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Correspondence

Reply to Koleva-Kolarova et al.☆

Dear editor,

We would like to sincerely thank the authors for their extensive overview on simulation models for breast cancer screening [1,2]. The multitude of papers cited clearly shows the utility of modelling in predicting harms and benefits of screening scenarios, guiding policy decisions and ultimately quantifying the effects of running programmes. Recent examples include the USPSTF-recommendations on lung, colorectal and breast cancer screening, partially based on CISNET modelling [3–5], but also the EU guidelines and IARC statements on (breast) cancer screening include simulation model-evidence. We therefore almost implicitly disagree with the authors' unfounded statement that there is high risk of bias in the model outcomes.

One main argument mentioned is the lack of external validation, defined as comparison of the output of the model to independent data sources. The essence of most models is a natural history model of cancer (by the way, contrary to what the authors claim, most models consider the possibility of non-progressive disease) with key estimates on screen-detectability (e.g., by age, density, histological type, race, risk) and sensitivity, estimated by using high quality data in the clinical situation and the screening situation. When going to another setting, this by nature means re-fitting these parameters; other radiologists, machinery, and screening protocol impact these durations and sensitivity estimates, as will differences in awareness and clinical stage distribution outside the (other) screening context. Most of the CISNET models have extensively reported on this. For example, the MISCAN model reported that German preliminary data implied a 12% difference in sensitivity, compared to Dutch parameters [6]. Conversely, we estimated that new evidence from the Swedish trials had to be interpreted as an 11% larger improvement in prognosis than the initially used estimate [7], and to be able to reproduce the findings of the UK-frequency trial, a relatively low sensitivity had to be assumed [8]. We may not have used a good terminology for these validations, but a good fit to new observed data is more important than sticking to a non-evolving model.

In fact, the importance of differences in settings is also implicitly highlighted by the authors by comparing the mortality reductions from randomized trials to those predicted by the models. The authors state that all models tended to overestimate the mortality reductions, but do not acknowledge that there are many important differences between the trials and the situation for which the model predictions were made. For example, MISCAN-Fadia simulated the Two County Study and predicted a mortality reduction after 11 years of 27%, as compared to an observed 30% reduction (and, thus, did not overestimate the mortality reduction from the trial) [9]. For a different setting (United States, 100% adherence to screening and indicated treatment) the same model predicted mortality reductions ranging from 13% to 49%, depending on the screening scenario (biennial screening from age 60–69 vs. annual screening from age 40–84) [4]. Simply comparing model predictions from one situation to observations from a completely different situation is therefore not very informative.

With regard to validation, two aspects are unfortunately not mentioned by the authors. First, external validation by others: in several instances, the CISNET models have been replicated by independent researchers based on the transparent reporting of all basic parameters in our papers, for example, the MISCAN model for prostate cancer [10,11], as well as breast cancer [12]. Secondly, it is crucial that the predictions, for which we build these models, ultimately unfold, referred to as predictive validation [13]. According to the ISPOR-SMDM Modeling Good Research Practices Task Force this type of validation is “the most desirable type, as it corresponds best to modelling's purpose: predicting what will happen” [13]. MISCAN model predictions for the impact of breast cancer screening on incidence, made in 1994 for a steady-state screening situation [14], closely resemble the actual breast cancer incidence rates in 2010 in the Netherlands (Fig. 1). It is a nice example of real and rather excellent external/predictive validation, given the time frames incorporated.

Another point of criticism that the authors mention is that the models did not report on the harms associated with screening. The only reason harms were not mentioned in the publications from the “original models” was that the research question was to estimate the contribution of screening and treatment on the mortality reduction [15]; answering this question did not involve mentioning harms. As the authors themselves note in the article, in many other papers, the harms of screening are reported extensively, highlighting the number of false-positive results [4,16], with some articles even focussing explicitly on harms, including radiation [17] and overdiagnosis [18].

The paper provides a nice overview of the important aspects that other modellers or new cancer type models have to incorporate into their work, in line with what others have reported recently [19]. It also shows the extensive work that goes into modelling, to us stressing the fact that it seems rather inefficient and waste of resources to start building new models on cancer types that already have an extensive track record.

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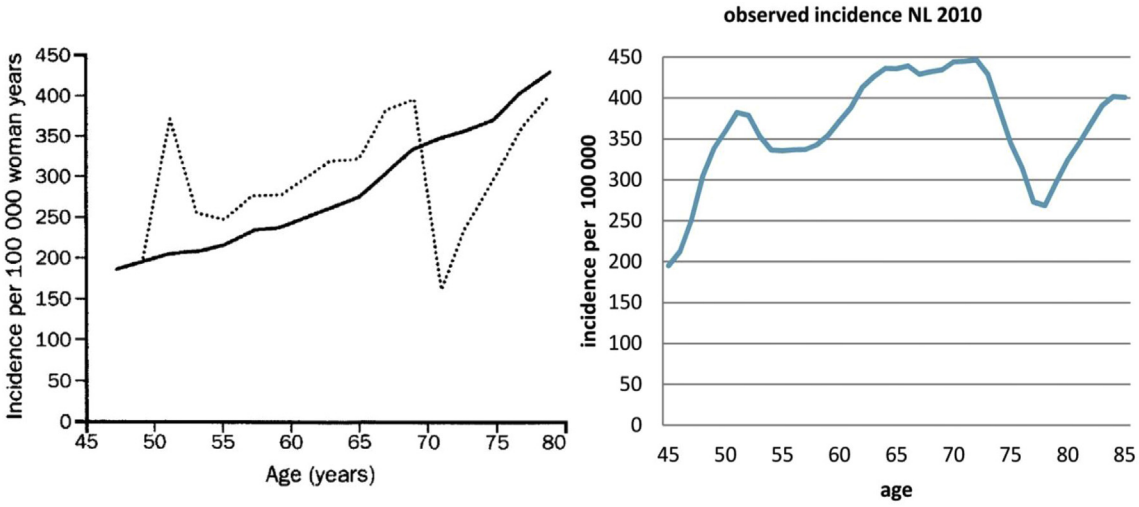

Fig. 1. Predicted breast cancer incidence in the Netherlands in a situation without and with screening from age 50 to 69 (left), compared with the observed breast cancer incidence in 2010 with screening up to age 75 (right). Solid line in left figure = not screened, dotted line = screened.
Left figure reprinted from Boer et al., the Lancet, 1994 with permission from Elsevier.

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