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ORIGINAL ARTICLE

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

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For numbered affiliations see end of article.

Correspondence to Professor Melissa C. Southey, Genetic Epidemiology Laboratory, Department of Pathology, The University of Melbourne, Melbourne, Victoria 3010, Australia; msouthey@unimelb.edu.au

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Melissa C Southey,¹ David E Goldgar,² Robert Winqvist,³ Katri Pylkäs,³ Fergus Couch,⁴ Marc Tischkowitz,⁵ William D Foulkes,⁶ Joe Dennis,⁷ Kyriaki Michailidou,⁷ Elizabeth J van Rensburg,⁸ Tuomas Heikkinen,⁹ Heli Nevanlinna,⁹ John L Hopper,¹⁰ Thilo Dörk,¹¹ Kathleen BM Claes,¹² Jorge Reis-Filho,¹³ Zhi Ling Teo,¹ Paolo Radice,¹⁴ Irene Catucci,¹⁵ Paolo Peterlongo,¹⁵ Helen Tsimiklis,¹ Fabrice A Odefrey,¹ James G Dowty,¹⁰ Marjanka K Schmidt,¹⁶ Annegien Broeks,¹⁶ Frans B Hogervorst,¹⁶ Senno Verhoef,¹⁶ Jane Carpenter,¹⁷ Christine Clarke,¹⁸ Rodney J Scott,¹⁹ Peter A Fasching,^{20,21} Lothar Haeberle,^{20,22} Arif B Ekici,²³ Matthias W Beckmann,²⁰ Julian Peto,²⁴ Isabel dos-Santos-Silva,²⁴ Olivia Fletcher,²⁵ Nichola Johnson,²⁵ Manjeet K Bolla,⁷ Elinor J Sawyer,²⁶ Ian Tomlinson,²⁷ Michael J Kerin,²⁸ Nicola Miller,²⁸ Federik Marme,^{29,30} Barbara Burwinkel,^{29,31} Rongxi Yang,^{29,31} Pascal Guénel,^{32,33} Thérèse Truong,^{32,33} Florence Menegaux,^{32,33} Marie Sanchez,^{32,33} Stig Bojesen,^{34,35} Sune F Nielsen,^{34,35} Henrik Flyger,³⁶ Javier Benitez,^{37,38} M Pilar Zamora,³⁹ Jose Ignacio Arias Perez,⁴⁰ Primitiva Menéndez,⁴¹ Hoda Anton-Culver,⁴² Susan Neuhausen,⁴³ Argyrios Ziogas,⁴⁴ Christina A Clarke,⁴⁵ Hermann Brenner,^{46,47,48} Volker Arndt,⁴⁶ Christa Stegmaier,⁴⁹ Hiltrud Brauch,^{48,50,51} Thomas Brüning,⁵² Yon-Dschun Ko,⁵³ Taru A Muranen,⁵⁴ Kristiina Aittomäki,⁵⁵ Carl Blomqvist,⁵⁶ Natalia V Bogdanova,^{11,57} Natalia N Antonenkova,⁵⁸ Annika Lindblom,⁵⁹ Sara Margolin,⁶⁰ Arto Mannermaa,^{61,62} Vesa Kataja,^{63,64} Veli-Matti Kosma,^{61,62} Jaana M Hartikainen,^{61,62} Amanda B Spurdle,⁶⁵ kConFab Investigators,⁶⁶ Australian Ovarian Cancer Study Group^{65,66} Els Wauters,^{67,68} Dominiek Smeets,^{67,68} Benoit Beuselinck,⁶⁹ Giuseppe Floris,⁶⁹ Jenny Chang-Claude,⁷⁰ Anja Rudolph,⁷⁰ Petra Seibold,⁷⁰ Dieter Flesch-Janys,⁷¹ Janet E Olson,⁷² Celine Vachon,⁷² Vernon S Pankratz,⁷² Catriona McLean,⁷³ Christopher A Haiman,⁷⁴ Brian E Henderson,⁷⁴ Fredrick Schumacher,⁷⁴ Loic Le Marchand,⁷⁵ Vessela Kristensen,^{76,77} Grethe Grenaker Alnæs,⁷⁶ Wei Zheng,⁷⁸ David J Hunter,^{79,80} Sara Lindstrom,^{79,80} Susan E Hankinson,^{80,81} Peter Kraft,^{79,80} Irene Andrulis,^{82,83} Julia A Knight,^{84,85} Gord Glendon,⁸² Anna Marie Mulligan,^{86,87} Arja Jukkola-Vuorinen,⁸⁸ Mervi Grip,⁸⁹ Saila Kauppila,⁹⁰ Peter Devilee,⁹¹ Robert A E M Tollenaar,⁹¹ Caroline Seynaeve,^{92,98} Antoinette Hollestelle,^{92,98} Montserrat Garcia-Closas,⁹³ Jonine Figueroa,⁹⁴ Stephen J Chanock,⁹⁴ Jolanta Lissowska,⁹⁵ Kamila Czene,⁹⁶ Hatf Darabi,⁹⁶ Mikael Eriksson,⁹⁶ Diana M Eccles,⁹⁷ Sajjad Rafiq,⁹⁷ William J Tapper,⁹⁷ Sue M Gerty,⁹⁷ Maartje J Hoening,⁹⁸ John W M Martens,⁹⁸ J Margriet Collée,⁹⁹ Madeleine Tilanus-Linthorst,¹⁰⁰ Per Hall,¹⁰¹ Jingmei Li,¹⁰² Judith S Brand,¹⁰¹ Keith Humphreys,¹⁰¹ Angela Cox,¹⁰³ Malcolm W R Reed,¹⁰³ Craig Luccarini,¹⁰⁴ Caroline Baynes,¹⁰⁴ Alison M Dunning,¹⁰⁴ Ute Hamann,¹⁰⁵ Diana Torres,^{105,106} Hans Ulrich Ulmer,¹⁰⁷ Thomas Rüdiger,¹⁰⁸ Anna Jakubowska,¹⁰⁹ Jan Lubinski,¹⁰⁹ Katarzyna Jaworska,^{109,110} Katarzyna Durda,¹⁰⁹ Susan Slager,⁷² Amanda E Toland,¹¹¹ Christine B Ambrosone,¹¹² Drakoulis Yannoukakos,¹¹³ Anthony Swerdlow,^{114,115} Alan Ashworth,⁹³ Nick Orr,⁹³ Michael Jones,¹¹⁴ Anna González-Neira,³⁷ Guillermo Pita,³⁷ M Rosario Alonso,³⁷ Nuria Álvarez,³⁷ Daniel Herrero,³⁷



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Daniel C Tessier,¹¹⁶ Daniel Vincent,¹¹⁷ Francois Bacot,¹¹⁷ Jacques Simard,¹¹⁸ Martine Dumont,¹¹⁸ Penny Soucy,¹¹⁸ Rosalind Eeles,^{119,120} Kenneth Muir,¹²¹ Fredrik Wiklund,¹²² Henrik Gronberg,¹²² Johanna Schleutker,^{123,124} Børge G Nordestgaard,¹²⁵ Maren Weischer,¹²⁶ Ruth C Travis,¹²⁷ David Neal,¹²⁸ Jenny L Donovan,¹²⁹ Freddie C Hamdy,¹³⁰ Kay-Tee Khaw,¹³¹ Janet L Stanford,^{132,133} William J Blot,¹³⁴ Stephen Thibodeau,⁴ Daniel J Schaid,⁷² Joseph L Kelley,¹³⁵ Christiane Maier,^{136,137} Adam S Kibel,^{138,139} Cezary Cybulski,¹⁴⁰ Lisa Cannon-Albright,¹⁴¹ Katja Butterbach,⁴⁶ Jong Park,¹⁴² Radka Kaneva,¹⁴³ Jyotsna Batra,¹⁴⁴ Manuel R Teixeira,¹⁴⁵ Zsafia Kote-Jarai,¹¹⁹ Ali Amin Al Olama,⁷ Sara Benlloch,⁷ Stefan P Renner,¹⁴⁶ Arndt Hartmann,¹⁴⁷ Alexander Hein,¹⁴⁶ Matthias Ruebner,¹⁴⁶ Diether Lambrechts,^{148,149} Els Van Nieuwenhuysen,¹⁵⁰ Ignace Vergote,¹⁵⁰ Sandrina Lambrechts,¹⁵⁰ Jennifer A Doherty,¹⁵¹ Mary Anne Rossing,^{152,153} Stefan Nickels,¹⁵⁴ Ursula Eilber,¹⁵⁴ Shan Wang-Gohrke,¹⁵⁵ Kunle Odunsi,¹⁵⁶ Lara E Sucheston-Campbell,¹⁵⁶ Grace Friel,¹⁵⁶ Galina Lurie,¹⁵⁷ Jeffrey L Killeen,¹⁵⁸ Lynne R Wilkens,¹⁵⁷ Marc T Goodman,^{159,160} Ingo Runnebaum,¹⁶¹ Peter A Hillemanns,¹⁶² Liisa M Peltari,⁹ Ralf Butzow,¹⁶³ Francesmary Modugno,^{164,165} Robert P Edwards,¹³⁵ Roberta B Ness,¹⁶⁶ Kirsten B Moysich,¹⁶⁷ Andreas du Bois,^{168,169} Florian Heitz,^{168,169} Philipp Harter,^{168,169} Stefan Kommos,^{169,170} Beth Y Karlan,¹⁷¹ Christine Walsh,¹⁷¹ Jenny Lester,¹⁷¹ Allan Jensen,¹⁷² Susanne Krüger Kjaer,^{172,173} Estrid Høgdall,^{172,174} Bernard Peissel,¹⁷⁵ Bernardo Bonanni,¹⁷⁶ Loris Bernard,¹⁷⁷ Ellen L Goode,⁷² Brooke L Fridley,¹⁷⁸ Robert A Vierkant,⁷² Julie M Cunningham,⁴ Melissa C Larson,⁷² Zachary C Fogarty,⁷² Kimberly R Kalli,¹⁷⁹ Dong Liang,¹⁸⁰ Karen H Lu,¹⁸¹ Michelle A T Hildebrandt,¹⁸² Xifeng Wu,¹⁸² Douglas A Levine,¹⁸³ Fanny Dao,¹⁸³ Maria Bisogna,¹⁸³ Andrew Berchuck,¹⁸⁴ Edwin S Iversen,¹⁸⁵ Jeffrey R Marks,¹⁸⁶ Lucy Akushevich,¹⁸⁷ Daniel W Cramer,¹⁸⁸ Joellen Schildkraut,¹⁸⁷ Kathryn L Terry,¹⁸⁸ Elizabeth M Poole,^{189,190} Meir Stampfer,^{80,189} Shelley S Tworoger,^{189,190} Elisa V Bandera,¹⁹¹ Irene Orlow,¹⁹² Sara H Olson,¹⁹² Line Bjorge,^{193,194} Helga B Salvesen,^{193,194} Anne M van Altena,¹⁹⁵ Katja K H Aben,^{196,197,198} Lambertus A Kiemeny,¹⁹⁶ Leon F A G Massuger,¹⁹⁵ Tanja Pejovic,¹⁹⁹ Yukie Bean,¹⁹⁹ Angela Brooks-Wilson,^{200,201} Linda E Kelemen,^{202,203} Linda S Cook,²⁰⁴ Nhu D Le,²⁰⁵ Bohdan Górski,²⁰⁶ Jacek Gronwald,²⁰⁶ Janusz Menkiszak,²⁰⁷ Claus K Høgdall,¹⁷³ Lene Lundvall,²⁰⁸ Lotte Nedergaard,²⁰⁹ Svend Aage Engelholm,²¹⁰ Ed Dicks,²¹¹ Jonathan Tyrer,²¹¹ Ian Campbell,²¹² Iain McNeish,²¹³ James Paul,²¹⁴ Nadeem Siddiqui,²¹⁵ Rosalind Glasspool,²¹⁵ Alice S Whittemore,²¹⁶ Joseph H Rothstein,²¹⁶ Valerie McGuire,²¹⁶ Weiva Sieh,²¹⁶ Hui Cai,⁷⁸ Xiao-Ou Shu,⁷⁸ Rachel T Teten,²¹⁷ Rebecca Sutphen,²¹⁷ John R McLaughlin,²¹⁸ Steven A Narod,²¹⁹ Catherine M Phelan,²²⁰ Alvaro N Monteiro,²²⁰ David Fenstermacher,²²¹ Hui-Yi Lin,²²¹ Jennifer B Permuth,²²⁰ Thomas A Sellers,²²⁰ Y Ann Chen,²²¹ Ya-Yu Tsai,²²⁰ Zhihua Chen,²²¹ Aleksandra Gentry-Maharaj,²²² Simon A Gayther,²²³ Susan J Ramus,²²³ Usha Menon,²²² Anna H Wu,²²³ Celeste L Pearce,²²³ David Van Den Berg,²²³ Malcolm C Pike,^{223,224} Agnieszka Dansonka-Mieszkowska,²²⁵ Joanna Plisiecka-Halasa,²²⁵ Joanna Moes-Sosnowska,²²⁵ Jolanta Kupryjanczyk,²²⁵ Paul DP Pharoah,²¹¹ Honglin Song,²¹¹ Ingrid Winship,^{226,227} Georgia Chenevix-Trench,⁶⁵ Graham G Giles,^{10,228} Sean V Tavtigian,² Doug F Easton,⁷ Roger L Milne^{10,228}

ABSTRACT

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.349A>G, c.538C>T, c.715G>A, c.1036C>T, c.1312G>T, and c.1343T>G 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 *PALB2* c.1592delT OR 3.44 (95% CI 1.39 to 8.52, $p=7.1\times 10^{-5}$), *PALB2* c.3113G>A OR 4.21 (95% CI 1.84 to 9.60, $p=6.9\times 10^{-8}$) and *ATM* c.7271T>G OR 11.0 (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.538C>T OR 1.33 (95% CI 1.05 to 1.67) ($p\leq 0.017$). Evidence for prostate cancer risk was observed for *CHEK2* c.1343T>G OR 3.03 (95% CI 1.53 to 6.03, $p=0.0006$) for African men and *CHEK2* c.1312G>T OR 2.21 (95% CI 1.06 to 4.63, $p=0.030$) for European

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*.¹⁻³ 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.⁴⁻⁷ 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%).⁸ 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.⁹⁻¹⁰ 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.¹¹⁻¹³ For example, Tavtigian *et al*¹² estimated an OR of 2.85 (95% CI 0.83 to 4.86) 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.⁷⁻¹³ Le Calvez-Kelm *et al*,¹¹ 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.¹¹

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.¹⁴⁻¹⁷ 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.^{4-8 18-20}

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)⁴ and c.3113G>A (p.Trp1038*)⁶ 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.Arg346Cys) predicted to be deleterious on the basis of evolutionary conservation,¹¹ c.538C>T (p.Arg180Cys), c.715G>A (p.Glu239Lys), c.1312G>T (p.Asp438Tyr) and c.1343T>G (p.Ile448Ser) and *ATM* c.7271T>G (p.Val2424Gly).⁷ 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.^{21 22}

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.^{22 23} 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;^{4 5 10} c.2323C>T p.Gln775*;²⁰ c.2816T>G, p. Leu939Trp;^{2 20} c.3113G>A, p.Trp1038*;^{2 6 20} c.3116delA, p. Asn1039Ilefs;^{2 6 20} c.3549C>G, p.Tyr1183*²), *CHEK2* (c.349A>G, p.ArgR117Gly; c.538C>T, p.Arg180Cys; c.715G>A p.Glu239Lys; c.1036C>T, p.Arg346Cys; c.1312G>T, p.Asp438Tyr; c.1343T>G, p.Ile448Ser)¹¹ and *ATM* (c.7271T>G, p.Val2424Gly)^{7 13 24} 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 *PALB2* variants c.2323C>T (p.Gln775*), c.3116delA (p.Asn1039Ilefs) and c.3549C>G (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 multicenter collaboration as described previously.²² Genotypes were called using Illumina's 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 0.05.²⁵ 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.^{23 26} All analyses were carried out using Stata: Release V.10 (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 (KBCP), Oulu Breast Cancer Study (OBCS) and Karolinska Mammography Project for Risk Prediction Breast Cancer (pKARMA); see online supplementary

Table 1 Rare genetic variants included in the iCOGS array.

Gene	Variant*	Amino acid*	dbSNP rs	Breast cancer risk estimates					
				OR (95% CI)	Penetrance† (95% CI)	Align-GVGD	Reference(s)	Designed‡	Genotyped
<i>PALB2</i>	c.1592delT	p.Leu531Cysfs	rs180177102	3.94 (1.5-12.1)§	40% (17-77)	na	4, 5, 10	Yes	Yes
	c.2323C>T	p.Gln775*	rs180177111			na	25, 26	No	No
	c.2816T>G	p.Leu939Trp	rs45478192			C55	20	Yes	Yes
	c.3113G>A	p.Trp1038*	rs180177132		95% (44-100)	na	2, 6, 20	Yes	Yes
	c.3116delA	p.Asn1039Ilefs	rs180177133			na	2	No	No
	c.3549C>G	p.Tyr1183*	rs118203998			na	2	No	No
<i>CHEK2</i>	c.349A>G	p.Arg117Gly	rs28909982	8.75 (1.06-72.2)¶		C65	11	Yes	Yes
	c.538C>T	p.Arg180Cys	rs77130927	2.47 (0.45-13.49)**		C25	11	Yes	Yes
	c.715G>A	p.Glu239Lys	rs121908702	1.82 (0.62-5.34)††		C15	11	Yes	Yes
	c.1036C>T	p.Arg346Cys	na	8.75 (1.06-72.2)¶		C65	11	Yes	Yes
	c.1312G>T	p.Asp438Tyr	na	2.47 (0.45-13.49)**		C25	11	Yes	Yes
	c.1343T>G	p.Ile448Ser	rs17886163	1.82 (0.62-5.34)††		C15	11	Yes	Yes
<i>ATM</i>	c.7271T>G	p.Val2424Gly	rs28904921		52% (28-80)	C65	7, 13, 23, 27	Yes	Yes

*Human Genome Variation Society (HGVS); reference sequences *PALB2*, NM_024675.3, NP_078951.2; *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.³⁻⁷

‡Able to be designed for measurement on the custom Illumina iSelect genotyping array.^{21 22}

§Breast cancer cases unselected for family history of breast cancer.⁴

¶OR estimated in a combined group of C65 *CHEK2* variants.¹¹

**OR estimated in a combined group of C25 *CHEK2* variants.¹¹

††OR estimated in a combined group of C15 *CHEK2* variants.¹¹

na, not available.

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)

Variant	Frequency* Controls	Frequency* Cases	OR (95% CI)	LRT p Value	OR† (95% CI)	LRT p Value‡
<i>PALB2</i> §						
c.1592delT (p.Leu531Cysfs)	0.00014	0.00082	4.52 (1.90 to 10.8)	7.1×10 ⁻⁵	3.44 (1.39 to 8.52)	0.003
c.2816T>G (p.Leu939Trp)	0.00342	0.00352	1.05 (0.83 to 1.32)	0.70	1.03 (0.80 to 1.32)	0.82
c.3113G>A (p.Trp1038*)	0.00019	0.00101	5.93 (2.77 to 12.7)	6.9×10 ⁻⁸	4.21 (1.84 to 9.60)	1.2×10 ⁻⁴
<i>CHEK2</i>						
c.349A>G (p.Arg117Gly)	0.00043	0.00103	2.26 (1.29 to 3.95)	0.003	2.03 (1.10 to 3.73)	0.020
c.538C>T (p.Arg180Cys)	0.00337	0.00370	1.33 (1.05 to 1.67)	0.016	1.34 (1.06 to 1.70)	0.015
c.715G>A (p.Glu239Lys)	0.00021	0.00035	1.70 (0.73 to 3.93)	0.210	1.47 (0.60 to 3.64)	0.40
c.1036C>T (p.Arg346Cys)	0.00005	0.00021	5.06 (1.09 to 23.5)	0.017	3.39 (0.68 to 16.9)	0.11
c.1312G>T (p.Asp438Tyr)	0.00078	0.00082	1.03 (0.62 to 1.71)	0.910	0.87 (0.49 to 1.52)	0.62
c.1343T>G (p.Ile448Ser)‡	0.00002	0	–	–	–	–
<i>ATM</i>						
c.7271T>G (p.Val2424Gly)	0.00002	0.00028	11.6 (1.50 to 89.9)	0.0012	11.0 (1.42 to 85.7)	0.0019

*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 the UK, Australia, the USA and Canada. *PALB2* c.1592delT (p.Leu531Cysfs) 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)

Variant	Frequency† Controls	Frequency† Cases	OR (95% CI)	LRT p Value
<i>PALB2</i>				
c.1592delT (p.Leu531Cysfs)	0.00018	0.00031	2.06 (0.59 to 7.11)	0.24
c.2816T>G (p.Leu939Trp)	0.00354	0.00381	0.95 (0.69 to 1.29)	0.73
c.3113G>A (p.Trp1038*)	0.00045	0.00027	0.49 (0.18 to 1.36)	0.16
<i>CHEK2</i> ‡				
c.349A>G (p.Arg117Gly)	0.00063	0.00081	1.46 (0.71 to 3.02)	0.30
c.538C>T (p.Arg180Cys)	0.00341	0.00296	1.02 (0.73 to 1.44)	0.90
c.715G>A (p.Glu239Lys)	0.00018	0.00027	1.47 (0.41 to 5.35)	0.55
c.1036C>T (p.Arg346Cys)	0.00018	0.00022	1.07 (0.28 to 4.07)	0.93
c.1312G>T (p.Asp438Tyr)	0.00049	0.00103	2.21 (1.06 to 4.63)	0.03
c.1343T>G (p.Ile448Ser)	0	0.00009	–	–
c.1343T>G (Africans§)	0.019	0.057	3.03 (1.53 to 6.03)	0.001
<i>ATM</i>				
c.7271T>G (p.Val2424Gly)	0.00004	0.00027	4.37 (0.52 to 36.4)	0.17

*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 ($p=7.1\times 10^{-5}$); 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 ($p=6.9\times 10^{-8}$), 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).

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)

Variant	Frequency* Controls	Frequency* Cases	OR (95% CI)	LRT p Value
<i>PALB2</i>				
c.1592delT (p.Leu531Cysfs)	0.00004	0.00012	2.50 (0.21 to 29.1)	0.45
c.2816T>G (p.Leu939Trp)	0.00413	0.00399	0.96 (0.69 to 1.34)	0.81
c.3113G>A (p.Trp1038*)	0.00034	0.00031	1.34 (0.36 to 4.97)	0.66
<i>CHEK2</i>				
c.349A>G (p.Arg117Gly)	0.00038	0.00031	1.07 (0.32 to 3.60)	0.92
c.538C>T (p.Arg180Cys)	0.00128	0.00160	1.49 (0.83 to 2.67)	0.18
c.715G>A (p.Glu239Lys)	0.00021	0.00037	1.47 (0.42 to 5.22)	0.54
c.1036C>T (p.Arg346Cys)‡	0	0	–	–
c.1312G>T (p.Asp438Tyr)	0.00081	0.00074	0.92 (0.42 to 1.99)	0.83
c.1343T>G (p.Ile448Ser)	0.00009	0	–	–
<i>ATM</i>				
c.7271T>G (p.Val2424Gly)	0	0.00012	–	–

*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.

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 (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 of European or Asian origin. It was detected in 48 cases and 29 controls of African origin, giving weak evidence of association (OR 1.52 (95% CI 0.95 to 2.43, $p=0.083$)). *CHEK2* c.1312G>T (p.Asp438Tyr) was identified in 23 cases and 11 controls from PRACTICAL, all European, providing evidence of association with prostate cancer risk (OR 2.21 (95% CI 1.06 to 4.63, $p=0.030$)). *CHEK2* c.1343T>G (p.Ile448Ser) was observed in 35 cases and 11 controls, all African, participating in PRACTICAL and was also associated with an increased risk of prostate cancer (OR 3.03 (95% CI 1.53 to 6.03,

$p=0.00059$)). 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).

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.^{27–29} 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,^{5–7 9 11–13} *PALB2* c.3113G>A (p.Trp1038*), *PALB2* c.1592delT (p.Leu531Cysfs) and *ATM* c.7271T>G (p.Val2424Gly) were found to be associated with substantially increased risk of breast cancer all with associated relative risk estimates of 3.44 or greater.

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.^{5 6 9} 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

Align-Grantham Variation Grantham Deviation (Align-GVGD) score and the observed impact on protein function.³⁰

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,³¹ thus this variant is likely to be acting as a dominant negative mutation.³²

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.³³ 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).³⁴ 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*,³⁵ 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 *PALB2*⁹ 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

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 Genetic Epidemiology, 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

¹⁵IFOM, the FIRG Institute of Molecular Oncology, Milan, Italy

¹⁶Netherlands Cancer Institute, Antoni van Leeuwenhoek hospital, Amsterdam, The Netherlands

¹⁷Australian 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

- ²¹David Geffen School of Medicine, Department of Medicine Division of Hematology and Oncology, University of California at Los Angeles, CA, USA
- ²²Unit of Biostatistics, Department of Gynecology and Obstetrics, University Hospital Erlangen, Friedrich-Alexander University Erlangen-Nuremberg, Erlangen, Germany
- ²³Institute of Human Genetics, University Hospital Erlangen, Friedrich Alexander University Erlangen-Nuremberg, Erlangen, Germany
- ²⁴Non-communicable Disease Epidemiology Department, London School of Hygiene and Tropical Medicine, London, UK
- ²⁵Breakthrough Breast Cancer Research Centre, The Institute of Cancer Research, London, UK
- ²⁶Division of Cancer Studies, NIHR Comprehensive Biomedical Research Centre, Guy's & St. Thomas' NHS Foundation Trust in partnership with King's College London, London, UK
- ²⁷Wellcome Trust Centre for Human Genetics and Oxford Biomedical Research Centre, University of Oxford, UK and Oxford NIHR Biomedical Research Centre, Headington, OX3 7LE
- ²⁸Surgery, Lambe Institute for Translational Science, NUI Galway, University Hospital Galway, Galway, Ireland
- ²⁹Department of Obstetrics and Gynecology, University of Heidelberg, Heidelberg, Germany
- ³⁰National Center for Tumor Diseases, University of Heidelberg, Heidelberg, Germany
- ³¹Molecular Epidemiology Group, German Cancer Research Center (DKFZ), Heidelberg, Germany
- ³²Inserm (National Institute of Health and Medical Research), CESP (Center for Research in Epidemiology and Population Health), U1018, Environmental Epidemiology of Cancer, Villejuif, France
- ³³University Paris-Sud, UMR5 1018, Villejuif, France
- ³⁴Copenhagen General Population Study, Herlev Hospital, Copenhagen University Hospital, University of Copenhagen, Copenhagen, Denmark
- ³⁵Department of Clinical Biochemistry, Herlev Hospital, Copenhagen University Hospital, University of Copenhagen, Copenhagen, Denmark
- ³⁶Department of Breast Surgery, Herlev Hospital, Copenhagen University Hospital, Copenhagen, Denmark
- ³⁷Human Genetics Group, Human Cancer Genetics Program, Spanish National Cancer Research Centre (CNIO), Madrid, Spain
- ³⁸Centro de Investigación en Red de Enfermedades Raras (CIBERER), Valencia, Spain
- ³⁹Servicio de Oncología Médica, Hospital Universitario La Paz, Madrid, Spain
- ⁴⁰Servicio de Cirugía General y Especialidades, Hospital Monte Naranco, Oviedo, Spain
- ⁴¹Servicio de Anatomía Patológica, Hospital Monte Naranco, Oviedo, Spain
- ⁴²Department of Epidemiology, University of California Irvine, Irvine, California, USA
- ⁴³Beckman Research Institute of City of Hope, Duarte, California, USA
- ⁴⁴Department of Epidemiology, University of California Irvine, Irvine, California, USA
- ⁴⁵Cancer Prevention Institute of California, Fremont, California, USA
- ⁴⁶Division of Clinical Epidemiology and Aging Research, German Cancer Research Center (DKFZ), Heidelberg, Germany
- ⁴⁷Division of Preventive Oncology, German Cancer Research Center (DKFZ), Heidelberg, Germany
- ⁴⁸German Cancer Consortium (DKTK), German Cancer Research Center (DKFZ), Heidelberg, Germany
- ⁴⁹Saarland Cancer Registry, Saarbrücken, Germany
- ⁵⁰Dr. Margarete Fischer-Bosch-Institute of Clinical Pharmacology, Stuttgart
- ⁵¹University of Tübingen, Tübingen, Germany
- ⁵²Institute for Prevention and Occupational Medicine of the German Social Accident Insurance, Institute of the Ruhr University, Bochum (IPA), Germany
- ⁵³Department of Internal Medicine, Evangelische Kliniken Bonn gGmbH, Johanner Krankenhaus, Bonn, Germany
- ⁵⁴Department of Obstetrics and Gynecology, University of Helsinki and Helsinki University Central Hospital, Helsinki, Finland
- ⁵⁵Department of Clinical Genetics, Helsinki University Central Hospital, Helsinki, Finland
- ⁵⁶Department of Oncology, Helsinki University Central Hospital, Helsinki, Finland
- ⁵⁷Department of Radiation Oncology, Hannover Medical School, Hannover, Germany
- ⁵⁸N.N. Alexandrov Research Institute of Oncology and Medical Radiology, Minsk, Belarus
- ⁵⁹Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden
- ⁶⁰Department of Oncology – Pathology, Karolinska Institutet, Stockholm, Sweden
- 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, Cancer 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
- ⁶⁷Vesalius Research Center (VRC), VIB, Leuven, Belgium
- ⁶⁸Laboratory for Translational Genetics, Department of Oncology, University of Leuven, Leuven, Belgium
- ⁶⁹University Hospital Gasthuisberg, Leuven, Belgium
- ⁷⁰Division of Cancer Epidemiology, German Cancer Research Center (DKFZ), Heidelberg, Germany
- ⁷¹Department of Cancer Epidemiology/Clinical Cancer Registry and Institute for Medical Biometrics and Epidemiology, University Clinic Hamburg-Eppendorf, Hamburg, Germany
- ⁷²Department of Health Sciences Research, Mayo Clinic, Rochester, MN, USA
- ⁷³Anatomical Pathology, The Alfred Hospital, Melbourne, Australia
- ⁷⁴Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA
- ⁷⁵Epidemiology Program, Cancer Research Center, University of Hawaii, Honolulu, HI, USA
- ⁷⁶Department of Genetics, Institute for Cancer Research, Oslo University Hospital, Radiumhospitalet, Oslo, Norway
- ⁷⁷Faculty of Medicine (Faculty Division Ahus), University of Oslo (UiO), Norway
- ⁷⁸Division of Epidemiology, Department of Medicine, Vanderbilt Epidemiology Center, Vanderbilt-Ingram Cancer Center, Vanderbilt University School of Medicine, Nashville, TN, USA
- ⁷⁹Program in Molecular and Genetic Epidemiology, Harvard School of Public Health, Boston, MA, USA
- ⁸⁰Department of Epidemiology, Harvard School of Public Health, Boston, MA, USA
- ⁸¹Channing Laboratory, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA
- ⁸²Ontario Cancer Genetics Network, Lunenfeld-Tanenbaum Research Institute of Mount Sinai Hospital, Toronto, Ontario, Canada
- ⁸³Department of Molecular Genetics, University of Toronto, Toronto, Ontario, Canada
- ⁸⁴Prosserman Centre for Health Research, Lunenfeld-Tanenbaum Research Institute of Mount Sinai Hospital, Toronto, Ontario, Canada
- ⁸⁵Division of Epidemiology, Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario, Canada
- ⁸⁶Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, ON, Canada
- ⁸⁷Laboratory Medicine Program, University Health Network, Toronto, Ontario; Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, ON, Canada
- ⁸⁸Department of Oncology, Oulu University Hospital, University of Oulu, Oulu, Finland
- ⁸⁹Department of Surgery, Oulu University Hospital, University of Oulu, Oulu, Finland
- ⁹⁰Department of Pathology, Oulu University Hospital, University of Oulu, Oulu, Finland
- ⁹¹Department of Surgical Oncology, Leiden University Medical Center, 2300 RC Leiden, The Netherlands
- ⁹²Family Cancer Clinic, Department of Medical Oncology, Erasmus MC-Daniel den Hoed Cancer Centre, Rotterdam, The Netherlands
- ⁹³The Breast Cancer Now Toby Robins Research Centre, The Institute of Cancer Research, London, SW3 6JB, UK
- ⁹⁴Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, Maryland, USA
- ⁹⁵Department of Cancer Epidemiology and Prevention, M. Sklodowska-Curie Memorial Cancer Center & Institute of Oncology, Warsaw, Poland
- ⁹⁶Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm 17177, Sweden
- ⁹⁷Faculty of Medicine, University of Southampton (UoS), Southampton UK
- ⁹⁸Department of Medical Oncology, Family Cancer Clinic, Erasmus MC Cancer Institute, Rotterdam, The Netherlands
- ⁹⁹Department of Clinical Genetics, Family Cancer Clinic, Erasmus University Medical Center, Rotterdam, The Netherlands
- ¹⁰⁰Department of Surgical Oncology, Family Cancer Clinic, Erasmus University Medical Center, Rotterdam, The Netherlands
- ¹⁰¹Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm 17177, Sweden
- ¹⁰²Human Genetics Division, Genome Institute of Singapore, Singapore 138672, Singapore
- ¹⁰³Sheffield Cancer Research, Department of Oncology, University of Sheffield, Sheffield, UK
- ¹⁰⁴Centre for Cancer Genetic Epidemiology, Department of Oncology, University of Cambridge, Cambridge, UK
- ¹⁰⁵Molecular Genetics of Breast Cancer, German Cancer Research Center (DKFZ), Heidelberg, Germany
- ¹⁰⁶Institute of Human Genetics, Pontificia Universidad Javeriana, Bogota, Colombia
- ¹⁰⁷Frauenklinik der Stadtklinik Baden-Baden, Baden-Baden, Germany
- ¹⁰⁸Institute of Pathology, Städtisches Klinikum Karlsruhe, Karlsruhe, Germany
- ¹⁰⁹Department of Genetics and Pathology, Pomeranian Medical University, Szczecin, Poland
- ¹¹⁰Postgraduate 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, IRRP, National Centre for Scientific Research "Demokritos", Aghia Paraskevi Attikis, 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, Canynge 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 0SR
- 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-3, 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-University Erlangen-Nuremberg, Comprehensive Cancer Center Erlangen-EMN, Universitaetsstrasse 21-23, 91054 Erlangen, Germany
- ¹⁴⁷University Hospital Erlangen, Institute of Pathology, Friedrich-Alexander-University Erlangen-Nuremberg, Comprehensive Cancer Center Erlangen-EMN, Universitaetsstrasse 21-23, 91054 Erlangen, German
- 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, Hannover, 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, Kapiolani 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 Gynaecology, 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 Womens 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, Kliniken Essen-Mitte/ Evang. Huysens-Stiftung/ Knappschaft GmbH, Essen, Germany
- ¹⁶⁹Department of Gynecology and Gynecologic Oncology, Dr. Horst Schmidt Kliniken 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 (INT), Milan, Italy
- ¹⁷⁶Division of Cancer Prevention and Genetics, Istituto Europeo di Oncologia (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

- ¹⁹⁵Radboud university medical center, Department of Gynaecology, Nijmegen, Netherlands
- ¹⁹⁶Radboud university medical centre, Radboud Institute for Health Sciences, Nijmegen, Netherlands
- ¹⁹⁷Netherlands Comprehensive Cancer Organisation, Utrecht, Netherlands
- ¹⁹⁸Department of Obstetrics & Gynecology, Oregon Health & Science University
- ¹⁹⁹Knight Cancer Institute, Oregon Health & Science University, Portland, Oregon, USA
- ²⁰⁰Canada's Michael Smith Genome Sciences Centre, BC Cancer Agency, Vancouver, BC, Canada
- ²⁰¹Department of Biomedical Physiology and Kinesiology, Simon Fraser University, Burnaby, BC Canada
- ²⁰²Department of Public Health Sciences, College of Medicine, Medical University of South Carolina, SC, USA
- ²⁰³Hollings Cancer Center, Medical University of South Carolina, SC, USA
- ²⁰⁴Division of Epidemiology and Biostatistics, Department of Internal Medicine, University of New Mexico, Albuquerque, New Mexico, USA
- ²⁰⁵Cancer Control Research, BC Cancer Agency, Vancouver, BC, Canada
- ²⁰⁶International Hereditary Cancer Center, Department of Genetics and Pathology, Pomeranian Medical University, Szczecin, Poland
- ²⁰⁷Department of Gynecological Surgery and Gynecological Oncology of Adults and Adolescents, Pomeranian Medical University, Szczecin, Poland
- ²⁰⁸Gyn Clinic, Rigshospitalet, University of Copenhagen, Denmark
- ²⁰⁹Department of Pathology, Rigshospitalet, University of Copenhagen, Denmark
- ²¹⁰Department of Oncology, Rigshospitalet, University of Copenhagen, Denmark
- ²¹¹Department of Oncology, University of Cambridge, Strangeways Research Laboratory, Cambridge, UK
- ²¹²Cancer Genetics Laboratory, Research Division, Peter MacCallum Cancer Centre, St Andrews Place, East Melbourne
- ²¹³Institute of Cancer Sciences, University of Glasgow, Wolfson Wohl Cancer Research Centre, Beatson Institute for Cancer Research, Glasgow, UK
- ²¹⁴The Cancer Research UK Clinical Trials Unit, Beatson West of Scotland Cancer Centre, 1053 Great Western Road, Glasgow, G12 0YN
- ²¹⁵Department of Gynaecological Oncology, Glasgow Royal Infirmary
- ²¹⁶Department of Health Research and Policy - Epidemiology, Stanford University School of Medicine, Stanford CA, USA
- ²¹⁷Epidemiology Center, College of Medicine, University of South Florida, Tampa, Florida, USA
- ²¹⁸Public Health Ontario, Toronto, Canada
- ²¹⁹Women's College Research Institute, University of Toronto, Toronto, Ontario, Canada
- ²²⁰Department of Cancer Epidemiology, Moffitt Cancer Center, Tampa, FL, USA
- ²²¹Department of Biostatistics and Bioinformatics, Moffitt Cancer Center, Tampa, FL, USA
- ²²²Women's Cancer, Institute for Women's Health, UCL, London, United Kingdom
- ²²³Department of Preventive Medicine, Keck School of Medicine, University of Southern California Norris Comprehensive Cancer Center, Los Angeles, California, USA
- ²²⁴Department of Epidemiology and Biostatistics, Memorial Sloan-Kettering Cancer Center, New York, New York, USA
- ²²⁵Department of Pathology and Laboratory Diagnostics, The Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology, Warsaw, Poland
- ²²⁶Department of Medicine, The University of Melbourne Health, Australia,
- ²²⁷The Royal Melbourne Hospital, Victoria 3050, Australia
- ²²⁸Cancer Epidemiology Centre, Cancer Council Victoria, Victoria, Australia

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