Editorial Commentary

Heritability of mammographic breast density

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A recent paper in the journal Cancer Research (1) has revisited the issue of the heritability of mammographic density (MD). This topic achieved a fair deal of attention between 2002–2010, with a number of twin studies showing heritability of MD of between 53–70% (*Table 1*), by comparing correlation in monozygous versus dizygous twins (2-5). Twin study correlations allow a distinction between shared environment and shared genetics with identical twins sharing all genetic information with dizygous twins only sharing 50% on average. As such they are the perfect cohorts to assess the 'hereditary component'. Dense areas that show white on X-ray mammography have been associated with an increased risk of breast cancer as well as masking of underlying cancers. There is an estimated 4–5 fold greater risk of breast cancer in women within the highest breast density quintile compared with the lowest quintile (after adjustment for age, menopausal status and BMI) (6,7). Because of the major impact of MD on risk even for BRCA1/2 mutation carriers (8), MD has been successfully included in several models to assess breast cancer risk (9-13).

Despite the much higher heritability of MD than breast cancer itself, with only 27–30% of breast cancer being attributable to heritable factors (14,15), far less is known about the genes or genetic factors that cause this. Around 4–5% of breast cancer was thought to be due to a putative single high risk gene (16) and most of this is now accounted for by at least 13 genes that confer at least a 2-fold relative risk (17). Although the BRIDGES study (17) of 60,466 female breast cancer cases and 53,461 controls confirmed BRCA1, BRCA2 and PALB2 in the high-risk category and ATM, BARD1, CHEK2, RAD51C and RAD51D in the moderate risk category. The risk estimates for MSH6, NF1, PTEN, STK11 and TP53 were not stable mainly due to their rarity (excepting MSH6), but these syndromic genes may have been excluded and there is strong cohort data to show they confer moderate (NF1) or high risk (PTEN, STK11 and TP53) (18). Genome wide association studies have shown that 210 confirmed single nucleotide polymorphisms (SNPs) and at least an additional 103 imputed SNPs (19) now explain 37.1% of the heritable component of breast cancer. These SNPs work in a multiplicative fashion that can be used in breast cancer risk estimation as a polygenic risk score (PRS). With the Mendelian moderate and high risk genes this means that including SNPs at least 60% of the heritable component of breast cancer is explained.

In contrast, despite a genetic analysis of MD showing that the most parsimonious model was a Mendelian single major gene model in which an allele with population

Table 1 Heritability of mammographic density from twin studies

Study	Country/region	Number of monozygous twins	Number of dizygous twins	Proportion of density heritable	Proportion of absolute dense area heritable
Boyd *et al.* 2010	Australia	353	246	61%	
Boyd *et al.* 2010	North America	218	134	67%	
Stone *et al.* 2006	Australia and North America	571	380		65%
Ursin *et al.* 2009	USA	257	296	53%	59%
Sung *et al.* 2010	Korea	122	28	58%	70%

frequency 0.39 (95% CI, 0.33–0.46) influenced MD in an additive fashion (5). No such gene has yet been identified despite this 'gene' potentially explaining 66% of the residual variance. In addition, none of the known breast cancer risk genes have been linked to any direct association with MD and any increase in MD has been pretty much refuted for BRCA1 and BRCA2 (7). Indeed to date only around 30 SNPs have been associated with MD in 20 loci in the last decade (ESR1, LSP1, ZNF365, RAD51L, TBX5, 8p11.23, AREG, IGF1, PRDM6, TMEM184B, MKL1, NTN4, TAB2, 2p24.1, EBF1, MIR1972-2:FTO, 1q12.21, HABP2, INHBB and LINC01483) (19-28). These SNPs barely account for more than 5% of the heritability of MD of which 22 are independent—the others are in high linkage disequilibrium with another and probably reflect part of the same signal.

The first paper to report on heritability of MD in 2002 showed that after adjustment for age the correlation coefficient for percentage MD was 0.61 for monozygotic twin pairs in Australia, 0.67 for monozygotic pairs in North America, 0.25 for dizygotic pairs in Australia, and 0.27 for dizygotic pairs in North America (2). Heritability accounted for 60% of the variation in MD in Australian twins, 67% in North American twins. A follow up study on the same twin cohorts estimated heritability to be 65% for dense area and 66% for non-dense area (3). A Korean study showed heritability accounted for 70% for dense area, 52% for non-dense area, and 58% for percent dense area (4). Since the original work on heritability of MD digital mammography has replaced film-screen imaging, paving the way for a variety of automated approaches to density measurement in addition to subjective visual estimation. This should enable the reproducible detection of more subtle changes and quantification of image features, although methodologies may be influenced by imaging parameters. In this paper, the selection of dense area rather than percent density is likely to have reduced the impact of errors introduced by differences in patient positioning.

The current Swedish study (1) using mammographic screening history and detailed questionnaire data from 56,820 women from the KARMA prospective cohort study also estimated heritability of mammographic features. The main aim of this study was to estimate the heritability of mammographically dense area (MDA), but also previously unstudied mammographic features including microcalcifications (mean number of clusters in both breasts), masses (not defined), and MD change (cm^2/year) and was estimated using 1,940 sister pairs. Heritability was estimated to be 58% (95% CI: 48–67%) for MD, 23% (95% CI: 2–45%) for microcalcifications, and 13% (95% CI: 1–25%) for masses. There was no association with MD change over time. The authors also found a positive association between breast cancer family history and PRS with MD ($P<0.0001$) as well as microcalcifications. The findings of a heritability component to two other mammographically measurable features (microcalcifications and masses) is novel and has important implications for assessment of future breast cancer risk. However, the heritable components of these additional risk factors are far smaller than MD. The absence of an association with another known factors associated with breast cancer risk, that of MD change association is perhaps not surprising. This is likely to be due to stochastic effects as well as non-genetic risk factors such as exposure to exogenous hormones (increase) and tamoxifen (decrease), which are known to change MD over time. There are also issues associated with the reproducibility of imaging.

The KARMA study paper is very well executed and although it contains large numbers of women does still produce data with wide confidence intervals that are close to showing no effect at the lower 95% CI for masses and calcifications. The study emphasises the complexity of using

MD and other mammographic features in breast cancer risk estimation. Some of these factors may be associated with a short-term risk, whereas MD itself confers increased risk for as long as the MD is higher than for a woman of the same age. The lack of overlap between MD SNPs in a PRS and family history have implications in ensuring that these interlinked factors are not double or triple counted in studies using multiple factors for risk estimation (9,12). However, the PRS also predicts MD in the KARMA study. There is still a very long way to go to determine markers of the hereditary component of MD. At present the discovered SNPs only scratch the surface of the strong inherited component of MD confirmed in this study.

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Footnote

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