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Commentary: A defence of the Health Insurance Plan (HIP) study and the Canadian National Breast Screening Study (CNBSS)

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The commentary of Freedman *et al.*¹ on the reviews by Gøtzsche and Olsen^{2,3} focuses largely on three of the screening trials, and they conclude, like the International Agency for Research on Cancer (IARC) working group that reviewed all the trials,⁴ that mammography screening does save lives.

I agree with their comments on the Health Insurance Plan (HIP) trial. I drew very similar conclusions when the first review of Gøtzsche and Olsen was published.⁵

Having been a participant in the IARC working group that reached similar conclusions to Freedman *et al.* on the Two County trial, and having found the analysis of Nixon *et al.*⁶ particularly compelling in largely dealing with the cluster randomization issue, I also agree with most of their comments

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on that trial, though I still have some caveats on its application at the present time. However, Freedman *et al.* cite the analysis of Nystrom *et al.*⁷ as demonstrating equivalence in breast cancer incidence prior to randomization. They neglect to mention that Nystrom *et al.*⁷ were only able to assess this in regard to Östergötland, as Tabar declined to produce the data for the Kopparberg component of the trial for this overview analysis. Thus we still do not have absolute certainty that the clusters in Kopparberg were balanced.

More important, it is not clear that either the HIP or the Two County trials are relevant to the present time, when women with stage 2 breast cancer invariably receive adjuvant chemotherapy or hormone therapy, not available at the time of HIP, and apparently not given in the Two Counties in Sweden when that trial was conducted.^{8,9} The availability of such therapy

could be one of the major reasons for the negative findings in both arms of the Canadian National Breast Screening Study (CNBSS); we were able to demonstrate that our participants with stage 2 breast cancer did receive such therapy.^{10,11}

With regard to the CNBSS, it is disappointing that Freedman *et al.* chose to largely restrict their attention to the deaths reported in the 1992 reports on these trials, and to fail to discuss the explanations we provided for the aspects on which they focus. They say the trials were underpowered, but in retrospect it is clear that the relative lack of deaths from breast cancer was due to the good therapy the women with breast cancer received, the impact of which had not been anticipated at the time the trials were initiated in 1980. Further, the numbers of breast cancer deaths exceeded the planned level with extended follow-up.^{10,11} As an example of the effect of good therapy, the 13-year survival for the breast cancers diagnosed in the physical examination screening alone arm in CNBSS 2 was 83%, identical to those in the CNBSS 2 mammography arm and for comparably aged women in the ASP (screened) arm in the Swedish Two County trial—all superior to the 75% survival in the women with breast cancer in the PSP (control) arm in the Two County Trial.

Freedman *et al.* also comment adversely on CNBSS mammography quality, citing our report of the work of the reference radiologist. Their comments would be more convincing if they were able to cite data showing that other trials did better, but they can not, as they have never been reported, while our cancer detection rates match or exceed those in other trials, and recent population-based screening programmes.

The issue which Freedman *et al.* call 'steering' has also been addressed numerous times, but our explanations were ignored by them.¹⁰ We have demonstrated that the numbers referred for review to the CNBSS review clinics were identical in the two arms, something that would not be anticipated if 'steering' (to the mammography allocation) had in fact occurred. However, the women with physical examination findings in the mammography allocation had mammograms available to facilitate the decisions on referral for further investigation, not so the women in the usual care arm. Further, the types of institutions to which those that were referred attended differed. Gotszche and Olsen correctly recognized this as a post-randomization diagnosis bias, not a fault of randomization.

Those who wish to discount the CNBSS must take note of its size, the time and circumstances when it was conducted, and the failure to show any mortality reduction from the addition of mammography to breast physical examination and breast self-examination in spite of the expected numbers of small, node-negative breast cancers detected through mammography.¹¹ The question asked in this trial was different from all other screening trials, and the IARC working group correctly therefore did not include the trial in assessing efficacy of mammography alone compared with no screening for women

age 50 or more. However, disappointingly, they did not consider the theoretical implications of our negative finding, which has led to renewed interest in alternatives to mammography in countries that cannot afford it.

In conclusion, we are now in an era where major advances in breast cancer therapy are having major impacts on breast cancer mortality. It is quite unclear whether the efficacy of mammography screening demonstrated in the pre-adjuvant therapy era will be replicated in effectiveness in the post-adjuvant era. Some initial analyses are not encouraging in this respect.^{12,13} Only time will tell if screening can achieve its promise in practice.

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