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Predicting breast cancer risk and implications for prevention

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Breast cancer risk can now be predicted using a combination of several hundred common genetic variants (SNPs), rare coding variants in susceptibility genes, lifestyle risk factors, breast density and family history. The effects of common variants can be efficiently summarised using polygenic risk scores (PRS) that provide good discrimination and are well calibrated in European populations. PRS are more predictive of risk for ER-positive breast cancer but can also predict ER-negative breast cancer risk. Current uncertainties include the performance of the PRS in non-European populations and its ability to predict clinical behaviour.

Rare coding variants in several genes are known to be associated with risk: however, in contrast to the PRS, risk estimates are still very imprecise, and the subset of missense variants that are risk-associated is unclear for most genes. The BRIDGES project is attempting to address this through targeted sequencing of more than 60,000 cases and 50,000 controls from the Breast Cancer Association Consortium, coupled with *in-silico* and functional analysis.
We find convincing evidence of risk for protein truncating variants in nine genes (*ATM*, *BARD1*, *BRCA1*, *BRCA2*, *CHEK2*, *RAD51C*, *RAD51D*, *PALB2*, and *TP53*). Risks vary by cancer subtype, with variants in *ATM* and *CHEK2* more associated with ER-positive disease and variants in the other genes more associated with ER-negative disease. Missense variants, in aggregate, in *CHEK2*, and missense variants in specific domains of *ATM* and *BRCA1,* are also risk associated. All these factors are incorporated into risk models, such as BOADICEA, which can be used for genetic counselling and stratified prevention, including modifying screening programmes or risk reducing medication. Studies are now ongoing to evaluate the acceptability and costs and benefits of applying such stratified prevention approaches at the population level.