Ovarian and breast cancer risks associated with pathogenic variants in *RAD51C* and *RAD51D*

Xin Yang, PhD¹; Honglin Song, PhD¹,²; Goska Leslie, MEng¹; Christoph Engel, MD³; Eric Hahnen, PhD⁴,⁵; Bernd Auber, PhD⁵; Judit Horváth, MD, PhD⁷; Karin Kast, PhD⁸; Dieter Niederacher, PhD⁹; Clare Turnbull, MD, PhD¹⁰; Richard Houlston, MD, PhD¹⁰; Helen Hanson, MD¹⁰; Chey Loveday, PhD¹⁰; Jill S. Dolinsky, MS, CGC¹¹; Holly LaDuca, MS, CGC¹¹; Susan J. Ramus, PhD¹²⁻¹⁴; Usha Menon, MD¹⁵; Adam N. Rosenthal, PhD¹⁶; Ian Jacobs, MD¹⁶⁻¹⁸; Simon A. Gayther, PhD¹⁹; Ed Dicks, PhD²; Heli Nevanlinna, PhD²⁰; Kristiina Aittomäki, MD, PhD²¹; Liisa M. Pelttari, MSc²⁰; Hans Ehrencrona, PhD²²,²³; Åke Borg, PhD²⁴; Anders Kvist, PhD²⁴; Barbara Rivera, PhD²⁵; Thomas V.O. Hansen, PhD²⁶,²⁷; Malene Djursby, MD²⁷; Andrew Lee, CASM¹; Joe Dennis, MSc¹; David D Bowtell, PhD²⁸,²⁹; Nadia Traficante, BSc²⁸,²⁹; Orland Diez, PhD³⁰,³¹; Judith Balmaña, MD, PhD³²,³³; Stephen B. Gruber, PhD³⁴; Georgia Chenevix-Trench, PhD³⁵; kConFab Investigators, MSc²⁸,²⁹; Allan Jensen, PhD³⁶; Susanne K. Kjær, MD, DMSc³⁶,³⁷; Estrid Høgdall, PhD, DMSc³⁶,³⁸; Laurent Castéra, PharmD, PhD³⁹; Judy Garber, MD, MPH⁴⁰; Ramunas Janavicius, MD, PhD⁴¹,⁴²; Ana Osorio, PhD⁴³,⁴⁴; Lisa Golmard, PharmD, PhD⁴⁵; Ana Vega, PhD⁴³,⁴⁶,⁴⁷; Fergus J. Couch, PhD⁴⁸; Mark Robson, MD⁴⁹; Jacek Gronwald, MD, PhD⁵⁰; Susan M. Domchek, PhD⁵¹; Julie O. Culver, MS⁵²; Miguel de la Hoya, PhD⁵³; Douglas F. Easton, PhD¹,²; William D. Foulkes, PhD⁵⁴; Marc Tischkowitz, MD, PhD⁵⁵; Alfons Meindl, PhD⁵⁶; Rita K. Schmutzler, MD⁴,⁵,⁵⁷; Paul D.P. Pharoah, PhD¹,²; Antonis C. Antoniou, PhD¹*
1 University of Cambridge, Centre for Cancer Genetic Epidemiology, Department of Public Health and Primary Care, Cambridge, UK.

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

3 University of Leipzig, Institute for Medical Informatics, Statistics and Epidemiology, Leipzig, Germany.

4 Faculty of Medicine and University Hospital Cologne, University of Cologne, Center for Familial Breast and Ovarian Cancer, Cologne, Germany.

5 Faculty of Medicine and University Hospital Cologne, University of Cologne, Center for Integrated Oncology (CIO), Cologne, Germany.

6 Hannover Medical School, Institute of Human Genetics, Hannover, Germany.

7 University of Münster, Institute of Human Genetics, Münster, Germany.

8 Medical Faculty and University Hospital Carl Gustav Carus, Technische Universität Dresden, Department of Gynecology and Obstetrics, Dresden, Germany.

9 University Hospital Düsseldorf, Heinrich-Heine University Düsseldorf, Department of Gynecology and Obstetrics, Düsseldorf, Germany.

10 The Institute of Cancer Research, Division of Genetics and Epidemiology, London, UK.

11 Ambry Genetics, Aliso Viejo, Canada.

12 University of NSW Sydney, School of Women’s and Children’s Health, Faculty of Medicine, Sydney, New South Wales, Australia.

13 The Kinghorn Cancer Centre, Garvan Institute of Medical Research, Sydney, New South Wales, Australia.

14 University of NSW Sydney, Adult Cancer Program, Lowy Cancer Research Centre, Sydney, New South Wales, Australia.
University College London, MRC Clinical Trials Unit at UCL, Institute of Clinical Trials & Methodology, London, UK.

University College London, Women’s Cancer, Institute for Women’s Health, London, UK.

University of New South Wales, Sydney, New South Wales, Australia.

University of Manchester, Manchester, UK.

Cedars-Sinai Medical Center, Center for Bioinformatics and Functional Genomics and the Cedars Sinai Genomics Core, Los Angeles, CA, USA.

University of Helsinki, Department of Obstetrics and Gynecology, Helsinki University Hospital, Helsinki, Finland.

University of Helsinki, Department of Clinical Genetics, Helsinki University Hospital, Helsinki, Finland.

Office for Medical Services, Region Skåne, Department of Clinical Genetics and Pathology, Laboratory Medicine, Lund, Sweden.

Lund University, Division of Clinical Genetics, Department of Laboratory Medicine, Lund, Sweden.

Lund University, Division of Oncology and Pathology, Department of Clinical Sciences Lund, Lund, Sweden.

McGill University and Lady Davis Institute, Jewish General Hospital, Gerald Bronfman Dept Oncology, Montréal, QC, Canada.

Rigshospitalet, Copenhagen University Hospital, Center for Genomic Medicine, Copenhagen, Denmark.

Rigshospitalet, Copenhagen University Hospital, Department of Clinical Genetics, Copenhagen, Denmark.

Peter MacCallum Cancer Center, Melbourne, Victoria, Australia.
29 The University of Melbourne, Sir Peter MacCallum Department of Oncology, Parkville, Victoria, Australia.

30 Vall d'Hebron Institute of Oncology (VHIO), Oncogenetics Group, Barcelona, Spain.

31 University Hospital Vall d'Hebron, Clinical and Molecular Genetics Area, Barcelona, Spain.

32 Vall d'Hebron Institute of Oncology, Hereditary Cancer Genetics Group, Barcelona, Spain.

33 University Hospital of Vall d'Hebron, Department of Medical Oncology, Barcelona, Spain.

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

35 QIMR Berghofer Medical Research Institute, Department of Genetics and Computational Biology, Brisbane, Queensland, Australia.

36 Danish Cancer Society Research Center, Department of Virus, Lifestyle and Genes, Copenhagen, Denmark.

37 University of Copenhagen, Department of Gynaecology, Rigshospitalet, Copenhagen, Denmark.

38 University of Copenhagen, Molecular Unit, Department of Pathology, Herlev Hospital, Copenhagen, Denmark.

39 Inserm U1245, Normandy Centre for Genomic and Personalized Medicine, François Baclesse Center, Department of Cancer Biology and Genetics, Caen, France.

40 Dana-Farber Cancer Institute, Cancer Risk and Prevention Clinic, Boston, MA, USA.

41 Vilnius University Hospital Santariskiu Clinics, Hematology, oncology and transfusion medicine center, Dept. of Molecular and Regenerative Medicine, Vilnius, Lithuania.
State Research Institute Centre for Innovative Medicine, Vilnius, Lithuania.

Centro de Investigación en Red de Enfermedades Raras (CIBERER), Madrid, Spain.

Spanish National Cancer Research Centre (CNIO), Human Cancer Genetics Programme, Madrid, Spain.

Institut Curie, Paris Sciences Lettres Research University, Service de Génétique, Paris, France.

Fundación Pública Galega de Medicina Xenómica, Santiago de Compostela, Spain.

Instituto de Investigación Sanitaria de Santiago de Compostela (IDIS), Complejo Hospitalario Universitario de Santiago, SERGAS, Santiago de Compostela, Spain.

Mayo Clinic, Department of Laboratory Medicine and Pathology, Rochester, MN, USA.

Memorial Sloan Kettering Cancer Center, Clinical Genetics Service, Department of Medicine, New York, NY, USA.

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

University of Pennsylvania, Basser Center for BRCA, Abramson Cancer Center, Philadelphia, PA, USA.

University of Southern California, Keck School of Medicine, Los Angeles, CA, USA.

CIBERONC, Hospital Clinico San Carlos, IdISSC (Instituto de Investigación Sanitaria del Hospital Clinico San Carlos), Molecular Oncology Laboratory, Madrid, Spain.

McGill University, Program in Cancer Genetics, Departments of Human Genetics and Oncology, Montréal, QC, Canada.
University of Cambridge, Department of Medical Genetics, National Institute for Health Research Cambridge Biomedical Research Centre, Cambridge, UK.

University of Munich, Campus Großhadern, Department of Gynecology and Obstetrics, Munich, Germany.

Faculty of Medicine and University Hospital Cologne, University of Cologne, Center for Molecular Medicine Cologne (CMMC), Cologne, Germany.

*Corresponding author
Antonis C. Antoniou
Centre for Cancer Genetic Epidemiology
University of Cambridge
Strangeways Research Laboratory
Worts Causeway
Cambridge
CB1 8RN
Tel: +44 (0)1223 748627
Fax: +44 (0)1223 748628
Email: aca20@medschl.cam.ac.uk
### Abbreviations

| Abbreviation | Description                    |
|--------------|--------------------------------|
| TOC          | Tubo-ovarian carcinoma         |
| BC           | Breast cancer                  |
| RR           | Relative risk                  |
| CI           | Confidence interval            |
| OR           | Odds ratio                     |
| AIC          | Akaike information criterion   |
| LRT          | Likelihood ratio test          |
| df           | Degree of freedom              |
| PRS          | Polygenic risk score           |
| GWAS         | Genome-wide association study  |
Abstract

Background

The purpose of this study was to estimate precise age-specific tubo-ovarian carcinoma (TOC) and breast cancer (BC) risks for carriers of pathogenic variants in \textit{RAD51C} and \textit{RAD51D}.

Methods

We analysed data from 6178 families, 125 with pathogenic variants in \textit{RAD51C}; and 6690 families, 60 with pathogenic variants in \textit{RAD51D}. TOC and BC relative and cumulative risks were estimated using complex segregation analysis to model the cancer inheritance patterns in families, while adjusting for the mode of ascertainment of each family. All statistical tests were two-sided.

Results

Pathogenic variants in both \textit{RAD51C} and \textit{RAD51D} were associated with TOC (\textit{RAD51C} RR=7.55, 95\%CI:5.60-10.19, \(p=5\times10^{-40}\); \textit{RAD51D} RR=7.60, 95\%CI:5.61-10.30, \(p=5\times10^{-39}\)) and BC (\textit{RAD51C} RR=1.99, 95\%CI:1.39-2.85, \(p=1.55\times10^{-4}\); \textit{RAD51D} RR=1.83, 95\%CI:1.24-2.72, \(p=0.002\)). For both \textit{RAD51C} and \textit{RAD51D}, there was a suggestion that the TOC RRs increased with age until around age 60 years and decreased thereafter. The estimated cumulative risks of developing TOC to age 80 were 11\% (95\%CI:6-21\%) for \textit{RAD51C} and 13\% (95\%CI:7-23\%) for \textit{RAD51D} pathogenic variant carriers. The estimated cumulative risks of developing BC to 80 were 21\% (95\%CI:15-29\%) for \textit{RAD51C} and 20\% (95\%CI:14-28\%) for \textit{RAD51D} pathogenic variant carriers. Both TOC and BC risks for \textit{RAD51C/D} pathogenic variant carriers varied by cancer family history, and could be as high as 32-36\% for TOC, for
carriers with two first degree relatives diagnosed with TOC; or 44-46% for BC, for carriers with two first degree relatives diagnosed with BC.

Conclusions

These estimates will facilitate the genetic counselling of RAD51C and RAD51D pathogenic variant carriers and justify the incorporation of RAD51C and RAD51D into cancer risk prediction models.
Genetic testing through multi-gene cancer panels is widely available and has become an integral part of the genetic counselling and oncologic practice used to inform clinical management options. *RAD51C* and *RAD51D* are included on widely available cancer panels due the reported associations of pathogenic variants in these genes with tubo-ovarian carcinoma (TOC) (1). However, the optimal interpretation of gene-panel testing results requires precise cancer risk estimates for pathogenic variants in *RAD51C*.

The reported TOC risks for *RAD51C* pathogenic variant carriers vary widely with odds ratio (OR) estimates ranging from 3.4 to 15.8 based on case-control studies and a relative risk (RR) of 5.9 using family-based segregation analysis (Supplementary Table 1). Similarly, the reported TOC ORs/RRs for *RAD51D* pathogenic variant carriers ranged from 6.3 to 12.0 (Supplementary Table 1). There has been conflicting evidence for the association of both *RAD51C* and *RAD51D* pathogenic variants with BC risk. Some studies reported an increased BC risk (OR estimates for *RAD51C*: 5.9-8.7; *RAD51D*: 3.1-8.3) but others reported no statistically significant associations (Supplementary Table 2) (2-4).

A concern with published risk estimates based on case-control studies, has been that cases may have been selected on the basis of cancer family history, which may confound the associations and/or lead to an overestimation of cancer risks due to the enrichment of cases for pathogenic variants. Furthermore, the pathogenic variant frequencies in controls come predominantly from publicly available resources and may come from populations that do not closely match the case population. Therefore, some of the published risk estimates may be susceptible to selection biases or biases due to population stratification and cannot be readily applied in the counselling process. Family- or pedigree-based approaches, with appropriate
ascertainment corrections in the analysis, which adjust for the ascertainment process of each family, address directly such potential biases and can result in more precise risk estimates due to the use of information on both genotyped and non-genotyped family members. Here, we use a large collection of families with RAD51C and/or RAD51D pathogenic variants, to estimate age-specific TOC and BC risks and assess how these vary by family history of cancer.

Methods

Families

Families were enrolled between 1996 and 2017 through 28 study centres from 12 countries from Europe and North America and were ascertained through: RAD51C/D variant screening of families with multiple TOC or BC affected members (24 studies); and RAD51C/D variant screening of TOC or BC patients unselected for cancer family history (3 studies). One study included families ascertained through both schemes. Four studies provided data on all families screened for RAD51C or RAD51D variants, irrespective of the result (Supplementary Table 3). Participants provided informed consent in accordance with institutional-review-board policies and local practices. The list of study centres and ascertainment criteria are provided in Supplementary Table 3.

Variants

Pathogenic variants including frameshift, nonsense, canonical splice sites and large genomic deletions were considered in the analyses. Variants in the last exon were excluded. We estimated the population RAD51C and RAD51D variant using the UK Biobank exome sequencing dataset (http://www.ukbiobank.ac.uk).
Statistical analysis

Cancer inheritance patterns and observed genotypes in families were modelled using complex segregation analysis to estimate TOC and BC RRls simultaneously (8, 9) in the pedigree analysis software Mendel, version 3.3 (10).

Family members were followed from birth until the age at first cancer diagnosis (excluding non-melanoma skin cancer), age at death, age at last follow-up, age at risk-reducing surgery (bilateral mastectomy in the BC analyses or bilateral salpingo-oophorectomy in the TOC analyses if they occurred at least one year prior to cancer diagnosis), or age 80 years, whichever occurred first. Women diagnosed with a first TOC or BC were assumed to be affected at the age of diagnosis whilst women with any other type of first cancer diagnosis were censored at the age of diagnosis and were assumed as unaffected. Missing ages were inferred from other information (Supplementary Methods). Individuals with unknown disease status and no age information were censored at age 0.

Each female was assumed to be at risk of developing TOC and BC assuming that the probability of developing each cancer was independent of one another conditional on genotype. We modelled the TOC and BC incidences so that they depend on the underlying assumed genetic effects (Supplementary Methods). Two main genetic models were fitted: a major-gene model that assumed all familial aggregation of TOC and BC to be due to RAD51C or RAD51D; and a major-gene plus polygenic component model that considered an additional residual familial component representing other unobserved genetic effects not due to RAD51C or RAD51D (11, 12) (Supplementary Methods). Models were fitted in which the log-Relative Risk (logRR) for RAD51C/D pathogenic variant carriers relative to population incidences was assumed to be either constant across the whole age range; constant
for specific age groups; or a piecewise linear function of age (Supplementary Methods). We used country-, cohort- and population- age-specific incidences and constrained the overall cancer age-specific incidences over all assumed genetic effects to agree with the population age-specific incidences (12, 13) (Supplementary Methods).

Since families were ascertained through different criteria across studies, we employed the “ascertainment assumption-free” approach to adjust for ascertainment by computing the pedigree likelihood conditional on all data relevant to the ascertainment (14-16) (Supplementary Methods). Non-informative families, for which no additional information was available beyond the data relevant to the ascertainment, were excluded from the analysis.

The most parsimonious models were selected by comparing either the Akaike information criterion (AIC) for non-nested models, by selecting the model with the smaller AIC, or using the likelihood ratio test (LRT) for nested models. The hypothesis that the RR is 1.00 was assessed using a Wald test statistic. All statistical tests were two-sided. Statistical significance was considered as a P-value<0.05.

Results

Variants and families

A total of 7,216 families eligible for pathogenic variant analysis were submitted to the coordinating centre, where 6,049 were identified through individuals with multiple relatives diagnosed with TOC or BC, and 1,167 were identified through women diagnosed with TOC or BC unselected for cancer family history. After adjustment for ascertainment, 6,178 and 6,690 families were eligible for the RAD51C and RAD51D penetrance analysis respectively (Supplementary Tables 3-4). These
included 215 women with *RAD51C* pathogenic variants (137 were TOC and/or BC cases) from 125 families, and 92 women with *RAD51D* pathogenic variants (66 were TOC or BC cases) from 60 families (Table 1). Full lists of the *RAD51C* and *RAD51D* pathogenic variants in this dataset are summarized in Supplementary Table 5-6. The pathogenic variant population frequencies used in the segregation analysis model were estimated to be 0.00022 for *RAD51C* and 0.00026 for *RAD51D* based on 42,325 cancer-free individuals from the UK Biobank exome sequencing data.

**Risk models**

The genetic models that included a residual polygenic/modifying familial component for TOC and BC provided better fits to the data than the major-gene models for both *RAD51C* and *RAD51D* (results for major gene models not shown). For *RAD51C*, using a constant RR with age, the AIC for the major gene model was 4363 compared with 4346 for the BC polygenic model and with 4336 for the TOC polygenic model (Table 2). For *RAD51D*, the AIC for the major-gene model was 4187 compared with 4178 for the BC polygenic model and with 4160 for the TOC polygenic model (Table 2). Therefore, we based all subsequent analyses on the major-gene plus polygenic component models.

**Tubo-ovarian carcinoma risk**

The estimated TOC RRs were 7.55 (95%CI: 5.60-10.19, p=5×10^{-40}) for *RAD51C* and 7.60 (95%CI: 5.61-10.30, p=5×10^{-39}) for *RAD51D* pathogenic variant carriers when RRs were assumed to be constant with age (Table 2). When separate RRs were estimated for each age-decade, there was a suggestion that RRs increased with age until 60-69 years and then decreased for *RAD51C* pathogenic variant carriers. A similar pattern was seen for *RAD51D* pathogenic variant carriers but the RR peaked in the 50-59 age group (Table 2). These models provided a better
fit to the data than the models with a constant RR for both \textit{RAD51C} (LRT-test, degrees of freedom (df)=4, \(p=0.04\)) and \textit{RAD51D} (LRT, df=4, \(p=0.02\)). When we partitioned age into <50 years and ≥50, the estimated TOC RRs were higher for ages ≥50 years for both \textit{RAD51C} (RR=9.44, 95\%CI:6.63-13.45 for ages≥50; RR=4.97, 95\%CI:2.75-8.97 for ages<50) and \textit{RAD51D} pathogenic variant carriers (RR=10.56, 95\%CI:7.48-14.91 for ages≥50; RR=3.23, 95\%CI:1.36-7.71 for ages<50). The model with separate RR parameters for each decade of age did not fit better than this two age-group model in either \textit{RAD51C} (LRT, df=3, \(p=0.12\)) or \textit{RAD51D} (LRT, df=3, \(p=0.51\)). To smooth the RR changes over age, we fitted models in which the logRR was assumed to be a piecewise linear function of age. For \textit{RAD51C}, there was statistically significant evidence that the RR increases with age (\(p=0.004\)) from age 30 to age 60 years and then decreases. Similarly for \textit{RAD51D}, there was statistically significant evidence that the RR increases with age (\(p=0.002\)) from age 30 to age 58 years and then decreases. The piecewise linear models were the most parsimonious with the lowest AIC (Table 2). Under these models, the estimated cumulative risks of developing TOC for a woman with a \textit{RAD51C} pathogenic variant to age 50 years was 1\% (95\% CI: 0.6-2\%) and 11\% (95\% CI: 6-21\%) to age 80 years; the corresponding cumulative TOC risks were 0.8\% (95\% CI: 0.5-2\%) to age 50 and 13\% (95\% CI: 7-23\%) to age 80 for a woman with a \textit{RAD51D} pathogenic variant, assuming the UK incidences (Figure 1 and Table 3). The corresponding risks using USA population incidences are shown in Supplementary Table 7.

Breast cancer risk

The estimated BC RR was 1.99 (95\%CI:1.39-2.85, \(p=1.55\times10^{-4}\)) for \textit{RAD51C} and 1.83 (95\%CI:1.24-2.72, \(p=0.002\)) for \textit{RAD51D} pathogenic variant carriers when RR was constant with age (Table 2). When RRs varied by age-decade, for \textit{RAD51C},
the statistically significant association was restricted to ages 30-49, but this model did not fit better than the model with a constant RR (LRT, df=5, p=0.37). When only two age groups were assumed, there was further evidence of higher BC RR in younger ages (20-49 years, RR=2.42, 95%CI:1.61-3.63) compared with age ≥50 (RR=1.36, 95%CI:0.70-2.63), but the model with a constant RR remained the most parsimonious. For RAD51D, a “U” shape pattern was observed with higher RR estimates in ages 20-39 and 70-79 years (Table 2), but the model with constant RR remained the most parsimonious (LRT, df=4, p=0.59 comparing against the age-specific RR model, Table 2). The estimated cumulative risks of developing BC to age 50 were 4% (95%CI:3-6%) for RAD51C and 4% (95%CI 2-5%) for RAD51D pathogenic variant carriers and to age 80 were 21% (95%CI:15-29%) for RAD51C and 20% (95 CI:14-28%) for RAD51D pathogenic variant carriers assuming UK incidences (Figure 1 and Table 3; Supplementary Table 7 assuming USA incidences).

Birth cohort and variant screening sensitivity

We assessed whether the estimated risks vary by birth cohort by estimating separate RRs for different birth cohort groupings (Supplementary Table 8). There was a suggestion of increasing BC risks with more recent birth cohort, but the differences were not statistically significant. Similarly, there were no statistically significant differences in the TOC RR estimates between cohort groupings for either RAD51C or RAD51D RRs. We also assessed the impact on the results of assuming a reduced mutation screening sensitivity when including RAD51C/D test-negative families (Supplementary Methods). As the mutation screening sensitivity parameter decreased, the estimated TOC and BC RRs increased (Supplementary Table 9).
Predicted risks by family history

The most parsimonious models included a residual familial polygenic component. Under this model, the risk of developing TOC or BC for RAD51C/D pathogenic variant differs by cancer family history. The predicted risk of developing TOC to age 80 years varies from 11% (95%CI:6-21%) for RAD51C and 13% (95%CI:7-23%) for RAD51D pathogenic variant carriers with no family history of TOC in first and second-degree relatives to 32% (95%CI:20-50%) for RAD51C and 36% (95%CI:23-53%) for RAD51D pathogenic variant carriers whose mother and sister developed TOC at age 50 years (Figure 2 and Supplementary Tables 10-11). Similarly, the predicted cumulative risk of developing BC to age 80 years varies from 20% (95%CI:15-28%) for RAD51C and 19% (95%CI:13-27%) for RAD51D pathogenic variant carriers with an unaffected mother at age 50 years and unaffected maternal grandmother at age 70 years to 46% (95%CI:6-56%) for RAD51C and 44% (95%CI:33-55%) for RAD51D pathogenic variant carriers with two first degree relatives diagnosed with.

Discussion

This is the largest family-based study to date to estimate age-specific relative and absolute TOC and BC risks for RAD51C and RAD51D pathogenic variant carriers, confirming that RAD51C and RAD51D pathogenic variants are associated with TOC and BC risks which vary by cancer-family history.

Several case-control studies have estimated the association between RAD51C and RAD51D pathogenic variants and TOC (Supplementary Table 1). However, these studies had limited statistical power and the OR estimates, ranging from 3.4 to 15.8, were (Supplementary Table 1). The reported associations with BC
risk have been unclear with conflicting evidence (Supplementary Table 2. A complicating factor in interpreting the results from some BC case-control studies includes the fact that BC cases may have been selected on the basis of family history of both BC and TOC, which may confound the BC associations given the known TOC association; and publicly-available controls were often not closely matched to the case populations. In contrast, the present analysis considered the ascertainment process for each family separately and modelled the simultaneous associations with TOC and BC. In addition, family-based analyses closely control for population stratification since genetic background is shared within families (17, 18).

For both \textit{RAD51C} and \textit{RAD51D} pathogenic variants the TOC incidence markedly increases and peaks around ages 58-60 years compared with the country- and cohort-specific population incidences. Even though this is the largest study to date, the age specific results were based on relatively small numbers in each age group. If this pattern is replicated by other studies this may have implications on the timing of risk-reducing interventions.

We used variant frequencies estimated from the UK (\textit{RAD51C}: 0.00022; \textit{RAD51D}: 0.00026). These are similar to other frequency estimates. Following the same pathogenic variant selection criteria, the variant frequencies were estimated to be 0.00055 for \textit{RAD51C} and 0.0003 for \textit{RAD51D} using European non-Finnish non cancer gnomAD data and 0.0007 for \textit{RAD51C} and 0.0004 for \textit{RAD51D} from Song et al (7). Therefore, our results are unlikely to have been influenced by incorrect assumptions for the population variant frequencies.

To maximise the number of families used in the analyses, for studies with data available for all families used in the mutation screening process, we used both
families in which pathogenic variants were detected and families without pathogenic variants, under the assumption that the mutation screening sensitivity is 100%. Our analyses which assumed reduced mutation screening sensitivity suggest that if this is substantially lower (~60%), the estimated risks may have been somewhat underestimated. The results were very similar to the main results for the most plausible values of 80-90%.

Women diagnosed with cancer were censored at the age of risk-reducing surgery if the surgery occurred at least one year prior to cancer diagnosis. We repeated the analysis assuming women were censored at the age of risk-reducing surgery plus one year for both affected and unaffected. The results were almost identical to the main analysis (Supplementary Table 12) suggesting that this assumption in unlikely to have led to bias in the results due to unequal counting of person-time.

The most parsimonious models incorporated a residual polygenic component, which also modifies the TOC and BC risk for pathogenic variant carriers. This indicates that other unobserved genetic or environmental risk factors shared in families may modify cancer risks for pathogenic variant carriers, consistent with results on other susceptibility genes e.g. BRCA1, BRCA2, PALB2 and CHEK2 (11, 12, 19-23). These may include the combined effects of common genetic variants (polygenic risk score, PRS) identified through genome-wide association studies which have been shown to modify TOC and BC risks for pathogenic variant carriers in other genes (24, 25). The results presented here imply that cancer family history should be considered when counselling carriers with RAD51C/D pathogenic variants as it can lead to large differences in the cumulative TOC and BC and thus influence clinical management. For example, the cumulative risk of TOC to age 80 could be as
high as 20-23% for a woman with a *RAD51C/D* pathogenic variant if her mother developed TOC at age 55 (Figure 2 and Supplementary Table 10-11). Similarly, a woman with a *RAD51C/D* pathogenic variant and a first degree relative diagnosed with BC at a young age would be classified as at “high-risk” (≥30%) of developing BC on the basis of the current NICE guidelines in the UK (26).

The current study has several limitations. Although this is the largest study of its kind to date, we were not able to assess variations in risks by variant type or location. Similarly, the number of TOC/BC cases in some age groups remains small and age specific RR estimates are associated with large standard errors (Table 2). Previous studies have suggested that pathogenic variants in *RAD51C* or *RAD51D* may be more strongly associated with specific BC subtypes, in particular estrogen receptor negative or triple-negative BC (3, 4). No cancer subtype analysis were performed for either BC or TOC. To estimate subtype-specific associations in this study design requires tumour pathology data being available on all family members diagnosed with BC/TOC but these were not available. Nevertheless, our BC risk estimates will still be of clinical relevance as current screening or other interventions do not distinguish between the risks for different BC subtypes. The analysis was restricted to studies from Europe and North America. Further studies are needed when applying our findings to other populations.

It has been recently suggested that risk-reducing salpingo-oophorectomy (RRSO) may be offered to women with lifetime risks of TOC of >4-5% (27, 28). The current cumulative risk estimates and associated confidence intervals place both *RAD51C* and *RAD51D* pathogenic variant carriers in the category of women for whom RRSO could be recommended for prevention. However, unlike *BRCA1* pathogenic variants this may only be warranted for women over the age 50, which
allows for women of childbearing age to complete their families. Although the average risk estimates of BC for \textit{RAD51C/RAD51D} pathogenic variant carriers would place these women in the moderate risk category, in combination with family history of BC, the cumulative risks could be as high as 46\% (Figure 2), which would place them in the high-risk category based on the NICE guidelines (26).

In summary, we refined and provided age-specific TOC risk estimates for women with \textit{RAD51C} and \textit{RAD51D} pathogenic variants. We also confirmed that both \textit{RAD51C} and \textit{RAD51D} pathogenic variants confer a moderate risk of BC. Our results suggest that the \textit{RAD51C} and \textit{RAD51D} genes should be included in gene panel testing for TOC and BC to guide cancer surveillance and prevention. Incorporation of \textit{RAD51C} and \textit{RAD51D} into risk prediction models should be considered to facilitate stratified TOC and BC risk management.

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Table 1  Summary of women by mutation, disease status and age among the families with *RAD51C* and *RAD51D* pathogenic variants.

| Age (years) | Pathogenic variant carriers | Tested non carriers | Untested |
|-------------|-----------------------------|---------------------|----------|
|             | Unaffected | BC  | TOC | Unaffected | BC  | TOC | Unaffected | BC  | TOC |
| **RAD51C**  | (N=1794 from 125 families) |        |     |            |     |     |            |     |     |
| <20         | 1          | 0   | 0   | 1          | 0   | 0   | 88         | 0   | 1   |
| 20-29       | 6          | 1   | 0   | 2          | 0   | 0   | 73         | 4   | 1   |
| 30-39       | 18         | 2   | 0   | 12         | 1   | 0   | 128        | 15  | 6   |
| 40-49       | 26         | 25  | 10  | 24         | 4   | 0   | 156        | 35  | 12  |
| 50-59       | 14         | 16  | 27  | 11         | 3   | 0   | 143        | 30  | 21  |
| 60-69       | 9          | 6   | 20  | 9          | 5   | 2   | 161        | 35  | 24  |
| 70-80       | 4          | 4   | 6   | 3          | 1   | 0   | 368        | 15  | 15  |
| missing*    | 0          | 0   | 0   | 0          | 0   | 0   | 172        | 0   | 0   |
| **Total†**  | 78         | 73  | 65  | 62         | 14  | 2   | 1289       | 134 | 80  |
| **RAD51D**  | (N=935 from 60 families)  |        |     |            |     |     |            |     |     |
| <20         | 1          | 0   | 0   | 2          | 0   | 0   | 26         | 0   | 0   |
| 20-29       | 2          | 1   | 0   | 2          | 0   | 0   | 40         | 0   | 0   |
| 30-39       | 7          | 7   | 2   | 6          | 0   | 0   | 54         | 7   | 4   |
| 40-49       | 7          | 11  | 4   | 8          | 2   | 1   | 80         | 19  | 7   |
| 50-59       | 7          | 8   | 17  | 8          | 0   | 0   | 85         | 28  | 19  |
| 60-69       | 1          | 3   | 10  | 5          | 2   | 0   | 87         | 13  | 14  |
| 70-80       | 1          | 0   | 3   | 0          | 0   | 0   | 192        | 7   | 5   |
| Missing*    | 0          | 0   | 0   | 0          | 0   | 0   | 120        | 0   | 0   |
| **Total**   | 26         | 30  | 36  | 31         | 4   | 1   | 684        | 74  | 49  |

*Individuals with missing phenotype information were censored at age 0.

†There are 3 individuals with two cancers diagnosed at the same age and counted in both BC and TOC: one is *RAD51C* pathogenic variant carrier and the other two were untested for *RAD51C*.

BC: Breast Cancer; TOC: Tubo-ovarian Carcinoma
Table 2  Estimated tubo-ovarian carcinoma and breast cancer RR for \textit{RAD51C} and \textit{RAD51D} pathogenic variant carriers.

| Cancer and Models considered | Age (years) | RR (95% CI) | P-value* | LRT P-value† | AIC       | Best fitting models |
|------------------------------|-------------|-------------|----------|--------------|-----------|--------------------|
| \textit{RAD51C}             |             |             |          |              |           |                    |
| Tubo-ovarian carcinoma      |             |             |          |              |           |                    |
| Age-constant model          | 30-79       | 7.55 (5.60-10.19) | 5x10^{-40} |              | 4335.8    | —                  |
| Age-specific model for each decade of age | 30-39 | 2.85 (0.46-17.70) | —        |              | 4334.0    | —                  |
|                              | 40-49       | 5.94 (3.09-11.43) | —        |              | —         | —                  |
|                              | 50-59       | 8.55 (5.10-14.33) | —        |              | —         | —                  |
|                              | 60-69       | 13.90 (8.45-22.88) | —        |              | —         | —                  |
|                              | 70-79       | 2.54 (0.53-12.27) | —        |              | —         | —                  |
| Age-specific model, separate parameters for 2 age groups: [30,50),(50,80) | 30-49 | 4.97 (2.75-8.97) | —        | 0.048        | 4333.8    | —                  |
|                              | 50-79       | 9.44 (6.63-13.45) | —        |              | —         | —                  |
| Piecewise linear model‡      | 35          | 2.40        | —        | 0.004        | 4328.6    | Yes                |
|                              | 45          | 5.14        | —        |              | —         | —                  |
|                              | 55          | 11.02       | —        |              | —         | —                  |
|                              | 65          | 9.02        | —        |              | —         | —                  |
|                              | 75          | 2.82        | —        |              | —         | —                  |
| Breast cancer                |             |             |          |              |           |                    |
| Age-constant model           | 20-79       | 1.99 (1.39-2.85) | 1.55x10^{-4} |              | 4346.4    | Yes                |
| Age-specific model, separate parameters for each decade of age | 20-29 | 1.19 (0.09-16.12) | —        | 0.37        | 4351.0    | —                  |
|                              | 30-39       | 3.25 (1.60-6.62) | —        |              | —         | —                  |
|                              | 40-49       | 2.50 (1.41-4.45) | —        |              | —         | —                  |
|                              | 50-59       | 0.96 (0.34-2.71) | —        |              | —         | —                  |
|                              | 60-69       | 1.54 (0.45-5.36) | —        |              | —         | —                  |
|                              | 70-79       | 2.57 (0.61-10.81) | —        |              | —         | —                  |
| Age-specific model, separate parameters for 2 age groups: [20,50),(50,80) | 20-49 | 2.42 (1.61-3.63) | —        | 0.12        | 4346.0    | —                  |
|                              | 50-79       | 1.36 (0.70-2.63) | —        |              | —         | —                  |
| \textit{RAD51D}             |             |             |          |              |           |                    |
| Tubo-ovarian carcinoma      |             |             |          |              |           |                    |
| Age-constant model           | 30-79       | 7.60 (5.61-10.30) | 5x10^{-39} |              | 4160.0    | —                  |
| Age-specific model for each decade of age | 30-39 | 3.60 (0.78-16.75) | —        | 0.02        | 4155.8    | —                  |
| Age Group | logRR (95% CI) | p-value | Likelihood Ratio Test (LRT) |
|-----------|----------------|---------|-----------------------------|
| 40-49     | 3.19 (1.04-9.72) | —       |                             |
| 50-59     | 12.54 (7.62-20.63) | —       |                             |
| 60-69     | 10.60 (6.10-18.41) | —       |                             |
| 70-79     | 4.94 (1.34-18.26) | —       |                             |
| 30-49     | 3.23 (1.36-7.71)  | 0.002   | 4152.1                      |
| 50-79     | 10.56 (7.48-14.91) | —       |                             |

### Age-specific model, separate parameters for 2 age groups: [30,50), [50,80)

| Age Group | logRR (95% CI) | p-value | Likelihood Ratio Test (LRT) |
|-----------|----------------|---------|-----------------------------|
| 30-49     | 3.23 (1.36-7.71) | 0.002   | 4152.1                      |
| 50-79     | 10.56 (7.48-14.91) | —       |                             |

### Piecewise linear model

| Age Group | logRR (95% CI) | p-value | Likelihood Ratio Test (LRT) |
|-----------|----------------|---------|-----------------------------|
| 35        | 1.64           | —       |                             |
| 45        | 4.30           | —       |                             |
| 55        | 11.29          | —       |                             |
| 65        | 10.16          | —       |                             |
| 75        | 5.77           | —       |                             |

### Breast cancer

#### Age-constant model

| Age Group | logRR (95% CI) | p-value | Likelihood Ratio Test (LRT) |
|-----------|----------------|---------|-----------------------------|
| 20-79     | 1.83 (1.24-2.72) | 0.0002  | 4177.9                      |

#### Age-specific model, separate parameters for each decade of age except for 20-39 age group

| Age Group | logRR (95% CI) | p-value | Likelihood Ratio Test (LRT) |
|-----------|----------------|---------|-----------------------------|
| 20-39     | 2.25 (1.25-4.04) | 0.59    | 4183.1                      |
| 40-49     | 1.46 (0.69-3.09) | —       |                             |
| 50-59     | 1.56 (0.69-3.51) | —       |                             |
| 60-69     | 1.63 (0.54-4.98) | —       |                             |
| 70-79     | 4.19 (1.51-11.62)| —       |                             |

#### Age-specific model, separate parameters for 2 age groups: [20,50), [50,80)

| Age Group | logRR (95% CI) | p-value | Likelihood Ratio Test (LRT) |
|-----------|----------------|---------|-----------------------------|
| 20-49     | 1.84 (1.12-3.02) | 1.00    | 4179.9                      |
| 50-79     | 1.83 (1.02-3.26) | —       |                             |

*The p-values assessing the null hypothesis of RR=1.00

†Likelihood ratio tests (LRT) comparing each model against the model with a constant RR.

‡logRR(t)=a+b1(t-30) if t ∈ [30,60); logRR(t)=a+b1×30+b2(t-60) if t ∈ [60,80) where a=0.49 (95% CI: -0.80 to 1.78), b1=0.076 (95% CI: 0.023 to 0.13), b2=-0.12 (95% CI: -0.23 to -0.0036)

§logRR(t)=a+b1(t-30) if t ∈ [30,58); logRR(t)=a+b1×28+b2(t-58) if t ∈ [58,80) where a=0.010 (95% CI: -1.49 to 1.51), b1=0.097 (95% CI: 0.034 to 0.16), b2=-0.057 (95% CI: -0.13 to 0.017)
Table 3 Estimated age-specific cancer incidences and cumulative cancer risks for *RAD51C* and *RAD51D* pathogenic variant carriers

| Age (years) | *RAD51C* pathogenic variant carriers | *RAD51D* pathogenic variant carriers |
|-------------|--------------------------------------|--------------------------------------|
|             | BC                                  | TOC                                  | BC                                  | TOC                                  |
| Estimated incidences per 1,000 person-years (95% Confidence Interval)* | | | | |
| 30          | 0.4 (0.2-0.5)                        | 0.05 (0.01-0.2)                      | 0.3 (0.2-0.5)                        | 0.03 (0.007-0.1)                      |
| 40          | 2 (1-3)                              | 0.3 (0.2-0.8)                        | 2 (1-2)                              | 0.3 (0.1-0.7)                        |
| 50          | 5 (3-6)                              | 2 (1-3)                              | 4 (3-6)                              | 2 (1-3)                              |
| 60          | 6 (4-9)                              | 7 (4-11)                             | 6 (4-9)                              | 6 (4-8)                              |
| 70          | 7 (5-10)                             | 3 (1-8)                              | 7 (4-10)                             | 5 (2-9)                              |
| 79          | 8 (5-11)                             | 1 (0.2-8)                            | 7 (5-11)                             | 3 (0.9-12)                           |
| Estimated cumulative risks, %, (95% Confidence Interval)* | | | | |
| 30          | 0.1 (0.08-0.2)                       | 0.02 (0.02-0.02)                     | 0.1 (0.07-0.2)                       | 0.02 (0.02-0.02)                     |
| 40          | 1 (0.7-1)                            | 0.2 (0.08-0.4)                       | 0.9 (0.6-1)                          | 0.1 (0.06-0.3)                       |
| 50          | 4 (3-6)                              | 1 (0.6-2)                            | 4 (2-5)                              | 0.8 (0.5-2)                          |
| 60          | 9 (6-12)                             | 4 (3-7)                              | 8 (6-12)                             | 4 (3-7)                              |
| 70          | 15 (11-21)                           | 9 (6-14)                             | 14 (10-20)                           | 9 (6-14)                             |
| 80          | 21 (15-29)                           | 11 (6-21)                            | 20 (14-28)                           | 13 (7-23)                            |

*Assuming the UK population calendar and cohort specific incidences for an individual born between 1950-1959. Mortality is not accounted for absolute risk estimates.

BC: Breast Cancer; TOC: Tubo-ovarian Carcinoma
Figure 1 Estimated age-specific tubo-ovarian carcinoma and breast cancer cumulative risks in RAD51C and RAD51D pathogenic variant carriers. The shaded areas correspond to the 95% confidence intervals.

**Figure 1**

Breast cancer

Tubo-ovarian carcinoma

Cumulative risk (%)

Age (years)

Group  | Pathogenic variant carriers | UK Population (birth cohort:1950–1959)
Figure 2 Estimated tubo-ovarian carcinoma and breast cancer cumulative risks for RAD51C and RAD51D pathogenic variant carriers by cancer family history.

**Figure 2**

![Graph showing cumulative risk for breast cancer and tubo-ovarian carcinoma for RAD51C and RAD51D pathogenic variant carriers by cancer family history.](image)

Family History:
- Red: Mother and sister with BC at age 50
- Blue: Mother and maternal grandmother with BC at age 50
- Black: Mother with BC at age 50
- Purple: Mother and sister with TOC at age 50
- Orange: Mother and maternal grandmother with TOC at age 50
- Brown: Without considering family history
- Pink: Mother unaffected at age 50 and maternal grandmother unaffected at age 70

Age (years) vs. Cumulative risk (%)
Supplementary Material

Methods

Variant frequencies

We estimated the \textit{RAD51C} and \textit{RAD51D} pathogenic variant frequencies in the population using the UK Biobank exome sequencing dataset (http://www.ukbiobank.ac.uk). Specifically, among the 49,960 available subjects, we selected cancer-free individuals (either self-reported or medical records) and removed relatives up to second degree, leaving 42,325 individuals for the variant frequency estimation. The pathogenic variants within \textit{RAD51C} and \textit{RAD51D} were extracted. Variants in the last exon were excluded. The pathogenic variant frequencies were estimated and were used as input parameters in the segregation analysis.

Missing age at cancer diagnosis

Individuals with missing age at cancer diagnosis but other age information available were assumed to develop the corresponding cancer at the minimum available age. For those without any age information available, we assigned the age at cancer diagnosis to be the “average cancer-specific age at diagnosis” obtained from: the family, within the study group and within the country, whichever was available in this order. A summary of the number of individuals with missing age is shown in Supplementary Table 13.

Statistical models

Two main genetic models were fitted: (1) a major-gene model that assumed all familial aggregation of tubo-ovarian carcinoma (TOC) and breast cancer (BC) to be due to \textit{RAD51C} or \textit{RAD51D}; and (2) a polygenic model that considered an additional residual familial component representing other unobserved genetic effects not due to \textit{RAD51C}.
or RAD51D (1, 2). Under each model, the cancer incidence for individual i at age t born in cohort k from country c was dependent on the underlying genetic effects through a model of the form

\[ \lambda_i(t, k, c) = \lambda_0(t, k, c) \exp(\beta(t)G_i + P_i), \]

where \( \lambda_0(t, k, c) \) is the baseline incidence for non-RAD51C/D carriers at age t for cohort k and country c, \( G_i \) is an indicator variable taking values 1 for RAD51C/D pathogenic variant carriers and 0 for non-carriers, and \( P_i \) is the polygenic component which was set to 0 under the single-gene models and was assumed to be normally distributed with mean 0 and variance \( \sigma^2_R \) under the polygenic models (3, 4). \( \beta(t) \) is the log-risk ratio for RAD51C/D pathogenic variant relative to non-carriers. To ease interpretation, the models were parameterised in terms of the cancer-specific log-relative risk (log-RR) for RAD51C and RAD51D pathogenic variant carriers relative to the population incidences for TOC and BC. Specifically, the RR at age t was defined as:

\[ \text{RR}(t) = \frac{i_{\text{RAD51C/D}+}(t, k, c)}{i_{\text{pop}}(t, k, c)} \]

where \( i_{\text{RAD51C/D}+}(t, k, c) \) denotes the average cancer incidence for RAD51C/D pathogenic variant carriers at age t born in cohort k from country c (over all polygenic effects) and \( i_{\text{pop}}(t, k, c) \) denotes the population incidence at age t for cohort k and country c.

We constrained the total genetic variance (\( \sigma^2_{\text{total}} \)), which was defined as the sum of the variance due to RAD51C/D pathogenic variant (\( \sigma^2_K \)) and the residual polygenic variance (\( \sigma^2_R \)), to agree with external estimates of the total polygenic variance. This was assumed be equal to 2.06 for TOC and 1.66 for BC, based on estimates from previously published segregation analyses (1, 5-7).
When the logRR for \(RAD51C/D\) pathogenic variant carriers relative to the population incidences was assumed to be a piecewise linear function of age, the \(\log RR(t)\) was modelled as:

\[
\log RR(t) = \begin{cases} 
    a + b_1(t - 30), & t \in [30, \tau) \\
    a + b_1(\tau - 30) + b_2(t - \tau), & t \in [\tau, 80)
\end{cases}
\]

where, \(t\) is the age, \(\tau\) is the age-breakpoint where the slope changes to \(b_2\). We optimised \(\tau\) by fitting a series of models in which \(\tau\) took values from age 55 to 65 (the plausible age range from the age-specific logRR models).

**Cancer incidences**

Country- and cohort-specific population cancer incidences (Cancer incidence in five continents, [http://ci5.iarc.fr/C5plus/Default.aspx](http://ci5.iarc.fr/C5plus/Default.aspx)) were used here to take into account differences in incidences by study group, study location and changes in incidences over time. The overall cancer incidences were constrained over all assumed genetic effects in the model to agree with the population incidences (5). The reported 5-year interval constant incidences were smoothed using the locally weighted regression LOWESS approach (8, 9). A total of eight cohort-specific incidences (<1920, 1920-1929, 1930-1939, 1940-1949, 1950-1959, 1960-1969, 1970-1979 and >1980) were used in the model by assuming each individual was born at the midpoint of each assumed cohort period (1915 for the first cohort and 1985 for the last cohort).

**Ascertainment adjustment**

We adjusted for ascertainment for each family separately by employing an assumption-free approach (10-12). We divided the data for each family into two parts depending on whether the data could be relevant to the ascertainment (F1) or not (F2). The conditional likelihood \(L=Pr(F1, F2)/Pr(F1)\) was then maximized, where \(Pr(F1, F2)\) is the probability of the observed data in the entire pedigree and \(Pr(F1)\) is the
probability of the observed data in the component relevant to the ascertainment. Specifically, for population-based families, F1 included the phenotype and genotype of the proband only. For families ascertained through multiple affected members, F1 included the genotype of the proband and phenotypes of all the family members. For the families from the four studies that provided data irrespective of the variant screening result (ICR, UKFOCSS, UKFOCR, and SEARCH), the proband’s genotype was excluded from F1 as it did not form part of the ascertainment (Supplementary Table 4).

**Variant screening sensitivity**

Four studies (ICR, UKFOCSS, UKFOCR and SEARCH) provided data on all families screened for *RAD51C* or *RAD51D* variants, irrespective of the mutation search result. Details of these studies and methods have been published elsewhere (13-15). In these families only the proband was screened for *RAD51C/D* mutations. To maximise the number of informative families included in the analysis (after ascertainment adjustment), for these four studies, the analysis included also the families in which the proband was found not to carry a pathogenic variant in *RAD51C* or *RAD51D* and these probands were treated as non-carriers in the analyses. However, this assumes that the variant screening sensitivity, describing the probability of detecting a variant given it exists, is 100%, which may not be necessarily true given the variant screening was carried in research setting in those studies. In practice variant screening sensitivity could be lower and some of the non-carrier families may carry pathogenic variants in *RAD51C* or *RAD51D*. To assess the impact of a reduced variant screening sensitivity on the risk estimates we extended the models to allow for a reduced variant screening sensitivity parameter (16) which was assumed to range from 0.6 to 0.9.
**Supplementary Table 1** Previously published studies on tubo-ovarian carcinoma (TOC) risks associated with germline mutations in *RAD51C* and *RAD51D*

| Published case-control studies | | Minor allele frequency | OR (95% CI) | Reference |
|---|---|---|---|---|
| **Population/country** | **Samples** | **Cases** | **Controls** | **RAD51C** | **RAD51D** | **RAD51C** | **RAD51D** | **Reference** |
| European | ~120,000 BC*/TOC† | ~120,000 | NA | NA | 4.24 (2.56-7.02) | 7.28 (4.03-13.14) | (17) |
| France | 5131 patients with FH‡ of BC or TOC | 571 geographically matched controls | 0.0012 | 0.00052 | 14.62 (5.39-29.52) | 11.84 (1.09-40.00) | (18) |
| United States | 1,915 patients unselected for FH | 4,300 ESP§ European American | 0.0002 | 0.0005 | 15.8 (1.9-128) | 9.0 (1.9-42.5) | (19) |
| | 3,6276 ExAC | | 0.0011 | 0.0004 | 3.4 (1.5-7.6) | 10.9 (4.6-26.0) | |
| Mixed population | 3.429 patients (including 3,135 unselected for FH and 294 with FH) | 2,772 controls (including 2,678 unselected for FH and 94 selected for FH) | 0.00036 | 0.00018 | 5.2 (1.1-24) | 12 (1.5-90) | (15) |

| Published family segregation studies | | Minor allele frequency | HR (95% CI) | Reference |
|---|---|---|---|---|
| **Population/country** | **Families** | **RAD51C** | **RAD51D** | **RAD51C** | **RAD51D** | **Reference** |
| European | 1132 families with FH | NA | NA | 5.88 (2.91-11.88) | NA | (14) |
| UK | 911 families with FH of BC/TOC | NA | NA | NA | 6.30 (2.86-13.85) | (13) |

*BC: breast cancer  
†TOC: tubo-ovarian carcinoma  
‡FH: family history  
§ESP: the National, Heart, Lung, and Blood Institute Exome Sequencing Project
### Supplementary Table 2

Previously published studies on breast cancer risks associated with germline mutations in *RAD51C* and *RAD51D*

#### Published case-control studies

| Population/country | Samples | Minor allele frequency | OR (95% CI) | Reference |
|--------------------|---------|------------------------|-------------|-----------|
| **Australia**      | 3080 patients with FH* of BC† or TOC‡ | 0.0004 | 8.67 (1.89-80.52) | (20) |
|                    | 4840 geographically matched controls | NA      | 1.13 (0.88-1.44) | (17) |
| **European**       | ~120,000 BC/TOC | NA | 2.42 (0.36-7.39) | (18) |
|                    | ~120,000 | NA | 1.25 (0.90-1.75) | (17) |
| **France**         | 5131 patients with FH of BC or TOC | 0.0012 | 1.92 (0.71-3.85) | (18) |
|                    | 571 geographically matched controls | 0.00052 | 2.42 (0.36-7.39) | (17) |
| **Germany**        | 5,589 Patients with FH or early-onset BC or bilateral BC or patients affected by BC and TOC | 0.00045 | 1.76 (0.38-8.17) | NA |
|                    | 2,189 geographically matched controls | 0 | NA |
|                    | 27,173 ExAC (European, non-Finnish, non-TCGA) | 0.00065 | 1.29 (0.62-2.69) | (21) |
|                    | 7,325 FLOSSIES (European American ancestry) | 0.00015 | 5.91 (1.28-27.34) | (21) |
| **United States (white or Ashkenazi Jewish)** | 38,326 patients quantifying for clinical genetic testing | 0.0006 | 0.78 (0.47-1.37) | (22) |
|                    | 26,911 ExAC (non-Finnish, non-TCGA) | 0.0001 | 3.07 (1.21-7.88) | (22) |
| **Mixed population** | 2,134 patients with FH of BC or TOC | 0.0007 | 0.39 (0.02-2.41) | (23) |
|                    | 26,375 ExAC (non-Finnish, non-TCGA European) | 0.0001 | 8.33 (2.20-30.48) | (23) |

#### Published family segregation studies

| Population/country | Families | Minor allele frequency | HR (95% CI) | Reference |
|--------------------|----------|------------------------|-------------|-----------|
| **European**       | 1132 families with FH | NA | 0.91 (0.45-1.86) | (14) |
| **UK**             | 911 families with FH of BC/TOC | NA | 1.32 (0.59-2.96) | (13) |

*FH: family history  
†BC: breast cancer
‡TOC: tubo-ovarian carcinoma
### Supplementary Table 3 List of contributing study groups and number of families

| Study group | Full name of study groups | Total number of families | Number of families by ascertainment type | Number of non-informative families excluded from the analysis due to ascertainment | Number of families eligible for inclusion in the analysis with pathogenic variants‡ | Reference |
|-------------|---------------------------|--------------------------|------------------------------------------|--------------------------------------------------------------------------------|-----------------------------------------------------------------------------|-----------|
| Ambry      | Ambry Genetics            | 18                       | 10                                       | 7                                                                          | 5                                                                           | 11        | 5         |
| AOCS       | Australian Ovarian Cancer Study | 3                       | 1                                        | 4                                                                          | 0                                                                           | 0         | 3         | 1         |
| BFBOCC-LT  | Baltic Familial Breast Ovarian Cancer Consortium (Lithuania) | 4                       | 0                                        | 4                                                                          | 0                                                                           | 2         | 0         |
| CBCS       | Copenhagen Breast Cancer Study | 7                       | 1                                        | 8                                                                          | 0                                                                           | 3         | 1         | 4         | 0         |
| CFB        |                           | 15                       | 5                                        | 20                                                                         | 0                                                                           | 13        | 5         | 2         | 0         |
| CNIO       | Spanish National Cancer Centre | 1                       | 0                                        | 1                                                                          | 0                                                                           | 1         | 0         | 0         | 0         |
| Curie      | Institut Curie            | 1                       | 3                                        | 4                                                                          | 0                                                                           | 0         | 3         | 1         | 0         |
| DFCI       | Dana Farber Cancer Institute | 4                       | 2                                        | 6                                                                          | 0                                                                           | 3         | 2         | 1         | 0         |
| FPGMX      | Fundación Pública Galega de Medicina Xenómica | 0                       | 1                                        | 1                                                                          | 0                                                                           | 0         | 0         | 0         | 1         |
| GC-HBOC    | German Consortium for Hereditary Breast and Ovarian Cancer | 74                      | 16                                       | 90                                                                         | 0                                                                           | 26        | 8         | 48        | 8         |
| Study group | Full name of study groups | Total number of families | Number of families by ascertainment type | Number of non-informative families excluded from the analysis due to ascertainment | Number of families eligible for inclusion in the analysis with pathogenic variants‡ | Reference |
|-------------|--------------------------|--------------------------|-----------------------------------------|---------------------------------------------------------------------------------|--------------------------------------------------------------------------------|----------|
|             |                          |                          | RAD51C | RAD51D | fhx* | pop† | RAD51C | RAD51D | RAD51C | RAD51D |
| HCSC        | Hospital Clinico San Carlos | 1                        | 1      | 2      | 0    | 0    | 1      | 1      | 0      |        |
| HEBCS       | Helsinki Breast Cancer Study | 6                        | 4      | 8      | 2    | 2    | 1      | 4      | 3      |        |
| HVH         | University Hospital Vall d’Hebron | 0                        | 3      | 3      | 0    | 0    | 1      | 0      | 2      | (24)   |
| IBOC        |                          | 1                        | 0      | 1      | 0    | 0    | 0      | 1      | 0      |        |
| ICR         | BOCS (Breast and Ovarian Cancer Study) formerly FBCS (Familial Breast Cancer Study) | 5354 (among these, 4451 families were screened for RAD51C and 5026 families were screened for RAD51D) | 5354   | 0      | 0    | 0    | 4451   | among these 24 with pathogenic variants | 5026   | among these 21 with pathogenic variants | (13, 14) Sequencing methods described in study references |
| kConFab     | Kathleen Cuningham Consortium for Research into Familial Breast Cancer | 2                        | 1      | 3      | 0    | 0    | 0      | 2      | 1      |        |
| MALOVA      | MALignant OVArian cancer study | 1                        | 2      | 0      | 3    | 0    | 0      | 1      | 2      | (25)   |
| MCBCS       |                          | 1                        | 0      | 1      | 0    | 1    | 0      | 0      | 0      |        |
| MCGILL      | McGill University        | 1                        | 1      | 2      | 0    | 1    | 0      | 0      | 1      | (26)   |
| MSKCC       | Memorial Sloane Kettering Cancer Center | 1                        | 0      | 1      | 0    | 0    | 0      | 1      | 0      |        |
| POC         |                          | 3                        | 0      | 3      | 0    | 3    | 0      | 0      | 0      |        |
| Study group       | Full name of study groups                                                                 | Total number of families | Number of families by ascertainment type | Number of non-informative families excluded from the analysis due to ascertainment | Number of families eligible for inclusion in the analysis with pathogenic variants‡ | Reference |
|------------------|------------------------------------------------------------------------------------------|--------------------------|------------------------------------------|----------------------------------------------------------------------------------|----------------------------------------------------------------------------------|-----------|
|                  |                                                                                         |                          | RAD51C | RAD51D | fhx* | pop† | RAD51C | RAD51D | RAD51C | RAD51D |                                               |           |
| UKFOCSS/UKFOCR  | UK Familial Ovarian Cancer Screening Study/UK Familial Ovarian Cancer Registry             | 491 (among these, 486 families were screened for RAD51C and 484 families were screened for RAD51D) | 491    | 0      | 0    | 0    | 486    | 0    | 484    | 0    | 486 among these 8 with pathogenic variants     | (27)     |
|                  |                                                                                         |                          |        |        |      |      |        |      |        |      | 484 among these 6 with pathogenic variants     |          |
|                  |                                                                                         |                          |        |        |      |      |        |      |        |      |                                               |          |
| SEARCH           |                                                                                         | 1158 (among these, 1151 families were screened for RAD51C and 1154 families were screened for RAD51D) | 0      | 1158   | 0    | 0    | 1151   | 0    | 1154   | 0    | 1151 among these 3 with pathogenic variants   | (15)     |
|                  |                                                                                         |                          |        |        |      |      |        |      |        |      | 1154 among these 7 with pathogenic variants   |          |
|                  |                                                                                         |                          |        |        |      |      |        |      |        |      |                                               |          |
| SWE-BRCA         | Swedish Breast Cancer Study                                                               | 9                        | 1      | 10     | 0    | 3    | 0      | 6    | 1      |                                               |           |
|                  |                                                                                         |                          |        |        |      |      |        |      |        |                                               |           |
| UCV              |                                                                                         | 0                        | 2      | 2      | 0    | 0    | 2      | 0    | 0      |                                               |           |
| UPENN            | University of Pennsylvania                                                                | 1                        | 0      | 1      | 0    | 1    | 0      | 0    | 0      |                                               |           |
| USC              | University of South California                                                            | 2                        | 2      | 4      | 0    | 0    | 1      | 2    | 1      |                                               |           |
|                  |                                                                                         |                          |        |        |      |      |        |      |        |                                               |           |
| Total            |                                                                                         |                          | 6244   | 6720   | 6049 | 1167 | 66     | 30   | 6178   | 6690 | 6178 among these 125 with pathogenic variants |           |
|                  |                                                                                         |                          |        |        |      |      |        |      | 6690   |        | 6690 among these 60 with pathogenic variants   |           |
|                  |                                                                                         |                          |        |        |      |      |        |      |        |                                               |           |

*fhx: family-based ascertainment
†pop: population-based ascertainment
‡For ICR, SEARCH and UKFOCSS/UKFOCR the cell contains the total number of families screened for RAD51C or RAD51D
Supplementary Table 4  Summary of types of ascertainment adjustment schemes used in the study

| Type of ascertainment | Study Groups | F1: Data relevant to ascertainment | F2: Data not relevant to ascertainment |
|-----------------------|--------------|-----------------------------------|----------------------------------------|
| Population-based      | SEARCH       | (1) Phenotype of the proband       | (1) Phenotypes of all family members except the proband; (2) mutation status of all family members |
|                       | Others       | (1) Phenotype of the proband; (2) mutation status of the proband | (1) Phenotypes of all family members except the proband; (2) mutation status of all family members except proband's |
| family-based          | ICR, UKFOCSS, UKFOCR | (1) All family phenotypes | Mutation status of all family members |
|                       | Others       | (1) All family phenotypes; (2) mutation status of the proband | Mutation status of all family members except proband's |
Supplementary Table 5  List of pathogenic variants in RAD51C among eligible families included in the analysis

| Variants HGVS (ref: ENST00000337432.9) | Type | Number of families |
|----------------------------------------|------|--------------------|
| c.158_160delinsTT                      | frameshift variant | 1 |
| c.158del                               | frameshift variant | 1 |
| c.181_182del                           | frameshift variant | 2 |
| c.186_187del                           | frameshift variant | 1 |
| c.216_220del                           | frameshift variant | 2 |
| c.224dup                               | frameshift variant | 6 |
| c.483_484insC                          | frameshift variant | 2 |
| c.498del                               | frameshift variant | 2 |
| c.501_502dup                           | frameshift variant | 1 |
| c.525dup                               | frameshift variant | 3 |
| c.622_623del                           | frameshift variant | 1 |
| c.651_652del                           | frameshift variant | 1 |
| c.704dup                               | frameshift variant | 1 |
| c.732del                               | frameshift variant | 4 |
| c.774del                               | frameshift variant | 3 |
| c.849_852del                           | frameshift variant | 1 |
| c.862del                               | frameshift variant | 3 |
| c.890del                               | frameshift variant | 1 |
| c.93del                                | frameshift variant | 14 |
| c.945dup                               | frameshift variant | 1 |
| c.966-?_c.1131+?del                    | frameshift variant | 1 |
| c.572-?_c.1131+?del                    | frameshift variant | 1 |
| c.706-?_c.1131+?del                    | frameshift variant | 1 |
| c.966-?_c.1026+?del                    | frameshift variant | 2 |
| c.706-?_c.837+?del                     | in-frame large deletion | 1 |
| c.145+1G>T                             | intron splicing site variant | 2 |
| c.146-4_146-2del                       | intron splicing site variant | 1 |
| c.404+2T>C                             | intron splicing site variant | 2 |
| c.571+1G>A                             | intron splicing site variant | 2 |
| c.572+1G>T                             | intron splicing site variant | 1 |
| c.705+1G>A                             | intron splicing site variant | 1 |
| c.706-1G>A                             | intron splicing site variant | 3 |
| c.706-2A>G                             | intron splicing site variant | 14 |
| c.837+1G>A                             | intron splicing site variant | 2 |
| c.905-2_905-1del                       | intron splicing site variant | 2 |
| c.905-2del                             | intron splicing site variant | 1 |
| c.397C>T                               | nonsense variant | 3 |
| c.502A>T                               | nonsense variant | 2 |
| c.577C>T                               | nonsense variant | 6 |
| c.664C>T                               | nonsense variant | 1 |
| c.701C>G                               | nonsense variant | 2 |
| c.955C>T                               | nonsense variant | 7 |
| c.97C>T                                | nonsense variant | 4 |
| c.994C>T                               | nonsense variant | 1 |
**Supplementary Table 6** List of pathogenic variants in *RAD51D* among eligible families included in the analysis

| Variants HGVS (ref: ENST00000345365.10) | Type                        | Number of families |
|---------------------------------------|-----------------------------|--------------------|
| c.140_141insAA                        | frameshift variant          | 1                  |
| c.255_256insCTCCCAAAGTGCTAGG          | frameshift variant          | 1                  |
| c.270_271dup                         | frameshift variant          | 1                  |
| c.363del                              | frameshift variant          | 2                  |
| c.416del                              | frameshift variant          | 1                  |
| c.480+1G>A                            | frameshift variant          | 1                  |
| c.564_567del                          | frameshift variant          | 2                  |
| c.564del                              | frameshift variant          | 2                  |
| c.623dup                              | frameshift variant          | 1                  |
| c.667_667+21del                       | frameshift variant          | 1                  |
| c.740_741dup                          | frameshift variant          | 1                  |
| c.748del                              | frameshift variant          | 5                  |
| c.83-?_577-?del                       | frameshift variant          | 1                  |
| c.145-?_263+?del                      | frameshift variant          | 1                  |
| c.451C>T                              | nonsense variant            | 1                  |
| c.478C>T                              | nonsense variant            | 1                  |
| c.547C>T                              | nonsense variant            | 1                  |
| c.556C>T                              | nonsense variant            | 11                 |
| c.620C>A                              | nonsense variant            | 1                  |
| c.649G>T; c.655C>T (cis)              | nonsense variant            | 1                  |
| c.694C>T                              | nonsense variant            | 4                  |
| c.757C>T                              | nonsense variant            | 2                  |
| c.803G>A                              | nonsense variant            | 3                  |
| c.898C>T                              | nonsense variant            | 4                  |
| c.263+1G>A                            | intron splicing site variant| 1                  |
| c.576+1G>A                            | intron splicing site variant| 5                  |
| c.577-2A>G                            | intron splicing site variant| 2                  |
| c.649_655delinsTGAGGTT                | intron splicing site variant| 1                  |
| c.83-1G>A                             | intron splicing site variant| 1                  |
**Supplementary Table 7** Estimated age-specific cancer incidences and cumulative cancer risks for *RAD51C* and *RAD51D* pathogenic variant carriers in the USA.

| Age (years) | Estimated incidences (per 1,000 person-years) for *RAD51C* and *RAD51D* pathogenic variant carriers (95% Confidence Interval)* | Estimated cumulative risks (%) for *RAD51C* and *RAD51D* pathogenic variant carriers by age (95% Confidence Interval)* |
|-------------|-------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|
|             | **RAD51C**                                                                                      | **RAD51D**                                                                                      |
|             | **BC**                                                                                           | **TOC**                                                                                           |
|             | **BC**                                                                                           | **TOC**                                                                                           |
| 30          | 0.4 (0.3-0.6)                                                                                    | 0.06 (0.02-0.2)                                                                                 | 0.4 (0.3-0.6)                                                                                    | 0.04 (0.009-0.2)                                                                                 |
| 40          | 2 (1-3)                                                                                          | 0.3 (0.1-0.7)                                                                                    | 2 (1-3)                                                                                          | 0.2 (0.1-0.6)                                                                                    |
| 50          | 4 (3-6)                                                                                          | 1 (1-2)                                                                                           | 4 (3-6)                                                                                          | 1 (0.9-2)                                                                                        |
| 60          | 7 (5-9)                                                                                          | 5 (3-8)                                                                                           | 6 (4-9)                                                                                          | 4 (3-6)                                                                                          |
| 70          | 9 (6-13)                                                                                         | 2 (0.9-6)                                                                                         | 8 (6-12)                                                                                         | 3 (2-7)                                                                                          |
| 79          | 9 (6-13)                                                                                         | 0.9 (0.1-6)                                                                                      | 8 (6-12)                                                                                         | 2 (0.6-9)                                                                                        |
| 30          | 0.1 (0.1-0.2)                                                                                    | 0.04 (0.04-0.04)                                                                                 | 0.1 (0.09-0.2)                                                                                  | 0.04 (0.04-0.04)                                                                                 |
| 40          | 1 (0.8-2)                                                                                        | 0.2 (0.09-0.4)                                                                                    | 1 (0.7-2)                                                                                       | 0.1 (0.07-0.4)                                                                                  |
| 50          | 4 (3-6)                                                                                          | 0.9 (0.5-2)                                                                                      | 4 (3-6)                                                                                          | 0.8 (0.4-1)                                                                                      |
| 60          | 9 (6-13)                                                                                         | 4 (2-6)                                                                                           | 8 (6-12)                                                                                         | 3 (2-6)                                                                                          |
| 70          | 16 (11-22)                                                                                       | 7 (4-11)                                                                                          | 15 (10-21)                                                                                       | 7 (5-11)                                                                                         |
| 80          | 23 (17-31)                                                                                       | 8 (5-17)                                                                                          | 21 (15-30)                                                                                       | 10 (6-18)                                                                                         |

*Assuming the USA population calendar and cohort specific incidences for an individual born between 1950-1959. Mortality is not accounted for absolute risk estimate.

BC: breast cancer; TOC: tubo-ovarian carcinoma
Supplementary Table 8  Estimated relative risks (RRs) of tubo-ovarian carcinoma (TOC) and breast cancer (BC) for *RAD51C* and *RAD51D* pathogenic variant carriers by birth cohort

| Cancer | Year of birth       | *RAD51C*         |          | *RAD51D*         |          |
|--------|---------------------|------------------|----------|------------------|----------|
|        |                     | RR (95% CI)      | p-value* | RR (95% CI)      | p-value* |
| BC     | Before 1940         | 1                |          | 1                |          |
|        | 1940-1959           | 2.47 (0.77-7.93) | 0.15     | 1.43 (0.5-4.09)  | 0.57     |
|        | in 1960 or later    | 2.68 (0.81-8.84) |          | 1.82 (0.57-5.81) |          |
| TOC    | Before 1940         | 1                |          | 1                |          |
|        | 1940-1959           | 1.19 (0.54-2.62) | 0.43     | 1.17 (0.53-2.61) | 0.75     |
|        | in 1960 or later    | 0.53 (0.13-2.16) |          | 0.76 (0.23-2.56) |          |

*Likelihood ratio test comparing against the model with a constant RR, degrees of freedom=2*
**Supplementary Table 9** Estimated breast cancer (BC) and tubo-ovarian carcinoma (TOC) relative risks for *RAD51C* and *RAD51D* pathogenic variant carriers by different variant screening sensitivity parameters*

| Gene  | Cancer | Assumed sensitivity of mutation screening |
|-------|--------|-----------------------------------------|
|       |        | 0.9          | 0.8          | 0.7          | 0.6          |
| **RAD51C** |        |              |              |              |              |
| BC    | 2.08 (1.46-2.98) | 2.16 (1.51-3.10) | 2.25 (1.57-3.24) | 2.37 (1.64-3.43) |
| TOC   | 8.29 (6.07-11.33) | 8.94 (6.45-12.37) | 9.75 (6.93-13.71) | 10.86 (7.58-15.56) |
| **RAD51D** |        |              |              |              |              |
| BC    | 1.90 (1.28-2.82) | 1.98 (1.33-2.94) | 2.06 (1.38-3.07) | 2.15 (1.44-3.22) |
| TOC   | 8.22 (5.98-11.29) | 8.86 (6.35-12.35) | 9.72 (6.87-13.75) | 10.89 (7.56-15.70) |

*Under the models assuming a constant RR across age groups.*
Supplementary Table 10 Age-specific cumulative breast cancer (BC) risks (%) for female RAD51C and RAD51D pathogenic variant carriers by cancer family history

| Age (years) | Without considering family history | Mother unaffected at 50, maternal grandmother unaffected at 70 | Mother with BC at 35 | Mother and sister with BC at 50 | Mother and maternal grandmother with BC at 50 |
|-------------|------------------------------------|---------------------------------------------------------------|----------------------|--------------------------------|-----------------------------------------------|
| *RAD51C*    |                                    |                                                               |                      |                                |                                               |
| 30          | 0.1 (0.1-0.2)                      | 0.1 (0.1-0.2)                                                 | 0.2 (0.2-0.3)        | 0.3 (0.2-0.5)                  | 0.2 (0.2-0.3)                                 |
| 35          | 0.4 (0.3-0.6)                      | 0.4 (0.3-0.5)                                                 | 0.7 (0.5-1)          | 1 (0.8-2)                      | 0.8 (0.6-1)                                   |
| 40          | 1 (0.7-1)                          | 1 (0.7-1)                                                     | 2 (1-3)              | 3 (2-4)                        | 2 (2-3)                                       |
| 45          | 2 (2-3)                            | 2 (2-3)                                                       | 4 (3-6)              | 6 (4-8)                        | 5 (3-6)                                       |
| 50          | 4 (3-6)                            | 4 (3-5)                                                       | 7 (5-10)             | 11 (8-14)                      | 8 (6-11)                                      |
| 55          | 6 (4-9)                            | 6 (4-9)                                                       | 11 (8-16)            | 16 (12-22)                     | 13 (9-17)                                     |
| 60          | 9 (6-13)                           | 9 (6-12)                                                      | 16 (11-22)           | 23 (17-30)                     | 18 (13-24)                                    |
| 65          | 12 (9-17)                          | 12 (8-16)                                                     | 21 (15-28)           | 29 (22-38)                     | 23 (17-31)                                    |
| 70          | 15 (11-21)                         | 15 (11-20)                                                    | 26 (19-34)           | 36 (27-45)                     | 29 (21-37)                                    |
| 75          | 18 (13-25)                         | 18 (13-24)                                                    | 30 (22-39)           | 41 (32-51)                     | 33 (25-43)                                    |
| 80          | 21 (15-29)                         | 21 (15-28)                                                    | 34 (26-45)           | 46 (36-57)                     | 38 (29-48)                                    |
| *RAD51D*    |                                    |                                                               |                      |                                |                                               |
| 30          | 0.1 (0.1-0.2)                      | 0.1 (0.1-0.2)                                                 | 0.2 (0.1-0.3)        | 0.3 (0.2-0.4)                  | 0.2 (0.2-0.3)                                 |
| 35          | 0.4 (0.2-0.5)                      | 0.4 (0.2-0.5)                                                 | 0.7 (0.5-1)          | 1 (0.7-2)                      | 0.8 (0.5-1)                                   |
| 40          | 0.9 (0.6-1)                        | 0.9 (0.6-1)                                                   | 2 (1-3)              | 3 (2-4)                        | 2 (1-3)                                       |
| 45          | 2 (1-3)                            | 2 (1-3)                                                       | 4 (3-5)              | 6 (4-8)                        | 4 (3-6)                                       |
| 50          | 4 (3-5)                            | 4 (2-5)                                                       | 7 (5-10)             | 10 (7-14)                      | 8 (5-11)                                      |
| 55          | 6 (4-9)                            | 6 (4-8)                                                       | 10 (7-15)            | 15 (11-21)                     | 12 (8-17)                                     |
| 60          | 8 (6-12)                           | 8 (6-12)                                                      | 15 (10-21)           | 21 (15-29)                     | 16 (12-23)                                    |
| 65          | 11 (8-16)                          | 11 (7-15)                                                     | 19 (14-27)           | 27 (20-36)                     | 22 (15-30)                                    |
| 70          | 14 (10-20)                         | 14 (9-19)                                                     | 24 (17-33)           | 33 (25-44)                     | 27 (19-36)                                    |
| 75          | 17 (12-24)                         | 16 (11-23)                                                    | 28 (20-38)           | 39 (29-50)                     | 31 (23-41)                                    |
| 80          | 20 (14-28)                         | 19 (13-27)                                                    | 32 (23-43)           | 44 (33-55)                     | 36 (26-47)                                    |
**Supplementary Table 11** Age-specific cumulative tubo-ovarian carcinoma (TOC) risks (%) for female *RAD51C* and *RAD51D* pathogenic variant carriers by cancer family history

| Age (years) | Without considering family history | Mother unaffected at 50, maternal grandmother unaffected at 70 | Mother with TOC at 55 | Mother and sister with TOC at 50 | Mother and maternal grandmother with TOC at 50 |
|-------------|-----------------------------------|---------------------------------------------------------------|-----------------------|---------------------------------|-----------------------------------------------|
| **RAD51C**  |                                   |                                                               |                       |                                 |                                               |
| 35          | 0.1 (0.0-0.2)                     | 0.1 (0.0-0.1)                                                 | 0.1 (0.1-0.3)         | 0.2 (0.1-0.5)                  | 0.2 (0.1-0.3)                                 |
| 40          | 0.2 (0.1-0.4)                     | 0.2 (0.1-0.4)                                                 | 0.3 (0.2-0.8)         | 0.6 (0.3-1)                    | 0.4 (0.2-0.9)                                 |
| 45          | 0.4 (0.2-0.9)                     | 0.4 (0.2-0.9)                                                 | 0.8 (0.4-2)           | 2 (0.7-3)                      | 1 (0.5-2)                                     |
| 50          | 1 (0.6-2)                         | 1 (0.6-2)                                                     | 2 (1-4)               | 4 (2-6)                        | 2 (1-4)                                       |
| 55          | 2 (1-4)                           | 2 (1-3)                                                       | 4 (3-7)               | 7 (5-11)                       | 5 (3-8)                                       |
| 60          | 4 (3-7)                           | 4 (3-7)                                                       | 9 (6-12)              | 14 (10-20)                     | 10 (7-15)                                     |
| 65          | 7 (5-11)                          | 7 (5-11)                                                      | 14 (9-20)             | 22 (16-31)                     | 16 (11-23)                                    |
| 70          | 9 (6-15)                          | 9 (6-14)                                                      | 17 (11-25)            | 27 (19-38)                     | 20 (13-29)                                    |
| 75          | 10 (6-18)                         | 10 (6-18)                                                     | 19 (12-30)            | 30 (20-45)                     | 22 (14-35)                                    |
| 80          | 11 (6-21)                         | 11 (6-21)                                                     | 20 (12-35)            | 32 (20-51)                     | 24 (14-40)                                    |
| **RAD51D**  |                                   |                                                               |                       |                                 |                                               |
| 35          | 0 (0-0.1)                         | 0 (0-0.1)                                                     | 0.1 (0.1-0.2)         | 0.2 (0.1-0.4)                  | 0.1 (0.1-0.3)                                 |
| 40          | 0.1 (0.1-0.3)                     | 0.1 (0.1-0.3)                                                 | 0.2 (0.1-0.6)         | 0.4 (0.2-1)                    | 0.3 (0.1-0.8)                                 |
| 45          | 0.3 (0.2-0.8)                     | 0.3 (0.2-0.8)                                                 | 0.6 (0.3-2)           | 1 (0.5-3)                      | 0.8 (0.4-2)                                   |
| 50          | 0.8 (0.5-2)                       | 0.8 (0.5-2)                                                   | 2 (0.9-3)             | 3 (2-5)                        | 2 (1-4)                                       |
| 55          | 2 (1-3)                           | 2 (1-3)                                                       | 4 (3-6)               | 7 (4-10)                       | 5 (3-7)                                       |
| 60          | 4 (3-7)                           | 4 (3-7)                                                       | 8 (6-12)              | 14 (9-20)                      | 10 (7-15)                                     |
| 65          | 7 (5-11)                          | 7 (5-10)                                                      | 13 (9-19)             | 22 (15-30)                     | 16 (11-22)                                    |
| 70          | 9 (6-14)                          | 9 (6-14)                                                      | 17 (12-25)            | 28 (19-38)                     | 20 (14-29)                                    |
| 75          | 11 (7-19)                         | 11 (7-18)                                                     | 20 (13-31)            | 32 (23-46)                     | 24 (16-36)                                    |
| 80          | 13 (7-23)                         | 13 (7-23)                                                     | 23 (14-37)            | 36 (23-54)                     | 27 (17-43)                                    |
**Supplementary Table 12** Estimated tubo-ovarian carcinoma (TOC) and breast cancer (BC) RR for *RAD51C* and *RAD51D* pathogenic variant carriers under the best fitting models in the main text assuming censoring for risk-reducing surgery occurs one year after surgery for both affected and unaffected*.

| Cancer | Models considered | Age (years) | *RAD51C* RR (95% CI) | AIC |
|--------|-------------------|-------------|----------------------|-----|
| **RAD51C** | | | | |
| TOC | Piecewise linear model† | 35 | 2.40 | 4328.6 |
| | | 45 | 5.14 | |
| | | 55 | 11.02 | |
| | | 65 | 9.01 | |
| | | 75 | 2.81 | |
| BC | Age-constant model | 20-79 | 1.99 (1.39-2.85) | 4346.5 |
| **RAD51D** | | | | |
| TOC | Piecewise linear model‡ | 35 | 1.64 | 4151.7 |
| | | 45 | 4.30 | |
| | | 55 | 11.29 | |
| | | 65 | 10.14 | |
| | | 75 | 5.75 | |
| BC | Age-constant model | 20-79 | 1.83 (1.24-2.72) | 4178.0 |

*There was only 1 unaffected woman in families with *RAD51D* pathogenic variants censored at risk-reducing bilateral mastectomy. The number of unaffected women who had undergone risk-reducing salpingo-oophorectomy were: 8 among the families with *RAD51C* pathogenic variants, and 5 among the families with *RAD51D* pathogenic variants.

†logRR(t)=a+b1(t-30) if t ∈ [30,60); logRR(t)=a+b1×30+b2(t-60) if t ∈ (60,80) where a=0.49 (95% CI: -0.75 to 1.74), b1=0.076 (95% CI: 0.025 to 0.13), b2=-0.12 (95% CI: -0.23 to -0.0043)

‡logRR(t)=a+b1(t-30) if t ∈ [30,58); logRR(t)=a+b1×28+b2(t-58) if t ∈ (58,80) where a=0.011 (95% CI: -1.52 to 1.55), b1=0.097 (95% CI: 0.033 to 0.16), b2=-0.057 (95% CI: -0.13 to 0.016)
**Supplementary Table 13** A summary of the number of individuals with missing age information at different events (based on all families used in the analysis).

| Event                               | Total number of individuals with event | Total number of individuals with missing ages at event (%) | Number of individuals with missing ages at each event and age inferred from: |  |
|-------------------------------------|----------------------------------------|----------------------------------------------------------|----------------------------------------------------------------------------|---|
|                                     |                                        |                                                          | other age information on the individual (%)                               | the mean event age within the family (%) | the mean event age within the study group (%) |
| First breast cancer (female)        | 15850                                  | 2378 (15%)                                              | 1426 (9%)                                                                  | 871 (5.5%)                         | 81 (0.5%)                                      |
| Ovarian cancer                      | 6742                                   | 920 (13.65%)                                            | 657 (9.7%)                                                                 | 166 (2.5%)                         | 97 (1.4%)                                      |
| First other cancer (female)         | 6172                                   | 1551 (25.13%)                                           | 1014 (16.4%)                                                               | 277 (4.5%)                         | 260 (4.2%)                                      |
| Bilateral mastectomy                | 144                                    | 29 (20.14%)                                             | 29 (20.1%)                                                                 | —                                  | —                                              |
| Bilateral salpingo-oophorectomy     | 624                                    | 42 (6.73%)                                              | 42 (6.7%)                                                                  | —                                  | —                                              |
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