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LETTER TO THE EDITOR

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Distribution of breast cancer risk from SNPs and classical risk factors in women of routine screening age in the UK

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The validation of breast cancer risk models is important, and that by MacInnis *et al* (2013) of the BOADICEA model, which is based solely on family history, is very welcome. A recent development has been the identification of 67 breast cancer risk SNPs (Michailidou *et al*, 2013), whose main use will be together as a panel to identify women at increased risk of breast cancer. We investigated how a polygenic SNP score based on these SNPs would compare with classical risk factors including family history, and how much information it might add to risk assessment.

Our analysis was based on simulated SNP scores from 100 000 women with population allele frequencies for the 67 SNPs, and treating them as independent so that a combined risk score can be obtained by multiplying their relative risks; and the Tyrer-Cuzick (TC) risk model (Tyrer *et al*, 2004) predictions from the first 10 000 women enrolled to the PROCAS study (predicting risk of breast cancer at screening) in Manchester, UK (Evans *et al*, 2012). The TC model is based on classical phenotypic factors including age, family history, age at menopause and menarche, and parity. The outcome measure was the 10-year relative risk of developing breast cancer.

Histograms are shown in Figure 1 for the TC model, the SNP score using 18 genes previously published (Turnbull *et al*, 2010) but with risks updated from the COGS analysis in Michailidou *et al* (2013), the full set of 67 SNPs, and a combined TC + SNP67 distribution assuming independence. Initial evaluations have shown the TC and SNP18 scores appear to be independent (Evans *et al*, 2012).

Of particular interest is the >8% 10-year risk group, where NICE (2013) guidelines in the UK advise offering the preventive use of tamoxifen. The SNP score was less able to identify women at high risk than the TC model (0.02% for SNP18, 0.37% for SNP67 and 0.77% for the TC model). However, adding SNP67 to TC gave a substantial increment to 2.85%, and similar effects were seen in the 5–8% 10-year risk group (1.72%, 4.28%, 6.64% and 8.17%, respectively), which is equivalent to the NICE moderate-risk

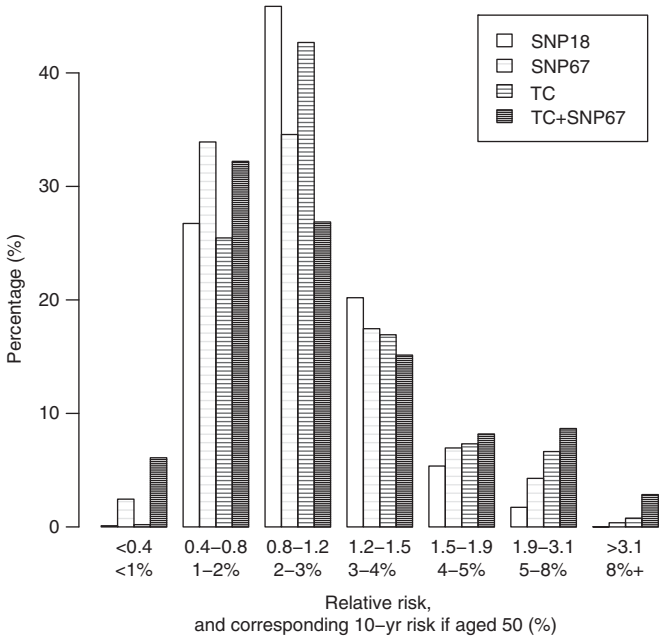

Figure 1. Predicted 10-year relative risk and corresponding absolute 10-year risk for a woman aged 50 using classical factors (TC), 18 SNPs from Turnbull *et al* (2010), the 67 COGS SNPs (SNP67) and combined (TC + SNP67). The phenotypic markers are from 10 000 women of routine screening age (46–70 years) in the UK.

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category where tamoxifen may be 'considered'. It is also noticeable that the SNPs identified more low-risk women than the TC model, which mainly uses uncommon high-risk phenotypes.

These data suggest that although the spread towards high-risk currently achieved by SNP67 is not as large as that obtained from classical phenotypic markers, SNPs may add substantially to classic factors when used together.

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