Title: Using observational data to estimate an upper bound on the reduction in cancer mortality due to periodic screening

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Reviewer: Stephen W Duffy

Level of interest: A paper whose findings are important to those with closely related research interests

Advice on publication: Accept after discretionary revisions

1. As always with Stuart Baker, this is an impressive piece of work. I have only one major comment, and that is to disagree with the statement that it is not meaningful to compare the PSE results with the intention to treat results of the trials. Of course the authors are correct to note that it would not be meaningful to compare the two on the expectation that the results would be equivalent. It is interesting, however, to compare them in the sense of seeing if one is compatible with the other, bearing in mind study group non-compliance and control group contamination rates. For example, the PSE estimates of relative benefit ought to be higher if there is poor compliance or if assumption 1 fails. I would therefore suggest that figure 2 be accompanied by statements of the PSE results in the text and that these should also be expressed as percent reductions in mortality. These could then be interpreted in the light of the intention to treat results, compliance/contamination rates and the likelihood of assumption 1 applying.

Some minor points:

2. Equation (3) needs a little signposting. I tried to prove it algebraically and got bogged down, then realised that in principle it simply expresses the probability of death from the disease within 5 years as a product of two separate components, the first being the probability of not succumbing to competing risks and the second the complement of survival from the disease in question. It would help the reader if this point were made explicitly.

3. There are occasions when the interval cancers have survival at least as good as those of an unscreened population, possibly through increased awareness thanks to the screening programme or possibly to effects of interval length. For example, in the Swedish Two-County Study, the interval cancers had marginally better survival than the tumours in the control group. In general, interval cases tend to be a mix of tumours with influences on prognosis including the length bias in reverse phenomenon noted by the authors, differing types of tumours arising at specific time phases after a negative screen, different kinds of tumours missed at screening due to mammographic-pathologic correlations, and the effect of increased awareness.

4. Should competing risks be a feature of the argument in the first paragraph of Step 3 (page 7)?
5. Equations (8) and (9) require a little explanation.

6. In the validation methodology section, it is worth referring to Cuzick J, Edwards R, Segnan N. Adjusting for non-compliance and contamination in randomized clinical trials. Stat Med 1997; 16: 1017-1029. This is strongly related to the noncompliance adjustment used.

**Competing interests:**

None declared.