Segregation analysis of 17,425 population-based breast cancer families: Evidence for genetic susceptibility and risk prediction

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A large population-based family study, with gene-panel sequencing data, investigated the genetic models that explain the residual breast cancer familial aggregation after considering known susceptibility genes. The results may have implications for strategies to identify new breast cancer-susceptibility genes and improve disease-risk prediction, especially at a young age.
Segregation analysis of 17,425 population-based breast cancer families: Evidence for genetic susceptibility and risk prediction

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Summary

Rare pathogenic variants in known breast cancer-susceptibility genes and known common susceptibility variants do not fully explain the familial aggregation of breast cancer. To investigate plausible genetic models for the residual familial aggregation, we studied 17,425 families ascertained through population-based probands, 86% of whom were screened for pathogenic variants in BRCA1, BRCA2, PALB2, CHEK2, ATM, and TP53 via gene-panel sequencing. We conducted complex segregation analyses and fitted genetic models in which breast cancer incidence depended on the effects of known susceptibility genes and other unidentified major genes and a normally distributed polygenic component. The proportion of familial variance explained by the six genes was 46% at age 20–29 years and decreased steadily with age thereafter. After allowing for these genes, the best fitting model for the residual familial variance included a recessive risk component with a combined genotype frequency of 1.7% (95% CI: 0.3%–5.4%) and a penetrance to age 80 years of 69% (95% CI: 38%–95%) for homozygotes, which may reflect the combined effects of multiple variants acting in a recessive manner, and a polygenic variance of 1.27 (95% CI: 0.94%–1.65), which did not vary with age. The proportion of the residual familial variance explained by the recessive risk component was 40% at age 20–29 years and decreased with age thereafter. The model predicted age-specific familial relative risks consistent with those observed by large epidemiological studies. The findings have implications for strategies to identify new breast cancer-susceptibility genes and improve disease-risk prediction, especially at a young age.

Introduction

There is a substantial familial aggregation of breast cancer (MIM: 114480). The familial relative risk (FRR) of breast cancer for having an affected first-degree relative is on average about 1.8 but is greater the younger the age at cancer diagnosis of the relative(s), the greater the number of affected relatives, and the younger the age of the consultant.1

High-risk pathogenic variants (PVs) in the currently known breast cancer-susceptibility genes BRCA1 (MIM: 113705), BRCA2 (MIM: 600185), and PALB2 (MIM: 610353) and intermediate-risk PVs in genes such as CHEK2 (MIM: 604373) and ATM (MIM: 607585)2–10 on average explain 20%–25% of the familial aggregation of breast cancer and much more at younger ages. A further on average ~20% of the familial aggregation is accounted for by a polygenic risk score (PRS) based on 313 common genetic variants identified by genome-wide association studies (GWASs).11 PVs in other genes, including BARD1 (MIM: 601593), RAD51C (MIM: 602774), RAD51D (MIM: 602954), TP53 (MIM: 191170), PTEN (MIM: 601728), and NF1 (MIM: 613113), are also associated with breast cancer risk, but to a lesser extent, and account for a small proportion of the familial aggregation.2 Consequently, a large proportion of the familial aggregation remains unexplained.

Segregation analyses have been used to develop pedigree-based statistical models of breast cancer susceptibility and predict breast cancer risk on the basis of family history, genotype, and other factors.12–15 For example, the Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA) for estimating a woman’s future risk of developing breast cancer16–20 was originally developed with data on 2,785 families and considered breast cancer familial risk to be determined by the joint effects of BRCA1 and BRCA2 PVs and a polygenic component representing the combined multiplicative effects of a large number of unknown genetic variants each making a small contribution to the variation in risk.12,14,17 The model was subsequently extended to incorporate PVs in PALB2, CHEK2, and ATM, polygenic risk scores, lifestyle- and
hormone-related risk factors, and mammographic density\(^{20}\) and more recently PVs in \(\text{BARD1, RAD51C, and RAD51D}\).\(^{21}\)

It was not previously possible to fit segregation analysis models that included the joint effects of all known breast cancer-susceptibility genes simultaneously because of the lack of data on PVs in some genes. Another challenge has been small sample sizes that limit the statistical power to distinguish different inheritance models. In this study, we conducted the analysis of this kind by using data from families ascertained through large population-based series of affected and unaffected probands for which data on PVs in \(\text{BRCA1, BRCA2, PALB2, CHEK2, ATM, and TP53}\) were available. Our objectives were (1) to estimate key genetic model parameters simultaneously to further improve the accuracy of existing genetic models and (2) to investigate the genetic models of inheritance that best explain the familial aggregation of breast cancer not accounted for by the known breast cancer-susceptibility genes and polygenic factors.

**Material and methods**

**Study sample**

The sample included 17,425 three-generation families ascertained via population-based sampling of breast cancer probands from two studies: 2,712 families from the population-based case-control family study within the Australian Breast Cancer Family Registry (ABCFR) and 14,713 families from the prospective Studies of Epidemiology and Risk Factors in Cancer Heredity (SEARCH) study in the UK.

ABCFR\(^{22–24}\) includes (1) 1,644 case families, ascertained independently of their family history through a sample of adult women living in the metropolitan areas of Melbourne and Sydney who were diagnosed between 1992 and 1999 (baseline) with a histologically confirmed first primary breast cancer (case probands) before age 70 years and (2) 1,068 control families ascertained through unaffected adult women (control probands) who were sampled at the same time via the Australian electoral rolls and frequency matched to case probands by age. Of these, 858 case families with a proband diagnosed with breast cancer before age 40 years were included in a previous segregation analysis.\(^{13}\) Case and control probands gave a blood sample and completed the same risk factor questionnaire and family history questionnaire involving the construction of a pedigree covering all known first- and second-degree adult relatives. In addition, each proband was asked to obtain permission from first- and second-degree relatives for their participation, which involved giving a blood sample, completing the same risk factor questionnaire, and providing additional information to complement the pedigree and family history information collected from the proband. This analysis used demographic data and breast and ovarian cancer (MIM: 167000) diagnoses of the probands and all their adult female first- and second-degree relatives identified at baseline. ABCFR was designed to be enriched for breast cancer diagnoses of the probands and all their adult female first-degree relatives and grandmothers collected at baseline. A total of 1,484 families with a proband diagnosed before age 55 years between 1991 and 1996 were included in previous segregation analyses.\(^{2,14}\) Of the probands included in this analysis, 94% were older than 40 years at diagnosis. Approximately three-quarters of the probands reported their ethnicity, and 99% had White European ancestry.

**SEARCH** was approved by the Human Research Ethics Committee of the University of Melbourne. SEARCH was approved by the National Research Ethics Service Committee East of England—Cambridge South. All participants provided written consent.

**PVs in breast cancer-susceptibility genes**

We studied six major cancer-susceptibility genes: \(\text{BRCA1, BRCA2, PALB2, CHEK2, ATM, and TP53}\). PVs included predicted protein-truncating variants (PTVs) and an additional subset of rare missense variants (population frequency < 0.001) for \(\text{BRCA1, BRCA2, and TP53}\). The risks associated with this subset of missense variants have been shown to be similar to those associated with PTVs\(^{7}\) and these were aggregated with the PTVs in the analysis.

In ABCFR, PVs were identified by gene-panel testing for 2,305 probands (85% of all probands) and 770 relatives and by other tests conducted before gene-panel testing was widely available (Table S1) for 2,317 probands and 1,765 relatives; 2,244 probands and 611 relatives tested by both regimes. In total, 88% of families were tested; see Southey et al.\(^{26}\) for more details about the gene-panel testing and pathogenicity definition. In SEARCH, PVs were identified by gene-panel testing for 12,654 probands (86% of all probands). No relatives were screened; see Dorling et al.\(^{2}\) for more details about the testing and pathogenicity definition. We effectively applied the American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP) criteria to classify variant pathogenicity, as our study used pathogenicity classification reviewed by the Evidence-based Network for the Interpretation of Germline Mutant Alleles (ENIGMA) Expert Panel.

**Statistical methods**

We conducted complex segregation analysis by using the pedigree analysis software MENDEL following a similar approach to that used in previous studies.\(^{12–14}\) Each woman was considered to be at risk of breast and ovarian cancer from birth until breast or ovarian cancer diagnosis, baseline interview, death, or age 80 years (whichever occurred first). The incidences of the two cancers were modeled simultaneously and assumed to be independent, conditional on genotype. For a woman \(i\) in birth cohort \(k\), from country \(c\) and at age \(t\), the incidence of cancer \(s\), \(\lambda_i(t, k, c, s)\), was assumed to depend on the genetic factors according to the following model:

\[
\lambda_i(t, k, c, s) = \lambda_0(t, k, c, s) \exp \left( \sum_{i=1}^{n} \beta_{MG_i}(t, s) G_i + P_i(t) \right)
\]

where \(\lambda_0(t, k, c, s)\) is the baseline incidence, \(\beta_{MG_i}(t, s)\) is the age-specific log-relative risk (log-RR) for a major gene that was assumed...
to be the same across countries and birth cohorts, $n$ is the number of major genotypes, and $G_{m}$ is an indicator variable that takes the value of 1 if the woman has major genotype $\mu$ and 0 otherwise. $P(t)$ is the breast cancer age-specific polygenic component that was assumed to be normally distributed with zero mean and variance $\sigma_{p}^{2}(t)$, the same across countries and birth cohorts, representing the multiplicative effects of a large number of variants each associated with a small increment in breast cancer risk. No polygenic component was included for ovarian cancer. The polygenic component was approximated by the hypergeometric polygenic model (HPM)\textsuperscript{27,28} as

$$P = \frac{R - N}{\sqrt{2}} \sigma_{p},$$

where $R$ has a binomial distribution ($2N$, $1/2$) and $N$, the number of loci used in the HPM, was 3.

We first fitted a model with a polygenic component only, without any major genes. The polygenic variance $\sigma_{p}^{2}(t)$ from this model reflects the total breast cancer familial variance under the polygenic susceptibility model.\textsuperscript{29} Note that while $\sigma_{p}^{2}(t)$ is termed the polygenic variance, it also captures the effects of non-genetic factors contributing to the risks for relatives being correlated and whose existence is suggested by analysis of twin pairs in the Nordic Twin Study.\textsuperscript{30} Given that breast cancer FRR decreases with age,\textsuperscript{31} we allowed $\sigma_{p}^{2}(t)$ to decrease linearly with age.

We then fitted a model equivalent to the BOADICEA (versions 4 and 5) in terms of the number of major genes, which included the effects of PVs in BRCA1, BRCA2, PALB2, CHEK2, and ATM, as well as the polygenic component. We sequentially extended this model to include the effects of PVs in TP53, and a hypothetical major gene for which we investigated different models of inheritance (dominant, recessive, general). We used the decrease in $\sigma_{p}^{2}(t)$ as major genes were included to express the proportions of breast cancer familial variance explained by PVs in those genes.

To reduce computational time, we fitted the major gene component by using a single locus comprising $m + 1$ alleles, where $m$ is the number of major genes considered in the model. That is, we assumed separate risk alleles representing the presence of a PV in BRCA1, BRCA2, PALB2, CHEK2, ATM, TP53, and the hypothetical gene and a normal allele. We assumed a dominant inheritance for the risk alleles in the order of the seven major genes above; therefore, there was a total of nine possible major genotypes: women with BRCA1 PVs, women with BRCA2 PVs, women with PALB2 PVs, women with CHEK2 PVs, women with ATM PVs, women with TP53 PVs, the hypothetical gene risk allele homozygotes, the hypothetical gene risk allele heterozygotes, and women without PVs. This simplification is unlikely to affect results because women with PVs in more than one major gene are very rare and would not contribute materially to the analysis; from our data, 0.1% of the women were such (Table 1). To compute the baseline incidence $\lambda(t, k, c, s)$, we used the method previously described\textsuperscript{12} to constrain the overall incidence across all genotypes to agree with the UK and Australian birth-cohort-specific smoothed population incidences used in the BOADICEA.\textsuperscript{15}

The age-specific breast and ovarian cancer RRs ($\beta_{G_{m}}(t, s)$) for BRCA1 and BRCA2 PVs and breast cancer RRs for PALB2, CHEK2, and ATM PVs were fixed at estimates from previous studies\textsuperscript{5,7,9,17}: log-RRs were functions of age for BRCA1, BRCA2, PALB2, and CHEK2 PVs (Table S2), and breast cancer RR was 2.8 for ATM PVs. Ovarian cancer RRs were assumed to be 1 for PALB2, CHEK2, and ATM PVs, i.e., ovarian cancer incidence depended on BRCA1 and BRCA2 PVs only. The risk allele frequencies for all major genes, the age-specific RRs for TP53 PVs and hypothetical gene risk allele, and the age-specific polygenic variance $\sigma_{p}^{2}(t)$ were estimated. The variances of the parameter estimates were obtained by inverting the observed information matrix. To allow for the restricted ranges of the parameter values and provide estimates likely to be more nearly normally distributed, we used transformed values for the parameters in the model: allele frequencies were logit transformed, RRs were log transformed, and $\sigma_{p}^{2}(t)$ was square-root transformed. We compared nested models by using the likelihood ratio test and non-nested models by using the Akaike information criterion. All statistical tests were two sided, and results with a $p < 0.05$ were treated as statistically significant.

Because not all PVs would be detected by the test methods used, we included a test sensitivity parameter defined as the probability of detecting a PV if one exists. In ABCFR, the test sensitivity was the weighted sum of the sensitivities of the test methods used (Table S1), and weights were the proportional lengths of the exons screened and taking into account whether multiplex ligation-dependent probe amplification had been conducted to detect large rearrangements and copy-number variations. The test sensitivity was assumed to be 100% for the relatives who had been only tested for their probands’ PV. For ABCFR probands, the average test sensitivity ranged from 88% to 90% across all genes. For SEARCH probands, the test sensitivity was assumed to be 90% for all genes. We also conducted a sensitivity analysis by assuming the test sensitivity to be 80% for all genes and all probands.

To adjust for family ascertainment, we computed the likelihood of observing the phenotypes and genotypes of each family conditional on observing the phenotypes of the proband, i.e., their cancer status and age of diagnosis or censoring. This ascertainment is justified because all families were ascertained through population-based sampling of probands, and the family history and genotype data could be assumed not to influence the ascertainment.

We computed age-specific breast cancer FRR predicted by the best fitting model by using the likelihoods from MENDEL.\textsuperscript{15} The FRR for a woman at age $t$ with a first-degree relative affected at age $t$ was computed as the ratio of two pedigree-likelihoods:

$$FRR = \frac{P(\text{The woman affected at age } t \text{ The relative affected at age } t)}{P(\text{The woman affected at age } t)} = \frac{P(\text{The woman affected at age } t \text{ The relative affected at age } t)}{P(\text{The woman affected at age } t)P(\text{The relative affected at age } t)}$$

We computed the FRRs separately for women with an affected mother and women with an affected sister. For TP53 PVs and the hypothetical gene risk allele, we estimated the age-specific cumulative risk (penetrance) to age $t$, $F(t)$, as

$$F(t) = 1 - \exp \left( - \int_{0}^{t} \lambda(t) dt \right)$$

where $\lambda(t)$ is the estimated incidence at age $t$ averaged over the polygenic effects, based on the UK population incidence for women born in 1940–1949 (the median birth year of the probands was 1948). The 95% confidence interval (CI) of $F(t)$ was calculated via a parametric bootstrap: a sample of 10,000 draws was taken from the multivariate normal distribution that the maximum likelihood estimates would be expected to follow under asymptotic likelihood theory; for each age, a corresponding sample of 10,000 cumulative risks was calculated with the
The formula above, and the 2.5th and 97.5th percentiles of this distribution were taken to be the 95% CI limits.

**Results**

A total of 15,032 (86%) probands were screened, and 892 (5.9%) were found to carry a PV in *BRCA1*, *BRCA2*, *PALB2*, *CHEK2*, *ATM*, or *TP53* (Table 1). Of the 1,924 ABCFR relatives tested, 142 from 88 families were found to carry a PV (Table S3), and 164 from 86 families did not carry the PV found in their affected probands. 2,449 (14.1%) and 1,521 (8.7%) probands had a family history of breast cancer in first-degree relatives and second-degree relatives, respectively; the corresponding numbers for a family history of ovarian cancer were 328 (1.9%) and 165 (0.9%), respectively (Table S4).

When a polygenic-component-only model was fitted, $\sigma^2_f(t)$ was 3.86 (95% CI: 3.27, 4.47) at age 20–29 years (calculated with the middle point, i.e., 25 years; the same for the age ranges below), decreasing to 0.72 (95% CI: 0.42, 1.03) at age 70–79 years (Table S5). After additionally fitting *BRCA1*, *BRCA2*, *PALB2*, *CHEK2*, and *ATM*, $\sigma^2_f(t)$ was 2.25 (95% CI: 1.61, 2.88) at age 20–29 years, decreasing to 1.11 (95% CI: 0.70, 1.51) at age 70–79 years. The proportion of the total breast cancer familial variance attributed to these five major genes was therefore 42% at 20–29 years and decreased steadily with age thereafter (Figure 1; Table S6).

We then additionally fitted a sixth hypothetical major gene (Table S5). All three inheritance models (dominant, recessive, and general) that included the hypothetical gene gave a better fit than their equivalent nested models (all $p < 0.03$). The dominant inheritance model gave the best fit, and the general inheritance model essentially converged to the dominant inheritance model. Under the dominant inheritance model, the hypothetical gene had a risk allele frequency of 0.003% (95% CI: 0.001%, 0.008%) and an RR of 340 (95% CI: 140, 810); $\sigma^2_f(t)$ was 1.53 (95% CI: 1.37, 1.70), and there was no evidence that $\sigma^2_f(t)$ depended on age ($p = 0.2$).

| Age group (years) | Total | Probands with *BRCA1* PVs | Probands with *BRCA2* PVs | Probands with *PALB2* PVs | Probands with *CHEK2* PVs | Probands with *ATM* PVs | Probands with *TP53* PVs | Probands without PVs | Untested |
|-------------------|-------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|---------------------|---------|
| ABCFR case families | <30   | 88                       | 7 (8.6%)                 | 6 (7.4%)                 | 1 (1.2%)                 | 2 (2.5%)                 | 2 (2.5%)                 | 3 (3.7%)            | 60 (74.1%) | 7       |
|                   | 30–39 | 810                      | 43 (6.0%)                | 27 (3.8%)                | 1 (0.1%)                 | 11 (1.5%)                | 5 (0.7%)                 | 5 (0.7%)            | 628 (87.3%) | 91      |
|                   | 40–49 | 368                      | 15 (4.3%)                | 5 (1.4%)                 | 4 (1.2%)                 | 6 (1.7%)                 | 3 (0.9%)                 | 0 (0%)              | 313 (90.7%) | 23      |
|                   | 50–59 | 346                      | 2 (0.6%)                 | 6 (1.8%)                 | 5 (1.5%)                 | 2 (0.6%)                 | 3 (0.9%)                 | 3 (0.9%)            | 315 (91.8%) | 10      |
|                   | 60–69 | 32                       | 0 (0%)                   | 0 (0%)                   | 0 (0%)                   | 1 (3.4%)                 | 1 (3.4%)                 | 27 (93.1%)          | 3       |
| Total             | 1,644 | 67                       | 4 (2.9%)                 | 11 (0.7%)                | 21 (1.4%)                | 14 (0.9%)                | 12 (0.8%)                | 1,343 (88.9%)       | 134     |
| ABCFR control families | <30   | 86                       | 0 (0%)                   | 1 (1.7%)                 | 0 (0%)                   | 1 (1.7%)                 | 3 (5.0%)                 | 0 (0%)              | 55 (91.7%) | 26      |
|                   | 30–39 | 468                      | 2 (0.5%)                 | 3 (0.8%)                 | 1 (0.3%)                 | 0 (0%)                   | 1 (0.3%)                 | 0 (0%)              | 366 (98.4%) | 96      |
|                   | 40–49 | 240                      | 2 (0.9%)                 | 1 (0.5%)                 | 0 (0%)                   | 2 (0.9%)                 | 0 (0%)                   | 0 (0%)              | 206 (97.6%) | 29      |
|                   | 50–59 | 218                      | 0 (0%)                   | 0 (0%)                   | 0 (0%)                   | 1 (0.5%)                 | 2 (1.1%)                 | 1 (0.5%)            | 179 (97.8%) | 35      |
|                   | 60–69 | 56                       | 0 (0%)                   | 0 (0%)                   | 0 (0%)                   | 0 (0%)                   | 0 (0%)                   | 0 (0%)              | 42 (100%)  | 14      |
| Total             | 1,068 | 4 (0.5%)                 | 6 (0.6%)                 | 1 (0.1%)                 | 4 (0.5%)                 | 6 (0.7%)                 | 1 (0.1%)                 | 848 (97.7%)         | 200     |
| SEARCH            | <30   | 60                       | 4 (8.9%)                 | 2 (4.4%)                 | 1 (2.2%)                 | 3 (6.7%)                 | 0 (0%)                   | 1 (2.2%)            | 35 (77.8%) | 15      |
|                   | 30–39 | 878                      | 19 (2.8%)                | 29 (4.2%)                | 1 (0.1%)                 | 15 (2.2%)                | 1 (0.1%)                 | 5 (0.7%)            | 614 (89.8%) | 194     |
|                   | 40–49 | 3,519                     | 40 (1.4%)                | 72 (2.5%)                | 23 (0.8%)                | 53 (1.8%)                | 21 (0.7%)                | 6 (0.2%)            | 2,665 (92.6%) | 642     |
|                   | 50–59 | 5,694                     | 27 (0.5%)                | 79 (1.6%)                | 39 (0.8%)                | 83 (1.7%)                | 37 (0.8%)                | 1 (0.02%)           | 4,648 (94.6%) | 782     |
|                   | 60–69 | 4,558                     | 10 (0.2%)                | 41 (1.0%)                | 18 (0.4%)                | 49 (1.2%)                | 31 (0.8%)                | 1 (0.02%)           | 3,983 (96.4%) | 426     |
|                   | 70–79 | 4                        | 0 (0%)                   | 0 (0%)                   | 0 (0%)                   | 0 (0%)                   | 0 (0%)                   | 0 (0%)              | 4 (100%)    | 0       |
| Total             | 14,713 | 100 (0.8%)               | 223 (1.8%)               | 82 (0.6%)                | 203 (1.6%)               | 90 (0.7%)                | 14 (0.1%)                | 11,949 (94.4%)       | 2,059    |

*Ten Probands had a PV in two genes: ABCFR case families—one proband (30–39 years) in *BRCA1* and *BRCA2* and one proband (40–49 years) in *BRCA1* and *CHEK2*; ABCFR control families—one proband (30–39 years) in *BRCA2* and *ATM*; SEARCH—two probands (40–49 years, 60–69 years) in *BRCA1* and *CHEK2*, one proband (50–59 years) in *BRCA2* and *PALB2*, and four probands (one <30 years, two 40–49 years, and one 50–59 years) in *BRCA2* and *CHEK2*. Within each age group, proportions (percentages in the parentheses) were calculated within the tested probands only, i.e., untested probands were excluded.*
Most of the difference in log-likelihoods between the dominant inheritance model for the hypothetical gene and its equivalent nested model without the gene was attributed to a small number of families (Figure S1). For all ten families contributing the most evidence for the hypothetical gene, the proband carried a PV in TP53. No PVS in the other genes were identified for the probands of these families from the gene-panel testing data. We therefore hypothesized that the hypothetical gene might reflect the effects of TP53 PVS and further extended the models to include TP53.

Incorporating TP53 in addition to the five major genes while fitting an age-decreasing $\sigma_2^2(t)$ improved the model fit ($p < 10^{-15}$; Table S8). The best fitting model included a TP53 RR, which decreased linearly with age on the log-RR scale over age 20–49 years and then was constant over age 50–79 years. Under this model, the frequency for TP53 PVs was 0.017% (95% CI: 0.009%, 0.034%) and the estimated cumulative risk of breast cancer to age 80 years for TP53 PVs was 45.0% (95% CI: 25.5%, 74.0%) (Figure 2). After fitting TP53, there was marginal evidence ($p = 0.07$) that $\sigma_2^2(t)$ decreased with age. On the basis of the model with an age-decreasing $\sigma_2^2(t)$, the proportion of the total breast cancer familial variance attributed to TP53 was 3.5% at age 20–29 years and decreased with age thereafter; in terms of the residual familial variance after adjusting for the effects of BRCA1, BRCA2, PALB2, CHEK2, and ATM, the proportion decreased from 6.1% at age 20–29 years (Figure 1; Table S6).

On the basis of the best fitting model that included TP53 and an age-constant $\sigma_2^2(t)$, we incorporated an additional hypothetical gene (Table 2). There was evidence for the hypothetical gene under both the recessive and general
inheritance models (both $p < 0.02$), and the general inheritance model essentially converged to the recessive inheritance model. Under the best fitting recessive inheritance model, the hypothetical gene had a risk allele frequency of 13% (95% CI: 5%, 23%) and an RR of 10 (95% CI: 4, 25), giving a cumulative risk to age 80 of 69.4% (95% CI: 37.9%, 94.7%) for homozygotes (Figure 2). Under this model, $\sigma^2(t)$ was estimated to be 1.27 (95% CI: 0.94, 1.65) and there was no evidence that it depended on age ($p = 0.81$). The proportion of the total breast cancer familial variance explained by the hypothetical gene was 21.6% at age 20–29 years and decreased steadily with age thereafter; in terms of the residual familial variance after adjusting for the effects of $BRCA1$, $BRCA2$, $PALB2$, $CHEK2$, $ATM$, and $TP53$, the proportion was 39.7% at age 20–29 years and decreased thereafter (Figure 1; Table S6). Under this model, the PV allele frequencies of $BRCA1$, $BRCA2$, $PALB2$, $CHEK2$, $ATM$, and $TP53$ were 0.080%, 0.141%, 0.059%, 0.385%, 0.167%, and 0.017%, respectively, corresponding to frequencies of individuals with $BRCA1$, $BRCA2$, $PALB2$, $CHEK2$, $ATM$, and $TP53$ PVs of 0.159%, 0.281%, 0.119%, 0.768%, 0.334%, and 0.034%, respectively.

No family contributed a large change in the log-likelihood when the hypothetical gene (recessive inheritance model) was added (Figure S1). For all ten families contributing most to the evidence for the hypothetical gene, the proband had at least one sister diagnosed with breast cancer before or at age 45 years (Table S9). No PV was identified for the probands of these ten families from the gene-panel testing data.

Similar results were found from the sensitivity analyses in which the PV test sensitivity was reduced to 80% (Table S10). With this sensitivity, the PV allele frequencies of $BRCA1$, $BRCA2$, $PALB2$, $CHEK2$, $ATM$, and $TP53$ genes were 0.089%, 0.157%, 0.067%, 0.432%, 0.187%, and 0.020%, respectively, corresponding to frequencies of individuals with $BRCA1$, $BRCA2$, $PALB2$, $CHEK2$, $ATM$, and $TP53$ PVs of 0.178%, 0.313%, 0.133%, 0.862%, 0.374%, and 0.039%, respectively.

The age-specific FRRs associated with a family history in a first-degree relative predicted by the best fitting recessive inheritance model were consistent with those observed by the largest combined analysis of epidemiological studies (Table 3). At each age, the FRR associated with a sister affected was slightly greater than the FRR associated with the mother affected.

**Discussion**

This study provides insights into the genetic susceptibility of breast cancer. In terms of explaining why women of the
same age differ in risk, the known susceptibility genes, including \(BRCA1\), \(BRCA2\), \(PALB2\), \(CHEK2\), \(ATM\), and \(TP53\), play more important roles at younger ages; the proportion of the total breast cancer familial variance explained by these genes was 46% at age 20–29 years and decreased steadily with age thereafter. GWASs have identified several hundred common genetic variants associated with breast cancer risk; these variants combine multiplicatively, and their effects can thus be summarized by a PRS. The most extensively validated PRS, comprising 313 common genetic variants, is associated with breast cancer risk with little evidence of variation in the relative risk by age, implying that the PRS explains a higher fraction of the breast cancer familial variance at older ages than at younger ages. The odds ratio (OR) per standard deviation of the PRS is 1.61, equivalent to a familial variance of \(~0.23\). Therefore, the PRS accounts for about 20% of the residual polygenic variance of 1.27 estimated after taking into account the known and predicted additional major gene(s), in line with previous estimates for the PRS contribution.\(^{11,20}\) The breast cancer familial variance explained by all imputable common genetic variants via the OncoArray (i.e., chip heritability) was estimated to be approximately twice that explained by the known common genetic variants (and thus about 40% of the residual polygenic variance).\(^{31}\) As illustrated in Figure 1, there is substantial breast cancer familial variance that cannot be explained by the known susceptibility genes and common genetic variants, and the unexplained familial variance is larger at younger ages. Therefore, breast cancer genomic studies focused on individuals diagnosed at younger ages may be a fruitful approach to identifying novel breast cancer susceptibility genes.

### Table 2. Models including \(BRCA1\), \(BRCA2\), \(PALB2\), \(CHEK2\), \(ATM\), \(TP53\), a hypothetical gene, and a polygenic component

| Parameters | Dominant inheritance model | Recessive inheritance model* | General inheritance model | Recessive inheritance model with an age-dependent \(\sigma^2(t)\)* |
|------------|----------------------------|----------------------------|---------------------------|--------------------------------------------------|
| \(\sigma^2(t)\) (95% CI) | 1.334 (1.448, 1.624) | 1.272 (0.944, 1.649) | 1.272 (0.908, 1.698) | \(\pi = 1.066 \text{ (95% CI: } -1.186, 3.318\), \(\beta = 0.004 \text{ (95\% CI: } -0.033, 0.040)\) |

### PV allele frequency (95% CI)

| Gene   | Frequency (95% CI) |
|--------|--------------------|
| BRCA1  | 0.080% (0.069%, 0.092%) |
| BRCA2  | 0.141% (0.126%, 0.158%) |
| PALB2  | 0.060% (0.049%, 0.073%) |
| CHEK2  | 0.385% (0.338%, 0.438%) |
| ATM    | 0.167% (0.139%, 0.200%) |
| TP53   | 0.018% (0.005%, 0.037%) |
| Hypothetical gene | 0.001% (0.0002%, 0.007%) |

### RR of TP53 PVs (95% CI)

| Age     | RR of TP53 PVs (95% CI) |
|---------|-------------------------|
| 20–29 years | 134.43 (44.84, 401.30) |
| 30–39 years | 30.81 (9.59, 98.44) |
| 40–49 years | 7.06 (1.58, 31.60) |
| 50–59 years | 3.01 (0.36, 25.45) |
| 60–69 years | 3.01 (0.36, 25.45) |
| 70–79 years | 3.01 (0.36, 25.45) |

### RR of the hypothetical gene (95% CI)

| Heterozygote | 282.55 (259.43, 307.72) |
| Homozygote | 282.55 (259.43, 307.72) |
| Log likelihood | –35,635.90 |
| Number of parameters estimated | 12 |
| Akaike information criterion | 71,295.80 |
| \(p^2\) | 0.23 |

\(\log RR = a + b \times (age - 20)\) in age 20–49 years, where \(a = 5.71 \text{ (95\% CI: } 4.72, 6.69\), \(b = -0.15 \text{ (95\% CI: } -0.21, -0.09)\).

\(\sigma^2(t) = \pi + \beta \times age.\)

\(\sigma^2(t) = \pi + \beta \times age.\)

\(\text{From the likelihood ratio test of comparing with the model including } BRCA1, BRCA2, PALB2, CHEK2, ATM, \text{ and an age-constant } \sigma^2(t).\)
cancer genetic susceptibility genes or variants. Our analyses predicted a recessively inherited risk component explaining a substantial proportion of the residual familial variance after taking into account PVs in *BRCA1, BRCA2, PALB2, CHEK2, ATM, TP53,* and the PRS, with the proportion greater at younger ages (44% at ages 20–29 years) and decreased steadily with age thereafter.

Although our study sample overlapped with the data used in three previous analyses, the current dataset was seven times larger. Moreover, we were able to include PV data for the large majority of probands, providing much more robust analyses. Our evidence for an additional recessively inherited major breast cancer-susceptibility gene, after considering the effects of PVs in *BRCA1, BRCA2, PALB2, CHEK2, ATM, TP53,* and the PRS, is consistent with the results from previous analyses. The best fitting model predicted age-specific FRRs consistent with the observed FRRs by epidemiological studies. The recessive risk component leads to the prediction that the FRR will be higher for sisters of affected women than for mothers of affected daughters, and this is consistent with observations in population-based epidemiological studies. Although the lower relative risk for mothers could be partly explained by them being parous by definition, the risk difference is more profound before age 50 years when mothers are pre-menopausal and the protective effect of parity is weaker. Our analysis used birth-cohort-specific incidences; therefore, the results are unlikely to be due to the higher incidence for sisters, who were born more recently than mothers. However, we cannot rule out the possibility that part of the increased risk to sisters may be due to surveillance because sisters of individuals with breast cancer are more likely to participate in screening programs.

We also cannot rule out the role of non-genetic familial factors in explaining familial aggregation of breast cancer, as we only considered genetic models. The Nordic Twin Study of breast cancer found evidence for non-genetic effects shared by twins, especially at younger ages, which would also be consistent with that the FRR is greater for sister pairs than for mother-daughter pairs and could reflect factors operating prior to adulthood such as puberty-related risk factors.

Our results also do not necessarily imply there is a single additional susceptibility gene (indeed this is highly unlikely), nor imply one or two genes contribute most of the effect, because such gene(s) would probably have been identified through linkage or association studies. It is more likely that the recessive component reflects the combined effects of multiple variants (and in more than one gene or non-coding region), each potentially being associated with different effects, although the actual number of variants and genes cannot be inferred from segregation analysis alone. Nevertheless, our results could inform the design of sequencing studies to try to identify such variants by focusing on analyzing the following types of samples that do not have PVs in the known genes: (1) families with multiple affected siblings; (2) families of young women (e.g., ≤40 years) with breast cancer; and (3) a combination of (1) and (2).

Breast cancer FRR depends on pathological subtype, and the risks associated with both known breast cancer-susceptibility genes and PRS differ across subtypes. However, our study was not able to investigate this in detail because, for most families, tumor features were only available for the affected probands. Further analyses of datasets with breast cancer subtype data for both probands and relatives are needed to investigate the extent to which the recessive risk component and the residual polygenic variance are subtype specific.

We calculated the age-specific proportion of breast cancer familial variance explained by PVs in major genes as the difference in the polygenic variance between nested models.
models. The results in Table S6 suggest the proportion at age 60 and older might be minimal, despite the fact the RRs for breast cancer associated with PVs at those ages are greater than 1. The estimated contribution of PVs at older ages may have been underestimated due to the fact that the total breast cancer familial variance used to calculate the contributions was based on a model without any major genes. Under this model, the polygenic variance decreased linearly with age, which may have resulted in imprecision of the estimated variance at older ages.

Although our study—by design—did not include probands diagnosed after age 70 years, the analyses are still informative for familial aggregation after age 70 years because it was the phenotypes (i.e., age of cancer diagnosis or censoring) of relatives, not of probands, that contributed to the analyses, as the likelihood of observing the family phenotypes was conditioned on the proband’s phenotype. Our study included 22,253 relatives from 12,393 families (71% of the total families) who were censored after age 70 years, and 470 of them were diagnosed with breast cancer.

Our study did not consider the PVs in other recently established breast cancer-susceptibility genes such as BARD1, RAD51C, and RAD51D, which are incorporated in the most recent version of BOADICEA (version 6). However, these PVs only explain on average 0.31% of residual breast cancer familial variance, so not considering these PVs is unlikely to have materially impacted our results.

We previously conducted a population-based study of women with breast cancer diagnosed at a young age in ABCFR and confirmed that germline TP53 PVs occur among women diagnosed at a very young age. Here, we estimated the PV frequency to be 0.017%, similar to the 1/5,000 estimated by a segregation analysis of 278 breast cancer families ascertained via population-based cases diagnosed before age 30 years. Reliable breast cancer risk estimates from population-based studies associated with TP53 PVs are lacking. Two studies of sarcoma families reported a breast cancer cumulative risk for TP53 PVs of approximately 37% to age 80 years and 54% to age 70 years, respectively. Although these studies did not report confidence intervals for their risk estimates, our confidence intervals include those point risk estimates and therefore are not significantly different. Another prospective analysis from the longitudinal Li-Fraumeni Syndrome Study reported a breast cancer cumulative risk of approximately 56% to age 60 years, higher than our estimate and outside our confidence intervals. However, the participants in that study were from families with Li-Fraumeni syndrome, who were ascertained on the basis of family history of cancer, including family history of breast cancer. That was a prospective study with no adjustments for the ascertainment of study participants. Therefore, the risk estimate of the longitudinal Li-Fraumeni Syndrome Study would be applicable to women with TP53 PVs with cancer family history. On the other hand, the estimates in our study are based on families from population-based studies of breast cancer, and our analysis has adjusted for the ascertainment process and allowed for the modification of cancer risks by the residual familial component. As a result, our estimate represents the average risk for women with TP53 PVs unselected for family history and would be expected to be lower than the estimates for those with family history of breast cancer—similar to the patterns observed previously for the risks for women with BRCA1/2 PVs. Since the TP53 PV risks are assumed to be modified by the residual familial component, the breast cancer risk predicted by the model will vary by the exact family history, and the risks for those with one or two affected relatives will be higher than the average risk.

The findings of the current study can be used to update breast cancer-risk models, in particular BOADICEA, which currently considers the effects of PVs in known major genes and a polygenic component. Thus, the model could be updated by incorporating the recessive component, using the revised estimate for the polygenic variance, and adding TP53 PVs. However, the extent to which including the additional genes and using the updated polygenic variance improves breast cancer-risk prediction overall needs to be investigated. Moreover, such a revised model would need to be validated with independent studies.

To allow for the possibility that not all PVs can be detected by the test methods used, our analysis included a test sensitivity parameter, which was assumed to be ~90%. The actual sensitivity is difficult to estimate and will depend on the methods used. The current implementation of BOADICEA assumes sensitivities of 89%, 96%, 92%, 98%, and 94% for BRCA1, BRCA2, PALB2, CHEK2, and ATM, respectively, on the basis of typical clinically testing approaches, but the sensitivity will be lower for research testing, particularly because large rearrangements would not have been detected in the targeted sequencing used in SEARCH. Using lower test sensitivities might have resulted in some underestimation of the polygenic component and some overestimation of the contributions of rare PVs to familial aggregation, through the estimation of higher PV frequencies. However, the differences would be small, as our estimates of PV frequencies for BRCA1 and BRCA2 were slightly greater than, and the estimates for PALB2, CHEK2, and ATM were similar to, those assumed in the BOADICEA, which had been derived from large population-based targeted-sequencing data and adjusted for the test sensitivity of targeted-sequencing. On the other hand, by using lower test sensitivities, our analysis reduced the possibility that the recessive risk component is simply due to unidentified variants in any of the considered major genes; our more conservative sensitivity analysis assuming the test sensitivity to be 80% still provided evidence for a recessive risk component.

Our study has several strengths. First, it included data from more than 17,000 three-generational families ascertained via probands from population-based studies and screened for high- and moderate-risk PVs in the major
known susceptibility genes. Second, our study incorporated the explicit age-specific effects of PVs in PALB2, CHEK2, ATM, and TP53 in addition to BRCA1 and BRCA2 while modeling the residual familial variance of breast cancer as a function of age with a polygenic component.

The study has also some limitations. First, family history in some families was self-reported and therefore subject to reporting errors, though reporting of breast cancer in first-degree relatives is generally considered to be accurate. Second, we modeled the major genes by using a single locus with eight alleles and assumed the genes were in a dominant hierarchy rather than seven loci each with two alleles. While this approach substantially reduces the computational time, it could introduce some imprecision in the parameter estimates, although the impact is likely to be minimal because the PVs in the known genes are rare. The polygenic component was also approximated with a binomial distribution inherited under the hypergeometric model; previous analyses had found that results are insensitive to the number of loci assumed, but this might not be true for more complex models. Third, the majority of our probands were of White European ancestry; therefore, our findings might not be applicable to other ethnicities.

In conclusion, by considering the explicit effects of established major breast cancer-susceptibility genes and polygenes and using the largest sample size of its kind, our analysis estimates the proportion of breast cancer familial aggregation that is explained by established susceptibility genes and variants and provides evidence for an additional recessive risk component, which could explain a substantial proportion of the residual familial aggregation, especially at a younger age. Our findings are informative for the design of sequencing studies to identify novel breast cancer-susceptibility genes and modeling breast cancer genetic susceptibility for disease risk prediction.

Data and code availability
The datasets supporting the current study have not been deposited in a public repository because of ethical requirements. Requests for access to the data analyzed in this study should be made to J.L.H. (ABCFR) and P.D.P. (SEARCH). Requests for access to the analytical code should be made to S.L. and A.C.A.

Supplemental information
Supplemental information can be found online at https://doi.org/10.1016/j.ajhg.2022.09.006.

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Declaration of interests
A.C.A., A.L., and D.F.E. are listed as creators of BOADICEA v.5, which has been licensed by Cambridge Enterprise. G.D.S. is an employee of Genetic Technologies Ltd.

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Web resources
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