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.

Authors’ Affiliations: 1Department of Oncology; 2Centre for Cancer Genetic Epidemiology, Department of Public Health and Primary Care, University of Cambridge, Cambridge, United Kingdom; 3Departments of Community and Family Medicine, and Obstetrics and Gynecology, Duke University Medical Center; 4Department of Statistical Science, Duke University, Durham, North Carolina; 5Department of Preventive Medicine, Keck School of Medicine and the USC Norris Comprehensive Cancer Center, University of Southern California; 5Department of Hematology and Oncology, Department of Medicine, David Geffen School of Medicine, University of California at Los Angeles; 5Women’s Cancer Research Institute at the Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, California; 5Ontario Cancer Genetics Network, Cancer Care Ontario and Samuel Lunenfeld Research Institute, Mount Sinai Hospital; 5Cancer Care Ontario; 5Women’s College Research Institute, University of Toronto, Toronto, Ontario, Canada; 5Department of Epidemiology, School of Medicine, University of California, Irvine, California; 5Belorussian Institute for Oncology and Medical Radiology Aleksandrov N.N., Minsk, Belarus; 5Breast Cancer Family Registry, Epidemiology and Genetics Research Program, DCCPS, National Cancer Institute, Rockville, Maryland; 5Cancer Risk Program, Departments of Medicine, Epidemiology, and Biostatistics, University of California at San Francisco, San Francisco, California; 5Department of Gynecology and Obstetrics, University Hospital Erlangen; 5Institute of Human Genetics, Friedrich-Alexander University Erlangen-Nuremberg, Erlangen, Bavaria, Germany; 5Department of Medicine, Massachusetts General Hospital; 5Obstetrics and Gynecology Epidemiology Center, Brigham and Women’s Hospital, Boston, Massachusetts; 5Clinics of Obstetrics and Gynaecology and 5Radiation Oncology, Hannover Medical School, Hannover, Germany; 5Division of Cancer Epidemiology and Genetics, National Cancer Institute, NIH, Bethesda, Maryland; 5Department of Obstetrics and Gynecology, School of Medicine, University of North Carolina at Chapel Hill, North Carolina; 5Genome Sciences Centre; 5Cancer Control Research, British Columbia Cancer Agency, Vancouver, British Columbia, Canada; 5Epigenetics Unit, Department of Surgery and Cancer, Imperial College London; 5Department of Gynaecological Oncology, University College London, EGA Institute for Women’s Health, London, United Kingdom; 5Department of Obstetrics and Gynecology, Helsinki University Central Hospital; 5Department of Pathology, University of Helsinki, Helsinki, Finland; 5Molecular Oncology Laboratory, Hospital Clinico San Carlos; 5Human Genetics Group, Human Cancer Genetics Programme, Spanish National Cancer Centre, Madrid, Spain; 5Section of Genetic Oncology, University Hospital of Pisa, Pisa, Italy; 5Centre for Cancer Genomics and Predictive Medicine, Peter MacCallum Cancer Centre, Melbourne; 5Department of Pathology, University of Melbourne, Parkville, Victoria, Australia; 5Division of Cancer Epidemiology, German Cancer Research Center (DKFZ), Heidelberg, Germany; 5H. Lee Moffitt Cancer Center and Research Institute; 5Department of Pediatrics, University of South Florida College of Medicine, Tampa, Florida; 5Division of Epidemiology and Biostatistics, Department of Internal Medicine, University of New Mexico, Albuquerque, New Mexico; 5Department of Laboratory Medicine and Pathology, Mayo Clinic; 5Genomics Shared Resource, Department of Laboratory Medicine and Pathology; 5Department of Health Sciences Research Divisions of Biostatistics and 5Epidemiology, Mayo Clinic College of Medicine, Rochester, Minnesota; 5Division of Gynaecologic Oncology, Department of Obstetrics and Gynaecology, University Hospitals Leuven, University of Leuven, Leuven, Belgium; 5Program in Epidemiology, Fred Hutchinson Cancer Research Center, Seattle, Washington; 5Clinic of Obstetrics and Gynaecology, Friedrich Schiller University, Jena, Germany;
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.
lies in a miRNA binding site, and associations between miRNA mutations or misexpression and risk of some human cancers have been seen. These observations suggested that miRNAs can function as tumor suppressors or oncogenes (6). An assay to determine genotype at rs61764370 has subsequently been marketed as a commercial test to determine risk in women with a family history of ovarian cancer (http://www.miradx.com). However, as with other candidate gene studies, the reported association was not at a level of statistical significance that is regarded as definitive for common susceptibility alleles (7), nor was the magnitude of risk sufficient for this SNP to be acceptable as a useful clinical marker of ovarian cancer risk. The present work therefore sought to achieve the following: (i) replicate the association in a robust manner in multiple study populations, genotyped to a high standard with stringent quality assurance procedures; (ii) assess the association between genotype at this locus and ovarian cancer risk in women with family histories or who carry deleterious mutations in \textit{BRCA1}; and (iii) examine the hypothesis that the SNP is associated with differences in postdiagnosis PFS or all-cause mortality.

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
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Case-only studies

| LAX | Case series | LAX | Los Angeles | Hospital based | 263 | Fluidigm |
| TCGA | The Cancer Genome Atlas | TCGA | USA | Hospital based | 359 | Illumina 1M Duo |

*Case 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 1 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 $\geq$ 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).

Discussion

This study provides no evidence to support the previously reported associations between rs61764370 and risk of EOC. The relative risk given by Ratner and colleagues for their replication data set of unselected cases was 1.70 (95% CI: 0.88–3.32, P = 0.07).
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

The content of this article does not necessarily reflect the views or policies of the National Cancer Institute or any of the collaborating centers in the BCFR, nor does mention of trade names, commercial products, or organizations imply endorsement by the US Government or the BCFR.

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Paul D. P. Pharoah, Rachel T. Palmieri, Susan J. Ramus, et al.

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