Conclusions

CONCLUSIONS

Research question 1: How can model description, comparison, and validation contribute to a better understanding of model predictions?

Describing the breast cancer natural history, screening, treatment, and demography component of micro simulation model MISCAN-Fadia provided necessary information to understand the workings of the model. The most important and distinct characteristics of the model are continuous tumor growth, the fatal diameter concept representing metastasized "fatal" breast cancer, and the use of tumor size as a proxy for screen detection and treatment effects. We concluded that the model is quite flexible and can synthesize data from different sources, but also requires recalibration of several inputs before these can be used in this tumor-size oriented model. In this detailed model description, we justified modeling choices, and listed considerations as well as limitations that should improve transparency.

The comparison of model predictions of overdiagnoses among screen detected DCIS was 34% to 72% and 2% to 12% among invasive breast cancers in a biennial 50-74 screening scenario. We concluded that regardless of differences in model structure and assumptions about breast cancer natural history, overdiagnoses among DCIS is extensive and as long as the standard of care is treatment of DCIS upon diagnosis, many women are overtreated. Convergence of overdiagnoses predictions can be achieved when data on, currently unobservable, DCIS progression rates becomes available from active surveillance trials.

The models´ predictive ability was formally assessed by the comparison of breast cancer incidence and mortality predictions of annual screening from ages 40 to 49 to observed outcomes in the Age trial. The models reproduced the patterns in breast cancer incidence, but underestimated breast cancer mortality reduction at 10- and were more accurate at 17-year follow-up. We concluded that the model structures, existing input parameters, and assumptions about breast cancer natural history are reasonable for estimating the impact of screening on mortality in the 40-49 age group.

The maximum clinical incidence reduction (MCLIR) method was used to compare models and disentangle the interplay between screening and treatment interventions with model-specific assumptions about unobservable breast cancer natural history. Overall, we concluded that in models, the timing of tumor inception and its effect on the length of the pre-clinical phase of breast cancer had substantial impact on predictions for breast cancer incidence and mortality reduction.

Research question 2: What are the benefits and harms of current age-based breast cancer screening in the United States?

The models consistently showed that biennial screening starting at age 40 instead of 50 lead to disproportionately more false-positives and overdiagnoses among average-risk women. Breast cancer mortality was only modestly lowered, but QALYs gained increased by 22%. Compared to annual screening strategies, biennial screening resulted in the greatest gain in benefits per mammogram and dominated annual strategies for average-risk women. Only for women at 2-to 4-fold average risk could consider annual screening at ages 40 or 50. Overall, we concluded that screening starting at age 40 has some benefits, but increased the harms substantially.

In light of the simultaneous improvements in breast cancer screening and treatment in the last decade, the models incorporated the transition from film to digital mammography and included molecular subtype specific breast cancer treatments to separate the contributions of either to breast cancer mortality reduction. In 2000, the contribution of screening to overall breast cancer mortality reduction was 44% vs. 56% explained by treatment. We showed that between 2000 and 2012 there has been a shift in relative contributions, screening was estimated to be responsible for 37% and treatment for 63% of the total breast cancer mortality reduction in 2012. The models concluded that dissemination and improved delivery of new molecularly targeted therapies has had a stronger impact than screening improvements on breast cancer mortality between 2000 and 2012.

The ionizing radiation associated with repeated mammography may increase breast cancer risk and could lead to radiation induced cancer. Annual screening including diagnostic work-up among women aged 40 to 74 years induced 125 breast cancers and 16 breast cancer deaths per 1.000 women screened. Biennial screening from ages 50 to 74 resulted in 27 breast cancers and only 4 breast cancer deaths. Overall, we concluded that it is important to account for variation in radiation amount caused by diagnostic work-up following an abnormal screening result, false-positive recalls, breast thickness, breast augmentation, breast biopsies, and follow-up screening examinations when quantifying the number of radiation induced breast cancer and breast cancer deaths

Research question 3: To what extent can risk-based breast cancer screening improve the harm-benefit ratio of current age-based screening guidelines?

The results of screening based on breast density and risk-level showed that increased breast cancer risk from either source was associated with more benefits of screening. Conversely, the number of false-positives and benign biopsies decreased with increasing risk and density while the number of overdiagnoses increased by risk. When considering a cost-effectiveness threshold of $100,000 per QALY, triennial screening was the only

effective strategy for women with low breast density at average risk. Biennial screening was cost-effective among women at increased risk regardless of density, and annual screening was only cost-effective across subgroups at the highest (4.0) risk level and breast density categories 3 and 4 (extremely dense). Overall, we concluded that breast density and risk level can be used to guide screening intervals.

We projected greater benefits (breast cancer deaths averted, life years gained) when screening was based on polygenic risk scores rather than family history. The screening approach combining risk from polygenic risk and family history resulted in the maximum improvement in benefits compared to current age-based screening guidelines. Women at high risk due to a first degree family history of breast cancer and/or high polygenic risk could initiate screening before age 50. Women with below-average polygenic risk could consider triennial screening. A large part of the projected increase in benefits was explained by the increase in cancer detection following from more screening examinations. Nevertheless, the benefits would still modestly increase at equal number of screens.