

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

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## Abbreviations

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 *RAD51C* and *RAD51D*.

## Methods

We analysed data from 6178 families, 125 with pathogenic variants in *RAD51C*; and 6690 families, 60 with pathogenic variants in *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 *RAD51C* and *RAD51D* were associated with TOC (*RAD51C* RR=7.55, 95%CI:5.60-10.19,  $p=5\times 10^{-40}$ ; *RAD51D* RR=7.60, 95%CI:5.61-10.30,  $p=5\times 10^{-39}$ ) and BC (*RAD51C* RR=1.99, 95%CI:1.39-2.85,  $p=1.55\times 10^{-4}$ ; *RAD51D* RR=1.83, 95%CI:1.24-2.72,  $p=0.002$ ). For both *RAD51C* and *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 *RAD51C* and 13% (95%CI:7-23%) for *RAD51D* pathogenic variant carriers. The estimated cumulative risks of developing BC to 80 were 21% (95%CI:15-29%) for *RAD51C* and 20% (95%CI:14-28%) for *RAD51D* pathogenic variant carriers. Both TOC and BC risks for *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 RRs 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,  $p=5\times 10^{-40}$ ) for *RAD51C* and 7.60 (95%CI: 5.61-10.30,  $p=5\times 10^{-39}$ ) 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 *RAD51C* (LRT-test, degrees of freedom (df)=4, p=0.04) and *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 *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 *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 *RAD51C* (LRT, df=3, p=0.12) or *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 *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 *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 *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 *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=1.55×10<sup>-4</sup>) for *RAD51C* and 1.83 (95%CI:1.24-2.72, p=0.002) for *RAD51D* pathogenic variant carriers when RR was constant with age (Table 2). When RRs varied by age-decade, for *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  $\geq 50$  ( $RR=1.36$ ,  $95\%CI:0.70-2.63$ ), 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 *RAD51C* and *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 (*RAD51C*: 0.00022; *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 *RAD51C* and 0.0003 for *RAD51D* using European non-Finnish non cancer gnomAD data and 0.0007 for *RAD51C* and 0.0004 for *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 is 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” ( $\geq 30\%$ ) 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 *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 *RAD51C* and *RAD51D* pathogenic variants. We also confirmed that both *RAD51C* and *RAD51D* pathogenic variants confer a moderate risk of BC. Our results suggest that the *RAD51C* and *RAD51D* genes should be included in gene panel testing for TOC and BC to guide cancer surveillance and prevention. Incorporation of *RAD51C* and *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
<i>RAD51C</i> (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	21	2	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
<i>RAD51D</i> (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 *RAD51C* and *RAD51D* pathogenic variant carriers.

Cancer and Models considered	Age (years)	RR (95% CI)	P-value*	LRT P-value†	AIC	Best fitting models
<i>RAD51C</i>						
Tubo-ovarian carcinoma						
Age-constant model	30-79	7.55 (5.60-10.19)	$5 \times 10^{-40}$		4335.8	—
Age-specific model for each decade of age	30-39	2.85 (0.46-17.70)	—	0.04	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)	$1.55 \times 10^{-4}$		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)	—			
<i>RAD51D</i>						
Tubo-ovarian carcinoma						
Age-constant model	30-79	7.60 (5.61-10.30)	$5 \times 10^{-39}$		4160.0	—
Age-specific model for each decade of age	30-39	3.60 (0.78-16.75)	—	0.02	4155.8	—

	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)	—			
Age-specific model, separate parameters for 2 age groups: [30,50],[50,80)	30-49	3.23 (1.36-7.71)	—	0.002	4152.1	—
	50-79	10.56 (7.48-14.91)	—			
Piecewise linear model§	35	1.64	—	0.002	4151.6	Yes
	45	4.30	—			
	55	11.29	—			
	65	10.16	—			
	75	5.77	—			
Breast cancer						
Age-constant model	20-79	1.83 (1.24-2.72)	0.0002		4177.9	Yes
Age-specific model, separate parameters for each decade of age except for 20-39 age group	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)	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.

‡ $\log RR(t) = a + b_1(t-30)$  if  $t \in [30,60)$ ;  $\log RR(t) = a + b_1 \times 30 + b_2(t-60)$  if  $t \in [60,80)$  where  $a = 0.49$  (95% CI: -0.80 to 1.78),  $b_1 = 0.076$  (95% CI: 0.023 to 0.13),  $b_2 = -0.12$  (95% CI: -0.23 to -0.0036)

§ $\log RR(t) = a + b_1(t-30)$  if  $t \in [30,58)$ ;  $\log RR(t) = a + b_1 \times 28 + b_2(t-58)$  if  $t \in [58,80)$  where  $a = 0.010$  (95% CI: -1.49 to 1.51),  $b_1 = 0.097$  (95% CI: 0.034 to 0.16),  $b_2 = -0.057$  (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

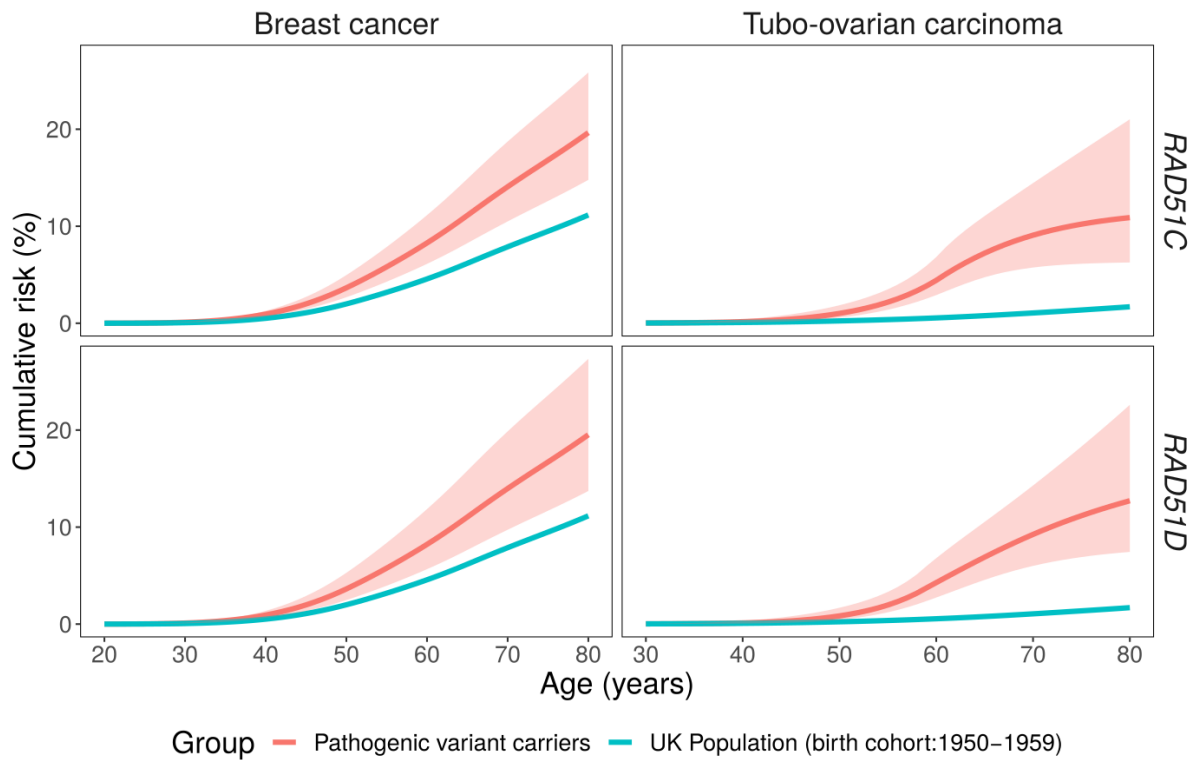
Age (years)	<i>RAD51C</i> pathogenic variant carriers		<i>RAD51D</i> pathogenic variant carriers	
	BC	TOC	BC	TOC
Estimated incidences per 1,000 person-years (95% Confidence Interval)*				
30	0.4 (0.2-0.5)	0.05 (0.01-0.2)	0.3 (0.2-0.5)	0.03 (0.007-0.1)
40	2 (1-3)	0.3 (0.2-0.8)	2 (1-2)	0.3 (0.1-0.7)
50	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

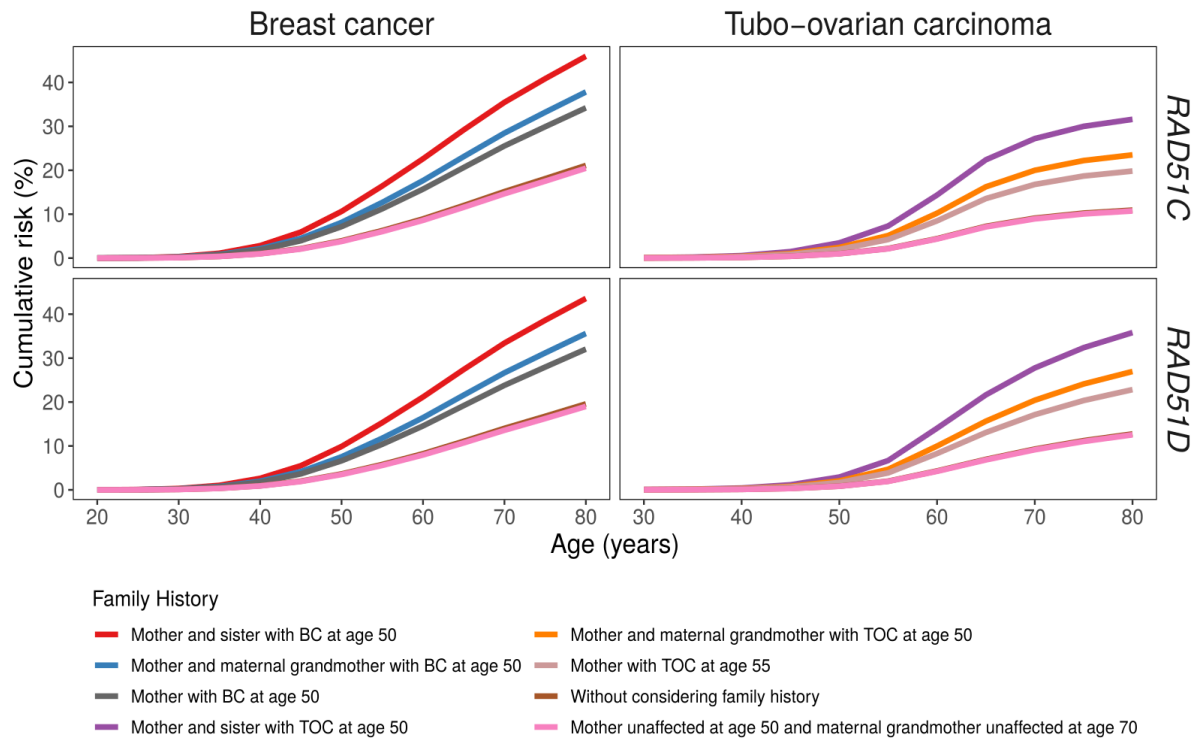
**Figure 1** Estimated age-specific tubo-ovarian carcinoma and breast cancer cumulative risks in *RAD51C* and *RAD51D* pathogenic variant carriers. The shaded areas correspond to the 95% confidence intervals.

**Figure 1**



**Figure 2 Estimated tubo-ovarian carcinoma and breast cancer cumulative risks for *RAD51C* and *RAD51D* pathogenic variant carriers by cancer family history.**

**Figure 2**





# Supplementary Material

## Methods

### Variant frequencies

We estimated the *RAD51C* and *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 *RAD51C* and *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 *RAD51C* or *RAD51D*; and (2) a polygenic model that considered an additional residual familial component representing other unobserved genetic effects not due to *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  $\sigma_R^2$  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:

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

where  $i_{RAD51C/D+}(t, k, c)$  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  $i_{pop}(t, k, c)$  denotes the population incidence at age *t* for cohort *k* and country *c*.

We constrained the total genetic variance ( $\sigma_{total}^2$ ), which was defined as the sum of the variance due to *RAD51C/D* pathogenic variant ( $\sigma_K^2$ ) and the residual polygenic variance ( $\sigma_R^2$ ), to agree with external estimates of the total polygenic variance. This was assumed to 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 logRR(t) was modelled as:

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

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/Ci5plus/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							
Population/ country	Samples		Minor allele frequency		OR (95% CI)		Reference
	Cases	Controls	<i>RAD51C</i>	<i>RAD51D</i>	<i>RAD51C</i>	<i>RAD51D</i>	
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							
Population/ country	Families	Minor allele frequency		HR (95% CI)		Reference	
		<i>RAD51C</i>	<i>RAD51D</i>	<i>RAD51C</i>	<i>RAD51D</i>		
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
	Cases	Controls	<i>RAD51C</i>	<i>RAD51D</i>	<i>RAD51C</i>	<i>RAD51D</i>	
Australia	3080 patients with FH* of BC† or TOC‡	4840 geographically matched controls	0.0004	NA	8.67 (1.89-80.52)	NA	(20)
European	~120,000 BC/TOC	~120,000	NA	NA	1.13 (0.88-1.44)	1.25 (0.90-1.75)	(17)
France	5131 patients with FH of BC or TOC	571 geographically matched controls	0.0012	0.00052	1.92 (0.71-3.85)	2.42 (0.36-7.39)	(18)
Germany	5,589 Patients with FH or early-onset BC or bilateral BC or patients affected by BC and TOC	2,189 geographically matched controls	0.00045	0	1.76 (0.38-8.17)	NA	(21)
		27,173 ExAC (European, non-Finnish, non-TCGA)	0.00065	0.00015	1.29 (0.62-2.69)	3.04 (0.99-9.30)	
		7,325 FLOSSIES (European American ancestry)	0.00015	0.00015	5.91 (1.28-27.34)	3.28 (0.64-16.91)	
United States (white or Ashkenazi Jewish)	38,326 patients quantifying for clinical genetic testing	26,911 ExAC (non-Finnish, non-TCGA)	0.0006	0.0001	0.78 (0.47-1.37)	3.07 (1.21-7.88)	(22)
Mixed population	2,134 patients with FH of BC or TOC	26,375 ExAC (non-Finnish, non-TCGA European)	0.0007	0.0001	0.39 (0.02-2.41)	8.33 (2.20-30.48)	(23)
Published family segregation studies							
Population/ country	Families	Minor allele frequency		HR (95% CI)		Reference	
		<i>RAD51C</i>	<i>RAD51D</i>	<i>RAD51C</i>	<i>RAD51D</i>		
European	1132 families with FH	NA	NA	0.91 (0.45-1.86)	NA	(14)	
UK	911 families with FH of BC/TOC	NA	NA	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
		<i>RAD51C</i>	<i>RAD51D</i>	fhx*	pop†	<i>RAD51C</i>	<i>RAD51D</i>	<i>RAD51C</i>	<i>RAD51D</i>	
Ambry	Ambry Genetics	18	10	28	0	7	5	11	5	
AOCS	Australian Ovarian Cancer Study	3	1	0	4	0	0	3	1	
BFBOCC-LT	Baltic Familial Breast Ovarian Cancer Consortium (Lithuania)	4	0	4	0	2	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
		<i>RAD51C</i>	<i>RAD51D</i>	fhx*	pop†	<i>RAD51C</i>	<i>RAD51D</i>	<i>RAD51C</i>	<i>RAD51D</i>	
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 <i>RAD51C</i> and 5026 families were screened for <i>RAD51D</i> )		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 OVArrian 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
		<i>RAD51C</i>	<i>RAD51D</i>	fhx*	pop†	<i>RAD51C</i>	<i>RAD51D</i>	<i>RAD51C</i>	<i>RAD51D</i>	
UKFOCSS/ UKFOCR	UK Familial Ovarian Cancer Screening Study/ UK Familial Ovarian Cancer Registry	491 (among these, 486 families were screened for <i>RAD51C</i> and 484 families were screened for <i>RAD51D</i> )		491	0	0	0	486 among these 8 with pathogenic variants	484 among these 6 with pathogenic variants	(27) Sequencing methods described in reference (15)
SEARCH		1158 (among these, 1151 families were screened for <i>RAD51C</i> and 1154 families were screened for <i>RAD51D</i> )		0	1158	0	0	1151 among these 3 with pathogenic variants	1154 among these 7 with pathogenic variants	(15) Sequencing methods described in study reference.
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 among these 125 with pathogenic variants	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

<b>Variants HGVS (ref: ENST00000337432.9)</b>	<b>Type</b>	<b>Number of families</b>
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	12
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

<b>Variants HGVS (ref: ENST00000345365.10)</b>	<b>Type</b>	<b>Number of families</b>
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 <i>RAD51C</i> and <i>RAD51D</i> pathogenic variant carriers (95% Confidence Interval)*			
	<i>RAD51C</i>		<i>RAD51D</i>	
	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)
Age (years)	Estimated cumulative risks (%) for <i>RAD51C</i> and <i>RAD51D</i> pathogenic variant carriers by age (95% Confidence Interval)*			
	<i>RAD51C</i>		<i>RAD51D</i>	
	BC	TOC	BC	TOC
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	<i>RAD51C</i>		<i>RAD51D</i>	
		RR (95% CI)	p-value*	RR (95% CI)	p-value*
BC	Before 1940	1	0.15	1	0.57
	1940-1959	2.47 (0.77-7.93)		1.43 (0.5-4.09)	
	in 1960 or later	2.68 (0.81-8.84)		1.82 (0.57-5.81)	
TOC	Before 1940	1	0.43	1	0.75
	1940-1959	1.19 (0.54-2.62)		1.17 (0.53-2.61)	
	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
<i>RAD51C</i>	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)
<i>RAD51D</i>	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
<b><i>RAD51C</i></b>					
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)
<b><i>RAD51D</i></b>					
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
<b><i>RAD51C</i></b>					
35	0.1 (0-0.2)	0.1 (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)
<b><i>RAD51D</i></b>					
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)	<i>RAD51C</i> RR (95% CI)	AIC
<b><i>RAD51C</i></b>				
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
<b><i>RAD51D</i></b>				
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.

† $\log RR(t) = a + b_1(t-30)$  if  $t \in [30,60)$ ;  $\log RR(t) = a + b_1 \times 30 + b_2(t-60)$  if  $t \in [60,80)$  where  $a = 0.49$  (95% CI: -0.75 to 1.74),  $b_1 = 0.076$  (95% CI: 0.025 to 0.13),  $b_2 = -0.12$  (95% CI: -0.23 to -0.0043)

‡ $\log RR(t) = a + b_1(t-30)$  if  $t \in [30,58)$ ;  $\log RR(t) = a + b_1 \times 28 + b_2(t-58)$  if  $t \in [58,80)$  where  $a = 0.011$  (95% CI: -1.52 to 1.55),  $b_1 = 0.097$  (95% CI: 0.033 to 0.16),  $b_2 = -0.057$  (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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