in the second overview[2] was not based on assessment 'done by committees unaware of the screening status of subjects that decided on likely cause of death using all available information'. The authors are ignoring the fact that in the first overview[3] an independent endpoint committee (EPC) was appointed that scrutinised all available information including medical records, histopathology reports, autopsy protocol and cause of death certificates of all breast cancer cases reported to the Swedish Cancer Register and deceased according to the Swedish Cause of Death Register and all breast cancer deaths not reported to the Swedish Cancer Register before end of follow-up. The EPC concluded that '"breast cancer as underlying cause of death" and "breast cancer as underlying or contributory cause of death" according to Statistics Sweden resulted in relative risk estimates very similar to those based on classification by the EPC,[5,6] (protocols are presented in Nyström,[6] Appendix 2.1–2.3). Further, an analysis of the overview using excess mortality, i.e. mortality in the breast cancer cases, resulted in almost identical relative risk estimates as

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using breast cancer as the underlying cause of death as the main outcome measure. The advantage of this approach is that the excess mortality estimate is independent of the cause of death determination.[7] Finally, the Nordic Cancer and Cause of Death Registers are constantly monitored and evaluated to maintain its well-known high quality.

The authors question the statistical analysis of the overview ignoring that an independent analysis of the first overview by Richard Peto's group in Oxford arrived at the same result as our analysis[6] (Appendix 3). Autier et al. make an 'alternative calculation of results of Swedish trials' using design 3 according to Duffy and Smith[4] in which they showed results in a crude underestimation of the intervention effect, and besides that the assumptions of the number of breast cancers resulting in breast cancer deaths during the first screening round of the control group is based on vague and unfortunately biased assumptions.

The authors also assume that there was a difference in the medical management between breast cancer cases diagnosed in the invited and control groups. This statement reveals the authors lack of knowledge about the Swedish healthcare system.

Declarations

Competing interests: None declared

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Lennarth Nyström
Umeå University, Umeå SE-90187, Sweden
Email: Lennarth.Nystrom@umu.se

Systematic review of the breast cancer screening trials is error-ridden

The article by Autier et al.[1] shows a most elementary lack of understanding of screening and is simply wrong.

The authors' assumption that, "during post-intervention periods, because screening (or absence of screening) activities are similar in the screening and in the control group, cancer detection rates in the two groups are also similar" is nonsense since a large number of cancers in the ASP will have been screen detected in the intervention period, which otherwise would have been detected in the post-intervention period. Thus, in the post-intervention period, cancer detection rates in the ASP will be *lower* than in the control group, and breast cancer mortality also will be lower. This is what they found, and is what they should expect if screening reduced breast cancer mortality.

This fundamental point also invalidates their argument against the closure screen of the control group; a closure screen of the control group is conservative, albeit less biased than the authors' preferred method.[2]

When arguing against the closure screen, the authors' adjusted estimates are wrong, since they subtract the deaths from cancers detected at screening of the control group, but not those detected contemporaneously in the study group. In the Two-County Trial, the reduction in mortality from breast cancers prior to the closure screen has been in the public domain since 1985,[3] *and was 31%,* similar to the reduction in mortality observed when the control group includes deaths from cases diagnosed in the closure screen and their counterparts in the study group.[4] Why resort to speculation when the empirical data are already published?

Their assumption that the 10% of breast cancer deaths in the control group in the Two-County Trial from cancers detected in the closure screen can be applied to other trials also is naïve, as is their argument that the smaller numbers of advanced