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Review Article

No clinical utility of *KRAS* variant rs61764370 for ovarian or breast cancer

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ABSTRACT

Objective. Clinical genetic testing is commercially available for rs61764370, an inherited variant residing in a *KRAS* 3′ UTR microRNA binding site, based on suggested associations with increased ovarian and breast cancer risk as well as with survival time. However, prior studies, emphasizing particular subgroups, were relatively small. Therefore, we comprehensively evaluated ovarian and breast cancer risks as well as clinical outcome associated with rs61764370.

Methods. Centralized genotyping and analysis were performed for 140,012 women enrolled in the Ovarian Cancer Association Consortium (15,357 ovarian cancer patients; 30,816 controls), the Breast Cancer Association Consortium (33,530 breast cancer patients; 37,640 controls), and the Consortium of Modifiers of *BRCA1* and *BRCA2* (14,765 *BRCA1* and 7904 *BRCA2* mutation carriers).

Results. We found no association with risk of ovarian cancer (OR = 0.99, 95% CI 0.94–1.04, p = 0.74) or breast cancer (OR = 0.98, 95% CI 0.94–1.01, p = 0.19) and results were consistent among mutation carriers (*BRCA1*, ovarian cancer HR = 1.09, 95% CI 0.97–1.23, p = 0.14, breast cancer HR = 1.04, 95% CI 0.97–1.12, p = 0.27; *BRCA2*, ovarian cancer HR = 0.89, 95% CI 0.71–1.13, p = 0.34, breast cancer HR = 1.06, 95% CI 0.94–1.19, p = 0.35). Null results were also obtained for associations with overall survival following ovarian cancer (HR = 0.94, 95% CI 0.83–1.07, p = 0.38), breast cancer (HR = 0.96, 95% CI 0.87–1.06, p = 0.38), and all other previously-reported associations.

Conclusions. rs61764370 is not associated with risk of ovarian or breast cancer nor with clinical outcome for patients with these cancers. Therefore, genotyping this variant has no clinical utility related to the prediction or management of these cancers.

Contents

1. Introduction

MicroRNAs (miRNAs) are a class of small non-coding RNA molecules that negatively regulate gene expression by binding partially complementary sites in the 3′ untranslated regions (UTRs) of their target mRNAs. In this way, miRNAs control many cancer-related biological pathways involved in cell proliferation, differentiation, and apoptosis [1]. To date, several inherited variants in microRNAs or miRNA target sites have been reported to confer increased cancer risks [2]. One such variant is located in the 3′ UTR of the *KRAS* gene (rs61764370 T > G) for which the rarer G allele has been reported to confer an increased risk of ovarian, breast, and lung cancer [3–7] as well as endometriosis [8], although not consistently [9–11].

For ovarian cancer, the rs61764370 G allele was also reported to be associated with increased risk (320 cases, 328 controls). Further increased risks were observed among 23 *BRCA1* mutation carriers and 31 women with familial ovarian cancer, but without *BRCA1* or *BRCA2* mutations [3]. In contrast, no association with ovarian cancer risk was seen in another, much larger study, based on 8669 cases, 10,012 controls, and 2682 *BRCA1* mutation carriers [9]. One criticism on the latter study was that some of the genotype data were for rs17388148, an imputed proxy for rs61764370; even though rs17388148 is highly correlated with rs61764370 ($r^2 = 0.97$) and was imputed with high accuracy ($r^2 = 0.977$) [12,13]. The minor allele of rs61764370 was also associated with shorter survival time in a study of 279 ovarian cancer patients diagnosed after age 52 years with platinum-resistant disease (28 resistant, 263 not resistant) and with sub-optimal debulking surgery after neoadjuvant chemotherapy (7 sub-optimal, 109 optimal) [14]. However, another study observed no association between rs61764370 and ovarian cancer outcome (329 cases) [15].

For breast cancer, a borderline significant increased frequency of the rs61764370 G allele was observed in 268 *BRCA1* mutation carriers with breast cancer, but not in 127 estrogen receptor (ER)-negative familial non-*BRCA1*/*BRCA2* breast cancer patients [5]. However, in a subsequent study, the variant was reported to be associated with increased risk of ER/PR negative disease (80 cases, 470 controls), as well as with triple negative breast cancer diagnosed before age 52 (111 cases, 250 controls), regardless of *BRCA1* mutation status [6]. The validity of these findings has been questioned given the very small sample sizes and the number of subgroups tested [16,17]. Another report found no association with sporadic or familial breast cancer risk (695 combined cases, 270 controls), but found that the variant was associated with ERBB2-positive and high grade disease, based on 153 cases who used post-menopausal hormone replacement therapy [18].

It has also been reported, based on 232 women with both primary ovarian and breast cancer, that the frequency of the G allele at rs61764370 was increased for those who were screened negative for *BRCA1* and *BRCA2* (92 cases), particularly among those enrolled within two years of their ovarian cancer diagnosis (to minimize survival bias, 30 cases), those diagnosed with post-menopausal ovarian cancer (63 cases), those with a family history of ovarian or breast cancer (24 cases), and those with a third primary cancer (16 cases) [4].

This notable lack of consistency in findings between studies might be expected when appropriate levels of statistical significance are not used to declare positive findings from multiple small subgroup comparisons or post-hoc hypotheses [19]. In this respect, the dangers of subgroup analyses in the context of clinical trials are well-recognized [20]. These are important caveats, particularly since a genetic test for rs61764370 is currently marketed in the US for risk prediction testing to women who are at increased risk for developing ovarian and/or breast cancer or women who have been diagnosed with either ovarian or breast cancer themselves [21]. In general, much larger studies, with sufficient power to detect positive findings at much more stringent levels of statistical significance ought to be required to establish the clinical validity of a genetic test. Therefore, we conducted centralized genotyping of rs61764370 and other variants in the genomic region around the *KRAS* gene in 140,012 women to examine associations with risk and clinical outcome of ovarian and breast cancer.

2. Methods

2.1. Study participants

The following three consortia contributed to these analyses: the Ovarian Cancer Association Consortium (OCAC: 41 studies, Supplementary Table S1) [22], the Breast Cancer Association Consortium (BCAC: 37 studies, Supplementary Table S2) [23], and the Consortium of Modifiers of *BRCA1* and *BRCA2* (CIMBA: 55 studies, Supplementary Table S3) [24,25]. OCAC and BCAC consisted of case–control studies of unrelated women, and CIMBA consisted of studies of women with germline

Table 1
Associations between *KRAS* rs61764370 and risk of ovarian and breast cancer.
For *BRCA1* and *BRCA2* mutation carrier analyses, cases are affected *BRCA1*/*BRCA2* mutation carriers and controls are unaffected *BRCA1*/*BRCA2* mutation carriers, and relative risks are estimated by hazard ratios; for other analyses, relative risks are estimated by odds ratios; ovarian cancer analyses used OCAC data adjusted for study, age, and the five European principal components; breast cancer analyses used BCAC data adjusted for study, age, and the seven European principal components; *BRCA1* and *BRCA2* mutation carrier analyses used CIMBA data with age as follow-up time and stratified for country; 95% CI, 95% confidence interval.

	Number		Minor allele frequency		Relative risk (95% CI)	
	Cases	Controls	Cases	Controls		p-Value
Ovarian cancer						
All invasive	15,357	30,816	0.0914	0.0949	0.99 (0.94–1.04)	0.74
Histology						
High-grade serous	6938	30,816	0.0946	0.0949	1.04 (0.97–1.11)	0.26
Endometrioid	2151	30,816	0.0834	0.0949	0.90 (0.80–1.00)	0.06
Clear cell	1015	30,816	0.0994	0.0949	1.09 (0.94–1.27)	0.27
Mucinous	1000	30,816	0.0902	0.0949	0.99 (0.85–1.16)	0.91
Low-grade serous	485	30,816	0.0705	0.0949	0.76 (0.59–0.97)	0.03
First-degree family history						
Ovarian cancer	483	342	0.0803	0.0849	0.87 (0.60–1.27)	0.47
Breast or ovarian cancer	477	18,442	0.0977	0.0915	1.09 (0.93–1.28)	0.28
BRCA1/2 mutation negative	346	15,492	0.1050	0.0997	1.09 (0.85–1.41)	0.49
BRCA1 mutation carriers	2332	12,433	0.0954	0.0922	1.09 (0.97–1.23)	0.14
BRCA2 mutation carriers	599	7305	0.0952	0.0966	0.89 (0.71–1.13)	0.34
Enrolled within two years of diagnosis						
All invasive	10,121	30,815	0.0942	0.0949	0.99 (0.95–1.04)	0.68
BRCA1 mutation carriers	1095	10,802	0.0950	0.0940	1.05 (0.90–1.23)	0.52
BRCA2 mutation carriers	270	6509	0.0907	0.0979	0.85 (0.60–1.20)	0.36
Menopausal status						
Pre- or peri-menopausal	4264	8789	0.0915	0.0927	1.02 (0.92–1.13)	0.68
Post-menopausal	11,058	15,903	0.0916	0.0951	0.99 (0.93–1.06)	0.81
Prior breast cancer						
Enrolled within two years of diagnosis	426	30,815	0.0943	0.0949	0.91 (0.71–1.17)	0.46
Post-menopausal ovarian cancer	341	15,903	0.0810	0.0951	0.90 (0.68–1.21)	0.49
First degree breast or ovarian cancer family history	202	30,815	0.0916	0.0949	0.99 (0.70–1.40)	0.95
Breast cancer						
All invasive	33,530	37,640	0.0904	0.0930	0.98 (0.94–1.01)	0.19
Receptor status						
ER−/PR−	4009	37,043	0.0940	0.0932	1.04 (0.96–1.13)	0.36
ER−/PR−/ERBB2−	1673	28,480	0.0885	0.0947	0.97 (0.85–1.10)	0.62
First-degree family history						
Breast cancer	4357	1943	0.0942	0.0954	0.96 (0.84–1.10)	0.59
Ovarian or breast cancer	4593	2265	0.0933	0.0949	0.96 (0.85–1.09)	0.52
Age diagnosis <52						
ER−/PR−	1530	37,043	0.0980	0.0932	1.07 (0.95–1.22)	0.28
ER−/PR−/ERBB2−	546	27,690	0.0908	0.0948	0.99 (0.81–1.20)	0.90
BRCA1/2 mutation negative	1431	1097	0.0853	0.0925	0.91 (0.75–1.11)	0.35
BRCA1 mutation carriers	7543	7222	0.0935	0.0919	1.04 (0.97–1.12)	0.27
BRCA2 mutation carriers	4138	3766	0.1005	0.0921	1.06 (0.94–1.19)	0.35
Enrolled within two years of diagnosis						
All invasive	20,444	34,349	0.0924	0.0934	0.99 (0.95–1.04)	0.73
BRCA1 mutation carriers	2595	5976	0.0896	0.0924	0.95 (0.85–1.05)	0.30
BRCA2 mutation carriers	1359	3365	0.0960	0.0926	1.05 (0.90–1.23)	0.52
Menopausal status						
Pre- or peri-menopausal	7086	8642	0.0934	0.0933	0.98 (0.91–1.07)	0.70
Post-menopausal	16,346	18,605	0.0904	0.0943	0.98 (0.93–1.03)	0.36

deleterious *BRCA1* or *BRCA2* mutations primarily identified through clinical genetics centers. For the purpose of the current analyses, only participants of European ancestry were included. Following genotyping, quality control exclusions (described below), and analysis-specific exclusions, data from the following women were available for analysis: 46,173 OCAC participants (15,357 patients with invasive epithelial ovarian cancer and 30,816 controls), 71,170 BCAC participants (33,530 patients with invasive breast cancer and 37,640 controls), and 22,669 CIMBA participants (for ovarian cancer analyses: 2332 affected and 12,433 unaffected *BRCA1* carriers, 599 affected and 7305 unaffected *BRCA2* carriers; for breast cancer analyses: 7543 affected and 7222 unaffected *BRCA1* carriers, 4138 affected and 3766 unaffected *BRCA2* carriers). For OCAC, overall and progression-free survival data were available for 3096 patients from 13 studies. Overall survival data were available for 28,471 patients from 26 BCAC studies and for 2623 mutation carriers with breast cancer from 11 CIMBA studies (excluding studies with less than ten deaths) as described previously [26,27]. Each study was approved by its relevant governing research ethics committee, and all study participants provided written informed consent.

2.2. Genotyping and imputation

Genotyping for rs61764370 was performed using the custom iCOGS Illumina Infinium iSelect BeadChip, as previously described [22–25]. In total, DNA from 185,443 women of varying ethnic background was genotyped (47,630 OCAC participants, 114,255 BCAC participants, 23,558 CIMBA participants), along with HapMap2 DNAs for European, African, and Asian populations. Genotype data were also available for three OCAC genome-wide association studies (UK GWAS, US GWAS, Mayo GWAS) that had been genotyped using either the Illumina Human610-Quad Beadchip (12,607 participants) [28] or the Illumina HumanOmni2.5-8 Beadchip (883 participants). Raw intensity data files underwent centralized genotype calling and quality control [22–25]. HapMap2 samples were used to identify women with predicted European intercontinental ancestry; among these women, a set of over 37,000 unlinked markers was used to perform principal component (PC) analysis [29]. The first five and seven European PCs were found to control adequately for residual population stratification in OCAC and BCAC data, respectively. Samples with low conversion rate, extreme heterozygosity, non-female sex, or one of a first-degree relative pair (the latter for OCAC and BCAC only) were excluded. Variants were excluded if they were monomorphic or had a call rate <95% (minor allele frequency (MAF) >0.05) or <99% (MAF <0.05), deviation from Hardy–Weinberg equilibrium ($p < 10^{-7}$), or >2% duplicate discordance.

In addition to rs61764370, 54 variants within 100 kb on either side of *KRAS* on chromosome 12 (25,258,179 to 25,503,854 bp in GRCh37.p12) were genotyped. Moreover, to provide a common set of variants across the region for analysis in all the data sets, we also used imputation to infer genotypes for another 1056 variants and for variants that failed genotyping. We performed imputation separately for OCAC samples, BCAC samples, *BRCA1* mutation carriers, *BRCA2* mutation carriers, and for each of the OCAC GWAS. We imputed variants from the 1000 Genomes Project data using the v3 April 2012 release as the reference panel [30]. To improve computation efficiency we initially used a two-step procedure, which involved pre-phasing using the SHAPEIT software [31] in the first step and imputation of the phased data in the second. We used the IMPUTE version 2 software [32] for the imputation for all studies with the exception of the US GWAS for which we used the MACH algorithm implemented in the minimac software version 2012.8.15 and MACH version 1.0.18 [33]. We excluded variants from association analyses if their imputation accuracy was $r^2 < 0.30$ or their MAF was <0.005, resulting in 974 variants genotyped and imputed for OCAC, 989 variants genotyped and imputed for BCAC, and 1001 variants genotyped and imputed for CIMBA, including rs61764370 (Supplementary Tables S5, S6, and S7).

2.3. Analysis

Genotypes were coded for genotype dosage as 0, 1, or 2, based on the number of copies of the minor allele. For ovarian cancer case–control analysis (i.e., OCAC studies), logistic regression provided estimated risks of invasive epithelial ovarian cancer with odds ratios (ORs) and 95% confidence intervals (CIs) adjusting for study, age, and the five European PCs. Subgroup analyses were conducted by histology, family ovarian and breast cancer history, menopausal status, time between ovarian cancer diagnosis and recruitment, and history of multiple primary cancers. For breast cancer case–control analysis (i.e., BCAC studies), the association between genotype and invasive breast cancer risk was evaluated by logistic regression, adjusting for study, age, and the seven European PCs, providing ORs and 95% CIs. Additional subgroup analyses were based on receptor status, first-degree family ovarian and breast cancer history, *BRCA1* and *BRCA2* mutation status, enrollment within two years of diagnosis, menopausal status (i.e. last menstruation longer than twelve months ago), age at diagnosis less than 52 years, and history of hormone replacement therapy use (i.e. longer than twelve months use). Risk analysis for *BRCA1* and *BRCA2* mutation carriers (i.e. CIMBA studies) was done using a Cox proportional hazard model to estimate hazard ratios (HRs) per copy of the minor allele, with age as follow-up time and stratified by country of residence; US and Canadian strata were further subdivided by self-reported Ashkenazi Jewish ancestry [24,25]. A weighted cohort approach was applied to correct for potential testing bias due to overrepresentation of cases in the study population [34]. We used robust variance estimation to allow for the non-independence of carriers within the same family [35]. To assess associations with ovarian cancer risk, mutation carriers were followed from birth until ovarian cancer diagnosis (event), a risk-reducing salpingo-oophorectomy (RRSO) or the age at enrollment,

Table 2
Associations between *KRAS* rs61764370 and outcome in ovarian and breast cancer.
Ovarian cancer analyses used OCAC data adjusted for age at diagnosis (overall survival only), the five European principal components, histology (serous, mucinous, endometrioid, clear cell, and other epithelial), grade (low versus high), FIGO stage (I–IV), residual disease after debulking surgery (nil versus any), and stratified by study; breast cancer analyses used BCAC data adjusted for age at diagnosis, tumor size, nodal status, grade, adjuvant hormonal and/or chemotherapy and was stratified by study; analyses for *BRCA1* and *BRCA2* mutation carriers used CIMBA data adjusted for age at diagnosis, tumor size, nodal status, grade, adjuvant hormonal and/or chemotherapy, and preventive bilateral oophorectomy and was stratified by study; 95% CI, 95% confidence interval.

	No. of patients	No. of events	Hazard ratio (95% CI)	p-Value
Ovarian cancer				
Overall survival				
All patients	3096	1421	0.94 (0.83–1.07)	0.38
Patients who were suboptimally debulked after cytoreductive surgery	1114	784	0.94 (0.78–1.13)	0.50
Post-menopausal patients > 52 years	2226	1276	0.97 (0.84–1.12)	0.70
Progression-free survival				
All patients	3096	2144	1.01 (0.90–1.13)	0.84
Patients who were suboptimally debulked after cytoreductive surgery	1114	961	1.03 (0.87–1.21)	0.74
Post-menopausal patients >52 years	2226	1603	1.02 (0.90–1.16)	0.76
Breast cancer				
Overall survival				
All patients	28,471	3013	0.96 (0.87–1.06)	0.38
ER-positive patients	20,071	1754	0.96 (0.85–1.10)	0.58
ER-negative patients	4778	771	0.97 (0.81–1.18)	0.78
Breast cancer-specific survival				
All patients	28,471	1693	0.95 (0.83–1.08)	0.40
Overall survival				
BRCA1 mutation carriers	1706	241	0.72 (0.48–1.08)	0.11
BRCA2 mutation carriers	917	162	0.98 (0.65–1.46)	0.90

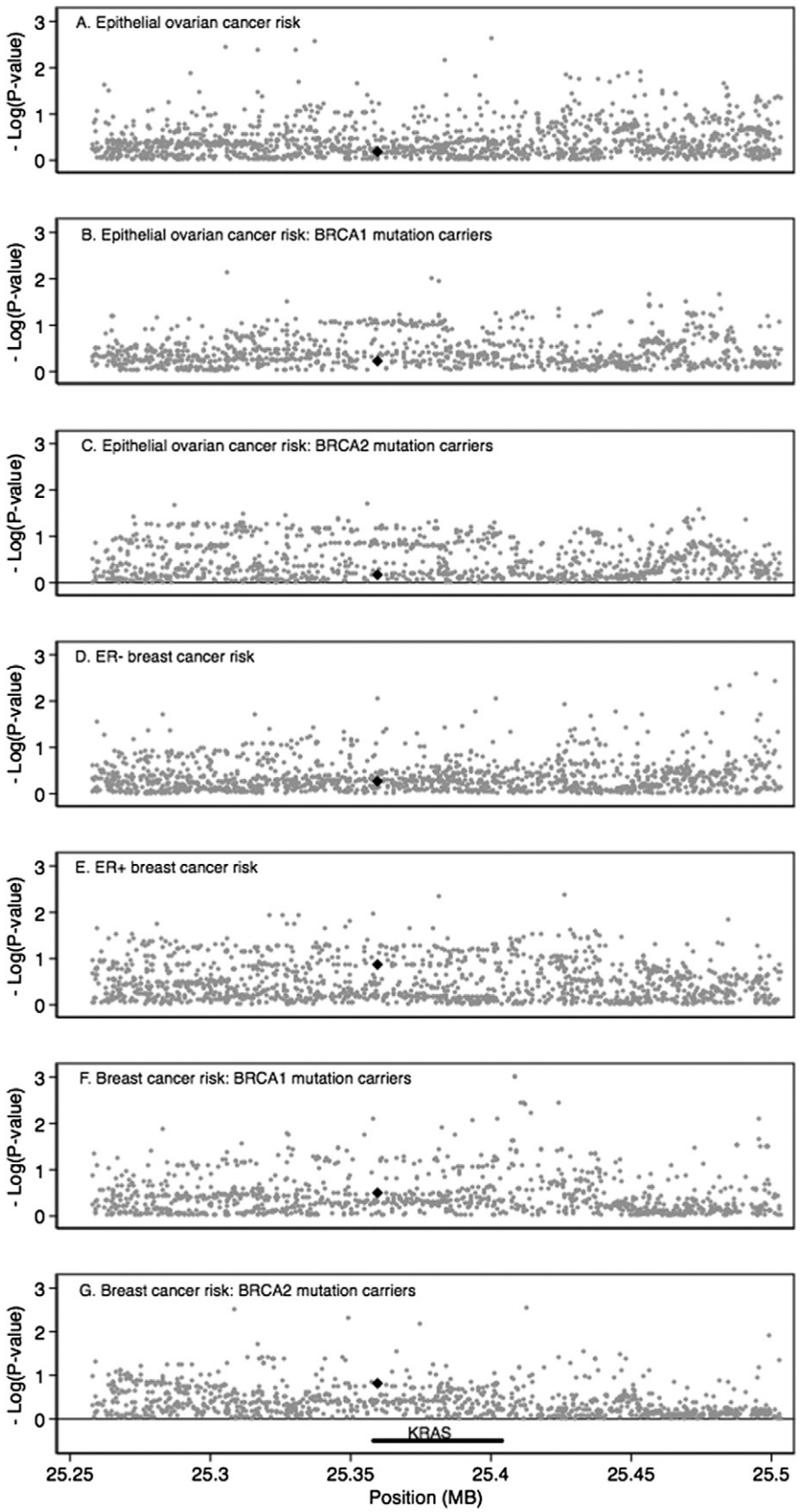

Fig. 1. Regional association plots for variants within the genomic region 100 kb either side of *KRAS* and risk of ovarian and breast cancer. X-axis position is referent to position (bp) on chromosome 12, build GRCh37.p12; yellow line indicates position of *KRAS*; red triangle indicates rs61764370. Y-axis is $-\log_{10}$(p-values) from association tests for risk of A) ER-negative breast cancer, B) ER-positive breast cancer, C) breast cancer in *BRCA1* mutation carriers, D) breast cancer in *BRCA2* mutation carriers, E) epithelial ovarian cancer, F) epithelial ovarian cancer in *BRCA1* mutation carriers, and G) epithelial ovarian cancer in *BRCA2* mutation carriers.

whichever occurred first. We also performed analyses restricted to women diagnosed or censored within two years before their enrollment. To assess associations with breast cancer risk, mutation carriers were followed from birth until a breast cancer diagnosis (i.e. either ductal carcinoma in situ or invasive breast cancer), ovarian cancer diagnosis, a risk-reducing bilateral prophylactic mastectomy or the age at enrollment, whichever occurred first.

Survival analysis of OCAC patients used Cox proportional hazards models estimating HRs and 95% CIs considering overall survival as well as progression-free survival following ovarian cancer diagnosis. Overall survival was adjusted for age at diagnosis, the five European PCs, histology, grade, FIGO stage, and residual disease after debulking surgery, and stratified by study, left truncating at the date of study entry and right censoring at five years to minimize events due to other causes. Progression-free survival was analyzed as for overall survival, but without adjustment for age and right censoring, and was defined as the time between the date of histologic diagnosis and the first confirmed sign of disease recurrence or progression, based on GCIG (Gynecological Cancer InterGroup) criteria [36]. We also performed subgroup analysis of patients suboptimally debulked after cytoreductive surgery (residual disease >1 cm) and of post-menopausal patients (age at diagnosis >52 years). Survival analysis of BCAC patients used Cox proportional hazard models estimating HRs and 95% CIs considering overall and breast cancer-specific survival following breast cancer diagnosis. Models were adjusted for age at diagnosis, tumor size, nodal status, grade, adjuvant hormonal and/or chemotherapy, and stratified by study, left-truncating at the date of study entry and right censoring at ten years. In addition, we performed subgroup analysis on ER-positive and ER-negative patients. For CIMBA breast cancer patients associations between genotype and overall survival were evaluated using Cox proportional hazard models estimating HRs and 95% CIs. Models were adjusted for age at diagnosis, tumor size, nodal status, grade, adjuvant hormonal and/or chemotherapy, and preventive bilateral oophorectomy and stratified by study, left-truncating at the date of study entry and right censoring at twenty years. Analyses were performed using STATA version 12.0 (StataCorp, Texas, USA).

3. Results

The results of the overall analysis as well as the subgroup analyses investigating the association between the minor allele at rs61764370 and ovarian cancer risk, breast cancer risk, and ovarian and breast cancer risks in *BRCA1* and *BRCA2* mutation carriers are shown in Table 1. Associations with clinical outcomes in and ovarian and breast cancer patients including *BRCA1* and *BRCA2* mutation carriers are shown in Table 2 and Supplementary Table S4.

We found no evidence for association between the rs61764370 G allele and ovarian or breast cancer risk. The most statistically significant association was observed for risk of low-grade serous ovarian cancer ($n = 485$; OR 0.76, 95% CI 0.59–0.97, $p = 0.031$), but this finding was not significant after Bonferroni correction for multiple testing. We also evaluated the association for additional specific subgroups in which an association with rs61764370 had been reported previously [3–6]. Ovarian cancer subgroups considered *BRCA1* mutation carriers as well as *BRCA1* and *BRCA2* screened-negative patients with first degree family histories of breast or ovarian cancer and patients who had been diagnosed with breast cancer before their ovarian cancer diagnoses. For breast cancer these included, among others, *BRCA1* mutation carriers, patients diagnosed with ER- and PR-negative tumors, and patients diagnosed with triple negative tumors before age 52 years. Importantly, we observed no evidence for association of rs61764370 with any of these subgroups (detailed in Table 1), with all ORs close to unity and very narrow CIs including unity.

Similarly, case-only analyses did not reveal any associations between rs61764370 genotype and ovarian and breast cancer clinical features or outcome (Table 2 and Supplementary Table S4). For example, the previously reported association between rs61764370 and risk of ERBB2-positive and high grade breast cancer in hormone replacement therapy users [18] was not replicated (Supplementary Table S4), and in ovarian cancer analyses we found no evidence of reduced survival among patients diagnosed after age 52 years or patients with suboptimal debulking after cytoreductive surgery (Table 2) [14]. The G allele of rs61764370 was also not associated with survival of breast cancer patients (Table 2).

Finally, we evaluated the association between the primary phenotypes of interest and common genetic variation (MAF > 0.02) in the genomic region of *KRAS* (i.e., within 100 kb on either side of the gene), using imputed and genotyped data on 974 variants for OCAC, 989 variants for BCAC, and 1001 variants genotyped and imputed for CIMBA (Supplementary Tables S5, S6, and S7). We found no evidence of association for any of these variants, including rs61764370 and rs17388148, with these phenotypes that would withstand Bonferroni correction for multiple testing, as detailed in Supplementary Tables S5, S6, and S7 and shown in regional association plots (Fig. 1).

4. Discussion

Our analysis of 140,012 women genotyped for inherited variants in the *KRAS* region provides definitive clarification of the role of these variants in ovarian and breast cancer susceptibility and outcome. We have found no evidence to support an association between rs61764370 and ovarian or breast cancer risk, or clinical outcomes in patients with ovarian or breast cancer. In the absence of any association and with ORs close to unity we would not typically consider sub-group analyses, particularly sub-groups for which differential associations would not be expected to occur. However, given the previous positive associations reported for a myriad of different subgroups, we tested for association among each of these subgroups and found no evidence to support the previously reported associations.

Our study has notable strengths. The vast majority (i.e. >95%) of the samples were genotyped using the same genotyping platform and employing a common approach to genotype calling and quality control; additional samples used denser arrays and nearly identical procedures. The very large sample sizes for all the major phenotypes of interest provide substantial statistical power to exclude any clinically relevant associated risks for the major phenotypes of interest (Fig. 2). The null results found here are thus not due to lack of statistical power, and this analysis also had greater than 80% power to detect association for most of the subgroups, although for some subgroups it was not possible to exclude

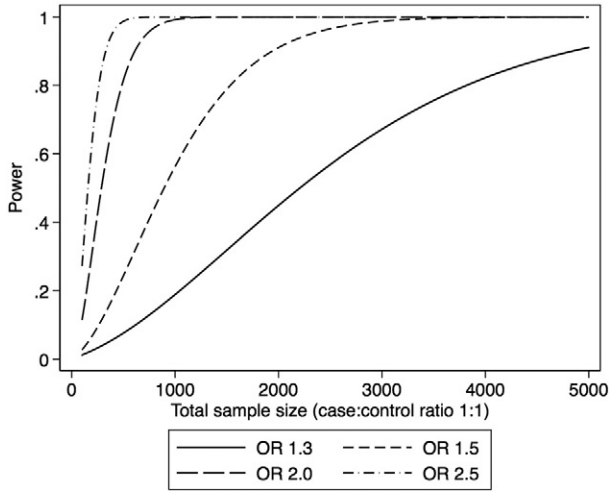

Fig. 2. Power curve for modest risk variants according to the total sample size. X-axis is total sample size for which case–control ratio is 1:1. Y-axis is the statistical power (range 0 · 5–1 · 0) for variants given a range of risks, assuming alpha = 0 · 01 and minor allele frequency 0 · 09.

modest risks. In contrast to the current findings, other genetic association analyses using the same genotyping platform and the same studies as included here have identified more than 90 common germline variants associated with ovarian or breast cancer risk at $p < 5 \times 10^{-8}$ [22,23,37]. While critiques on a previous null *KRAS* report have suggested that inclusion of male controls, use of "prevalent" cases, and reliance on a surrogate genetic variant may have led to falsely negative conclusions, these are not issues in the present data set. Rather, we demonstrate the importance of international collaboration to identify true associations as well as to refute false associations, an equally important objective.

The rise of individualized medicine including the use of panels of common variants to predict cancer risk more accurately than using family history alone holds great promise [38]. For example, the 31 prostate cancer susceptibility alleles confirmed as of 2011 (at $p < 5 \times 10^{-8}$) can be combined to identify men in the top one percent of the risk distribution having a 3.2-fold increased risk [39]. Prediction has since then improved with now over 70 prostate cancer susceptibility alleles [40] and the utility of these genetic tests is currently under clinical evaluation. A similar clinical examination in ovarian and breast cancer is not far behind, with now over 18 and 77 confirmed susceptibility alleles, respectively, for these cancers [22,23]. The genotype at rs61764370, however, does not predict ovarian or breast cancer risk, even among particular subgroups of women or for particular subtypes of disease, nor is it a marker of differential outcome following diagnosis with these cancers. Therefore, genetic test results for rs61764370 should not be used to counsel women about their ovarian or breast cancer risks or outcome. Our results highlight the dangers of developing clinical tests without appropriate data from carefully conducted, large-scale studies to establish clinical validity.

Conflict of interest statement

There are no conflicts of interest to disclose.

Antoinette Hollestelle and Ellen L. Goode had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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