ORIGINAL ARTICLE

PALB2, CHEK2 and ATM rare variants and cancer risk: data from COGS


Background  The rarity of mutations in PALB2, CHEK2 and ATM make it difficult to estimate precisely associated cancer risks. Population-based family studies have provided evidence that at least some of these mutations are associated with breast cancer risk as high as those associated with rare BRCA2 mutations. We aimed to estimate the relative risks associated with specific rare variants in PALB2, CHEK2 and ATM via a multicentre case-control study.

Methods  We genotyped 10 rare mutations using the custom iCOGS array: PALB2 c.1592delT, c.2816T>G and c.3113G>A, CHEK2 c.1343T>G, c.349A>G, c.7271T>G, c.1312G>T, c.538C>T, c.1036C>T, c.1312G>T and ATM c.7271T>G. We assessed associations with breast cancer risk (42 671 cases and 42 164 controls), as well as prostate (22 301 cases and 22 320 controls) and ovarian (14 542 cases and 23 491 controls) cancer risk, for each variant. Results  For European women, strong evidence of association with breast cancer risk was observed for CHEK2 c.3113G>A OR 4.21 (95% CI 1.29 to 3.95), c.1036C>T OR 5.06 (95% CI 1.09 to 23.5) and c.7271T>G OR 11.0 (95% CI 1.84 to 9.60) for African men and c.1343T>G OR 3.03 (95% CI 1.42 to 85.7, p=0.0012). We also found evidence of association with ATM c.1592delT OR 3.44 (95% CI 1.39 to 8.52, p=7.1×10^{-5}), PALB2 c.3113G>A OR 11.0 (95% CI 1.84 to 9.60) and ATM c.7271T>G OR 11.0 (95% CI 1.84 to 9.60) for European women. For European men, strong evidence of association with prostate cancer risk was observed for CHEK2 c.1343T>G OR 3.03 (95% CI 1.42 to 85.7, p=0.0012). We also found evidence of association with breast cancer risk for three variants in CHEK2, c.349A>G OR 2.26 (95% CI 1.29 to 3.95), c.1036C>T OR 5.06 (95% CI 1.09 to 23.5) and c.7271T>G OR 11.0 (95% CI 1.84 to 9.60) for African men and CHEK2 c.1312G>T OR 2.21 (95% CI 1.06 to 4.63, p=0.030) for European women.
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men. No evidence of association with ovarian cancer was found for any of these variants.

Conclusions This report adds to accumulating evidence that at least some variants in these genes are associated with an increased risk of breast cancer that is clinically important.

INTRODUCTION

The rapid introduction of massive parallel sequencing (MPS) into clinical genetics services is enabling the screening of multiple breast cancer susceptibility genes in one assay at reduced cost for women who are at increased risk of breast (and other) cancer. These gene panels now typically include the so-called ‘moderate-risk’ breast cancer susceptibility genes, including PALB2, CHEK2 and ATM. However, mutations in these genes are individually extremely rare and limited data are available with which to accurately estimate the risk of cancer associated with them.

Estimation of the age-specific cumulative risk (penetrance) of breast cancer associated with specific mutations in these three genes has been limited to those that have been observed more frequently, such as PALB2 c.1592delT (a Finnish founder mutation), PALB2 c.3113G>A and ATM c.7271T>G. These mutations have been estimated to be associated with a 40% (95% CI 17% to 77%), 91% (95% CI 44% to 100%) and 52% (95% CI 28% to 80%) cumulative risk of breast cancer to the age of 70 years, respectively. These findings, based on segregation analyses in families of population-based case series, indicate that at least some mutations in these ‘moderate-risk’ genes are associated with a breast cancer risk comparable to that of the average pathogenic mutation in BRCA2: 45% (95% CI 31% to 56%). However, such estimates are imprecise and, moreover, may be confounded by modifying genetic variants or other familial risk factors.

Case-control studies provide an alternative approach to estimating cancer risks associated with specific variants. This design can estimate the relative risk directly, without making assumptions about the modifying effects of other risk factors. However, because these variants are rare, such studies need to be extremely large to provide precise estimates.

The clearest evidence for association, and the most precise breast cancer risk estimates, for rare variants in PALB2, CHEK2 and ATM relate to protein truncating and splice-junction variants. However, studies based on mutation screening in case-control studies, combined with stratification of variants by their evolutionary likelihood suggest that at least some evolutionarily unlikely missense substitutions are associated with a similar risk to those conferred by truncating mutations. For example, Tavtigan et al. estimated an OR of 2.85 (95% CI 0.83 to 8.66) for evolutionarily unlikely missense substitutions in the 3′ third of ATM, which is comparable to that for truncating variants. Specifically, ATM c.7271C>G has been associated with a more substantial breast cancer risk in several studies. Le Calvez-Kelm et al. estimated that the ORs associated with rare mutations in CHEK2 from similarly designed studies were 6.18 (95% CI 1.76 to 21.8) for rare protein-truncating and splice-junction variants and 8.75 (95% CI 1.06 to 72.2) for evolutionarily unlikely missense substitutions.

It is plausible that monoallelic mutations in PALB2, CHEK2 and ATM could be associated with increased risk of cancers other than breast cancer, as has been observed for BRCA1 and BRCA2 and both ovarian and prostate cancers. However, with the exception of pancreatic cancer in PALB2 carriers, there is little evidence to support or refute the existence of such associations, although a few individually striking pedigrees have been observed.

In this study we selected rare genetic variants on the basis that they had been observed in breast cancer candidate gene case-control screening projects involving PALB2, CHEK2 or ATM. These included three rare variants in PALB2: the protein truncating variants c.1592delT (p.Leu531Cysfs) and c.3113 G>A (p.Trp1038*) and the missense variant c.2816T>G, (p. Leu939Trp), six rare missense variants in CHEK2: c.349A>G (p.Arg117Gly) and c.1036C>T (p.Arg346Gly) predicted to be deleterious on the basis of evolutionary conservation, c.538C>T (p.Arg180Cys), c.715G>A (p.Glu239Lys), c.1312G>T (p.Asp437Tyr) and c.1343T>G (p.Ile448Ser) and ATM c.7271T>G (p.Val2424Gly). We assessed the association of these variants with breast, ovarian and prostate risk by case-control analyses in three large consortia participating in the Collaborative Oncological Gene-environment Study.

METHODS

Participants

Participants were drawn from studies participating in three consortia as follows:

The Breast Cancer Association Consortium (BCAC), involving a total of 48 studies: 37 of women from populations with predominantly European ancestry (42,671 cases and 42,164 controls), 9 of Asian women (5795 cases and 6624 controls) and 2 of African-American women (1046 cases and 932 controls). All cases had invasive breast cancer. The majority of studies were population-based or hospital-based case-control studies, but some studies of European women oversampled cases with a family history or with bilateral disease (see online supplementary table S1). Overall, 79% of BCAC cases with known ER status were ER-positive. The proportion of cases selected by family history that are ER-positive is 78% (38% missing).

The Prostate Cancer Association Group to Investigate Cancer Associated Alterations in the Genome (PRACTICAL) involving a total of 26 studies: 25 included men with European ancestry (22,301 cases and 22,320 controls) and 3 included African-American men (623 cases and 569 controls). The majority of studies were population-based or hospital-based case-control studies (see online supplementary table S2).

The Ovarian Cancer Association Consortium (OCAC), involving a total of 46 studies. Some studies were case-only and their data were combined with case-control studies from the same geographical region (leaving 36 study groupings). Of these groupings, 33 included women from populations with predominantly European ancestry (16,287 cases (14,542 with invasive disease) and 23,491 controls), 25 included Asian women (813 cases (720 with invasive disease) and 1574 controls), 17 included African-American women (813 cases (720 with invasive disease) and 1574 controls), 29 included women of other ethnic origin (893 cases (709 with invasive disease) and 864 controls). The majority of studies were population-based or hospital-based case-control studies (see online supplementary table S3).

Details regarding sample quality control have been published previously. All study participants gave informed consent and all studies were approved by the corresponding local ethics committees (see online supplementary tables S1–S3).

Variant selection

We selected for genotyping 13 rare mutations that had been observed in population-based case-control mutation screening studies. These variants were PALB2 (c.1592delT, p.
Leu531Cysfs\textsuperscript{4}\textsuperscript{,5}\textsuperscript{,10} c.2323C>T p.Gln775fs\textsuperscript{20} c.2816T>G, p.Leu939Trp\textsuperscript{12}\textsuperscript{,20} c.3113G>A p.Trp1183*\textsuperscript{2}, c.3549G>C p.Arg1183*\textsuperscript{2}, CHEK2 (c.349A>G p.Arg117Gly; c.538C>T p.Arg180Cys; c.715G>A p.Gln239Lys; c.1036C>T p.Arg346Cys; c.1312G>T p.Asp438Tyr; c.1343T>G p.Ile448Ser)\textsuperscript{11} and ATM (c.7271T>G, p.Val2424Gly)\textsuperscript{7}\textsuperscript{,13} see table 1. A DNA sample carrying each of these variants was included in a plate of control DNAs that was distributed to each genotyping centre to assist with quality control and genotype calling.

Genotyping

Three \textit{PALB2} variants c.2323C>T (p.Gln775*), c.3116delA (p.Asn1039Ilefs) and c.3549G>C (p.Tyr1183*) were unable to be designed for measurement on the custom Illumina iSelect genotyping array and were not considered further (table 1). Genotyping was conducted using a custom Illumina Infinium array (iCOGS) in four centres, as part of a multiconsortia collaboration.

Statistical methods

The association of each variant with breast, prostate and ovarian cancer risk was assessed using unconditional logistic regression, the \textit{ℓ}-distributed to each genotyping centre to assist with quality control and genotype calling. Inclusion was based on personal or family history of breast cancer in the general population of white European women (leaving 37 039 cases and 38 260 controls from 32 studies). Multiple testing was adjusted for using the Benjamini-Hochberg procedure to control the false discovery rate, with a significance level of 0.05.\textsuperscript{25} Reported \(p\) values are unadjusted unless otherwise stated. Reported CIs are all nominal. We included two race-specific principal components in each of the main breast cancer analyses of Asian and African-American women. Similar analyses were conducted using the data from PRACTICAL and OCAC, consistent with those used previously.\textsuperscript{23}\textsuperscript{,26} All analyses were carried out using Stata: Release V10 (StataCorp, 2008).

RESULTS

\textit{PALB2}

In BCAC, \textit{PALB2} c.1592delT (Leu531Cysfs) was only observed in 35 cases and 6 controls, all from four studies from Sweden and Finland (Helsinki Breast Cancer Study (HEBCS), Kuopio Breast Cancer Project (KBPC), Oulu Breast Cancer Study (OBCS) and Karolinska Mamography Project for Risk Prediction Breast Cancer (pKARMA); see online supplementary...
Table 2  Summary results from Breast Cancer Association Consortium studies of white Europeans (42 671 invasive breast cancer cases and 42 164 controls)

<table>
<thead>
<tr>
<th>Variant</th>
<th>Frequency* Controls</th>
<th>Frequency* Cases</th>
<th>OR (95% CI)</th>
<th>LRT p Value</th>
<th>OR† (95% CI)</th>
<th>LRT p Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>PALB2‡</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>c.1592delT (p.Leu531Cysfs)</td>
<td>0.00014</td>
<td>0.00082</td>
<td>4.52 (1.90 to 10.8)</td>
<td>7.1×10⁻⁵</td>
<td>3.44 (1.39 to 8.52)</td>
<td>0.003</td>
</tr>
<tr>
<td>c.2816T&gt;G (p.Leu939Trp)</td>
<td>0.00342</td>
<td>0.00352</td>
<td>1.05 (0.83 to 1.32)</td>
<td>0.70</td>
<td>1.03 (0.80 to 1.32)</td>
<td>0.82</td>
</tr>
<tr>
<td>c.3113G&gt;A (p.Trp1038*)</td>
<td>0.00019</td>
<td>0.00101</td>
<td>5.93 (2.77 to 12.7)</td>
<td>6.9×10⁻⁴</td>
<td>4.21 (1.84 to 9.60)</td>
<td>1.2×10⁻¹</td>
</tr>
<tr>
<td>CHEK2</td>
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<tr>
<td>c.349A&gt;G (p.Arg117Gly)</td>
<td>0.00043</td>
<td>0.00103</td>
<td>2.26 (1.29 to 3.95)</td>
<td>0.003</td>
<td>2.03 (1.10 to 3.73)</td>
<td>0.020</td>
</tr>
<tr>
<td>c.538C&gt;T (p.Arg180Cys)</td>
<td>0.00337</td>
<td>0.00370</td>
<td>1.33 (1.05 to 1.67)</td>
<td>0.016</td>
<td>1.34 (1.06 to 1.70)</td>
<td>0.015</td>
</tr>
<tr>
<td>c.715G&gt;A (p.Glu239lys)</td>
<td>0.00021</td>
<td>0.00035</td>
<td>1.70 (0.73 to 3.93)</td>
<td>0.210</td>
<td>1.47 (0.60 to 3.64)</td>
<td>0.40</td>
</tr>
<tr>
<td>c.1036C&gt;T (p.Arg334Cys)</td>
<td>0.00005</td>
<td>0.00021</td>
<td>5.06 (1.09 to 23.5)</td>
<td>0.017</td>
<td>3.39 (0.68 to 16.9)</td>
<td>0.11</td>
</tr>
<tr>
<td>c.1312G&gt;T (p.Asp438Tyr)</td>
<td>0.00078</td>
<td>0.00082</td>
<td>1.03 (0.62 to 1.71)</td>
<td>0.910</td>
<td>0.87 (0.49 to 1.52)</td>
<td>0.62</td>
</tr>
<tr>
<td>c.1343T&gt;G (p.Ile448Ser)†</td>
<td>0.00002</td>
<td>0</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>ATM</td>
<td></td>
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</tr>
<tr>
<td>c.771T&gt;G (p.Val2424Gly)</td>
<td>0.00002</td>
<td>0.00028</td>
<td>11.6 (1.50 to 89.9)</td>
<td>0.0012</td>
<td>11.0 (1.42 to 85.7)</td>
<td>0.0019</td>
</tr>
</tbody>
</table>

*Proportion of subjects carrying the variant.
†Excluding women from five studies that selected all cases based on family history or bilateral disease and the subset of selected cases from other studies (based on 34 488 unselected cases and 34 059 controls).
‡CHEK2 c.1343T>G (p.Ile448Ser) was only observed in one control and no cases of white European origin.
§PALB2 c.3113G>A (p.Trp1038*) only observed in Finland and Sweden.
LRT, likelihood ratio test; OR, OR for carriers of the variant versus common-allele homozygotes, adjusted for study and seven principal components.

Table 3  Summary results from the Prostate Cancer Association Group to Investigate Cancer Associated Alterations in the Genome studies for white European men* (22 301 prostate cancer cases and 22 320 controls)

<table>
<thead>
<tr>
<th>Variant</th>
<th>Frequency† Controls</th>
<th>Frequency† Cases</th>
<th>OR (95% CI)</th>
<th>LRT p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PALB2</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>c.1592delT (p.Leu531Cysfs)</td>
<td>0.00018</td>
<td>0.00031</td>
<td>2.06 (0.59 to 7.11)</td>
<td>0.24</td>
</tr>
<tr>
<td>c.2816T&gt;G (p.Leu939Trp)</td>
<td>0.00354</td>
<td>0.00381</td>
<td>0.95 (0.69 to 1.29)</td>
<td>0.73</td>
</tr>
<tr>
<td>c.3113G&gt;A (p.Trp1038*)‡</td>
<td>0.00045</td>
<td>0.00027</td>
<td>0.49 (0.18 to 1.36)</td>
<td>0.16</td>
</tr>
<tr>
<td>CHEK2‡</td>
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<td></td>
</tr>
<tr>
<td>c.349A&gt;G (p.Arg117Gly)</td>
<td>0.00063</td>
<td>0.00081</td>
<td>1.46 (0.71 to 3.02)</td>
<td>0.30</td>
</tr>
<tr>
<td>c.538C&gt;T (p.Arg180Cys)</td>
<td>0.00341</td>
<td>0.00296</td>
<td>1.02 (0.73 to 1.44)</td>
<td>0.90</td>
</tr>
<tr>
<td>c.715G&gt;A (p.Glu239lys)</td>
<td>0.00018</td>
<td>0.00027</td>
<td>1.47 (0.41 to 5.35)</td>
<td>0.55</td>
</tr>
<tr>
<td>c.1036C&gt;T (p.Arg334Cys)</td>
<td>0.00018</td>
<td>0.00022</td>
<td>1.07 (0.28 to 4.07)</td>
<td>0.93</td>
</tr>
<tr>
<td>c.1312G&gt;T (p.Asp438Tyr)</td>
<td>0.00049</td>
<td>0.00103</td>
<td>2.21 (1.06 to 4.63)</td>
<td>0.03</td>
</tr>
<tr>
<td>c.1343T&gt;G (p.Ile448Ser)†</td>
<td>0</td>
<td>0.00009</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>ATM</td>
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<td></td>
</tr>
<tr>
<td>c.771T&gt;G (p.Val2424Gly)</td>
<td>0.00004</td>
<td>0.00027</td>
<td>4.37 (0.52 to 36.4)</td>
<td>0.17</td>
</tr>
</tbody>
</table>

*For white European men, unless otherwise indicated.
†Proportion of subjects carrying the variant.
‡CHEK2 c.1343T>G (p.Ile448Ser) was the only CHEK2 variant observed in African men and was identified in two cases and no controls of white European origin.
§Based on data from 623 and 569 African-American cases and controls, respectively.
LRT, likelihood ratio test; OR, OR for carriers of the variant versus common-allele homozygotes, adjusted for study and seven principal components.
**CHEK2**

CHEK2 c.349A>G (p.Arg117Gly) was identified in 44 cases and 18 controls in studies participating in BCAC; all of these women were of European origin. We found evidence of association with breast cancer (p=0.003), with little change in the OR after excluding selected cases (OR 2.03 (95% CI 1.10 to 3.73)).

CHEK2 c.538C>T (p.Arg180Cys) was identified in 158 breast cancer cases and 142 controls in studies of white Europeans. Evidence of association with breast cancer risk (p=0.016) was observed, with an unbiased OR estimate of 1.34 (95% CI 1.06 to 1.70). A consistent OR estimate was observed for Asian women, based on 45 case and 45 control carriers (OR 1.16 (95% CI 0.75 to 1.76)).

CHEK2 c.715G>A (p.Glu239Lys) mutations were identified in 15 cases and 9 controls, all European women participating in BCAC and no evidence of association with risk of breast cancer was observed (p=0.21).

CHEK2 c.1036C>T (p.Arg346Cys) was identified in nine cases from seven studies and two controls from two different studies in BCAC (neither control carrier was from a study that had case carriers), all of European origin. We found evidence of association with breast cancer risk (p=0.017) with reduced OR estimate of 3.39 (95% CI 0.68 to 16.9) after excluding selected cases.

None of the above four CHEK2 variants (CHEK2 c.349A>G (p.Arg117Gly); c.538C>T (p.Arg180Cys); c.715G>A (p.Glu239Lys) and c.1036C>T (p.Arg346Cys)) were found to be associated with an increased risk of prostate or ovarian cancer (table 3 and 4).

**DISCUSSION**

The present report adds to an accumulating body of evidence that at least some rare variants in so-called ‘moderate-risk’ genes are associated with an increased risk of breast cancer that is of clinical relevance. These findings are presented at a time when detailed information about variants in these genes is becoming more readily available via the translation of diagnostic genetic testing from Sanger sequencing-based testing platforms to MPS platforms that test panels of genes in single assays. There are associations with increased risk of breast cancer for PALB2 c.3113G>A (p.Trp1038*) and ATM c.7271T>G (p.Val2424Gly) were found to be associated with substantial increased risk of breast cancer associated with relative risk estimates of 3.44 or greater.

### Table 4 Summary results from the Ovarian Cancer Association Consortium studies for white European women (14,542 invasive ovarian cancer cases and 23,491 controls)

<table>
<thead>
<tr>
<th>Variant</th>
<th>Frequency* Controls</th>
<th>OR (95% CI)</th>
<th>Frequency* Cases</th>
<th>LRT p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PALB2</strong></td>
<td></td>
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<tr>
<td>c.1592delT (p.Leu531Cysfs)</td>
<td>0.00004</td>
<td>2.50 (0.21 to 29.1)</td>
<td>0.00012</td>
<td>0.45</td>
</tr>
<tr>
<td>c.2816T&gt;G (p.Leu939Trp)</td>
<td>0.00413</td>
<td>0.966 (0.69 to 1.34)</td>
<td>0.00399</td>
<td>0.81</td>
</tr>
<tr>
<td>c.3113G&gt;A (p.Trp1038*)</td>
<td>0.00034</td>
<td>1.34 (0.36 to 4.97)</td>
<td>0.00031</td>
<td>0.66</td>
</tr>
<tr>
<td><strong>CHEK2</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>c.349A&gt;G (p.Arg117Gly)</td>
<td>0.00038</td>
<td>1.07 (0.32 to 3.60)</td>
<td>0.00031</td>
<td>0.92</td>
</tr>
<tr>
<td>c.538C&gt;T (p.Arg180Cys)</td>
<td>0.00128</td>
<td>1.49 (0.83 to 2.67)</td>
<td>0.00037</td>
<td>0.18</td>
</tr>
<tr>
<td>c.715G&gt;A (p.Glu239Lys)</td>
<td>0.00021</td>
<td>1.47 (0.42 to 5.22)</td>
<td>0.00027</td>
<td>0.54</td>
</tr>
<tr>
<td>c.1036C&gt;T (p.Arg346Cys)</td>
<td>0</td>
<td>--</td>
<td>0</td>
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<tr>
<td><strong>ATM</strong></td>
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<tr>
<td>c.7271T&gt;G (p.Val2424Gly)</td>
<td>0</td>
<td>--</td>
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</table>

*Proportion of subjects carrying the variant.
‡ c.1036C>T (p.Arg346Cys) was not observed in any sample.
LRT, likelihood ratio test; OR, OR for carriers of the variant versus common-allele homozygotes, adjusted for study and seven principal components.

There was no evidence that these CHEK2 variants were associated with risk of ovarian cancer (table 4).

**ATM**

ATM c.7271T>G (p.Val2424Gly) was identified in 12 cases and 1 control in studies participating in BCAC, all of European origin, giving evidence of association with breast cancer risk (p=0.0012). The OR estimate based on unselected studies was 11.0 (95% CI 1.42 to 85.7). There was no evidence of association of this variant with prostate or ovarian cancer risk (see tables 3 and 4).

The estimates for the two loss-of-function PALB2 variants (c.1592delT and c.3113G>A) were consistent with each other and with estimates based on segregation analysis. We found no evidence of association with breast cancer for PALB2 c.2816T>G (p.Leu939Trp), with an upper 95% confidence limit excluding an OR >1.5 which is notable given the
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Align-Grantham Variation Granthan Deviation (Align-GVGD) score and the observed impact on protein function. The estimate for ATM c.7271T>G (p.Val2424Gly) was also consistent with that found by segregation analysis.7 13 The substantial increased risk of breast cancer associated with ATM c.7271T>G (p.Val2424Gly) could be due to the reduction in kinase activity (with near-normal protein levels) observed for ATM p.Val2424Gly,13 thus this variant is likely to be acting as a dominant negative mutation.12

In contrast, we found no evidence of an association with risk of prostate or ovarian cancer with any of these three variants: however, the confidence limits were wide; based on the upper 95% confidence limit we could exclude an OR of >1.4 for prostate cancer for the loss-of-function PALB2 c.3113G>A and 1.9 for c.1592delT and c.3113G>A combined.

We analysed six rare missense variants in CHEK2. Two of these (CHEK2 c.349A>G (p.Arg117Gly); rs28909982) and c.1036C>T (p.Arg346Cys) had evidence of a significant impact on the protein based on in silico prediction. We proposed these variants for inclusion in the iCOGS design as they had been identified in 3/1242 cases and 1/1089 controls and 3/1242 cases and 0/1089 controls, respectively, in a population-based case-control mutation screening study of CHEK2.11 In that study, Le Calvez-Kelm et al, estimated an OR of 8.75 (95% CI 1.06 to 72.2) for variants with an Align-GVGD score C65 (based on nine cases and one control). The current analysis provides confirmatory evidence of this association in a much larger sample (OR 2.18 (95% CI 1.23 to 3.85)) including 40 unselected case and 18 control carriers. The evidence that CHEK2 is a breast cancer susceptibility gene is largely based on studies of protein truncating variants, in particular CHEK2 1100delC.13 Reports of the association of the missense variant I157T, (C15) and breast cancer risk have been conflicting but a large meta-analysis involving 15 985 breast cancer cases and 16 869 controls estimated a modest OR of 1.58 (95% CI 1.42 to 1.75).14 We also found evidence (p=0.015) of an association for c.538C>T (Align-GVGD C25); OR 1.34 (95% CI 1.06 to 1.70), a risk comparable to I157T.

The p values reported above have not been adjusted for multiple testing. This was not considered appropriate for the associations with breast cancer risk of PALB2 c.1592delT, c.3113G>A and ATM c.7271T>G because these associations had previously been reported; our aim was to more precisely estimate the associated relative risks. All three associations with breast cancer risk reported for CHEK2 variants remained statistically significant after adjusting for the other tests conducted in relation to breast cancer risk, but not after correcting for all tests for all cancers. Nevertheless, the findings for CHEK2 c.349A>G and c.1036C>T confirmed those reported previously, although collectively. The association observed with CHEK2 c.538C>T requires independent replication.

Do this approach and new data have an impact on clinical recommendations for women and families carrying these rare genetic variants? Although age-specific cumulative risks for cancer are more informative for genetic counselling and clinical management of carriers, our study provides information that is relevant to clinical recommendations. As discussed in Easton et al,15 a relative risk of 4 will place a woman in a ‘high-risk’ category (in the absence of any other risk factor) and a relative risk between 2 and 4 will place a woman in this category if other risk factors are present. Thus, several of the variants included in this report (PALB2 c.1592delT; c.3113G>A ATM c.7271T>G) would place the carrier in a high-risk group, especially if other risk factors, such as a family history, are present. The high level of breast cancer risk associated with PALB2 c.1592delT and c.3113G>A reported here is consistent with the penetrance estimate reported for a group of loss-of-function mutations in PALB212 and has an advantage in terms of clinical utility that the estimates in this study have been made at a mutation-specific level. Therefore, this work provides important information for risk reduction recommendations (such as prophylactic mastectomy and potentially salpingo-oophorectomy) for carriers of these variants. However, further prospective research is required to characterise these risks and to understand the potential of other risk-reducing strategies such as salpingo-oophorectomy and chemoprevention.

The consistency of the relative risk estimates with those derived through family based studies supports the hypothesis that these variants combine multiplicatively with other genetic loci and familial risk factors; this information is critical for deriving comprehensive risk models. Even with very large sample sizes such as those studied here, however, it is still only possible to derive individual risk estimates for a limited set of variants, and even for these variants the estimates are still imprecise. This internationally collaborative approach also has limited capacity to improve risk estimates for rare variants that are only observed in specific populations. Inevitably, therefore, risk models will depend on combining data across multiple variants, using improved in silico predictions and potentially biochemical/functional evidence to synthesise these estimates efficiently. It will also be necessary to develop counselling and patient management strategies that can accommodate a multifactorial approach to variant classification.

Author affiliations

1Genetic Epidemiology Laboratory, Department of Pathology, The University of Melbourne, Melbourne, Australia
2Huntsman Cancer Institute, Salt Lake City, UT, USA
3Laboratory of Cancer Genetics and Tumor Biology, Cancer and Translational Medicine Research Unit and Biocenter Oulu, University of Oulu, Nordlab Oulu, Oulu, Finland
4Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN, USA
5Department of Medical Genetics and National Institute for Health Research Cambridge Biomedical Research Centre, University of Cambridge, and the Department of Clinical Genetics, East Anglian Regional Genetics Service, Addenbrooke’s Hospital
6Program in Cancer Genetics, Department of Human Genetics and Oncology, Lady Davis Institute, and Research Institute, McGill University Health Centre, McGill University, Montreal, Canada
7Centre for Cancer Gene Therapy, Department of Public Health and Primary Care, University of Cambridge, Strangeways Laboratory, Worts Causeway, Cambridge, UK
8Department of Genetics, University of Pretoria, South Africa
9Department of Obstetrics and Gynecology, University of Helsinki and Helsinki University Central Hospital, Helsinki, Finland
10Centre for Epidemiology and Biostatistics, School of Population and Global Health, The University of Melbourne, Melbourne, Australia,
11Gynaecology Research Unit, Hannover Medical School, Hannover, Germany
12Center for Medical Genetics, Ghent University Hospital, De Pintelaan 185, 9000 Ghent, Belgium,
13Department of Pathology and Human Oncology and Pathogenesis Program, Memorial Sloan-Kettering Cancer Center, New York, New York, USA
14Unit of Molecular Bases of Genetic Risk and Genetic Testing, Department of Preventive and Predictive Medicine, Fondazione IRCCS Istituto Nazionale dei Tumori (INT), Milan, Italy
15FOOM, the FIRC Institute of Molecular Oncology, Milan, Italy
16Netherlands Cancer Institute, Antoni van Leeuwenhoek hospital, Amsterdam, The Netherlands
17Austrian Breast Cancer Tissue Bank, University of Sydney at the Westmead Institute for Medical Research, NSW, Australia
18Centre for Cancer Research, University of Sydney at the Westmead Institute for Medical Research, NSW, Australia
19Division of Molecular Medicine, Pathology North, Newcastle and University of Newcastle, NSW, Australia
20University Breast Center Franconia, Department of Gynecology and Obstetrics, University Hospital Erlangen, Friedrich-Alexander University Erlangen-Nuremberg, Comprehensive Cancer Center Erlangen-EMN, Erlangen, Germany


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Cancer Research Centre (CNIO), Madrid, Spain
Hospital, University of Copenhagen, Copenhagen, Denmark
Epidemiology of Cancer, Villejuif, France
Heidelberg, Germany
Galway, Galway, Ireland
Department of Obstetrics and Gynecology, University of Heidelberg, Heidelberg, Germany
National Center for Tumor Diseases, University of Heidelberg, Heidelberg, Germany
Molecular Epidemiology Group, German Cancer Research Center (DKFZ), Heidelberg, Germany
Inserm (National Institute of Health and Medical Research), CESP (Center for Research in Epidemiology and Population Health), U1018, Environmental Epidemiology of Cancer, Villejuif, France
University Paris-Sud, UMR 1018, Villejuif, France
Copenhagen General Population Study, Herlev Hospital, Copenhagen University Hospital, University of Copenhagen, Copenhagen, Denmark
Department of Clinical Biochemistry, Herlev Hospital, Copenhagen University Hospital, University of Copenhagen, Copenhagen, Denmark
Department of Breast Surgery, Herlev Hospital, Copenhagen University Hospital, Copenhagen, Denmark
Human Genetics Group, Human Cancer Genetics Program, Spanish National Cancer Research Centre (CNIO), Madrid, Spain
Centre de Investigación en Red de Enfermedades Raras (CIBERER), Valencia, Spain
Servicio de Oncología Médica, Hospital Universitario La Paz, Madrid, Spain
Servicio de Cirugía General y Especialidades, Hospital Monte Naranco, Oviedo, Spain
Servicio de Anatomía Patológica, Hospital Monte Naranco, Oviedo, Spain
Department of Epidemiology, University of California Irvine, Irvine, California, USA
Beckman Research Institute of City of Hope, Duarte, California, USA
Division of Epidemiology, University of California Irvine, Irvine, California, USA
Cancer Prevention Institute of California, Fremont, California, USA
Division of Clinical Epidemiology and Aging Research, German Cancer Research Center (DKFZ), Heidelberg, Germany
Division of Preventive Oncology, German Cancer Research Center (DKFZ), Heidelberg, Germany
German Cancer Consortium (DKTK), German Cancer Research Center (DKFZ), Heidelberg, Germany
Saarland Cancer Registry, Saarbrücken, Germany
Dr. Margarete Fischer-Bosch-Institute of Clinical Pharmacology, Stuttgart
University of Tübingen, Tübingen, Germany
Institute for Prevention and Occupational Medicine of the German Social Accident Insurance, Institute of the Ruhr University, Bochum (IPA), Germany
Department of Internal Medicine, Evangelische Kliniken Bonn gGmbH, Johanniter Krankenhaus, Bonn, Germany
Department of Obstetrics and Gynecology, University of Helsinki and Helsinki University Central Hospital, Helsinki, Finland
Department of Clinical Genetics, Helsinki University Central Hospital, Helsinki, Finland
Department of Radiation Oncology, Hannover Medical School, Hannover, Germany
N.N. Alexandrov Research Institute of Oncology and Medical Radiology, Minsk, Belarus
Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden
Department of Oncology – Pathology, Karolinska Institutet, Stockholm, Sweden
School of Medicine, Institute of Clinical Medicine, Pathology and Forensic Medicine, and Cancer Center of Eastern Finland, University of Eastern Finland, Kuopio, Finland
Imaging Center, Department of Clinical Pathology, Kuopio University Hospital, Kuopio, Finland
School of Medicine, Institute of Clinical Medicine, Oncology, University of Eastern Finland, Kuopio, Finland
Biocenter Kuopio, Cancer Center of Eastern Finland, Kuopio University Hospital, Kuopio, Finland
QIMR Berghofer Medical Research Institute, Brisbane, Australia
Research Department, Peter MacCallum Cancer Centre and The Sir Peter MacCallum Department of Oncology, University of Melbourne, Victoria, Australia
Vesalius Research Center (VRC), VIB, Leuven, Belgium
Laboratory for Translational Genetics, Department of Oncology, University of Leuven, Leuven, Belgium
University Hospital Gasthuisberg, Leuven, Belgium
Division of Cancer Epidemiology, German Cancer Research Center (DKFZ), Heidelberg, Germany
Department of Cancer Epidemiology/Clinical Cancer Registry and Institute for Medical Biometrics and Epidemiology, University Clinic Hamburg-Eppendorf, Hamburg, Germany
Department of Health Sciences Research, Mayo Clinic, Rochester, MN, USA
Anatomical Pathology, The Alfred Hospital, Melbourne, Australia
Division of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA
Epidemiology Program, Cancer Research Center, University of Hawaii, Honolulu, HI, USA
Department of Genetics, Institute for Cancer Research, Oslo University Hospital, Radiumhospitalet, Oslo, Norway
Faculty of Medicine (Faculty Division Allhus), University of Oslo (UiO), Norway
Division of Epidemiology, Department of Medicine, Vanderbilt Ingram Cancer Center, Vanderbilt University School of Medicine, Nashville, TN, USA
Program in Molecular and Genetic Epidemiology, Harvard School of Public Health, Boston, MA, USA
Department of Epidemiology, Harvard School of Public Health, Boston, MA, USA
Channing Laboratory, Department of Medicine, Brigham and Women’s Hospital and Harvard Medical School, Boston, MA, USA
Ontario Cancer Genetics Network, Lunenfeld-Tanenbaum Research Institute of Mount Sinai Hospital, Toronto, Ontario, Canada
Department of Molecular Genetics, University of Toronto, Toronto, Ontario, Canada
Prosserman Centre for Health Research, Lunenfeld-Tanenbaum Research Institute of Mount Sinai Hospital, Toronto, Ontario, Canada
Division of Epidemiology, Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario, Canada
Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, ON, Canada
Laboratory Medicine Program, University Health Network, Toronto, Ontario
Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, ON, Canada
Department of Oncology, Oulu University Hospital, University of Oulu, Oulu, Finland
Department of Surgery, Oulu University Hospital, University of Oulu, Oulu, Finland
Department of Pathology, Oulu University Hospital, University of Oulu, Oulu, Finland
Department of Surgical Oncology, Leiden University Medical Center, 2300 RC Leiden, The Netherlands
Family Cancer Clinic, Department of Medical Oncology, Erasmus MC-Daniel den Hoed Cancer Centre, Rotterdam, The Netherlands
Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, Maryland, USA
Department of Cancer Epidemiology and Prevention, M. Sklodowska-Curie Memorial Cancer Center & Institute of Oncology, Warsaw, Poland
Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm 17177, Sweden
Faculty of Medicine, University of Southampton (UoS), Southampton UK
Department of Medical Oncology, Family Cancer Clinic, Erasmus MC Cancer Institute, Rotterdam, The Netherlands
Department of Clinical Genetics, Family Cancer Clinic, Erasmus University Medical Center, Rotterdam, The Netherlands
Department of Surgical Oncology, Family Cancer Clinic, Erasmus University Medical Center, Rotterdam, The Netherlands
Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm 17177, Sweden
Human Genetics Division, Genome Institute of Singapore, Singapore 138672, Singapore
Sheffield Cancer Research, Department of Oncology, University of Sheffield, Sheffield, UK
Centre for Cancer Gene Epidemiology, Department of Oncology, University of Cambridge, Cambridge, UK
Molecular Genetics of Breast Cancer, German Cancer Research Center (DKFZ), Heidelberg, Germany
Institute of Human Genetics, Pontificia Universidad Javeriana, Bogota, Colombia
Frauenklinik der Stadtklinik Baden-Baden, Baden-Baden, Germany
Institute of Pathology, Städtisches Klinikum Karlsruhe, Karlsruhe, Germany
Department of Genetics and Pathology, Pomeranian Medical University, Szczecin, Poland
Postgraduate School of Molecular Medicine, Warsaw Medical University, Warsaw, Poland
Cancer genetics

111Department of Molecular Virology, Immunology and Medical Genetics, Comprehensive Cancer Center, The Ohio State University, Columbus, OH, USA
112Roswell Park Cancer Institute, Buffalo, New York, USA
113Molecular Diagnostics Laboratory, IRPP, National Centre for Scientific Research "Demokritos", Aghia Paraskevi Attiki, Athens, Greece
114Division of Genetics and Epidemiology, Institute of Cancer Research, London, UK
115Division of Breast Cancer Research, Institute of Cancer Research, London, UK
116Centre d’innovation Genome Quebec et University McGill Montreal Quebec, Canada
117McGill University, Montreal, Quebec, Canada
118Cancer Genomics Laboratory, Centre Hospitalier Universitaire de Quebec Research Center, Laval University, Quebec, Canada
119The Institute of Cancer Research, London, SM2 5NG, UK
120Royal Marsden NHS Foundation Trust, Fulham, London, SW3 6JJ, UK
121University of Warwick, Coventry, UK
122Department of Medical Epidemiology and Biostatistics, Karolinska Institute, Stockholm, Sweden
123Department of Medical Biochemistry and Genetics, University of Turku, and Tyks Microbiology and Genetics, Department of Medical Genetics, Turku University Hospital, Turku, Finland
124Institute of Biomedical Technology/BioMediTech, University of Tampere, Tampere, Finland
125Department of Clinical Biochemistry, Herlev Hospital, Copenhagen University Hospital, Herlev Ringvej 75, DK-2730 Herlev, Denmark
126Department of Human Genetics University of Utah, Salt Lake City, UT, USA and Department of Clinical Biochemistry, Herlev Hospital, Copenhagen University Hospital, University of Copenhagen, Copenhagen, Denmark
127Cancer Epidemiology Unit, Nuffield Department of Population Health, University of Oxford, Oxford, UK
128Surgical Oncology (Uro-Oncology): S4, University of Cambridge, Box 279, Addenbrooke’s Hospital, Hills Road, Cambridge, UK and Cancer Research UK Cambridge Research Institute, Li Ka Shing Centre, Cambridge, UK
129Professor of Social Medicine, University of Bristol, Cynghame Hall, 39 Whatley Road, Bristol BS8 2PS
130Nuffield Department of Surgical Sciences, Old Road Campus Research Building (off Roosevelt Drive), University of Oxford, Headington, Oxford, OX3 7DQ
131Cambridge Institute of Public Health, University of Cambridge, Forvie Site, Robinson Way, Cambridge CB2 2SR
132Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, Washington, USA
133Department of Epidemiology, School of Public Health, University of Washington, Seattle, Washington, USA
134International Epidemiology Institute, 1455 Research Blvd., Suite 550, Rockville, MD 20850
135Department of Obstetrics, Gynecology and Reproductive Sciences, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA
136Department of Urology, University Hospital Ulm, Germany
137Institute of Human Genetics University Hospital Ulm, Germany
138Brigham and Women’s Hospital/Dana-Farber Cancer Institute, 45 Francis Street-ASB II, Boston, MA 02115
139Washington University, St Louis, Missouri
140International Hereditary Cancer Center, Department of Genetics and Pathology, Pomeranian Medical University, Szczecin, Poland
141Division of Genetic Epidemiology, Department of Medicine, University of Utah School of Medicine
142Division of Cancer Prevention and Control, H. Lee Moffitt Cancer Center, 12902 Magnolia Dr., Tampa, Florida, USA
143Molecular Medicine Center and Department of Medical Chemistry and Biochemistry, Medical University – Sofia, 2 Zdrave St, 1431, Sofia, Bulgaria
144Australian Prostate Cancer Research Centre-Qld, Institute of Health and Biomedical Innovation and Schools of Life Science and Public Health, Queensland University of Technology, Brisbane, Australia
145Department of Genetics, Portuguese Oncology Institute, Porto, Portugal and Biomedical Sciences Institute (ICBAS), Porto University, Porto, Portugal
146University Hospital Erlangen, Department of Gynecology and Obstetrics, Friedrich-Alexander-Universität Erlangen-Nuremberg, Comprehensive Cancer Center Erlangen-EMN, Universitätsstrasse 21-23, 91054 Erlangen, Germany
147University Hospital Erlangen, Institute of Pathology, Friedrich-Alexander-Universität Erlangen-Nuremberg, Comprehensive Cancer Center Erlangen-EMN, Universitätsstrasse 21-23, 91054 Erlangen, Germany
148Vesalius Research Center, VIB, Leuven, Belgium
149Laboratory for Translational Genetics, Department of Oncology, University of Leuven, Belgium
150Department of Epidemiology, The Geisel School of Medicine at Dartmouth, Lebanon, NH, USA
151Department of Epidemiology, The Geisel School of Medicine at Dartmouth, Hanover, NH, USA
152Program in Epidemiology, Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA, USA
153Department of Epidemiology, University of Washington, Seattle, WA, USA
154German Cancer Research Center, Division of Cancer Epidemiology, Heidelberg, Germany
155Department of Obstetrics and Gynecology, University of Ulm, Ulm, Germany
156Department of Gynecological Oncology, Roswell Park Cancer Institute, Buffalo, NY
157Cancer Epidemiology Program, University of Hawaii Cancer Center, Hawaii, USA
158Department of Pathology, Kapolani Medical Center for Women and Children, John A. Burns School of Medicine, University of Hawaii, Honolulu, Hawaii 96826, USA
159Cancer Prevention and Control, Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, California, USA
160Community and Population Health Research Institute, Department of Biomedical Sciences, Cedars-Sinai Medical Center, Los Angeles, California, USA
161Department of Gynecology and Obstetrics, Friedrich Schiller University, Jena University Hospital, Jena, Germany
162Clinics of Obstetrics and Gynecology, Hannover Medical School, Hannover, Germany
163Department of Pathology, Helsinki University Central Hospital, Helsinki, 00029 HUS, Finland
164University of Pittsburgh Department of Obstetrics, Gynecology and Reproductive Sciences and Ovarian Cancer Center of Excellence Pittsburgh PA USA
165University of Pittsburgh Department of Epidemiology, University of Pittsburgh Graduate School of Public Health and Womans Cancer Research Program, Magee-Womens Research Institute and University of Pittsburgh Cancer Institute Pittsburgh PA USA
166The University of Texas School of Public Health, Houston, TX, USA
167Department of Cancer Prevention and Control, Roswell Park Cancer Institute, Buffalo, NY
168Department of Gynecology and Gynecologic Oncology, Klinik en Essel-Mittel/ Evang. Huyssen-Stiftung/ Knappschaft GmbH, Essen, Germany
169Department of Gynecology and Gynecologic Oncology, Dr. Horst Schmidt Klinik Wiesbaden, Wiesbaden, Germany
170Tuebingen University Hospital, Department of Women’s Health, Tuebingen, Germany
171Women’s Cancer Program at the Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, California
172Department of Virus, Lifestyle and Genes, Danish Cancer Society Research Center, Copenhagen, Denmark
173Department of Obstetrics and Gynecology, Rigshospitalet, Copenhagen, Denmark
174Molecular Unit, Department of Pathology, Herlev Hospital, University of Copenhagen, Copenhagen, Denmark
175Unit of Medical Genetics, Department of Preventive and Predictive Medicine, Fondazione IRCCS Istituto Nazionale dei Tumori (IIT), Milan, Italy
176Division of Cancer Prevention and Genetics, Istituto Europeo di Oncoologia (IEO), Milan, Italy
177Department of Experimental Oncology, Istituto Europeo di Oncologia (IEO), Milan, Italy and Cogentech Cancer Genetic Test Laboratory, Milan, Italy
178University of Kansas Medical Center, Kansas City, KS, USA
179Department of Medical Oncology, Mayo Clinic, Rochester, Minnesota, USA
180College of Pharmacy and Health Sciences, Texas Southern University, Houston, Texas, USA
181Department of Gynecologic Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA
182Department of Epidemiology, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA
183Gynecology Service, Department of Surgery, Memorial Sloan-Kettering Cancer Center, New York, NY, USA
184Department of Obstetrics and Gynecology, Duke University Medical Center, Durham, North Carolina, USA
185Department of Statistical Science, Duke University, Durham, North Carolina, USA
186Department of Surgery, Duke University Medical Center, Durham, North Carolina, USA
187Cancer Prevention, Detection & Control Research Program, Duke Cancer Institute, Durham, North Carolina, USA
188Obstetrics and Gynecology Epidemiology Center, Brigham and Women’s Hospital, Boston, Massachusetts, USA
189Channing Division of Network Medicine, Brigham and Women’s Hospital and Harvard Medical School
190Department of Epidemiology, Harvard TH Chan School of Public Health, Boston, Massachusetts, USA
191Cancer Prevention and Control Program, Rutgers Cancer Institute of New Jersey, The State University of New Jersey, New Brunswick, NJ, USA
192Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY, USA
193Department of Gynecology and Obstetrics, Haukeland University Hospital, Bergen, Norway
194Centre for Cancer Biomarkers, Department of Clinical Sciences, University of Bergen, Bergen, Norway
The Breast Cancer Association Consortium through attendance at regular meetings and planning of the iCOGS experiment. Each author has made substantial contribution through design and coordinating the studies listed in the supplemental material and therefore have made substantial contributions to the conception or design of this work. Many authors played multiple roles across these activities. Specifically, MICS conceived this study, worked to include the rare variants on the iCOGS and drafted the manuscript. RLM led the statistical analysis and drafted the paper. Members of the PALB2 interest group, MCS, DEG, RW, KP, FC, MT, WF, JD, KM, Ejvr, TH, HN, JLH, TD, KC, JR-F, ZLT, PR, IC, PF, HT, FAO, JGD contributed to the inclusion of the PALB2 rare variants on iCOGS. DFE coordinated the BCAC project and contributed to statistical analysis along with DEG. SVT contributed to the selection of CHEK2 rare variants. GC-T contributed to the selection of rare variants in ATM, AD, CL and JD made significant contribution to the data quality related to the calling of the rare genetics variants on iCOGS. MKS, AB, FBH, SV, JC, CI, RS, PAF, LH, AME, MBB, JP, ISD, OF, N, MJ, KBE, ESJ, IT, MIK, NM, FM, BB, PY, GT, TM, FT, MS, SB, SFN, HF, JB, MPZ, IM, JAC, HN, SC, AZ, CDD, HB, VA, CS, HB, TD, YDK, TAM, KA, CB, NBV, NNA, AL, SM, AM, VK, V-MK, JM, AS, EK, DS, GB, GF, JCC, AR, PS, DJJ, JEO, CV, CSP, CM, CAH, BEH, FS, LLM, VK, GGA, WJ, DHI, SL, SEH, PK, IA, JAK, GIS, AMM, AVJ, MG, SK, PD, RAEMT, CS, AH, MSGC, IF, SIC, JL, KC, HD, ME, DME, SR, WIT, SMG, MJH, IWWM, JMC, MTL, PH, JL, ISB, KH, AC, MWWR, CL, CB, AD, UH, DT, HUO, TR, AJ, KL, KD, SS, AET, CBA, DY, AS, AA, NO, MI, AGN, GPR, MA, NA, DH, DFT, DV, JS, BD, MS, PD, RE, KM, FW, HG, JS, MW, BGN, RCT, JD, FLD, JKH, KT, JLS, WIB, ST, DIS, JLK, CM, ASK, CC, LCA, KB, JP, JR, RB, MRT, ZKJ, AAAOB, SB, SPR, AH, AT, MR, DL, ERN, IV, N, IAD, MAR, SN, UE, SWG, KO, LES, GF, JG, JLK, LRMG, ISDN, NAM, ABH, FM, RPE, HUG, IC, MNO, CDA, ED, JRN, KMC, EH, BP, BB, LB, ELF, BGF, RAW, JMC, MCL, ZCF, KRK, DL, KHAL, MW, XAL, DAL, FD, MB, AE, ESI, JRN, LA, DWC, KLT, ELP, MS, SST, EBP, IO, SHO, LB, ABWA, AVAVA, KKH, LAJ, LAFGM, TP, YB, ABW, LEK, LSD, NDL, BG, JG, JM, CHK, LL, LN, SAE, ED, JT, IC, IN, JP, NS, RG, ASW, JHR, VG, WS, HC, XOS, RTT, RS, JRM, SAN, CP, ANM, DF, HYL, JPM, TAS, TAC, YYT, ZCM, AGM, SAD, SJJM, UHM, AHW, CLP, DVBW, BARNM, UJH, JMS, JK, PF, JRA, ZNM, SGB, JCG, SGG, SFT, DFL, RLM provided DNA samples and/or phenotypical data. All authors read and approved the final manuscript.

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Data sharing statement

This would vary for each study—each study is listed in the supplemental material.

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PALB2, CHEK2 and ATM rare variants and cancer risk: data from COGS

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