Hereditary breast cancer and the clinical significance of variants in the BRCA1 and BRCA2 genes

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The *BRCA1* c.5096G>A p.Arg1699Gln (R1699Q) intermediate risk variant: breast and ovarian cancer risk estimation and recommendations for clinical management from the ENIGMA consortium

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ABSTRACT

Background

We previously showed that the *BRCA1* variant c.5096G>A p.Arg1699Gln (R1699Q) was associated with an intermediate risk of breast cancer (BC) and ovarian cancer (OC). This study aimed to assess these cancer risks for R1699Q carriers in a larger cohort, including follow-up of previously studied families, to further define cancer risks and to propose adjusted clinical management of female *BRCA1**R1699Q carriers.

Methods

Data were collected from 129 *BRCA1**R1699Q families ascertained internationally by ENIGMA (Evidence-based Network for the Interpretation of Germline Mutant Alleles) consortium members. A modified segregation analysis was used to calculate BC and OC risks. Relative risks were calculated under both monogenic model and major gene plus polygenic model assumptions.

Results

In this cohort the cumulative risk of BC and OC by age 70 years was 20% and 6%, respectively. The relative risk for developing cancer was higher when using a model that included the effects of both the R1699Q variant and a residual polygenic component compared with monogenic model (for BC 3.67 vs 2.83, and for OC 6.41 vs 5.83).

Conclusion

Our results confirm that *BRCA1**R1699Q confers an intermediate risk for BC and OC. Breast surveillance for female carriers based on mammogram annually from age 40 is advised. Bilateral salpingo-oophorectomy should be considered based on family history.

INTRODUCTION

In 2008, the International Agency for Research on Cancer (IARC) proposed a standardised five-tier classification system applicable to sequence-based results in highly penetrant cancer predisposition genes and linked the likelihood of pathogenicity to clinical actions.[1] The multifactorial likelihood model (MLM) is commonly used to calculate the probability of pathogenicity[2] of individual *BRCA1* and *BRCA2* variants. It is used in the IARC five-tier classification system to categorise each variant into a specific class. The MLM combines complementary sources of data (ie, physicochemical proper- ties,[3] family history,[4] cosegregation of the variant with disease in a family[5] and co-occurrence of the variant with a pathogenic *BRCA1* or *BRCA2* variant in trans)[6] to determine the probability that a given variant has a cancer risk equivalent to known high- risk pathogenic (predominantly truncating) variants.

The *BRCA1* variant c.5096G>A p.Arg1699Gln (hereafter termed *BRCA1**R1699Q) was initially classified as class 3 (variant of uncertain significance) using the MLM method.[1] A subsequent study[7] included functional assays to assess pathogenicity, but did not yield conclusive results. Indeed this variant, located in the *BRCA1* carboxyl terminal region of the transcriptional transactivation domain, and at the interface of the phosphopeptide binding region, demonstrated ambiguous behaviour in a variety of functional assays, when compared with the pathogenic *BRCA1* variant c.5095C>T p.Arg1699Trp (*BRCA1**R1699W) at the same residue, wild-type *BRCA1* and other known pathogenic missense variants.[7] Other models based on family history analysis of *BRCA*-ness[8] or cosegregation within a family[5] also gave inconclusive results.

In 2012, members of the ENIGMA consortium (Evidence- based Network for the Interpretation of Germline Mutant Alleles)[9] reported on the family histories of 69 families carrying *BRCA1**R1699Q.[10] Comparison of *BRCA1* carrier prediction scores of probands using the BOADICEA risk prediction tool[11] showed that *BRCA1**R1699Q variant carriers had family histories that were less 'BRCA1-like' than *BRCA1**R1699W carriers but more 'BRCA1-like' than BRCA-X families (families with no detectable *BRCA1* or *BRCA2* pathogenic mutation). Second, modified segregation analysis was used in a subset of 30 families and showed lower risks of breast cancer (BC) or ovarian cancer (OC) (estimated cumulative risk to age 70: 24%) than *BRCA1**R1699W (58%) and the 'average' pathogenic *BRCA1* truncating variant (68%).[10] Due to the relatively small number of families with cosegregation data in that study, age-specific cancer risks could not be established with a high degree of precision.

The aim of the present study was to update the BC and OC risk estimates associated with *BRCA1**R1699Q in a larger series that included newly identified families, as well as some of the previously studied families, which had been updated with cosegregation data as a result of cascade screening. Based on these results, we propose recommendations for the clinical management of the carriers and their family members.

MATERIALS AND METHODS

Data collection

All families participating in this study included one or more individuals referred to a cancer family clinic because of a personal history of BC and/or OC, and/or a family history consistent with hereditary BC and/or OC.

Each index case had a confirmed *BRCA1**R1699Q variant. ENIGMA members, including those from centres that had contributed pedigrees to the previous study, were asked to provide updated pedigrees (if possible) and additional families segregating *BRCA1**R1699Q identified after the close of enrolment of the previous study. Pedigrees and patient-specific data such as ages at diagnoses and genotypes were collected from a total of 129 families from 11 different countries, of which 91 families had at least one additional person genotyped, and were thus informative for estimating BC and OC risks. From these 91 families, 30 had been included in the segregation analysis in our previous study[10] (see online supplementary table S1). When ages of diagnosis were missing, we conservatively assumed them to be age 65, and for unaffected women we imputed their age using other pedigree members using the PedPro suite of programs (www.bjfenglab.org, accessed 21 September 2016).

Statistical analysis

Data sets

In order to account for ascertainment bias, the likelihood of the pedigree phenotypes and *BRCA1**R1699Q genotypes was calculated conditional on the pedigree phenotypes and the *BRCA1**R1699Q genotype of the index case. Cancer risks were estimated using the following data sets:

The primary analysis (hereafter termed main analysis) included all 129 informative pedigrees from both the previous study and the present recruitment. The second analysis (subanalysis 1) was similar to the main analysis, except that for the genotypes and phenotypes from the previous study only information gathered since the previous study is included. In this analysis, the likelihood was conditioned on the genotype of the index case and pedigree phenotypes of the new families and all genotypes and pedigree phenotypes in the previous pedigrees as they were in the previous analysis in 2012. In fact the index patients carrier status and affected status are not used to estimate the hazard/ risk ratios on which the cumulative risks are based. The last analysis (subanalysis 2) included only the 60 pedigrees that were recruited for this study. Data from subanalyses 1 and 2 are shown in the online supplementary materials.

Cancer risk estimation methods

BC and OC risks were estimated using modified segregation analysis with the MENDEL package of programs.[12] For each data set, the analysis was performed under each of the following assumptions: (1) the relative risk (RR) across age groups was assumed to be constant; and (2) the RR was assumed to be a continuous, piecewise linear function of age,

which was constant before age 40 years and after age 60 years and linear between ages 40 and 60 years. For both models, baseline population incidence rates were assumed to be those for the UK 2003–2007 (Cancer Incidence in Five Continents Reports (IARC-WHO; update November 2010).[13]

For both these analyses we first used a model assuming a single major gene only (the *BRCA1**R1699Q variant) and second a model that included the major gene and a polygenic background effect. From the resulting estimates of BC and OC relative risk, age-specific cumulative risk estimates were calculated based on the cumulative incidence A(t): F(t)=1 − exp(A(t)), and the corresponding CIs were calculated using a parametric bootstrap with 5000 replications.[14]

RESULTS

Descriptive characteristics of the cohort

Our cohort included 129 separate families with a total of 4024 family members, from whom 309 women were proven *BRCA1**R1699Q carriers and 173 were proven non-carriers. For 91 families, in addition to genotyping data of the proband, at least one additional genotype was available (see online supplementary table S2). Descriptive characteristics of the cohort about BC and OC cancer history and age distribution are listed in the online supplementary table S2.

BC and OC risks

Online supplementary figure S1 and supplementary table S2 show the age distribution for BC and OC for the female carriers. The sharpest increase of BC occurred between ages 40 and 49. For OC this was between ages 50 and 59. The youngest case of BC was diagnosed at age 25, for OC this was age 35.

Cumulative risks for this variant by age 70 years are estimated to be 20% (95% CI 13% to 32%) for BC and 6% (95% CI 3% to 25%) for OC. The risks are lower than for high-risk *BRCA1* truncating variants and higher than for the general population in all the three data sets. Figure 1 shows the corresponding curves for the main analysis. Online supplementary figures S2 and S3 and supplementary tables S3 and S4 show comparable results for all the data sets under both assumptions.

Effect of other genetic factors on cancer risks

In order to study the effect of other (genetic) factors on risk, HRs were calculated based on the 'major gene only' model and the 'major gene and polygenic' model under both assumptions.

For the main analysis, HRs for BC are higher in the major gene plus polygenic model compared with the major gene only model, both when assuming constant RR across age groups, and when modelled as a continuous piecewise linear function of age.

HRs for OC are higher in the major gene plus polygenic model when assuming constant RR. When assuming RR as a continuous, piecewise linear function of age, the HR is higher

for the major gene plus polygenic model when the individual is older than 60 years old, suggesting that modifiers might be especially important for the late-onset disease (table 1). Online supplementary table S5 shows the HRs for the subanalyses.

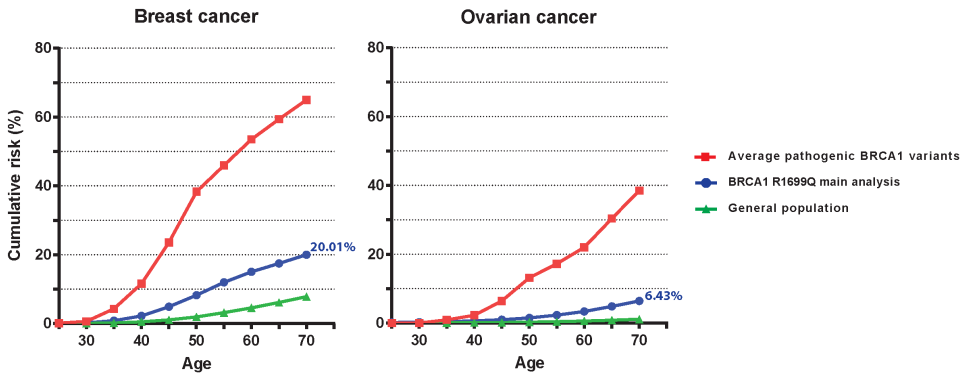

Figure 1. Cumulative risks (%) for breast cancer (left graph) and ovarian cancer (right graph) by age for carriers of *BRCA1**R1699Q based on the main analysis (blue line). The corresponding curves or the cumulative risk conferred by average pathogenic *BRCA1* variants (red line) and for the general population (green line) are also shown. Cumulative risks are calculated using segregation analysis, major gene model assuming relative risk as a continuous, piecewise linear function of age.

Table 1. Modified segregation analysis results from MENDEL in the main analysis a) assuming constant relative risk across age groups and b) assuming relative risk as a continuous, piecewise linear function of age.

	Model	HR (a)	Age	HR (b)
Breast	Major Gene Only	2.83 (1.76, 4.57)	< 40	4.72 (2.22, 10.02)
			> 60	1.75 (0.75, 4.05)
	Major and Polygenic	3.67 (1.97, 6.81)	< 40	5.05 (2.07, 12.34)
			> 60	2.71 (1.09, 6.75)
Ovarian	Major Gene Only	5.83 (2.19, 15.49)	< 40	5.91 (0.58, 60.20)
			> 60	5.81 (1.80, 18.76)
	Major and Polygenic	6.41(2.19, 18.75)	< 40	5.39 (0.48, 61.10)
			> 60	6.75 (1.96, 23.22)

DISCUSSION

After publication of the study by Spurdle *et al*[10] in 2012, many cancer clinics started offering cascade screening to relatives of carriers of the *BRCA1**R1699Q variant. However, in the absence of robust estimates of cancer risks, it was not clear whether available guidelines for *BRCA* carriers would also be suitable for female carriers of *BRCA1**R1699Q.

The cumulative risks estimated from the main analysis and the two subanalyses were lower than for the average *BRCA1* truncating pathogenic variant, yet still substantially higher than the rates in the general population. Cumulative risk by age 70 years was estimated to be 20% (95% CI 13% to 32%) for BC and 6% (95% CI 3% to 25%) for OC.

Our results strongly confirm our previous findings that this variant has reduced penetrance,[10] and can thus be termed an intermediate risk variant conferring risks lower than that for the average pathogenic variant in a high-risk cancer predisposition gene. These risk estimates are consistent with those reported for disease-associated variants in so-called 'moderate risk' genes, defined as genes in which pathogenic variants have an RR between 2 and 5. [15, 16]

Interestingly, our results show that the estimated HRs are in general slightly higher when the 'major gene plus polygenic' model is used compared with the 'major gene only' model, which is especially evident in the late-onset disease (>60 years) group. This means that in addition to *BRCA1**R1699Q, other genetic and/or environmental factors seem to contribute to the magnitude of the BC and OC risk in carriers. Indeed, recent literature[15-17] indicates that single nucleotide polymorphisms are important determinants of personal cancer risk in women carrying a deleterious disease-associated variant especially in moderate risk genes. As those factors are mostly unmeasured or unknown, an indirect estimation of clustering of risk factors can be deduced taking the family history into account. This is particularly relevant to consider when deciding surveillance for healthy relatives who are non-carriers of deleterious variants in the moderate risk genes, or non-carriers of intermediate risk variants in 'high-risk cancer predisposition genes' such as *BRCA1* or *BRCA2*.

The relevance of these findings for clinical management of *BRCA1**R1699Q carriers and their relatives was considered during the Clinical Working Group meeting at the April 2016 ENIGMA conference, held in Prague, which was attended by 38 members with expertise in laboratory research, statistics and clinical genetics. Recommendations for *CHEK2* c.1100delC carriers[17, 18] and country-specific guidelines including Oncoline (The Netherlands: http://www.oncoline.nl, accessed 21 September 2016), National Institute for Health and Care Excellence (UK: https:// www.nice.org.uk, accessed 21 September 2016) and National Comprehensive Cancer Network (USA: https://www.nccn.org, accessed 21 September 2016) were used as a framework to guide discussion. A consensus and majority-based discussion led to the following opinions and recommendations:

Female non-carriers of *BRCA1**R1699Q from BRCA1*R1699Q families

Surveillance should depend on (family) history of cancer, for example, on the risk calculated using programs like BOADICEA.[11]

Female carriers of *BRCA1**R1699Q

A cumulative risk of BC (20% (95% CI 13% to 32%)) does not by itself justify preventive mastectomy or breast MRI. Breast surveillance for female carriers based on annual mammogram from age 40 up to 50 years and inclusion in population screening afterwards is advised.

Combining with family history, the BC risk might be estimated to be higher than the risk conferred by the variant alone. If this is the case, the surveillance advice for *BRCA1**R1699Q carriers can be 'overruled' by the higher family history risk and additional genetic testing can be considered.

The specific genes included will vary across countries dependent on testing practices, which incorporate availability and extent of panel-based testing, eligibility for health insurance or state-based testing, clinical guidelines for ascertainment including number and types of cancer reported in families, etc (ENIGMA, unpublished findings). Genetic testing for variants in other genes using a panel approach for a range of BC/OC susceptibility genes may offer some additional genotype-based information about risk in those cases; however, penetrance estimates for the majority of other genes beyond *BRCA1*, *BRCA2* and *PALB2* are imprecise.[16] Furthermore, it is still unclear how genetic risks are best combined to produce more accurate, individualised, risk estimates.

The *BRCA1**R1699Q variant carriers have lower OC risk (6% (95% CI 3% to 25%)), compared with that for *BRCA1* carriers (39% (95% CI 22% to 51%)) and *BRCA2* carriers (11% (95% CI 4.1% to 18%)).[19] Bilateral salpingo-oophorectomy (BSO) is the standard preventive treatment in the Netherlands for high- risk pathogenic variant carriers, performed at age 35–40 for *BRCA1* and 40–45 for *BRCA2* (http://www.oncoline.nl). Routine surveillance for OC is not effective and is no longer offered to carriers.[20] The magnitude of OC risk for R1699Q carriers suggests that BSO, if performed, may be postponed until age 50. We advise BSO surgery should be offered at age 50, based on the age-related cumulative risks for OC obtained from the study. The cumulative lifetime risk of OC for someone in the general population is approximately 1.5%, but the vast majority of risk occurs after 50 years of age. From our study the cumulative OC risk for *BRCA1**R1699Q carriers by age 50 is lower than the cumulative population risk for OC and rises significantly after age 55. Although BSO surgery could be offered at any age after the genetic risk is identified, we base our guidance on a pragmatic balance between cancer prevention and minimum adverse effects from early oestrogen deprivation, achieved if the surgery is timed around the current average age for the menopause in the Western society (52 years).

However, as for BC risk management, and considering the wide CI for the estimated risk of OC, information about cancer history in the family should be taken into account for decision making.

CONCLUSION

Our analysis of a large cohort of 129 families, using several analytical approaches, confirms that the *BRCA1**R1699Q variant is associated with intermediate cancer risks (compared

with the average *BRCA1* truncating variant). It also provides evidence that cancer risk in carriers is likely to be influenced by other genetic factors. Based on our findings, we propose recommendations for the clinical management of *BRCA1**R1699Q carriers and non-carriers. We recommend that follow-up and screening in these families are performed in a research setting in order to enable future assessment of the utility of the proposed surveillance.

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SUPPLEMENTARY DATA

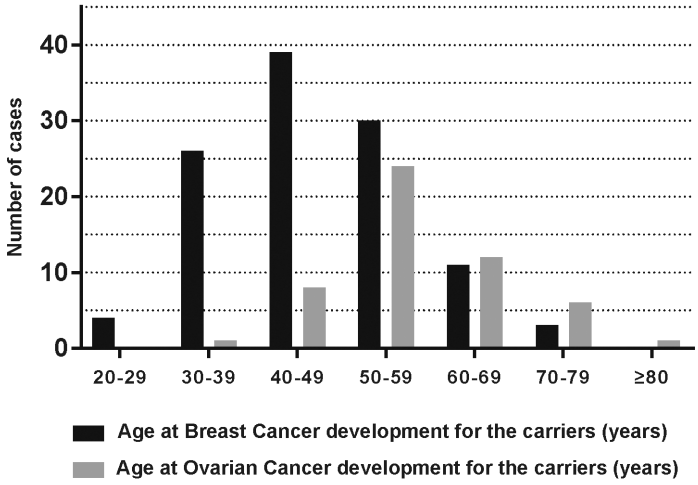

Figure S1. Age at breast cancer development (black bars) and ovarian cancer development (grey bars) for the carriers of *BRCA1**R1699Q.

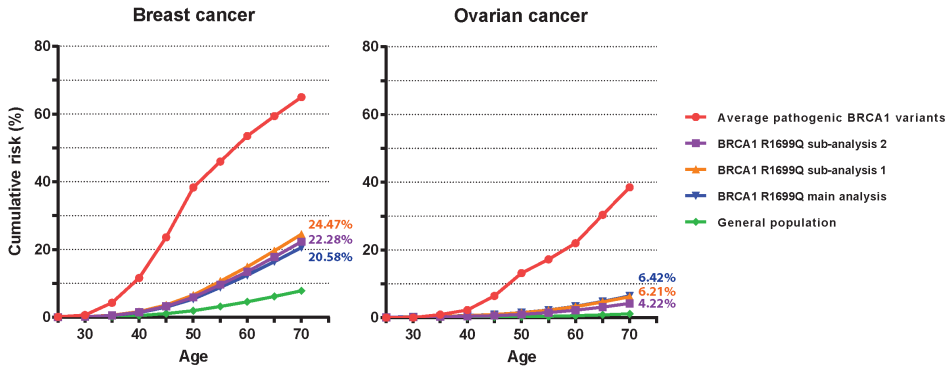

Figure S2. Cumulative risks (%) for breast cancer (left graph) and ovarian cancer (right graph) by age for carriers of *BRCA1**R1699Q based on the main analysis (blue line), sub-analysis 1 (orange line) and sub-analysis 2 (purple line). The corresponding curves or the cumulative risk conferred by average pathogenic *BRCA1* variants (red line) and for the general population (green line) are also shown. Cumulative risks are calculated using segregation analysis, major gene model assuming constant relative risk.

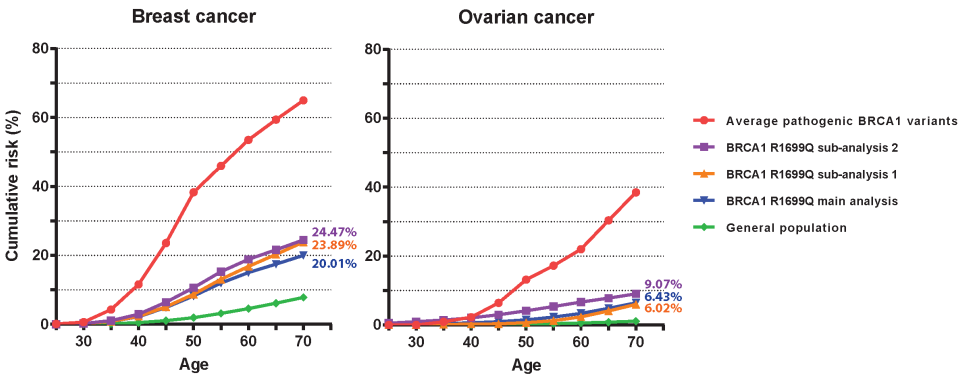

Figure S3. Cumulative risks (%) for breast cancer (left graph) and ovarian cancer (right graph) by age for carriers of *BRCA1**R1699Q based on the main analysis (blue line), sub-analysis 1 (orange line) and sub-analysis 2 (purple line). The corresponding curves or the cumulative risk conferred by average pathogenic *BRCA1* variants (red line) and for the general population (green line) are also shown. Cumulative risks are calculated using segregation analysis, major gene model assuming relative risk as a continuous, piecewise linear function of age.

Table S1. Number and origin of families in the previous study and current study (previous plus newly included families) .

	Previous study[10]		Current study	
Country	# Families	# Families with additional genotyping (*)	# Families	# Families with additional genotyping (*)
Australia	6	2	6	2
The Netherlands	12	3	20	15
Belgium	3	2	8	6
Denmark	10	4	22	19
France	5	3	14	7
Germany	5	1	19	10
South Africa	1	1	1	1
Sweden	14	5	20	17
Switzerland	0	0	1	1
United Kingdom	4	2	4	2
U.S.A.	9	7	14	11
Total	69	30	129	91

(*): additional genotyping means at least one other relative tested in addition to the index.

Table S2. Descriptive characteristics of the 129 families.

	Unknown Carriership			Non-carriers			Carriers		
Age	Total	BC[#]	OC[&]	Total	BC	OC	Total	BC	OC
<30	2935	1	0	100	0	0	105	4	0
30-39	89	18	2	8	1	0	37	26	1
40-49	94	26	5	27	5	0	60	39	8
50-59	124	40	26	24	4	1	53	30	24
60-69	122	36	15	6	2	0	39	11	12
70-79	96	16	7	4	2	1	11	3	6
>=80	82	10	2	4	1	0	4	0	1
Total	3542	147	57	173	15	2	309	113	52

#BC: Breast cancer
&OC: Ovarian cancer

Table S3. Cumulative risk (95% Confidence Interval) using segregation analysis, major gene models assuming constant relative risk.

	Main Analysis Cumulative risk (95% Confidence Interval)		Sub-Analysis 1 Cumulative risk (95% Confidence Interval)		Sub-Analysis 2 Cumulative risk (95% Confidence Interval)	
Age	Breast cancer	Ovarian cancer	Breast cancer	Ovarian cancer	Breast cancer	Ovarian cancer
25	0.017 (0.010, 0.024)	0.15 (0.06, 0.24)	0.02 (0.01, 0.03)	0.14 (0.04, 0.24)	0.02 (0.01, 0.03)	0.10 (0.03, 0.17)
30	0.13 (0.07, 0.18)	0.26 (0.12, 0.41)	0.16 (0.07, 0.24)	0.26 (0.10, 0.41)	0.14 (0.05, 0.23)	0.17 (0.06, 0.28)
35	0.49 (0.31, 0.68)	0.42 (0.21, 0.62)	0.60 (0.32, 0.88)	0.40 (0.17, 0.63)	0.54 (0.23, 0.85)	0.27 (0.11, 0.43)
40	1.34 (0.90, 1.78)	0.63 (0.34, 0.92)	1.63 (0.95, 2.31)	0.61 (0.29, 0.93)	1.47 (0.72, 2.21)	0.41 (0.18, 0.63)
45	2.97 (2.08, 3.85)	0.95 (0.52, 1.38)	3.60 (2.23, 4.96)	0.92 (0.45, 1.38)	3.24 (1.74, 4.72)	0.62 (0.29, 0.95)
50	5.40 (3.96, 6.82)	1.49 (0.81, 2.17)	6.54 (4.31, 8.71)	1.44 (0.69, 2.18)	5.89 (3.45, 8.28)	0.97 (0.45, 1.49)
55	8.82 (6.68, 10.90)	2.28 (1.25, 3.29)	10.63 (7.36, 13.79)	2.20 (1.08, 3.31)	9.61 (5.99, 13.09)	1.49 (0.70, 2.27)
60	12.38 (9.72, 14.97)	3.36 (1.89, 4.81)	14.87 (10.81, 18.74)	3.25 (1.64, 4.83)	13.47 (8.96, 17.75)	2.20 (1.07, 3.32)
65	16.42 (13.23, 19.49)	4.81 (2.78, 6.79)	19.62 (14.80, 24.16)	4.65 (2.42, 6.82)	17.82 (12.43, 22.87)	3.15 (1.58, 4.70)
70	20.58 (16.95, 24.05)	6.42 (3.87, 8.90)	24.47 (19.04, 29.53)	6.21 (3.41, 8.92)	22.28 (16.17, 27.95)	4.22 (2.24, 6.17)

Table S4. Cumulative risk (95% Confidence Interval) using segregation analysis, major gene models assuming relative risk as a continuous, piecewise linear function of age.

	Main Analysis Cumulative risk (95% Confidence Interval)		Sub-Analysis 1 Cumulative risk (95% Confidence Interval)		Sub-Analysis 2 Cumulative risk (95% Confidence Interval)	
Age	Breast cancer	Ovarian cancer	Breast cancer	Ovarian cancer	Breast cancer	Ovarian cancer
25	0.03 (0.01, 0.06)	0.15 (0.02, 1.57)	0.03 (0.01, 0.08)	0.06 ($3.94x10^{-4}$, 7.50)	0.04 (0.01, 0.10)	0.56 (0.003, 3.73)
30	0.21 (0.10, 0.45)	0.27 (0.03, 2.79)	0.22 (0.08, 0.57)	0.10 ($7.01x10^{-4}$, 12.98)	0.28 (0.08, 0.73)	0.96 (0.005, 6.56)
35	0.82 (0.38, 1.75)	0.42 (0.04, 4.34)	0.86 (0.32, 2.21)	0.16 ($1.10x10^{-3}$, 19.63)	1.09 (0.31, 2.81)	1.44 (0.008, 10.11)
40	2.22 (1.04, 4.70)	0.64 (0.06, 6.49)	2.32 (0.87, 5.92)	0.24 ($1.66x10^{-3}$, 28.11)	2.95 (0.85, 7.49)	2.08 (0.01, 14.87)
45	4.89 (2.30, 10.19)	0.96 (0.10, 9.66)	5.10 (1.94, 12.72)	0.36 ($2.52x10^{-3}$, 39.32)	6.41 (1.89, 15.95)	2.98 (0.02, 21.63)
50	8.22 (4.22, 16.40)	1.51 (0.30, 13.68)	8.72 (3.86, 20.34)	0.67 (0.12, 51.16)	10.62 (3.69, 24.88)	4.13 (0.13, 29.53)
55	11.99 (6.82, 22.50)	2.30 (0.66, 17.66)	13.05 (6.73, 28.18)	1.29 (0.36, 60.48)	15.25 (6.06, 32.87)	5.39 (0.34, 36.61)
60	15.02 (9.35, 26.46)	3.39 (1.21, 20.74)	16.82 (9.53, 33.35)	2.37 (0.80, 66.01)	18.87 (8.15, 37.55)	6.65 (0.66, 41.30)
65	17.46 (11.37, 28.80)	4.83 (1.99, 21.94)	20.28 (12.18, 36.99)	4.10 (1.51, 66.40)	21.64 (9.93, 40.72)	7.80 (1.14, 41.82)
70	20.01 (13.26, 32.01)	6.43 (2.78, 24.53)	23.89 (14.51, 42.42)	6.02 (2.25, 66.73)	24.47 (11.29, 46.03)	9.07 (1.58, 42.50)

Table S5. Modified segregation analysis results from MENDEL in the sub-analysis 1 and sub-analysis 2, a) assuming constant relative risk across age groups and b) assuming relative risk as a continuous, piecewise linear function of age.

	Analysis	Model	HR (a)	Age	HR (b)
Breast	Sub-Analysis 1	Major Gene Only	3.45 (1.88, 6.34)	< 40	4.93 (1.87, 12.99)
				> 60	2.56 (0.96, 6.82)
		Major and Polygenic	4.14 (1.93, 8.91)	< 40	4.66 (1.53, 14.23)
				> 60	3.75 (1.32, 10.72)
	Sub-Analysis 2	Major Gene Only	3.10 (1.48, 6.49)	< 40	5.50 (1.80, 16.81)
				> 60	1.59 (0.36, 7.09)
		Major and Polygenic	3.93 (1.56, 9.90)	< 40	5.07 (1.26, 20.43)
				> 60	2.91 (0.47, 14.92)
Ovarian	Sub-Analysis 1	Major Gene Only	5.63 (1.86, 17.03)	< 40	2.18 (0.01, 337.05)
				> 60	6.92 (1.80, 26.58)
		Major and Polygenic	5.96 (1.83, 19.44)	< 40	1.50 (0.01, 406.07)
				> 60	7.86 (1.99, 31.09)
	Sub-Analysis 2	Major Gene Only	3.79 (1.20, 11.96)	< 40	4.32 (0.12, 159.24)
				> 60	3.68 (0.89, 15.13)
		Major and Polygenic	4.06 (1.99, 8.26)	< 40	3.48 (0.05, 259.56)
				> 60	4.19 (0.95, 18.47)

HR: hazard ratio