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


Cancer genetics

ORIGINAL ARTICLE

PALB2, CHEK2 and ATM rare variants and cancer risk: data from COGS
estimated precisely associated cancer risks.

Conclusion We found evidence of association with breast cancer risk for three variants in CHEK2, c.1312G>T OR 2.21 (95% CI 1.06 to 4.63, p=0.030) for European men, c.1592delT OR 3.44 (95% CI 1.91 to 6.15), c.3113G>A OR 4.21 (95% CI 1.53 to 6.03, p=0.0006) for African men and c.7271T>G OR 11.0 (95% CI 1.53 to 31.9), c.2816T>G OR 2.26 (95% CI 1.42 to 85.7, p=0.0012). We also found evidence of association with breast cancer risk for three variants in ATM, c.7271T>G OR 3.44 (95% CI 1.91 to 6.15), c.1592delT OR 3.44 (95% CI 1.91 to 6.15), c.3113G>A OR 4.21 (95% CI 1.53 to 6.03, p=0.0006) for African men and c.7271T>G OR 11.0 (95% CI 1.53 to 31.9), c.2816T>G OR 2.26 (95% CI 1.42 to 85.7, p=0.0012). We also found evidence of association with breast cancer risk for three variants in ATM, c.7271T>G OR 3.44 (95% CI 1.91 to 6.15), c.1592delT OR 3.44 (95% CI 1.91 to 6.15), c.3113G>A OR 4.21 (95% CI 1.53 to 6.03, p=0.0006) for African men and c.7271T>G OR 11.0 (95% CI 1.53 to 31.9), c.2816T>G OR 2.26 (95% CI 1.42 to 85.7, p=0.0012).
Cancer genetics

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, Tavtigian 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.3113G>A (p.Trp1038*) and the missense variant c.2816T>G (p.Leu939Thr), six rare missense variants in CHEK2: c.349A>G (p.Arg117Gly) and c.1036C>T (p.Arg346Cys) predicted to be deleterious on the basis of evolutionary conservation, c.538C>T (p.Ala180Ser), c.715G>A (p.Glu239Lys), c.3132G>T (p.Asp438Tyr) 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 Estrogen Receptor (ER) status (23% missing) are 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 (186 cases (150 with invasive disease) and 200 controls) and 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.

Genotyping

Three PALB2 variants c.2323C>T (p.Gln775*), c.3116delA (p.Asn1039Ilefs) and c.3549C>G (p.Tryr1183*) 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, as described previously. Genotypes were called using the Illumina proprietary GenCall algorithm and then, for the data generated from the rare variant probes, manually confirmed with reference to the positive control sample. Two per cent of samples were provided in duplicate by all studies and 270 HapMap2 samples were genotyped in all four genotyping centres. Subjects with an overall call rate <95% were excluded. Plates with call rates <90% were excluded on a variant-by-variant basis. Cluster plots generated for all of the 10 rare variants were manually checked to confirm automated calls (see online supplementary figure S1).

Statistical methods

The association of each variant with breast, prostate and ovarian cancer risk was assessed using unconditional logistic regression to estimate ORs for carriers versus non-carriers, adjusting for study (categorical). p Values were determined by the likelihood ratio test comparing models with and without carrier status as a covariate. We also applied conditional logistic regression, defining risk sets by study, and found that this made no difference to the OR estimates, CIs or p values to two significant figures; since model convergence was a problem for this latter regression analysis, all subsequent analyses were based on unconditional logistic regression. For the main analyses of breast cancer risk in European women, we also included as covariates the first six principal components, together with a seventh component specific to one study (Leuven Multidisciplinary Breast Centre (LMBC)) for which there was substantial inflation not accounted for by the components derived from the analysis of all studies. Addition of further principal components did not reduce inflation further. Data from all breast cancer studies were included to assess statistical significance. Data from cases selected for inclusion based on personal or family history of breast cancer were excluded in order to obtain unbiased OR estimates for 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 threshold of 0.05. 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. All analyses were carried out using Stata: Release V10 (StataCorp, 2008).

RESULTS

PALB2

In BCAC, 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 Mammography Project for Risk Prediction Breast Cancer (pKARMA); see online supplementary materials for details).

<table>
<thead>
<tr>
<th>Gene</th>
<th>Variant*</th>
<th>Amino acid*</th>
<th>dbSNP rs</th>
<th>OR (95% CI)</th>
<th>Penetrance† (95% CI)</th>
<th>Align-GVGD</th>
<th>Reference(s)</th>
<th>Designed‡</th>
<th>Genotyped</th>
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<tbody>
<tr>
<td>PALB2</td>
<td>c.1592delT</td>
<td>p.Leu531Cysfs</td>
<td>rs1801771102</td>
<td>3.94 (1.5-12.1)$</td>
<td>40% (17-77)</td>
<td>na</td>
<td>4, 5, 10</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>c.2323C&gt;T</td>
<td>p.Gln775*</td>
<td>rs180177111</td>
<td>25.26</td>
<td>95% (44-100)</td>
<td>na</td>
<td>2, 6, 20</td>
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<td>Yes</td>
</tr>
<tr>
<td></td>
<td>c.3549C&gt;G</td>
<td>p.Tryr1183*</td>
<td>rs180203998</td>
<td>na</td>
<td>2, 2</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>CHEK2</td>
<td>c.349A&gt;G</td>
<td>p.Arg117Gly</td>
<td>rs28909982</td>
<td>8.75 (1.06-72.2)$</td>
<td>95% (44-100)</td>
<td>na</td>
<td>2, 6, 20</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
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<td>c.538C&gt;T</td>
<td>p.Arg180Cys</td>
<td>rs278130927</td>
<td>2.47 (0.45-13.49)</td>
<td>95% (44-100)</td>
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<td>20</td>
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<td>Yes</td>
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<tr>
<td></td>
<td>c.715G&gt;A</td>
<td>p.Glu397Gly</td>
<td>rs121908702</td>
<td>1.82 (0.62-5.34)</td>
<td>95% (44-100)</td>
<td>C55</td>
<td>20</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td></td>
<td>c.1036C&gt;T</td>
<td>p.Arg346Cys</td>
<td>rs17886163</td>
<td>8.75 (1.06-72.2)$</td>
<td>95% (44-100)</td>
<td>C55</td>
<td>20</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>c.1316G&gt;A</td>
<td>p.Asp343Tyr</td>
<td>rs180177132</td>
<td>1.82 (0.62-5.34)</td>
<td>95% (44-100)</td>
<td>C55</td>
<td>20</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>c.3116delA</td>
<td>p.Asn1039Ilefs</td>
<td>rs180177133</td>
<td>na</td>
<td>2</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>c.3549C&gt;G</td>
<td>p.Tryr1183*</td>
<td>rs180203998</td>
<td>na</td>
<td>2</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

*Human Genome Variation Society (HGVS); reference sequences PALB2, NM_024675.3, NP_077194.3; CHEK2, NM_007194.3, NP_009125.1; ATM, NM_000051.3, NP_000042.3.
†Age-specific cumulative risk of breast cancer to age 70 years.
‡Able to be designed for measurement on the custom Illumina iSelect genotyping array.
§Breast cancer cases unselected for family history of breast cancer.
¶OR estimated in a combined group of C25 CHEK2 variants.
††OR estimated in a combined group of C15 CHEK2 variants.
‡‡OR estimated in a combined group of C65 CHEK2 variants.
Cancer genetics

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</th>
<th>p Value</th>
<th>OR† (95% CI)</th>
<th>LRT</th>
<th>p Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>PALB2§</td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<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>7.1×10⁻⁶</td>
<td>3.44 (1.39 to 8.52)</td>
<td>0.003</td>
<td></td>
<td></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>
<td></td>
<td></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>6.9×10⁻⁶</td>
<td>4.21 (1.84 to 9.60)</td>
<td>1.2×10⁻⁴</td>
<td></td>
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</tr>
<tr>
<td>CHEK2‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<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>
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<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>
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</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>
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<tr>
<td>c.1036C&gt;T (p.Arg336Cys)</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>
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<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>
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</tr>
<tr>
<td>c.1343T&gt;G (p.Ile448Ser)</td>
<td>0.00002</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td></td>
<td></td>
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<td>ATM</td>
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</tr>
<tr>
<td>c.7217T&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>
<td></td>
<td></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</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PALB2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>c.1592delT (p.Leu531Cysfs)</td>
<td>0.00018</td>
<td>0.00301</td>
<td>2.06 (0.59 to 7.11)</td>
<td>0.24</td>
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<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>
<td></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>
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<tr>
<td>CHEK2‡</td>
<td></td>
<td></td>
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<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>
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<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>
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<td>c.715G&gt;A (p.Glu239Lys)</td>
<td>0.00021</td>
<td>0.00027</td>
<td>1.47 (0.41 to 5.35)</td>
<td>0.55</td>
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<tr>
<td>c.1036C&gt;T (p.Arg336Cys)</td>
<td>0.00018</td>
<td>0.00022</td>
<td>1.07 (0.28 to 4.07)</td>
<td>0.93</td>
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<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>
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<tr>
<td>c.1343T&gt;G (p.Ile448Ser)</td>
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<td>0.0009</td>
<td>—</td>
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<td>ATM</td>
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<tr>
<td>c.7217T&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>
<td></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.

Table S1, giving strong evidence of association with breast cancer risk ($p=7.1\times10^{-8}$); the OR estimate was $4.52$ (95% CI $1.90$ to $10.8$) based on all studies and $3.44$ (95% CI $1.39$ to $8.52$) based on unselected cases and controls (Table 2). We also found evidence of heterogeneity by ER status ($p=0.0023$), the association being stronger for ER-negative disease (OR $6.49$ (95% CI $2.17$ to $19.4$) versus $2.24$ (95% CI $1.05$ to $7.24$) for ER-positive disease).

PALB2 c.3113G>A (p.Trp1038*) was identified in 44 cases and 8 controls from nine BCAC studies. Only one carrier of the variant was of non-European origin. Strong evidence of association with breast cancer risk was observed ($p=6.9\times10^{-8}$), with an estimated OR of $5.93$ (95% CI $2.77$ to $12.7$) based on all studies and $4.21$ (95% CI $1.85$ to $9.61$) based on unselected cases and controls. There was no evidence of a differential association by ER status ($p=0.15$).

Based on unselected cases, the estimated OR associated with carrying either of these PALB2 variants (c.1592delT or c.3113G>A) was $3.85$ (95% CI $2.09$ to $7.09$).

PALB2 c.2816T>G (p.Leu939Trp) was identified in 150 cases and 145 controls and there was no evidence of association with risk of breast cancer. There was no evidence of association with risk of prostate or ovarian cancer for any of the three PALB2 variants (see Tables 3 and 4).
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.358C>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 1.70)). Variant c.1312G>T (p.Asp438Tyr) was not associated with risk of breast cancer for European 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.358C>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 (tables 3 and 4). CHEK2 variant c.1312G>T (p.Asp438Tyr) was not associated with risk of breast cancer for European women (p=0.91). Variant c.1343T>G (p.Ile448Ser) was not observed in any breast cancer cases and 142 controls in studies participating in BCAC; all of these women were of European origin. 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).

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. The vast majority of information about PALB2, CHEK2 and ATM, variants generated from these new testing platforms is not being used in clinical genetics services due to lack of reliable estimates of the cancer risk associated with individual variants, or groups of variants, in each gene. Previous analyses have been largely based on selected families, relying on data on the segregation of the variant. The present study is by far the largest to take a case-control approach. Consistent with previous reports, we found no evidence of association with risk of breast cancer for PALB2 variants (c.1592delT (p.Leu531Cysfs) and c.1592delT (p.Leu939Trp), p=0.98) or PALB2 c.2816T>G (p.Leu939Trp), with an upper 95% confidence limit excluding an OR >1.5 which is notable given the
Cancer genetics

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. 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, thus this variant is likely to be acting as a dominant negative mutation.

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. 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. 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 18,609 controls estimated a modest OR of 1.58 (95% CI 1.42 to 1.75). 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., a relative risk of 4 would place a woman in a ‘high-risk’ category (in the absence of any other risk factor) and a relative risk between 2 and 4 would 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 PALB2 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 develop counselling and patient management strategies that can accommodate a multifactorial approach to variant classification.

Author affiliations

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

doi:10.1136/jmedgenet-2016-103839

Cancer genetics

2David Geffen School of Medicine, Department of Medicine Division of Hematology and Oncology, University of California at Los Angeles, CA, USA

3University of Biostatistics, Department of Gynecology and Obstetrics, University Hospital Erlangen, Friedrich-Alexander University Erlangen-Nuremberg, Erlangen, Germany

4Institute of Human Genetics, University Hospital Erlangen, Friedrich Alexander University Erlangen-Nuremberg, Erlangen, Germany

5Non-communicable Disease Epidemiology Department, London School of Hygiene and Tropical Medicine, London, UK

6Breakthrough Breast Cancer Research Centre, The Institute of Cancer Research, London, UK

7Division of Cancer Studies, NIHR Comprehensive Biomedical Research Centre, Guy’s & St Thomas’ NHS Foundation Trust in partnership with King’s College London, London, UK

8Wellcome Trust Centre for Human Genetics and Oxford Biomedical Research Centre, University of Oxford, UK and Oxford NIHR Biomedical Research Centre, Headington, OX3 7LE

9Surgey, Lambe Institute for Translational Science, NILGalway, University Hospital Galway, Galway, Ireland

10Department of Obstetrics and Gynecology, University of Heidelberg, Heidelberg, Germany

11National Center for Tumor Diseases, University of Heidelberg, Heidelberg, Germany

12Molecular Epidemiology Group, German Cancer Research Center (DKFZ), Heidelberg, Germany

13Inserm (National Institute of Health and Medical Research), CESP (Center for Research in Epidemiology and Population Health), U1018, Environmental Epidemiology of Cancer, Villejuif, France

14University Paris-Sud, UMRS 1018, Villejuif, France

15Copenhagen General Population Study, Herlev Hospital, Copenhagen University Hospital, University of Copenhagen, Copenhagen, Denmark

16Department of Clinical Biochemistry, Herlev Hospital, Copenhagen University Hospital, University of Copenhagen, Copenhagen, Denmark

17Department of Breast Surgery, Herlev Hospital, Copenhagen University Hospital, Copenhagen, Denmark

18Human Genetics Group, Human Cancer Genetics Program, Spanish National Cancer Research Centre (CNIO), Madrid, Spain

19Centro de Investigación en Red de Enfermedades Raras (CIBERER), Valencia, Spain

20Servicio de Oncología Médica, Hospital Universitario La Paz, Madrid, Spain

21Servicio de Cirugía General y Especialidades, Hospital Monte Naranco, Oviedo, Spain

22Servicio de Anatomía Patológica, Hospital Monte Naranco, Oviedo, Spain

23Department of Epidemiology, University of California Irvine, Irvine, California, USA

24Beckman Research Institute of City of Hope, Duarte, California, USA

25Department of Epidemiology, University of California Irvine, Irvine, California, USA

26Department of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, Maryland, USA

27Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, Maryland, USA

28Division of Cancer Epidemiology and Prevention, M. Sklodowska-Curie Memorial Cancer Center & Institute of Oncology, Warsaw, Poland

29Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm 17177, Sweden

30Department of Pharmacy, University of Southampton (UoS), Southampton UK

31Department of Molecular Genetics, University of Toronto, Toronto, Ontario, Canada

32Division of Epidemiology, Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario, Canada

33University Paris-Sud, UMRS 1018, Villejuif, France

34Department of Clinical Biochemistry, Herlev Hospital, Copenhagen University Hospital, University of Copenhagen, Copenhagen, Denmark

35Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, ON, Canada

36Department of Breast Surgery, Herlev Hospital, Copenhagen University Hospital, Copenhagen, Denmark

37Division of Clinical Epidemiology and Aging Research, German Cancer Research Center (DKFZ), Heidelberg, Germany

38Division of Preventive Oncology, German Cancer Research Center (DKFZ), Heidelberg, Germany

39German Cancer Consortium (DKTK), German Cancer Research Center (DKFZ), Heidelberg, Germany

40Saarland Cancer Registry, Saarbrücken, Germany

41Dr. Margarete Fischer-Bosch-Institute of Clinical Pharmacology, Stuttgart

42University of Tübingen, Tübingen, Germany

43Institute for Prevention and Occupational Medicine of the German Social Accident Insurance, Institute of the Ruhr University, Bochum (IPA), Germany

44Department of Internal Medicine, Evangelische Kliniken Bonn gGmbH, Johanniter Krankenhaus, Bonn, Germany

45Department of Obstetrics and Gynecology, University of Helsinki and Helsinki University Central Hospital, Helsinki, Finland

46Department of Clinical Genetics, Helsinki University Central Hospital, Helsinki, Finland

47Department of Radiation Oncology, Hannover Medical School, Hannover, Germany

48N.N. Alexandrov Research Institute of Oncology and Medical Radiology, Vinnytsya, Ukraine

49Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden

50Institute of Oncology – Pathology, Karolinska Institutet, Stockholm, Sweden

51School of Medicine, Institute of Clinical Medicine, Pathology and Forensic Medicine, and Cancer Center of Eastern Finland, University of Eastern Finland, Kuopio, Finland

52Imaging Center, Department of Clinical Pathology, Kuopio University Hospital, Kuopio, Finland

53School of Medicine, Institute of Clinical Medicine, Oncology, University of Eastern Finland, Kuopio, Finland

54Biocenter Kuopio, Center of Eastern Finland, Kuopio University Hospital, Kuopio, Finland

55QIMR Berghofer Medical Research Institute, Brisbane, Australia

56Research Department, Peter MacCallum Cancer Centre and The Sir Peter MacCallum Department of Oncology, University of Melbourne, Victoria, Australia

57Department of Radiation Oncology, Hannover Medical School, Hannover, Germany

58N.N. Alexandrov Research Institute of Oncology and Medical Radiology, Vinnytsya, Ukraine

59Department of Medical Genetics, University of Toronto, Toronto, Ontario, Canada

60Department of Molecular Genetics, University of Toronto, Toronto, Ontario, Canada

61School of Medicine, Institute of Clinical Medicine, Pathology and Forensic Medicine, and Cancer Center of Eastern Finland, University of Eastern Finland, Kuopio, Finland

62Imaging Center, Department of Clinical Pathology, Kuopio University Hospital, Kuopio, Finland

63School of Medicine, Institute of Clinical Medicine, Oncology, University of Eastern Finland, Kuopio, Finland

64Biocenter Kuopio, Center of Eastern Finland, Kuopio University Hospital, Kuopio, Finland

65QIMR Berghofer Medical Research Institute, Brisbane, Australia

66Research Department, Peter MacCallum Cancer Centre and The Sir Peter MacCallum Department of Oncology, University of Melbourne, Victoria, Australia

67Division of Cancer Epidemiology, German Cancer Research Center (DKFZ), Heidelberg, Germany

68Division of Cancer Epidemiology/Clinical Cancer Registry and Institute for Medical Biometrics and Epidemiology, University Clinic Hamburg-Eppendorf, Hamburg, Germany

69Department of Health Sciences Research, Mayo Clinic, Rochester, MN, USA

70Anatomical Pathology, The Alfred Hospital, Melbourne, Australia

71Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA

72Epidemiology Program, Cancer Research Center, University of Hawaii, Honolulu, HI, USA

73Department of Genetics, Institute for Cancer Research, Oslo University Hospital, Radiumhospitalet, Oslo, Norway

74Faculty of Medicine (Faculty Division Ahus), University of Oslo (UiO), Norway

75Division of Epidemiology, Department of Medicine, Vanderbilt Epidemiology Center, Vanderbilt-Ingram Cancer Center, Vanderbilt University School of Medicine, Nashville, TN, USA

76Program in Molecular and Genetic Epidemiology, Harvard School of Public Health, Boston, MA, USA

77Department of Epidemiology, Harvard School of Public Health, Boston, MA, USA

78Channing Laboratory, Department of Medicine, Brigham and Women’s Hospital and Harvard Medical School, Boston, MA, USA

79Ontario Cancer Genetics Network, Lunenfeld-Tanenbaum Research Institute of Mount Sinai Hospital, Toronto, Ontario, Canada

80Department of Molecular Genetics, University of Toronto, Toronto, Ontario, Canada

81Prosperman Centre for Health Research, Lunenfeld-Tanenbaum Research Institute of Mount Sinai Hospital, Toronto, Ontario, Canada

82Division of Epidemiology, Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario, Canada

83Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, ON, Canada

84Laboratory Medicine Program, University Health Network, Toronto, Ontario

85Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, ON, Canada

86Department of Oncology, Oulu University Hospital, University of Oulu, Oulu, Finland

87Department of Surgery, Oulu University Hospital, University of Oulu, Oulu, Finland

88Department of Oncology, Oulu University Hospital, University of Oulu, Oulu, Finland

89Department of Surgical Oncology, Leiden University Medical Center, 2300 RC Leiden, The Netherlands

90Family Cancer Clinic, Department of Medical Oncology, Erasmus MC-Daniel den Hoed Cancer Centre, Rotterdam, The Netherlands


92Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, Maryland, USA

93Department of Cancer Epidemiology and Prevention, M. Sklodowska-Curie Memorial Cancer Center & Institute of Oncology, Warsaw, Poland

94Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm 17177, Sweden

95Faculty of Medicine, University of Southampton (UoS), Southampton UK

96Department of Medical Oncology, Family Cancer Clinic, Erasmus MC Cancer Institute, Rotterdam, The Netherlands

97Department of Clinical Genetics, Family Cancer Clinic, Erasmus University Medical Center, Rotterdam, The Netherlands

98Department of Surgical Oncology, Family Cancer Clinic, Erasmus University Medical Center, Rotterdam, The Netherlands

99Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm 17177, Sweden

100Human Genetics Division, Genome Institute of Singapore, Singapore 138672, Singapore

101Sheffield Cancer Research, Department of Oncology, University of Sheffield, Sheffield, UK

102Centre for Cancer Genetic Epidemiology, Department of Oncology, University of Cambridge, Cambridge, UK

103Molecular Genetics of Breast Cancer, German Cancer Research Center (DKFZ), Heidelberg, Germany

104Institute of Human Genetics, Pontificia Universidad Javeriana, Bogota, Colombia

105Department of Medical Genetics, University of Toronto, Toronto, Ontario, Canada

106Institute of Human Genetics, Pontificia Universidad Javeriana, Bogota, Colombia

107Department of Genetics and Pathology, Pomeranian Medical University, Szczecin, Poland

108Postgraduate School of Molecular Medicine, Warsaw Medical University, Warsaw, Poland
and planning of the iCOGS experiment. Each author has made substantial contribution through designing 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, EVr, TH, HN, JHL, TD, KC, JRF, 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 data quality related to the calling of the rare genetics variants on iCOGS. MKS, AB, FBH, SV, JC, CV, RJ, PFS, LAFH, AE, MB, JW, JP, IDSS, OF, NJ, MKB, EJS, IT, MIK, NM, FM, BB, RG, PT, TM, FF, MS, SB, SFN, HF, JB, MPZ, JIAM, PM, HAC, SN, AZ, CACD, HS, VA, CS, HB, TD, YDK, TAM, KA, CB, NVB, NNA, AL, SM, AM, VM, V-KM, JHM, AS, EW, DS, BF, GG, JC, AR, PS, DJJ, CEO, CV, CSP, CM, CAH, BEH, FS, LLM, VK, GGA, WJ, DH, SL, SEH, PK, IA, JAK, GGS, AMV, AIV, MG, SK, FD, RAEMT, BS, AH, MGS, IF, SJ, IC, JL, KC, HD, ME, DME, SR, WIT, SMG, MJH, JWMM, JMC, MTL, PH, JL, ISB, KB, AC, MMWR, CL, CB, AD, UH, DT, HU, TR, AJ, JK, KD, SS, AET, CBA, DY, AS, AA, NO, MI, AGN, GPR, MA, NA, DH, DTF, CV, BS, MD, PS, RE, KM, FW, HG, JS, NW, BGM, RTC, JD, FLD, KXT, JLS, WIB, ST, DIJ, JSK, CM, ASK, CC, LCA, KB, JP, RJ, RB, MRT, ZKQ, AAAB, SB, SPR, AH, AM, DR, EMN, IV, NV, JAD, MAR, SN, UWE, SWG, KO, LES, GF, JS, GLK, LR, LGT, MTD, RMD, AR, NAM, RR, RB, RPB, FM, RPE, NZW, KA, RPS, ARD, AH, FH, PH, NRS, GM, SH, EN, EH, BP, BB, LB, ELG, BLF, RA, JMC, MCL, ZCF, KRK, DL, KHL, MATH, XW, DAL, FD, MB, AB, ESI, JRM, LA, DWC, KL, ELT, MSP, SST, EVO, IB, SHO, LB, HBS, AAVA, KKKH, LAK, LFAGM, TP, YB, ABW, LEC, LND, NDL, BG, JG, JIM, CKL, HH, LN, SAE, ED, JT, IC, JP, IS, RG, ASW, JH, VR, WS, HG, XCS, RIT, RS, JRM, SAN, CP, AMV, DF, FYL, JIM, TACS, YFT, ZCM, AGM, SAO, SJ, UR, AMH, CLP, DDB, CKN, UJH, JMS, JK, PHJ, MD, RWMM, MCG, GT, DFF, DMT, DLF, SMT, DFC, DFE, RLM provided DNA supplemental material and therefore have made substantial contribution to the primary manuscript. All authors read and approved the final manuscript.

Funding Funding for the iCOGS infrastructure came from: the European Community’s Seventh Framework Programme under grant agreement n° 223175 (HEALTH-F2-2009-223175) (COGS), Cancer Research UK (C1287/A10118, C1287/A 10710, C12292/A11174, C5047/A8388, C5047/A15007, C5047/A10692, CRUK C18197/A10123), the National Institutes of Health (CA128978) and Post-Cancer GWAS initiative (No. 1 U19 CA 148537— the GAME-ON initiative), the Department of Defense (WB1X1H-10-1-0341), the Canadian Institutes of Health Research (CIHR) for the CIHR Team in Familial Risks of Breast Cancer, Komen Foundation for the Cure, the Breast Cancer Research Foundation, the Ovarian Cancer Research Fund and Susan G Komen (WF).

Further information about the financial report received is outlined in the supplementary file online.

Competing interests None declared.

Provenance and peer review Not commissioned; externally peer reviewed.

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