The Role of KRAS rs61764370 in Invasive Epithelial Ovarian Cancer: Implications for Clinical Testing


Abstract

**Purpose:** An assay for the single-nucleotide polymorphism (SNP), rs61764370, has recently been commercially marketed as a clinical test to aid ovarian cancer risk evaluation in women with family histories of the disease. rs61764370 is in a 3'-UTR miRNA binding site of the KRAS oncogene and is a candidate for epithelial ovarian cancer (EOC) susceptibility. However, only one published article, analyzing fewer than 1,000 subjects in total, has examined this association.

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Experimental Design: Risk association was evaluated in 8,669 cases of invasive EOC and 10,012 controls from 19 studies participating in the Ovarian Cancer Association Consortium, and in 683 cases and 2,044 controls carrying BRCA1 mutations from studies in the Consortium of Investigators of Modifiers of BRCA1/2. Prognosis association was also examined in a subset of five studies with progression-free survival (PFS) data and 18 studies with all-cause mortality data.

Results: No evidence of association was observed between genotype and risk of unselected EOC (OR = 1.02, 95% CI: 0.95–1.10), serous EOC (OR = 1.08, 95% CI: 0.98–1.18), familial EOC (OR = 1.09, 95% CI: 0.78–1.54), or among women carrying deleterious mutations in BRCA1 (OR = 1.09, 95% CI: 0.88–1.36). There was little evidence for association with survival time among unselected cases (HR = 1.10, 95% CI: 0.99–1.22), among serous cases (HR = 1.12, 95% CI = 0.99–1.28), or with PFS in 540 cases treated with carboplatin and paclitaxel (HR = 1.18, 95% CI: 0.93–1.52).

Conclusions: These data exclude the possibility of an association between rs61764370 and a clinically significant risk of ovarian cancer or of familial ovarian cancer. Use of this SNP for ovarian cancer clinical risk prediction, therefore, seems unwarranted. Clin Cancer Res; 17(11): 3742–50. ©2011 AACR.

Introduction

Epithelial ovarian cancer (EOC) is the fifth-most common cancer in women. It generally presents as advanced disease with poor prognosis. Family and twin studies have suggested that inherited genetic variation plays an appreciable part in determining individual risk. However, until recently, knowledge of genetic susceptibility was limited to rare, highly penetrant alleles in a handful of genes including BRCA1, BRCA2 and the mismatch repair genes (1). In the past 2 years, genome-wide association studies have identified common susceptibility alleles at 4 loci at highly stringent levels of statistical significance (P < 10^−8), but these alleles have small effects on disease risk (per-allele OR < 1.3) and explain a small fraction of the genetic component of disease risk (2–4). Many candidate gene studies have identified possible common ovarian cancer susceptibility alleles, but most are likely to represent false-positive associations as none have been reported at the levels of statistical significance required, when testing hypotheses with low prior probabilities of association (1).

In July 2010, a single-nucleotide polymorphism (SNP), rs61764370, located in the 3′-UTR of the KRAS oncogene, was reported to be associated with risk of unselected EOC (5). The variant was also reported to be associated with a stronger risk in women carrying BRCA1 mutations, in women not carrying BRCA1 or BRCA2 mutations but with a family history of the disease, as well as with associated with poorer progression-free survival (PFS: ref. 5). This SNP was thought to be a strong candidate for cancer risk as it...
Translational Relevance

An assay for a single-nucleotide polymorphism (SNP) in a 3’-UTR miRNA binding site of the KRAS gene has recently been commercially marketed as a clinical test to aid epithelial ovarian cancer (EOC) risk assessment in women with family histories of the disease. The justification for use of this assay was based on one published article which analyzed fewer than 1,000 subjects in total, including only 67 EOC cases carrying BRCA1 mutations or with family histories of EOC. The present article found no association between this SNP and ovarian cancer risk among 8,669 cases of unselected invasive EOC and 10,012 controls, or in 683 cases and 2,044 controls carrying BRCA1 mutations. The results suggest that evaluation of this SNP is not clinically useful for risk prediction in sporadic or familial ovarian cancer.

Materials and Methods

Study populations

Nineteen ovarian cancer case–control sets and 1 case series participating in the Ovarian Cancer Association Consortium (OCAC), and 1 additional case series, contributed data to the analyses (Table 1). Three of the case–control sets were each comprised of a case series matched to controls from the same geographic region: PVM, UK2, and UK-GWAS (genome-wide association studies). Survival time analysis was based on data from 18 case series, including the additional publicly available data for 359 ovarian cancer cases from The Cancer Genome Atlas (http://cancergenome.nih.gov/) that had information on...
Table 1. Description of participating studies (Cont’d)

<table>
<thead>
<tr>
<th>Analysis set</th>
<th>Study name</th>
<th>Study abbrev.</th>
<th>Study population</th>
<th>Study type</th>
<th>Number of subjects</th>
<th>Genotyping method</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>HOP Hormones and Ovarian Cancer Prediction Study</td>
<td>HOPb</td>
<td>Pittsburgh</td>
<td>Population based</td>
<td>368 365</td>
<td>TaqMan</td>
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<tr>
<td></td>
<td>MAY Mayo Clinic Ovarian Cancer Study</td>
<td>MAYa</td>
<td>Upper Midwest</td>
<td>Hospital based</td>
<td>520 358</td>
<td>Illumina 610 Quad</td>
</tr>
<tr>
<td></td>
<td>NCO North Carolina Ovarian Cancer Study</td>
<td>NCOb</td>
<td>North Carolina</td>
<td>Population based</td>
<td>655 494</td>
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<tr>
<td></td>
<td>NTH Nijmegen Ovarian Cancer Study</td>
<td>NTH</td>
<td>Netherlands</td>
<td>Population based</td>
<td>327 296</td>
<td>Fluidigm</td>
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<td>OVA Ovarian Cancer Study</td>
<td>OVA</td>
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<td>Fluidigm</td>
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<td>PVDb</td>
<td>Copenhagen, Denmark</td>
<td>Hospital based</td>
<td>215 201</td>
<td>Fluidigm</td>
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<tr>
<td></td>
<td>TBO Tampa Bay Ovarian Cancer Study</td>
<td>TBOa</td>
<td>Tampa</td>
<td>Population based</td>
<td>168 227</td>
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</tr>
<tr>
<td></td>
<td>TOR Familial Ovarian Tumour Study</td>
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<td>Ontario, Canada</td>
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<td>UK2 SEARCH Southampton Ovarian Cancer Study</td>
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<td>Fluidigm</td>
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<tr>
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<td>UK</td>
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<td>UK-GWAS Cancer Research UK Familial Ovarian Ovarian Cancer Register</td>
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<td></td>
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<td>5BBCa, NSCRa</td>
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<td>Cohort</td>
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<td></td>
<td>UK Colorectal control</td>
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<td>Population based</td>
<td>917 917</td>
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<tr>
<td></td>
<td>USC Los Angeles County Case-Control Studies</td>
<td>USC</td>
<td>Los Angeles</td>
<td>Population based</td>
<td>343 260</td>
<td>TaqMan</td>
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Case-only studies

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<th>Study name</th>
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<th>Study population</th>
<th>Study type</th>
<th>Number of subjects</th>
<th>Genotyping method</th>
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<td>TCGA</td>
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<td>USA</td>
<td>Hospital based</td>
<td>359</td>
<td>Illumina 1M Duo</td>
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</table>

aCase data included in analysis of all-cause mortality and PFS.
bCase data included in analysis of all-cause mortality.
all-cause mortality. The analysis of PFS was based on data from 5 case series. Finally, data from 683 cases and 2,044 controls enrolled in a stage I project of the Consortium of Investigators of Modifiers of BRCA1/2 (see ref. 8 for details of studies participating in CIMBA) were used to examine risk among women carrying deleterious BRCA1 mutations. Each study was approved by a governing research ethics committee and all study subjects provided written informed consent. Clinical and questionnaire data included tumor behavior, histology, stage and grade, age at diagnosis (or at comparable date for controls), family history of ovarian cancer, and ethnicity/race.

Survival time data were available for cases from 18 studies (BEL, DOV, UCR, GER, HOP, LAX, MAY, NCO, PVD, RMH, SEA, SOC, SRO, TBO, TCGA, UCI, UKO, and USC) and clinical information on chemotherapy, residual disease after surgery, and time to progression was collected in 5 studies (BEL, LAX, MAY, SRO, and TCGA). All of the women included in the analysis of PFS had at least 4 cycles of carboplatin and paclitaxel as part of primary treatment. PFS was defined as the time interval between the date of histologic diagnosis and the first confirmed sign of disease recurrence or progression (9).

Genotyping

Genotyping of 13 case–control sets was done in a single laboratory by using a 5′-nuclease TaqMan allelic discrimination assay (Applied Biosystems) as part of a 96-SNP Fluidigm multiplex (10 studies) or—with the same batch of TaqMan reagents—using the 7900HT Sequence Detection Software (Applied Biosystems; 3 studies; Table 1). Details of quality control criteria of OCAC have been described previously (10): they include genotyping of a common set of 95 DNAs (90 CEPH trios and 5 duplicate samples) and comparison with the genotypes for the same samples as reported by HapMap. However, rs61764370 was not genotyped in the HapMap project. On the basis of sequence data for 57 individuals of European origin from the 1000 Genomes project (http://www.1000genomes.org), a HapMap SNP, rs17388148, was found to be strongly correlated ($r^2 = 0.97$) with rs61764370. The concordance between the CEPH trio genotype data for rs61764370 and the HapMap genotypes for rs17388148 was 100%. Therefore, data on rs17388148 were obtained from 3 GWAS, in which cases and controls had been genotyped by using Illumina genome-wide SNP arrays (refs. 1, 2, 4, 8; Table 1). Neither rs61764370 nor rs17388148 were included on the Illumina arrays used in these GWAS studies, but imputed genotypes were available for rs17388148. These genotypes were provided as the estimated number of rare alleles carried (0 to 2 on a continuous scale). The accuracy of the imputation as calculated by the program MACH of Li and Abecasis (11) for the North American studies (BWH, MAY, NCO, TBO, and TOR) was $r^2 = 0.977$. This high accuracy of the imputation was evidently because of the presence of a nearby SNP (rs12305513, 17 kb away) in high LD ($r^2 = 1$ in HapMap) with rs17388148.

Statistical analyses

Analyses were restricted to white non-Hispanic women based on self-reported ethnic origin for all of the studies, with the exception of the TCGA, MAY, NCO, TOR, TBO, and UK-GWAS controls. For these studies, genome-wide genotype data were used to estimate intercontinental ancestry and women of less than 90% European ancestry were excluded (see methods in ref. 3 for details). Cases with borderline (low malignant potential) EOC were also excluded, as were 22 cases from TCGA that had been provided to TCGA as part of the MAY case–control study. Departure of genotype frequencies from those expected under Hardy–Weinberg equilibrium was assessed by using a $\chi^2$ test for each study that was directly genotyped. The association between SNP and disease risk was evaluated by using unconditional logistic regression in which number of copies of the minor (infrequent) allele was treated as a continuous variable. This provides an estimate of the per-allele OR and 95% CI. Models adjusted for age categories (<40, 40–49, 50–59, 60–69, and ≥70 years) were also considered. Each case–control set was analyzed individually and the pooled result was obtained by combining the log odds-ratios by using standard inverse variance-weighted meta-analytic methods. Analysis of the BRCA1 mutation carrier cohort was carried out by using a time-to-event analysis framework that models the association between genotype and ovarian cancer risk as a HR. Because mutation carriers were not sampled randomly with respect to their disease status, standard methods of survival analysis may lead to biased estimates of associations. Therefore, analyses were carried out by modeling the retrospective likelihood of observed genotype conditional on disease phenotype (see refs. 8, 12 for details).

Associations between genotype and PFS and all-cause mortality were evaluated by using proportional hazards regression. Because the EOC cases were recruited at variable times after diagnosis, regression analysis of all-cause mortality allowed for left truncation, with time at risk starting on date of diagnosis and time under observation beginning at the time of study entry. This method generates an unbiased estimate of the HR, provided that the proportional hazards assumption is reasonably correct (13). Cause-specific mortality was not available for most studies, so the analysis of all-cause mortality was right censored at 5 years after diagnosis to minimize the proportion of deaths from causes other than ovarian cancer. The analysis of PFS was adjusted for stage and residual disease, and survival time ended at time of progression or was censored at time of last follow-up.

Results

Details of the 19 case–control sets used in our analyses are given in Table 1. Genotype data from these sets were available for 8,669 cases and 10,012 controls (Table 2). All studies passed the OCAC criteria for genotyping quality. Genotype frequencies were close to those expected under
Hardy–Weinberg equilibrium in both cases and controls for the 13 directly genotyped studies. No evidence was found for association between rs61764370 and invasive EOC in univariate analysis (OR = 1.02, 95% CI: 0.95–1.10, \( P = 0.44 \)), with minimal heterogeneity of risk between studies (\( P = 0.28 \)). Study-specific ORs are shown in Figure 1A. When studies with directly genotyped data and with imputed data were analyzed separately, the overall OR in the genotyped studies was 0.96 (95% CI: 0.87–1.06, \( P = 0.42 \)) compared with 1.08 (95% CI: 0.97–1.20, \( P = 0.15 \)) in the imputed data studies. Adjusting for age at diagnosis/interview made little difference to the results (data not shown). No differences in risk were observed when analyses were restricted to cases who provided blood samples within 18 months of diagnosis (\( n = 6,550, \ OR = 1.02, \ 95\% \ CI: 0.93–1.10, \ P = 0.72 \)), cases with serous tumors (Fig. 1B, \( n = 4,706, \ OR = 1.08, \ 95\% \ CI: 0.98–1.18, \ P = 0.11 \)), or cases reporting a family history of ovarian cancer in a first-degree relative (from 6 studies; Fig. 1C, \( n = 249, \ OR = 1.09, \ 95\% \ CI: 0.78–1.54, \ P = 0.62 \)). Tests for heterogeneity of risk between studies in all analyses were not statistically significant. A similar result was seen for risk of EOC by genotype among 683 cases and 2,044 controls who were carriers of BRCA1 mutations (\( HR = 1.09, \ 95\% \ CI: 0.88–1.36, \ P = 0.40 \)).

Survival time data were available for 6,002 cases of the 6,826 total from 18 case series, including 13,696 person-years at risk and 2,044 deaths. Little evidence of association was observed between rs61764370 genotype and all-cause mortality within 5 years of diagnosis (\( HR = 1.10, \ 95\% \ CI: 0.99–1.22, \ P = 0.08 \)), with no evidence of heterogeneity of the HR between studies (\( P = 0.89 \)). Results of analyses restricted to serous subtype (\( HR = 1.12, \ 95\% \ CI: 0.99–1.28, \ P = 0.08 \)) or adjusted for tumor stage and grade (\( HR = 1.06, \ 95\% \ CI: 0.96–1.18, \ P = 0.27 \)) were similar. There was also little evidence for association between genotype and PFS in 540 high-grade serous cases known to have been treated with carboplatin and paclitaxel (\( HR = 1.18, \ 95\% \ CI: 0.93–1.52, \ P = 0.16 \)).

**Table 2. Genotype frequency numbers of controls and cases by study**

<table>
<thead>
<tr>
<th>Study abbreviation</th>
<th>Control genotypes(^a)</th>
<th>Case genotypes(^a)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Allele freq.(^b)</td>
<td>Allele freq.(^b)</td>
</tr>
<tr>
<td>BEL</td>
<td>0.105</td>
<td>0.098</td>
</tr>
<tr>
<td>DOV</td>
<td>0.082</td>
<td>0.095</td>
</tr>
<tr>
<td>GER</td>
<td>0.091</td>
<td>0.076</td>
</tr>
<tr>
<td>HJO</td>
<td>0.092</td>
<td>0.052</td>
</tr>
<tr>
<td>HMO</td>
<td>0.102</td>
<td>0.102</td>
</tr>
<tr>
<td>HOC</td>
<td>0.102</td>
<td>0.081</td>
</tr>
<tr>
<td>HOP</td>
<td>0.102</td>
<td>0.082</td>
</tr>
<tr>
<td>LAX</td>
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<td>0.112</td>
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<tr>
<td>NTH</td>
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<td>0.081</td>
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<tr>
<td>OVA</td>
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<td>0.081</td>
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<tr>
<td>PVM</td>
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<td>0.112</td>
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<tr>
<td>UCI</td>
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<tr>
<td>UK2</td>
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<td>0.092</td>
</tr>
<tr>
<td>USC</td>
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<td>0.090</td>
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<tr>
<td>BWH(^c)</td>
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<td>MAY(^c)</td>
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<td>NCO(^c)</td>
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<td>TBO(^c)</td>
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<td>TCGA(^c)</td>
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<td>0.107</td>
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<tr>
<td>TOR(^c)</td>
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<tr>
<td>UK-GWAS(^c)</td>
<td>0.096</td>
<td>0.096</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>9,291</td>
<td>9,291</td>
</tr>
</tbody>
</table>

\(^a\)Columns labeled 0, 1, and 2 refer to common homozygote, heterozygote, and infrequent homozygote, respectively.

\(^b\)Estimated frequency of minor (infrequent) allele: \( f_2 + \frac{1}{2} f_1 / (f_2 + f_1 + f_0) \).

\(^c\)Estimated genotype frequencies based on imputed data.
Clinical Cancer Research

To detect an allele conferring a relative risk of 1.3 under a dominant or log-additive genetic model with a type 1 error rate of $10^{-3}$ was greater than 99%, strongly suggesting that the association observed by Ratner and colleagues was a chance finding or possibly because of subtle genotyping errors. This observation is not surprising. Associations with modest $P$ values that are declared as positive are very likely to be false positives, when the prior probability of association is low (14). In genetic association studies, even if evidence exists that a variant has functional effects, the prior probability of association at a relative risk of 1.5 is unlikely to be more than 1:100 and, given that only a handful of loci conferring relative risks of more than 1.5 have been found for any cancer, the prior probability is likely to be much less. On the basis of the methodology of Wacholder and colleagues (14), assuming a prior of 1:100, the probability that the association reported by Ratner and colleagues was a false positive is 86%. Under more likely, smaller prior probabilities, the false positive probability will approach 100%. For familial ovarian cancer, the power of the present study to detect a relative risk of 2.0 was over 95% at a type 1 error rate of 0.05, again suggesting that it is unlikely that the present analyses have missed a true association of this magnitude with familial ovarian cancer.

In summary, the possibility that the minor (infrequent) allele of rs61764340 is associated with an appreciable risk of EOC is excluded. Furthermore, it is debatable whether a single-risk allele, even one conferring a relative risk as high as 2.0, has clinical utility, particularly in a disease with lifetime risk as low as it is in invasive EOC (1 in 70), and even among women with a family history of the disease (16). The marketing of a commercial assay for rs61764370 and ovarian cancer risk. A, all cases; B, serous cases; and C, cases with a family history of ovarian cancer in a first-degree relative.

**Figure 1.** Funnel plots of study-specific ORs for association between rs61764370 and ovarian cancer risk. A, all cases; B, serous cases; and C, cases with a family history of ovarian cancer in a first-degree relative.
Disclosure of Potential Conflicts of Interest

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