The impact of risk stratification by polygenic risk and age on breast cancer screening in women aged 40–49 years: a modelling study

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Abstract

Background **Polygenic Risk Scores (PRSs) have been proposed as a mechanism for risk-stratification of screening, increasing efficiency and enabling extension of existing programmes to improve survival in our aging population. We sought to model the impact of three hypothetical programmes of annual breast cancer screening in women aged 40–49 years: screening the PRS-defined high-risk quintile, screening the oldest quintile, and screening the full population.**

Methods **In this UK-based modelling study, we used the published estimate of the area under the curve (AUC) of a currently available breast cancer PRS (0·64) to calculate the proportion of cancers captured by the PRS-defined high-risk quintile. We used population size estimates from the Office for National Statistics alongside age-stratified incidence rates of breast cancer, and age or stage-specific survival data from the National Cancer Registry, to build our model. We used stage-specific route-to-diagnosis data to reassign stage-specific survival for screen-detected cancers. Ethics approval was not required.**

Findings **The PRS-defined high-risk quintile, oldest quintile, and full population capture 37% (n=2811), 29% (n=2198), and 100% (n=7533) of breast cancers occurring in women aged 40–49 each year. Annual screening of each group using digital mammography (sensitivity 70%, specificity 92%) would identify 1968, 1538, and 5273 breast cancers per year, respectively. This corresponds to an improvement in survival of 1·4% (102 deaths averted), 1·1% (80 deaths averted) and 3·6% (274 deaths averted) compared with baseline (no screening). Full population screening would require 4 369 703 mammograms and 354 246 confirmatory tests (breast biopsies) every year, while screening the oldest quintile would require 937 850 mammograms and 76 390 biopsies. Screening the PRS-defined high-risk quintile would require 873 941 mammograms and 71 658 biopsies, in addition to a PRS for all women in the age group (4 369 703).**

Interpretation **Under favourable assumptions, stratifying screening by PRS rather than age results in modest gains in survival but increases overdiagnoses, logistical complexity, and economic costs. Our study is limited by our modelling parameters (anticipated to maximise survival estimates), including complete uptake of PRS profiling and cancer screening, no interval cancers, and application of screening tools superior to those currently available in the UK. Only with randomised controlled trials, can the uptake, clinical impact, costs, and harms of PRS-stratified screening be definitively assessed.**

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Contributors

CT, AS, MEJ, and RSH designed the analyses. MEJ provided models for lifetime cancer risk and age quintile risk. ADH provided models for PRS tool discrimination. CH undertook literature review for parameterisation of the models. CH and BT did statistical analyses and generated tables for presentation. BT assembled figures for presentation. CT drafted the manuscript. All authors contributed to the final manuscript. CT, CH, BT, and MEJ have accessed and verified the raw data. CT and CH were responsible for the decision to submit the manuscript for publication.

Declaration of interests

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