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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 was 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 7,904 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.

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Gynecologic Oncology

Dear Editors,

We are pleased to submit our manuscript "No Clinical Utility of *KRAS* Variant rs61764370 for Ovarian or Breast Cancer" for consideration for publication. This single nucleotide polymorphism (SNP) in the 3' untranslated region of *KRAS* was initially reported in 2010 by Dr. Joanne Weidhaas et al. from Yale University to be associated with risk and outcome of ovarian or breast cancer. Subsequent publications by her group have suggested relationships with risk and/or outcome of several other cancer types as well as endometriosis.

Since 2010, Dr. Weidhaas' company MiraDx has commercially marketed a test that utilizes this single SNP as a breast/ovarian cancer risk predictor.

"If your patient tests positive for this mutation, this may impact how you follow her for cancer detection. Women who carry this mutation have > 20% lifetime risk of developing breast cancer, and a 10% risk of developing an additional independent breast cancer after their first diagnosis. Thus, they may be considered for higher-level breast cancer screenings, such as MRIs, especially in the setting of dense breast tissue, as is common for *KRAS*-variant patients. Since women with this mutation are also at increased risk for ovarian cancer, consideration should be made for appropriate screening and management of their ovaries by a qualified physician, such as yourself or an OBGYN."

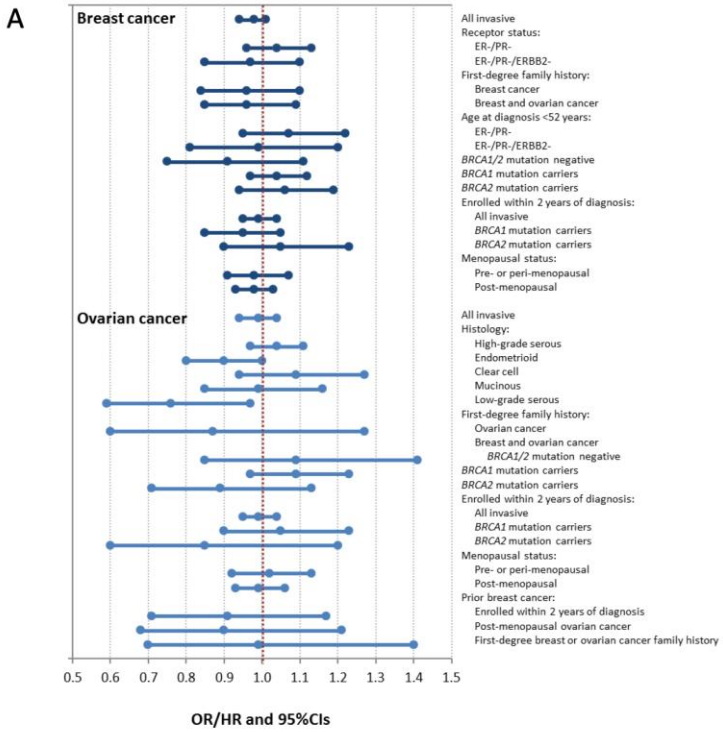
https://miradx.com/preovar-kras-variant-test-populations/
accessed 9/24/2014

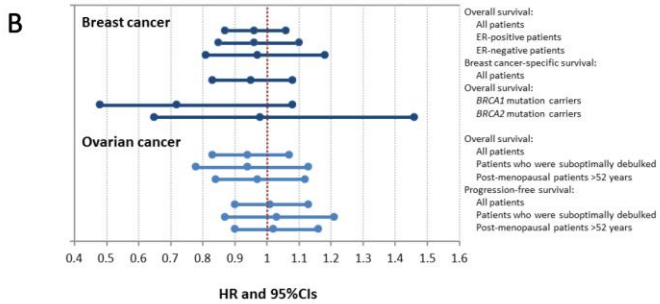
However, the publications by the Weidhaas group have been based on relatively small studies of a few hundred cases and controls, and, in many instances, subgroup analyses of much smaller numbers of subjects. By way of example, one paper by the Weidhaas group in 2011 suggesting that the *KRAS* SNP was associated with triple negative breast cancer was based on the risk allele being present in eight of 24 breast cancer cases (*Lancet Oncol*. 2011;12:377-86).

The *KRAS* SNP data we present in this paper is based on genotyping of 140,012 women in the context of the Collaborative Oncological Gene-Environment Study (COGS). Our analysis was conducted by three well-established international consortia, including the Ovarian Cancer Association Consortium (OCAC), the Breast Cancer Association Consortium (BCAC) and the Consortium of Modifiers of *BRCA1* and *BRCA2* (CIMBA). These groups came together because of the need for

large studies and rigorous validation of ovarian and breast cancer risk variants with small effect sizes. Over the past five years, our consortia have used genome wide association studies to discover and validate more than 100 common variants that are associated with risk of these cancers at a genome-wide level of significance (p values < $5x10^{-8}$). Here, we definitively show that this *KRAS* SNP is not associated with risk or outcome of ovarian or breast cancer; a forest plot of risk results is included below.

Figure. Associations between *KRAS* rs61764370 and breast and ovarian cancer (A) Risk: For *BRCA1* and *BRCA2* mutation carrier analyses, cases were affected *BRCA1/BRCA2* mutation carriers and controls were unaffected *BRCA1/BRCA2* mutation carriers, and relative risks were estimated by hazard ratios; for other analyses, relative risks are estimated by odds ratios; breast cancer risk analyses used BCAC data adjusted for study, age, and the seven European principal components; ovarian cancer analyses used OCAC data adjusted for study, age, and the five European principal components; *BRCA1* and *BRCA2* mutation carrier analyses used CIMBA data with age as follow-up time and stratified for country; (B) Outcome: 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; 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; 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.





Although null results generally are less likely to be published (*Science* 2014,345:992), this paper warrants acceptance for two reasons. First, the large size of this study refutes beyond any doubt the findings published previously. Second, and more importantly, MiraDx's test for the *KRAS* SNP continues to be marketed commercially. Thus, it is in the public interest for these null data to be widely visible to the scientific and lay communities. I will be presenting the ovarian cancer results at the 2015 SGO meeting.

We believe that the marketing of this test is a disservice to women who are concerned about risk or prognosis of ovarian and breast cancer and that our work will ignite an important dialogue about marketing of predictive genetic tests. Due to conflict of interest, we advise against the use of reviewers that are involved in MiraDx (i.e., Dr. Weidhaas and colleagues, see https://miradx.com/about/).

Lastly, we realize that the numbers of authors, 366, is large. Nonetheless, all of the authors of this paper fulfill the criteria for authorship, contributed to writing, and approved the submitted manuscript; other contributions are enumerated on the following pages.

Thank you in advance for consideration of this timely and important translational paper.

Sincerely,

Andrew Berchuck, MD
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on behalf of
the Ovarian Cancer Association Consortium (OCAC),
the Breast Cancer Association Consortium (BCAC), and
the Consortium of Modifiers of *BRCA1/2* Penetrance (CIMBA).

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51	Ralf		Butzow	PhD	Department of Pathology, Helsinki University Central Hospital, Helsinki, Finland; Department of Obstetrics and Gynecology, Helsinki University Central Hospital, University of Helsinki, Helsinki, Finland	contributed samples and data, edited manuscript	ralf.butzow@hus.fi	52	4
52	Saundra	S	Buys	MD	Department of Oncological Sciences, Huntsman Cancer Institute, University of Utah School of Medicine, Salt Lake City, UT, USA	contributed samples and data, edited manuscript	saundra.buys@hci.utah.edu	53	1
53	Maria	A	Caligo	PhD	Section of Genetic Oncology, Department of Laboratory Medicine, University Hospital of Pisa, University of Pisa, Pisa, Italy	contributed samples and data, edited manuscript	adelaide.caligo@do.unipi.it	54	1
54	Ian		Campbell	PhD	Cancer Genetics Laboratory, Research Division, Peter MacCallum Cancer Centre, Melbourne, Australia; Sir Peter MacCallum Department of Oncology, The University of Melbourne, Australia; Department of Pathology, University of Melbourne, Melbourne, Victoria, Australia	contributed samples and data, edited manuscript	ian.campbell@petermac.org	55	1
55	Jonathan		Carter	MD	Gynaecological Oncology, The Chris O'Brien Lifehouse and The University of Sydney, Sydney, Australia	contributed samples and data, edited manuscript	j.carter@sydney.edu.au	56	1
56	Jenny		Chang-Claude	PhD	Division of Cancer Epidemiology, German Cancer Research Center (DKFZ), Heidelberg, Germany	contributed samples and data, edited manuscript	j.chang-claude@dkfz-heidelberg.de	57	1
57	Stephen	J	Chanock	MD, PhD	Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD, USA	contributed samples and data, edited manuscript	chanocks@mail.nih.gov	58	1

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58	Kathleen	B M	Claes	PhD	Center for Medical Genetics, Ghent University, Ghent, Belgium	contributed samples and data, edited manuscript	Kathleen.Claes@UGent.be	59	3
59	J	Margriet	Collée	MD	Department of Clinical Genetics, Erasmus University Medical Center, Rotterdam, The Netherlands	contributed samples and data, edited manuscript	j.collee@erasmusmc.nl	60	1
60	Linda	S	Cook	PhD	Division of Epidemiology and Biostatistics, University of New Mexico, Albuquerque, NM, USA	contributed samples and data, edited manuscript	lcook@salud.unm.edu	61	1
61	Fergus	J	Couch	PhD	Department of Health Sciences Research, Division of Epidemiology, Mayo Clinic, Rochester, MN, USA; Department of Laboratory Medicine and Pathology, Division of Experimental Pathology, Mayo Clinic, Rochester, MN, USA	provided funding and contributed samples and data, edited manuscript	Couch.fergus@mayo.edu	62	1
62	Angela		Cox	PhD	Sheffield Cancer Research Centre, Department of Oncology, University of Sheffield, Sheffield, UK	contributed samples and data, edited manuscript	a.cox@sheffield.ac.uk	63	1
63	Daniel		Cramer	MD	Obstetrics and Gynecology Epidemiology Center, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA; Department of Epidemiology, Harvard School of Public Health, Boston, MA, USA	contributed samples and data, edited manuscript	dcramer@partners.org	64	1
64	Simon	S	Cross	PhD	Academic Unit of Pathology, Department of Neuroscience, University of Sheffield, Sheffield, UK	contributed samples and data, edited manuscript	s.s.cross@sheffield.ac.uk	65	1
65	Julie	M	Cunningham	PhD	Department of Laboratory Medicine and Pathology, Division of Experimental Pathology, Mayo Clinic, Rochester, MN, USA	performed genotyping and contributed samples and data, edited manuscript	cunningham.julie@mayo.edu	66	1
66	Cezary		Cybulski	PhD	International Hereditary Cancer Center, Department of Genetics and Pathology, Pomeranian Medical Academy, Szczecin, Poland	contributed samples and data, edited manuscript	cezarycy@sci.pam.szczecin.pl	67	1
67	Kamila		Czene	PhD	Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden	contributed samples and data, edited manuscript	kamila.czene@ki.se	68	1
68	Francesca		Damiola	PhD	INSERM U1052, CNRS UMR5286, Université Lyon 1, Centre de Recherche en Cancérologie de Lyon, Lyon, France	contributed samples and data, edited manuscript	francesca.damiola@lyon.unicancer.fr	70	1
69	Agnieszka		Dansonka-Mieszkowska	PhD	Department of Pathology and Laboratory Diagnostics the Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Warsaw, Poland	contributed samples and data, edited manuscript	agad@coi.waw.pl	71	1
70	Hatef		Darabi	PhD	Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden	contributed samples and data, edited manuscript	hatef.darabi@ki.se	72	1
71	Miguel		de la Hoya	PhD	Molecular Oncology Laboratory, Hospital Clinico San Carlos, Madrid, Spain	contributed samples and data, edited manuscript	mdhoya@hotmail.com	73	1
72	Anna		deFazio	PhD	Center for Cancer Research, University of Sydney at Westmead Millennium Institute, Sydney, Australia; Department of Gynaecological Oncology, Westmead Hospital, Sydney, Australia	contributed samples and data, edited manuscript	anna.defazio@sydney.edu.au	74	1
73	Joseph		Dennis	PhD	Centre for Cancer Genetic Epidemiology, Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK	contributed samples and data, edited manuscript	jgd29@cam.ac.uk	75	1

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74	Peter		Devilee	PhD	Department of Human Genetics, Leiden University Medical Center, Leiden, The Netherlands; Department of Pathology, Leiden University Medical Center, Leiden, The Netherlands	contributed samples and data, edited manuscript	p.devilee@lumc.nl	76	1
75	Ed	M	Dicks	PhD	Centre for Cancer Genetic Epidemiology, Department of Oncology, University of Cambridge, Cambridge, UK	contributed samples and data, edited manuscript	emd43@medschl.cam.ac.uk	77	1
76	Orland		Diez	PhD	Oncogenetics Laboratory, University Hospital Vall d'Hebron and Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain	contributed samples and data, edited manuscript	odiez@vhebron.net	78	1
77	Jennifer	A	Doherty	PhD	Section of Biostatistics and Epidemiology, The Geisel School of Medicine at Dartmouth, Lebanon, NH, USA	contributed samples and data, edited manuscript	jennifer.a.doherty@dartmouth.edu	79	1
78	Susan	M	Domchek	MD	Department of Medicine, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA; Basser Research Centre, Abramson Cancer Center, The University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA	contributed samples and data, edited manuscript	Susan.Domchek@uphs.upenn.edu	80	1
79	Cecilia	M	Dorfling	MS	Department of Genetics, University of Pretoria, Pretoria, South Africa	contributed samples and data, edited manuscript	Celmari.dorfling@up.ac.za	81	1
80	Thilo		Dörk	PhD	Department of Obstetrics and Gynaecology, Hannover Medical School, Hannover, Germany	contributed samples and data, edited manuscript	doerk.thilo@mh-hannover.de	82	1
81	Isabel		Dos Santos Silva	PhD	Non-Communicable Disease Epidemiology Department, London School of Hygiene and Tropical Medicine, London, UK	contributed samples and data, edited manuscript	isabel.silva@lshtm.ac.uk	83	1
82	Andreas		du Bois	MD	Department of Gynecology and Gynecologic Oncology, Dr. Horst Schmidt Klinik Wiesbaden, Wiesbaden, Germany; Department of Gynecology and Gynecologic Oncology, Kliniken Essen-Mitte, Essen, Germany	contributed samples and data, edited manuscript	Prof.duBois@googlemail.com	84	1
83	Martine		Dumont	PhD	Centre Hospitalier Universitaire de Québec Research Center and Laval University, Quebec, Canada	contributed samples and data, edited manuscript	martine.dumont@crchul.ulaval.ca	85	1
84	Alison	M	Dunning	PhD	Centre for Cancer Genetic Epidemiology, Department of Oncology, University of Cambridge, Cambridge, UK	contributed samples and data, edited manuscript	amd24@medschl.cam.ac.uk	86	1
85	Mercedes		Duran	PhD	Institute of Biology and Molecular Genetics, Universidad de Valladolid (IBGM-UVA), Valladolid, Spain	contributed samples and data, edited manuscript	merche@ibgm.uva.es	87	2
86	Douglas	F	Easton	PhD	Centre for Cancer Genetic Epidemiology, Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK; Centre for Cancer Genetic Epidemiology, Department of Oncology, University of Cambridge, Cambridge, UK	provided funding and contributed samples and data, edited manuscript	dfe20@medschl.cam.ac.uk	88	1
87	Diana		Eccles	PhD	Faculty of Medicine, University of Southampton, University Hospital Southampton, Southampton, UK	contributed samples and data, edited manuscript	d.m.eccles@soton.ac.uk	89	1
88	Robert		Edwards	MD	Department of Obstetrics, Gynecology and Reproductive Sciences, Division of Gynecologic Oncology, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA	contributed samples and data, edited manuscript	redwards@mail.magee.edu	90	1
89	Hans		Ehrencrona	MD	Department of Clinical Genetics, Lund University, Lund, Sweden	contributed samples and data, edited manuscript	hans.ehrencrona@med.lu.se	91	1

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90	Bent		Ejlertsen	MD	Department of Oncology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark	contributed samples and data, edited manuscript	bent.ejlertsen@rh.regionh.dk	92	1
91	Arif	B	Ekici	PhD	Institute of Human Genetics, Friedrich Alexander University Erlangen-Nuremberg, Erlangen, Germany	contributed samples and data, edited manuscript	arif.ekici@uk-erlangen.de	93	1
92	Steve	D	Ellis	MS	Centre for Cancer Genetic Epidemiology, Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK	contributed samples and data, edited manuscript	sde26@medschl.cam.ac.uk	94	1
93			EMBRACE		Centre for Cancer Genetic Epidemiology, Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK	contributed samples and data, edited manuscript	sde26@medschl.cam.ac.uk	95	1
94	Christoph		Engel	MD	Institute for Medical Informatics, Statistics and Epidemiology, University of Leipzig, Leipzig, Germany	contributed samples and data, edited manuscript	christoph.engel@imise.uni-leipzig.de	96	1
95	Mikael		Eriksson	PhD	Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden	contributed samples and data, edited manuscript	mikael.eriksson@ki.se	97	1
96	Peter	A	Fasching	MD	University Breast Center Franconia, Department of Gynecology and Obstetrics, University Hospital Erlangen, Erlangen, Germany; David Geffen School of Medicine, Department of Medicine Division of Hematology and Oncology, University of California at Los Angeles, CA, USA	contributed samples and data, edited manuscript	peter.fasching@uk-erlangen.de	98	1
97	Lidia		Feliubadalo	PhD	Molecular Diagnostic Unit, Hereditary Cancer Program, IDIBELL-Catalan Institute of Oncology, Barcelona, Spain	contributed samples and data, edited manuscript	lfeliubadalo@iconcologia.net	99	1
98	Jonine		Figueroa	PhD	Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD, USA	contributed samples and data, edited manuscript	figueroaj@mail.nih.gov	100	1
99	Dieter		Flesch-Janys	PhD	Department of Cancer Epidemiology/Clinical Cancer Registry and Institute for Medical Biometrics and Epidemiology, University Clinic Hamburg-Eppendorf, Hamburg, Germany	contributed samples and data, edited manuscript	flesch@uke.de	69	1
100	Olivia		Fletcher	PhD	Breakthrough Breast Cancer Research Centre, Division of Breast Cancer Research, The Institute of Cancer Research, London, UK	contributed samples and data, edited manuscript	Olivia.fletcher@icr.ac.uk	101	1
101	Annette		Fontaine	MD	Clinical Cancer Genetics, City of Hope, Duarte, CA, USA; New Mexico Cancer Center, Albuquerque, NM, USA	contributed samples and data, edited manuscript	afontaine@nmohc.com	102	3
102	Stefano		Fortuzzi	PhD	Fondazione Istituto FIRC di Oncologia Molecolare (IFOM), Milan, Italy; Cogentech Cancer Genetic Test Laboratory, Milan, Italy	contributed samples and data, edited manuscript	stefano.fortuzzi@ifom.eu	103	1
103	Florentia		Fostira	PhD	Molecular Diagnostics Laboratory, Institute of Nuclear & Radiological Sciences & Technology, Energy & Safety, National Centre for Scientific Research Demokritos, Aghia Paraskevi Attikis, Athens, Greece	contributed samples and data, edited manuscript	florentia@rrp.demokritos.gr	104	1
104	Brooke	L	Fridley	PhD	Kansas IDeA Network of Biomedical Research Excellence Bioinformatics Core, The University of Kansas Cancer Center, Kansas City, KS, USA	contributed samples and data, edited manuscript	bfridley@kumc.edu	105	1
105	Tara		Friebel	MPH	University of Pennsylvania, Philadelphia, PA, USA	contributed samples and data, edited manuscript	tfriebel@mail.med.upenn.edu	106	1

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106	Eitan		Friedman	MD	The Susanne Levy Gertner Oncogenetics Unit, Sheba Medical Center, Tel-Hashomer, Israel; Institute of Oncology, Sheba Medical Center, Tel-Hashomer, Israel	contributed samples and data, edited manuscript	feitan@post.tau.ac.il	107	2
107	Grace		Friel	MS	Department of Cancer Prevention and Control, Roswell Park Cancer Institute, Buffalo, NY, USA	contributed samples and data, edited manuscript	Grace.Friel@roswellpark.org	108	1
108	Debra		Frost	ONC	Centre for Cancer Genetic Epidemiology, Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK	contributed samples and data, edited manuscript	djsf2@medschl.cam.ac.uk	109	1
109	Judy		Garber	MD	Center for Cancer Genetics and Prevention, Dana-Farber Cancer Institute, Boston, MA, USA	contributed samples and data, edited manuscript	Judy_Garber@dfci.harvard.edu	110	1
110	Montserrat		García-Closas	PhD	Breakthrough Breast Cancer Research Centre, Division of Breast Cancer Research, The Institute of Cancer Research, London, UK	contributed samples and data, edited manuscript	Montse.GarciaClosas@icr.ac.uk	111	1
111	Simon	A	Gayther	PhD	Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA	contributed samples and data, edited manuscript	gayther@usc.edu	112	1
112			GEMO Study Collaborators		GEMO Study : National Cancer Genetics Network, UNICANCER Genetic Group, France	contributed samples and data	contributed samples and data, edited manuscript	113	1
113			GENICA Network		Dr. Margarete Fischer-Bosch-Institute of Clinical Pharmacology, Stuttgart, Germany; University of Tübingen, Tübingen, Germany; German Cancer Consortium (DKTK) and German Cancer Research Center (DKFZ), Heidelberg, Germany; Institute for Prevention and Occupational Medicine of the German Social Accident Insurance, Institute of the Ruhr-Universität Bochum (IPA), Bochum, Germany; Department of Internal Medicine, Evangelische Kliniken Bonn gGmbH, Johanniter Krankenhaus, Bonn, Germany; Institute of Pathology, Medical Faculty of the University of Bonn, Bonn, Germany; Institute of Occupational Medicine and Maritime Medicine, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; Molecular Genetics of Breast Cancer, German Cancer Research Center (DKFZ), Heidelberg, Germany	contributed samples and data, edited manuscript	hiltrud.brauch@ikp-stuttgart.de	114	1
114	Aleksandra		Gentry-Maharaj	PhD	Gynaecological Cancer Research Centre, Department of Women's Cancer, Institute for Women's Health, UCL, London, UK	contributed samples and data, edited manuscript	a.gentry-maharaj@ucl.ac.uk	115	1
115	Anne-Marie		Gerdes	MD	Department of Clinical Genetics, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark	contributed samples and data, edited manuscript	anne-marie.gerdes@regionh.dk	116	1

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116	Graham	G	Giles	PhD	Centre for Epidemiology and Biostatistics, School of Population and Global Health, University of Melbourne, Melbourne, VIC, Australia; Cancer Epidemiology Centre, Cancer Council Victoria, Melbourne, VIC, Australia; Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, VIC, Australia	contributed samples and data, edited manuscript	Graham.Giles@cancervic.org.au	117	1
117	Rosalind		Glasspool	PhD	Cancer Research UK Clinical Trials Unit, The Beatson West of Scotland Cancer Centre, Glasgow, UK	contributed samples and data, edited manuscript	ros.glasspool@ggc.scot.nhs.uk	118	1
118	Gord		Glendon	MS	Ontario Cancer Genetics Network, Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital, Toronto, ON, Canada	contributed samples and data, edited manuscript	gglendon@uhnresearch.ca	119	1
119	Andrew	K	Godwin	PhD	Department of Pathology and Laboratory Medicine, University of Kansas Medical Center, Kansas City, KS, USA	contributed samples and data, edited manuscript	agodwin@kumc.edu	120	1
120	Marc	T	Goodman	PhD	Samuel Oschin Comprehensive Cancer Institute, Cedars Sinai Medical Center, Los Angeles, CA, USA	provided funding and contributed samples and data, edited manuscript	marc.goodman@cshs.org	121	1
121	Martin		Gore	PhD	Gynecological Oncology Unit, The Royal Marsden Hospital, London, UK	contributed samples and data, edited manuscript	Martin.Gore@rmh.nhs.uk	122	1
122	Mark	H	Greene	MD	Clinical Genetics Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Rockville, MD, USA	contributed samples and data, edited manuscript	greenem@mail.nih.gov	123	1
123	Mervi		Grip	PhD	Department of Surgery, Oulu University Hospital, University of Oulu, Oulu, Finland	contributed samples and data, edited manuscript	mervi.grip@ppshp.fi	124	1
124	Jacek		Gronwald	MD	Department of Genetics and Pathology, Pomeranian Medical University, Szczecin, Poland	contributed samples and data, edited manuscript	jgron@sci.pum.edu.pl	125	1
125	Daphne		Gschwantler Kaulich	MD	Department of Obstetrics and Gynecology, Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria	contributed samples and data, edited manuscript	daphne.gschwantler-kaulich@meduniwien.ac.at	126	1
126	Pascal		Guénel	PhD	INSERM U1018, CESP (Center for Research in Epidemiology and Population Health), Environmental Epidemiology of Cancer, Villejuif, France; University Paris-Sud, UMRS 1018, Villejuif, France	contributed samples and data, edited manuscript	pascal.guenel@inserm.fr	127	1
127	Starr	R	Guzman	BS	Department of Health Sciences Research, Division of Epidemiology, Mayo Clinic, Rochester, MN, USA	contributed samples and data, edited manuscript	guzman.starr@mayo.edu	128	1
128	Lothar		Haeberle	PhD	University Breast Center Franconia, Department of Gynecology and Obstetrics, University Hospital Erlangen, Erlangen, Germany	contributed samples and data, edited manuscript	lothar.haeberle@uk-erlangen.de	129	1
129	Christopher	A	Haiman	PhD	Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA	contributed samples and data, edited manuscript	Christopher.Haiman@med.usc.edu	130	1
130	Per		Hall	PhD	Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden	contributed samples and data, edited manuscript	Per.Hall@ki.se	131	1
131	Sandra	L	Halverson	PhD	Division of Epidemiology, Department of Medicine, Vanderbilt Epidemiology Center, Vanderbilt-Ingram Cancer Center, Vanderbilt University School of Medicine, Nashville, TN, USA	contributed samples and data, edited manuscript	sandra.l.deming@vanderbilt.edu	132	1

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132	Ute		Hamann	PhD	Molecular Genetics of Breast Cancer, German Cancer Research Center (DKFZ), Heidelberg, Germany	contributed samples and data, edited manuscript	u.hamann@dkfz-heidelberg.de	133	1
133	Thomas	V O	Hansen	PhD	Center for Genomic Medicine, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark	contributed samples and data, edited manuscript	tvoh@rh.dk	134	1
134	Philipp		Harter	MD	Department of Gynecology and Gynecologic Oncology, Dr. Horst Schmidt Klinik Wiesbaden, Wiesbaden, Germany; Department of Gynecology and Gynecologic Oncology, Kliniken Essen-Mitte, Essen, Germany	contributed samples and data, edited manuscript	p.harter@gmx.de	135	1
135	Jaana	M	Hartikainen	PhD	Imaging Center, Department of Clinical Pathology, Kuopio University Hospital, Kuopio, Finland; School of Medicine, Institute of Clinical Medicine, Pathology and Forensic Medicine, Biocenter Kuopio, Cancer Center of Eastern Finland, University of Eastern Finland, Kuopio, Finland	contributed samples and data, edited manuscript	jaana.hartikainen@uef.fi	136	1
136	Sue		Healey	BS	Department of Genetics, QIMR Berghofer Medical Research Institute, Brisbane, Australia	contributed samples and data, edited manuscript	sueH@qimr.edu.au	137	1
137			HEBON		The Hereditary Breast and Ovarian Cancer Research Group Netherlands (HEBON),Coordinating Center: Netherlands Cancer Institute, Amsterdam, The Netherlands	contributed samples and data, edited manuscript	m.hooning@erasmusmc.nl	138	1
138	Alexander		Hein	PhD	University Hospital Erlangen, Department of Gynecology and Obstetrics, Friedrich-Alexander-University Erlangen-Nuremberg, Comprehensive Cancer Center, Erlangen, Germany	contributed samples and data, edited manuscript	alexander.hein@uk-erlangen.de	139	1
139	Florian		Heitz	MD	Department of Gynecology and Gynecologic Oncology, Dr. Horst Schmidt Klinik Wiesbaden, Wiesbaden, Germany; Department of Gynecology and Gynecologic Oncology, Kliniken Essen-Mitte, Essen, Germany	contributed samples and data, edited manuscript	florian.heitz@gmx.net	140	1
140	Brian	E	Henderson	MD	Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA	contributed samples and data, edited manuscript	Behender@usc.edu	141	1
141	Josef		Herzog	BS	Clinical Cancer Genetics, City of Hope, Duarte, CA, USA	contributed samples and data, edited manuscript	jherzog@coh.org	142	1
142	Michelle	A T	Hildebrandt	PhD	Department of Epidemiology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA	contributed samples and data, edited manuscript	mhildebr@mdanderson.org	143	1
143	Claus	K	Høgdall	PhD	Department of Gynecology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark	contributed samples and data, edited manuscript	hogdall@rh.dk	144	1
144	Estrid		Høgdall	PhD	Virus, Lifestyle and Genes, Danish Cancer Society Research Center, Copenhagen, Denmark; Molecular Unit, Department of Pathology, Herlev Hospital, University of Copenhagen, Copenhagen, Denmark	contributed samples and data, edited manuscript	hogdall@dadlnet.dk	145	1
145	Frans	B L	Hogervorst	PhD	Netherlands Cancer Institute, Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands	contributed samples and data, edited manuscript	f.hogervorst@nki.nl	146	1

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146	John	L	Hopper	PhD	Centre for Epidemiology and Biostatistics, School of Population and Global Health, University of Melbourne, Melbourne, VIC, Australia	contributed samples and data, edited manuscript	j.hopper@unimelb.edu.au	147	1
147	Keith		Humphreys	PhD	Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden	contributed samples and data, edited manuscript	Keith.Humphreys@ki.se	148	1
148	Tomasz		Huzarski	PhD	Department of Genetics and Pathology, Pomeranian Medical University, Szczecin, Poland	contributed samples and data, edited manuscript	huzarski@pum.edu.pl	149	1
149	Evgeny	N	Imyanitov	PhD	N.N. Petrov Institute of Oncology, St. Petersburg, Russia	contributed samples and data, edited manuscript	evgeny@imyanitov.spb.ru	150	1
150	Claudine		Isaacs	MD	Lombardi Comprehensive Cancer Center, Georgetown University, Washington, DC, USA	contributed samples and data, edited manuscript	isaacsc@georgetown.edu	151	1
151	Anna		Jakubowska	PhD	Department of Genetics and Pathology, Pomeranian Medical University, Szczecin, Poland	contributed samples and data, edited manuscript	aniaj@sci.pam.szczecin.pl	152	1
152	Ramunas		Janavicius	MD	Vilnius University Hospital Santariskiu Clinics, Hematology, Oncology and Transfusion Medicine Center, Department of Molecular and Regenerative Medicine; State Research Centre Institute for Innovative Medicine, Vilnius, Lithuania	contributed samples and data, edited manuscript	Ramunas.Janavicius@santa.lt	153	2
153	Katarzyna		Jaworska	PhD	Department of Genetics and Pathology, Pomeranian Medical University, Szczecin, Poland; Postgraduate School of Molecular Medicine, Warsaw Medical University, Warsaw, Poland	contributed samples and data, edited manuscript	ka_jaworska@wp.pl	154	1
154	Allan		Jensen	PhD	Virus, Lifestyle and Genes, Danish Cancer Society Research Center, Copenhagen, Denmark	contributed samples and data, edited manuscript	allan@cancer.dk	155	1
155	Uffe Birk		Jensen	PhD	Department of Clinical Genetics, Aarhus University Hospital, Aarhus, Denmark	contributed samples and data, edited manuscript	uffejens@rm.dk	156	1
156	Nichola		Johnson	PhD	Breakthrough Breast Cancer Research Centre, Division of Breast Cancer Research, The Institute of Cancer Research, London, UK	contributed samples and data, edited manuscript	Nichola.johnson@icr.ac.uk	157	1
157	Arja		Jukkola-Vuorinen	PhD	Department of Oncology, Oulu University Hospital, University of Oulu, Oulu, Finland	contributed samples and data, edited manuscript	arja.jukkola-vuorinen@ppshp.fi	158	1
158	Maria		Kabisch	PhD	Molecular Genetics of Breast Cancer, German Cancer Research Center (DKFZ), Heidelberg, Germany	contributed samples and data, edited manuscript	m.kabisch@dkfz.de	159	1
159	Beth	Y	Karlan	MD	Women's Cancer Program, Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, CA, USA	contributed samples and data, edited manuscript	beth.karlan@cshs.org	160	1
160	Vesa		Kataja	PhD	School of Medicine, Institute of Clinical Medicine, Pathology and Forensic Medicine, Biocenter Kuopio, Cancer Center of Eastern Finland, University of Eastern Finland, Kuopio, Finland; Jyväskylä Central Hospital, Jyväskylä, Finland	contributed samples and data, edited manuscript	vesa.kataja@ksshp.fi	161	1
161	Noah		Kauff	MD	Clinical Genetics Research Laboratory, Memorial Sloan-Kettering Cancer Center, New York, NY, USA	contributed samples and data, edited manuscript	kauffn@mskcc.org	162	1
162	KConFab		KConFab Investigators		kConFab: Kathleen Cuningham Consortium for Research into Familial Breast Cancer – Peter MacCallum Cancer Center, Melbourne, Australia	contributed samples and data, edited manuscript	heather.thorne@petermac.org	163	1

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163	Linda	E	Kelemen	PhD	Department of Population Health Research, Alberta Health Services-Cancer Care, Calgary, Alberta, Canada; Department of Medical Genetics, University of Calgary, Calgary, Alberta, Canada; Department of Oncology, University of Calgary, Calgary, Alberta, Canada	provided funding and contributed samples and data, edited manuscript	LKelemen@post.harvard.edu	164	1
164	Michael	J	Kerin	PhD	School of Medicine, National University of Ireland, Galway, Ireland	contributed samples and data, edited manuscript	michael.kerin@nuigalway.ie	165	1
165	Lambertus	A	Kiemeney	PhD	Department for Health Evidence, Radboud University Medical Centre, Nijmegen, Netherlands; Department of Urology, Radboud University Medical Centre, Nijmegen, Netherlands	contributed samples and data, edited manuscript	bart.kiemeney@radboudumc.nl	166	1
166	Susanne	K	Kjaer	PhD	Department of Gynecology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark; Virus, Lifestyle and Genes, Danish Cancer Society Research Center, Copenhagen, Denmark	contributed samples and data, edited manuscript	susanne@cancer.dk	167	1
167	Julia	A	Knight	PhD	Division of Epidemiology, Dalla Lana School of Public Health, University of Toronto, Toronto, ON, Canada; Prosserman Centre for Health Research, Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital, Toronto, ON, Canada	contributed samples and data, edited manuscript	knight@lunenfeld.ca	168	1
168	Jacoba	P	Knol-Bout	MS	Department of Epidemiology, Netherlands Cancer Institute, Amsterdam, The Netherlands	contributed samples and data, edited manuscript	cora.knol@gmail.com	169	1
169	Irene		Konstantopoulou	PhD	Molecular Diagnostics Laboratory, Institute of Nuclear & Radiological Sciences & Technology, Energy & Safety, National Centre for Scientific Research Demokritos, Aghia Paraskevi Attikis, Athens, Greece	contributed samples and data, edited manuscript	reena@rrp.demokritos.gr	170	1
170	Veli-Matti		Kosma	PhD	Imaging Center, Department of Clinical Pathology, Kuopio University Hospital, Kuopio, Finland; School of Medicine, Institute of Clinical Medicine, Pathology and Forensic Medicine, Biocenter Kuopio, Cancer Center of Eastern Finland, University of Eastern Finland, Kuopio, Finland	contributed samples and data, edited manuscript	veli-matti.kosma@uef.fi	171	1
171	Camilla		Krakstad	PhD	Department of Gynecology and Obstetrics, Haukeland University Hospital, Bergen, Norway; Department of Clinical Science, University of Bergen, Bergen, Norway	contributed samples and data, edited manuscript	camilla.krakstad@med.uib.no	172	1
172	Vessela		Kristensen	PhD	Department of Genetics, Institute for Cancer Research, Oslo University Hospital, Radiumhospitalet, Oslo, Norway; Faculty of Medicine (Faculty Division Ahus), Universitetet i Oslo, Norway	contributed samples and data, edited manuscript	Vessela.N.Kristensen@rr-research.no	173	2
173	Karoline	B	Kuchenbaecker	MS	Centre for Cancer Genetic Epidemiology, Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK	contributed samples and data, edited manuscript	karoline@srl.cam.ac.uk	174	2
174	Jolanta		Kupryjanczyk	MD, PhD	Department of Pathology and Laboratory Diagnostics the Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Warsaw, Poland	contributed samples and data, edited manuscript	jkupry@coi.waw.pl	175	1

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175	Yael		Laitman	MS	The Susanne Levy Gertner Oncogenetics Unit, Sheba Medical Center, Tel-Hashomer, Israel; Institute of Oncology, Sheba Medical Center, Tel-Hashomer, Israel	contributed samples and data, edited manuscript	yael.laitman@gmail.com; yael.laitman@sheba.health.gov.il	176	1
176	Diether		Lambrechts	PhD	Laboratory for Translational Genetics, Department of Oncology, University of Leuven, Belgium; Vesalius Research Center (VRC), VIB, Leuven, Belgium	contributed samples and data, edited manuscript	Diether.Lambrechts@med.kuleuven.be	177	1
177	Sandrina		Lambrechts	PhD	Division of Gynecologic Oncology , Department of Obstetrics and Gynaecology, University Hospitals Leuven, Leuven, Belgium; Leuven Cancer Institute, University Hospitals Leuven, Leuven, Belgium	contributed samples and data, edited manuscript	Sandrina.Lambrechts@uzleuven.be	178	2
178	Melissa	C	Larson	MS	Department of Health Sciences Research, Division of Biomedical Statistics and Informatics, Mayo Clinic, Rochester, MN, USA	contributed samples and data, edited manuscript	melissa.larson@mayo.edu	179	1
179	Adriana		Lasa	PhD	Genetic and Molecular Epidemiology Group, Human Cancer Genetics Program, Spanish National Cancer Research Centre (CNIO), Madrid, Spain	contributed samples and data, edited manuscript	ALasa@santpau.cat	180	4
180	Pierre		Laurent-Puig	PhD	Université Paris Sorbonne Cité, UMR-S775 Inserm, Paris, France	contributed samples and data, edited manuscript	pierre.laurent-puig@parisdescartes.fr	181	1
181	Conxi		Lazaro	PhD	Molecular Diagnostic Unit, Hereditary Cancer Program, IDIBELL-Catalan Institute of Oncology, Barcelona, Spain	contributed samples and data, edited manuscript	clazaro@iconcologia.net	182	1
182	Nhu	D	Le	PhD	Cancer Control Research, BC Cancer Agency, Vancouver, BC, Canada	contributed samples and data, edited manuscript	nle@bccrc.ca	183	1
183	Loic		Le Marchand	PhD	Cancer Epidemiology Program, University of Hawaii Cancer Center, Honolulu, HI, USA	contributed samples and data, edited manuscript	loic@crch.hawaii.edu	184	1
184	Arto		Leminen	PhD	Department of Obstetrics and Gynecology, Helsinki University Central Hospital, University of Helsinki, Helsinki, Finland	contributed samples and data, edited manuscript	arto.leminen@hus.fi	185	1
185	Jenny		Lester	MPH	Women's Cancer Program, Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, CA, USA	contributed samples and data, edited manuscript	jenny.lester@cshs.org	186	1
186	Douglas	A	Levine	MD	Gynecology Service, Department of Surgery, Memorial Sloan-Kettering Cancer Center, New York, NY, USA	contributed samples and data, edited manuscript	levine2@MSKCC.ORG	187	1
187	Jingmei		Li	PhD	Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden	contributed samples and data, edited manuscript	jingmei@gmail.com	188	1
188	Dong		Liang	PhD	College of Pharmacy and Health Sciences, Texas Southern University, Houston, TX, USA	provided funding and contributed samples and data, edited manuscript	Liang_DX@tsu.edu	189	1
189	Annika		Lindblom	PhD	Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden	contributed samples and data, edited manuscript	Annika.Lindblom@ki.se	190	4
190	Noralane		Lindor	MD	Center for Individualized Medicine, Mayo Clinic, Scottsdale, AZ, USA	contributed samples and data, edited manuscript	lindor.noralane@mayo.edu	191	1
191	Jolanta		Lissowska	PhD	Department of Cancer Epidemiology and Prevention, M. Sklodowska-Curie Memorial Cancer Center & Institute of Oncology, Warsaw, Poland	contributed samples and data, edited manuscript	lissowsj@coi.waw.pl	192	1

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192	Jirong		Long	PhD	Division of Epidemiology, Department of Medicine, Vanderbilt Epidemiology Center, Vanderbilt-Ingram Cancer Center, Vanderbilt University School of Medicine, Nashville, TN, USA	contributed samples and data, edited manuscript	jirong.long@vanderbilt.edu	194	1
193	Karen	H	Lu	MD	Department of Gynecologic Oncology, University of Texas MD Anderson Cancer Center, Houston, TX, USA	contributed samples and data, edited manuscript	khlu@mdanderson.org	195	1
194	Jan		Lubinski	MD	Department of Genetics and Pathology, Pomeranian Medical University, Szczecin, Poland	contributed samples and data, edited manuscript	lubinski@sci.pam.szczecin.pl	196	1
195	Lene		Lundvall	PhD	Department of Gynecology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark	contributed samples and data, edited manuscript	lundvall@rh.dk	197	1
196	Galina		Lurie	PhD	Cancer Epidemiology Program, University of Hawaii Cancer Center, Honolulu, HI, USA	contributed samples and data, edited manuscript	galina9@yahoo.com	198	1
197	Phuong	L	Mai	MD	Clinical Genetics Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Rockville, MD, USA	contributed samples and data, edited manuscript	maip@mail.nih.gov	199	1
198	Arto		Mannermaa	PhD	Imaging Center, Department of Clinical Pathology, Kuopio University Hospital, Kuopio, Finland; School of Medicine, Institute of Clinical Medicine, Pathology and Forensic Medicine, Biocenter Kuopio, Cancer Center of Eastern Finland, University of Eastern Finland, Kuopio, Finland	contributed samples and data, edited manuscript	arto.mannermaa@uef.fi	200	1
199	Sara		Margolin	PhD	Department of Oncology and Pathology, Karolinska Institutet, Stockholm, Sweden	contributed samples and data, edited manuscript	Sara.Margolin@karolinska.se	201	1
200	Frederique		Mariette	PhD	Fondazione Istituto FIRC di Oncologia Molecolare (IFOM), Milan, Italy; Cogentech Cancer Genetic Test Laboratory, Milan, Italy	contributed samples and data, edited manuscript	frederique.mariette@ifom.eu	202	1
201	Frederik		Marme	PhD	Department of Obstetrics and Gynecology, University of Heidelberg, Heidelberg, Germany; National Center for Tumor Diseases, University of Heidelberg, Heidelberg, Germany	contributed samples and data, edited manuscript	frederikmarme@gmail.com	203	4
202	John	W M	Martens	PhD	Department of Medical Oncology, Erasmus MC Cancer Institute, Rotterdam, The Netherlands	contributed samples and data, edited manuscript	j.martens@erasmusmc.nl	204	1
203	Leon	F A G	Massuger	PhD	Department of Gynecology, Radboud University Medical Centre, Nijmegen, Netherlands	contributed samples and data, edited manuscript	leon.massuger@radboudumc.nl	205	1
204	Christine		Maugard	MD	Laboratoire de Diagnostic Génétique et Service d'Onco-hématologie, Hopitaux Universitaire de Strasbourg, CHRU Nouvel Hôpital Civil, Strasbourg, France	contributed samples and data, edited manuscript	christinemaugard@gmail.com	206	4
205	Sylvie		Mazoyer	PhD	INSERM U1052, CNRS UMR5286, Université Lyon 1, Centre de Recherche en Cancérologie de Lyon, Lyon, France	contributed samples and data, edited manuscript	sylvie.mazoyer@lyon.unicancer.fr	207	1
206	Lesley		McGuffog	BS	Centre for Cancer Genetic Epidemiology, Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK	contributed samples and data, edited manuscript	lesley@srl.cam.ac.uk	208	1
207	Valerie		McGuire	PhD	Department of Health Research and Policy, Stanford University School of Medicine, Stanford, CA, USA	contributed samples and data, edited manuscript	vmcguire@stanford.edu	209	1

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208	Catriona		McLean	PhD	Anatomical Pathology, The Alfred Hospital, Melbourne, Australia	contributed samples and data, edited manuscript	C.McLean@alfred.org.au	210	1
209	Iain		McNeish	MD	Institute of Cancer Sciences, University of Glasgow, Wolfson Wohl Cancer Research Centre, Beatson Institute for Cancer Research, Glasgow, UK	contributed samples and data, edited manuscript	iain.mcneish@glasgow.ac.uk	211	1
210	Alfons		Meindl	PhD	Department of Gynecology and Obstetrics, Division of Tumor Genetics, Klinikum rechts der Isar, Technical University Munich, Munich, Germany	contributed samples and data, edited manuscript	Alfons.Meindl@lrz.tu-muenchen.de	212	1
211	Florence		Menegaux	PhD	INSERM U1018, CESP (Center for Research in Epidemiology and Population Health), Environmental Epidemiology of Cancer, Villejuif, France; University Paris-Sud, UMRS 1018, Villejuif, France	contributed samples and data, edited manuscript	florence.menegaux@inserm.fr	213	1
212	Primitiva		Menéndez	PhD	Servicio de Anatomía Patológica, Hospital Monte Naranco, Oviedo, Spain	contributed samples and data, edited manuscript	tiva@hca.es	214	1
213	Janusz		Menkiszak	PhD	Department of Surgical Gynecology and Gynecological Oncology of Adults and Adolescents, Pomeranian Medical University, Szczecin, Poland	contributed samples and data, edited manuscript	nbz@list.pl	215	1
214	Usha		Menon	PhD	Gynaecological Cancer Research Centre, Department of Women's Cancer, Institute for Women's Health, UCL, London, UK	contributed samples and data, edited manuscript	u.menon@ucl.ac.uk	216	1
215	Arjen	R	Mensenkamp	PhD	Department of Human Genetics, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands	contributed samples and data, edited manuscript	a.mensenkamp@gen.umcn.nl	217	1
216	Nicola		Miller	PhD	School of Medicine, National University of Ireland, Galway, Ireland	contributed samples and data, edited manuscript	nicola.miller@nuigalway.ie	218	1
217	Roger	L	Milne	PhD	Centre for Epidemiology and Biostatistics, School of Population and Global Health, University of Melbourne, Melbourne, VIC, Australia; Cancer Epidemiology Centre, Cancer Council Victoria, Melbourne, VIC, Australia	contributed samples and data, edited manuscript	roger.milne@cancervic.org.au	219	1
218	Francesmary		Modugno	PhD	Department of Epidemiology, University of Pittsburgh Graduate School of Public Health, Pittsburgh, PA, USA; Department of Obstetrics, Gynecology and Reproductive Sciences, Division of Gynecologic Oncology, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA; Womens Cancer Research Program, Magee-Women's Research Institute and University of Pittsburgh Cancer Institute, Pittsburgh, PA, USA	contributed samples and data, edited manuscript	fm@cs.cmu.edu	220	1
219	Marco		Montagna	PhD	Immunology and Molecular Oncology Unit, Veneto Institute of Oncology IOV-IRCCS, Padua, Italy	contributed samples and data, edited manuscript	montagna@unipd.it	221	1
220	Kirsten	B	Moysich	PhD	Department of Cancer Prevention and Control, Roswell Park Cancer Institute, Buffalo, NY, USA	provided funding and contributed samples and data, edited manuscript	kirsten.moysich@roswellpark.org	222	1
221	Heiko		Müller	PhD	Division of Clinical Epidemiology and Aging Research, German Cancer Research Center, Heidelberg, Germany	contributed samples and data, edited manuscript	h1.mueller@web.de	223	2

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222	Anna Marie		Mulligan	MD	Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, ON, Canada; Laboratory Medicine Program, University Health Network, Toronto, ON, Canada	contributed samples and data, edited manuscript	AnnaMarie.Mulligan@uhn.ca	224	1
223	Taru	A	Muranen	MS	Department of Obstetrics and Gynecology, Helsinki University Central Hospital, University of Helsinki, Helsinki, Finland	contributed samples and data, edited manuscript	taru.a.muranen@helsinki.fi	225	1
224	Steven	A	Narod	MD	Women's College Research Institute, University of Toronto, Toronto, Ontario, Canada	contributed samples and data, edited manuscript	Steven.Narod@wchospital.ca	226	1
225	Katherine	L	Nathanson	MD	Department of Medicine, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA; Basser Research Centre, Abramson Cancer Center, The University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA	contributed samples and data, edited manuscript	knathans@exchange.upenn.edu	227	1
226	Roberta	B	Ness	PhD	The University of Texas School of Public Health, Houston, TX, USA	contributed samples and data, edited manuscript	roberta.b.ness@uth.tmc.edu	228	1
227	Susan	L	Neuhausen	PhD	Department of Population Sciences, Beckman Research Institute of City of Hope, Duarte, CA, USA	contributed samples and data, edited manuscript	sneuhausen@coh.org	229	1
228	Heli		Nevanlinna	PhD	Department of Obstetrics and Gynecology, Helsinki University Central Hospital, University of Helsinki, Helsinki, Finland	contributed samples and data, edited manuscript	Heli.Nevanlinna@hus.fi	230	1
229	Patrick		Neven	PhD	Multidisciplinary Breast Center, University Hospital Leuven, University of Leuven, Belgium	contributed samples and data, edited manuscript	Patrick.Neven@uzleuven.be	231	1
230	Finn	C	Nielsen	MD	Center for Genomic Medicine, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark	contributed samples and data, edited manuscript	fcn@rh.dk	232	1
231	Sune	F	Nielsen	PhD	Copenhagen General Population Study, Herlev Hospital, Copenhagen University Hospital, University of Copenhagen, Copenhagen, Denmark; Department of Clinical Biochemistry, Herlev Hospital, Copenhagen University Hospital, University of Copenhagen, Copenhagen, Denmark	contributed samples and data, edited manuscript	sune.fallgaard.nielsen@regionh.dk	233	1
232	Børge	G	Nordestgaard	PhD	Copenhagen General Population Study, Herlev Hospital, Copenhagen University Hospital, University of Copenhagen, Copenhagen, Denmark; Department of Clinical Biochemistry, Herlev Hospital, Copenhagen University Hospital, University of Copenhagen, Copenhagen, Denmark	contributed samples and data, edited manuscript	boerge.nordestgaard@regionh.dk	234	1
233	Robert	L	Nussbaum	MD	Department of Medicine and Institute for Human Genetics, University of California, San Francisco, CA, USA	contributed samples and data, edited manuscript	nussbaumr@humgen.ucsf.edu	235	1
234	Kunle		Odunsi	MD	Department of Cancer Prevention and Control, Roswell Park Cancer Institute, Buffalo, NY, USA	contributed samples and data, edited manuscript	Kunle.Odunsi@roswellpark.org	236	1
235	Kenneth		Offit	MD	Clinical Genetics Service, Memorial Sloan-Kettering Cancer Center, New York, NY, USA	provided funding and contributed samples and data, edited manuscript	offitk@mskcc.org	237	1
236	Edith		Olah	PhD	Department of Molecular Genetics, National Institute of Oncology, Budapest, Hungary	contributed samples and data, edited manuscript	e.olah@oncol.hu	238	1

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237	Olufunmilayo	I	Olopade	MD	Center for Clinical Cancer Genetics and Global Health, University of Chicago Medical Center, Chicago, IL, USA	contributed samples and data, edited manuscript	folopade@medicine.bsd.uchicago.edu	239	1
238	Janet	E	Olson	PhD	Department of Health Sciences Research, Division of Epidemiology, Mayo Clinic, Rochester, MN, USA	contributed samples and data, edited manuscript	olsonj@mayo.edu	240	1
239	Sara	H	Olson	PhD	Department of Epidemiology and Biostatistics, Memorial Sloan-Kettering Cancer Center, New York, NY, USA	contributed samples and data, edited manuscript	olsons@mskcc.org	241	1
240	Jan	C	Oosterwijk	PhD	University of Groningen, University Medical Center, Department of Genetics, Groningen, The Netherlands	contributed samples and data, edited manuscript	j.c.oosterwijk@medgen.umcg.nl	242	1
241	Irene		Orlow	PhD	Department of Epidemiology and Biostatistics, Memorial Sloan-Kettering Cancer Center, New York, NY, USA	contributed samples and data, edited manuscript	orlowi@mskcc.org	243	1
242	Nick		Orr	PhD	Breakthrough Breast Cancer Research Centre, Division of Breast Cancer Research, The Institute of Cancer Research, London, UK	contributed samples and data, edited manuscript	Nicholas.Orr@icr.ac.uk	244	1
243	Sandra		Orsulic	PhD	Women's Cancer Program, Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, CA, USA	contributed samples and data, edited manuscript	sandra.orsulic@cshs.org	245	1
244	Ana		Osorio	PhD	Human Genetics Group, Spanish National Cancer Research Centre (CNIO), Madrid, Spain; Biomedical Network on Rare Diseases (CIBERER), Madrid, Spain; Genetic and Molecular Epidemiology Group, Human Cancer Genetics Program, Spanish National Cancer Research Centre (CNIO), Madrid, Spain	contributed samples and data, edited manuscript	aosorio@cnio.es	246	1
245	Laura		Ottini	MD	Department of Molecular Medicine, Sapienza University, Rome, Italy	contributed samples and data, edited manuscript	laura.ottini@uniroma1.it	247	1
246	James		Paul	PhD	Cancer Research UK Clinical Trials Unit, The Beatson West of Scotland Cancer Centre, Glasgow, UK	contributed samples and data, edited manuscript	James.Paul@glasgow.ac.uk	250	1
247	Celeste	L	Pearce	PhD	Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA	contributed samples and data, edited manuscript	pearce_l@med.usc.edu	251	1
248	Inge Sokilde		Pedersen	PhD	Section of Molecular Diagnostics, Department of Clinical Biochemistry, Aalborg University Hospital, Aalborg, Denmark	contributed samples and data, edited manuscript	isp@rn.dk	252	1
249	Bernard		Peissel	MD	Unit of Medical Genetics, Department of Preventive and Predictive Medicine, Fondazione Istituto di Ricovero e Cura a Carattere Scientifico Istituto Nazionale Tumori (INT), Milan, Italy	contributed samples and data, edited manuscript	bernard.peissel@istitutotumori.mi.it	253	1
250	Tanja		Pejovic	PhD	Department of Obstetrics and Gynecology, Oregon Health and Science University, Portland, OR, USA; Knight Cancer Institute, Oregon Health and Science University, Portland, OR, USA	contributed samples and data, edited manuscript	pejovict@ohsu.edu	254	1
251	Liisa	M	Pelttari	PhD	Department of Obstetrics and Gynecology, Helsinki University Central Hospital, University of Helsinki, Helsinki, Finland	contributed samples and data, edited manuscript	liisa.pelttari@helsinki.fi	255	1

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252	Jo		Perkins	PhD	Centre for Cancer Genetic Epidemiology, Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK	contributed samples and data, edited manuscript	jp410@medschl.cam.ac.uk	256	2
253	Jenny		Permuth-Wey	PhD	Department of Cancer Epidemiology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA	contributed samples and data, edited manuscript	jenny.wey@moffitt.org	257	1
254	Paolo		Peterlongo	PhD	Fondazione Istituto FIRC di Oncologia Molecolare (IFOM), Milan, Italy	contributed samples and data, edited manuscript	paolo.peterlongo@ifom-ieo-campus.it	258	1
255	Julian		Peto	PhD	Non-Communicable Disease Epidemiology Department, London School of Hygiene and Tropical Medicine, London, UK	contributed samples and data, edited manuscript	Julian.Peto@lshtm.ac.uk	259	1
256	Catherine	M	Phelan	MD	Department of Cancer Epidemiology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA	provided funding and contributed samples and data, edited manuscript	Catherine.Phelan@moffitt.org	260	1
257	Kelly-Anne		Phillips	PhD	Centre for Epidemiology and Biostatistics, School of Population and Global Health, University of Melbourne, Melbourne, VIC, Australia; Sir Peter MacCallum Department of Oncology, The University of Melbourne, Australia; Division of Cancer Medicine, Peter MacCallum Cancer Centre, Melbourne, Australia; Department of Medicine, St Vincent's Hospital, The University of Melbourne, Victoria, Australia	contributed samples and data, edited manuscript	Kelly.Phillips@petermac.org	261	1
258	Marion		Piedmonte	MA	NRG Oncology Statistics and Data Management Center, Buffalo, NY, USA	contributed samples and data, edited manuscript	marion.piedmonte@gmail.com	262	1
259	Malcolm	C	Pike	PhD	Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA; Department of Epidemiology and Biostatistics, Memorial Sloan-Kettering Cancer Center, New York, NY, USA	contributed samples and data, edited manuscript	pikem@mskcc.org	263	1
260	Radka		Platte	BS	Centre for Cancer Genetic Epidemiology, Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK	contributed samples and data, edited manuscript	rp356@medschl.cam.ac.uk	264	1
261	Joanna		Plisiecka-Halasa	MD	Department of Pathology and Laboratory Diagnostics the Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Warsaw, Poland	contributed samples and data, edited manuscript	jopliha@coi.waw.pl	265	1
262	Elizabeth	M	Poole	PhD	Department of Epidemiology, Harvard School of Public Health, Boston, MA, USA; Channing Division of Network Medicine, Harvard Medical School and Brigham and Women's Hospital, Boston, MA, USA	contributed samples and data, edited manuscript	liz.poole@channing.harvard.edu	266	1
263	Bruce		Poppe	MD	Center for Medical Genetics, Ghent University, Ghent, Belgium	contributed samples and data, edited manuscript	Bruce.Poppe@UGent.be	267	1
264	Katri		Pylkäs	PhD	Laboratory of Cancer Genetics and Tumor Biology, Department of Clinical Genetics, University of Oulu, Oulu University Hospital, Oulu, Finland; Biocenter Oulu, University of Oulu, Oulu, Finland	contributed samples and data, edited manuscript	katri.pylkas@oulu.fi	268	1

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266	Susan	J	Ramus	PhD	Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA	contributed samples and data, edited manuscript	sramus@usc.edu	270	1
267	Timothy	R	Rebbeck	PhD	Basser Research Centre, Abramson Cancer Center, The University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA; Center for Clinical Epidemiology and Biostatistics, The University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA	contributed samples and data, edited manuscript	rebbeck@exchange.upenn.edu	271	1
268	Malcolm	W R	Reed	MD	Sheffield Cancer Research Centre, Department of Oncology, University of Sheffield, Sheffield, UK	contributed samples and data, edited manuscript	m.reed@bsms.ac.uk	272	4
269	Gad		Rennert	MD	Clalit National Israeli Cancer Control Center, Haifa, Israel; Department of Community Medicine and Epidemiology, Carmel Medical Center and B. Rappaport Faculty of Medicine, Technion, Haifa, Israel	contributed samples and data, edited manuscript	rennert@tx.technion.ac.il	273	1
270	Harvey	A	Risch	PhD	Department of Chronic Disease Epidemiology, Yale School of Public Health, New Haven, CT, USA	contributed samples and data, edited manuscript	harvey.risch@yale.edu	274	1
271	Mark		Robson	MD	Clinical Genetics Service, Memorial Sloan-Kettering Cancer Center, New York, NY, USA	contributed samples and data, edited manuscript	robsonm@mskcc.org	275	1
272	Gustavo	C	Rodriguez	MD	NorthShore University Health System, University of Chicago, Evanston, IL, USA	contributed samples and data, edited manuscript	grodriguez@northshore.org	276	1
273	Atocha		Romero	PhD	Molecular Oncology Laboratory, Hospital Clinico San Carlos, Madrid, Spain	contributed samples and data, edited manuscript	atocha10@hotmail.com	277	1
274	Mary Anne		Rossing	PhD	Department of Epidemiology, University of Washington, Seattle, WA, USA; Program in Epidemiology, Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA, USA	contributed samples and data, edited manuscript	mrossing@fhcrc.org	278	1
275	Joseph	H	Rothstein	PhD	Department of Health Research and Policy, Stanford University School of Medicine, Stanford, CA, USA	contributed samples and data, edited manuscript	joe.rothstein@stanford.edu	279	1
276	Anja		Rudolph	PhD	Division of Cancer Epidemiology, German Cancer Research Center (DKFZ), Heidelberg, Germany	contributed samples and data, edited manuscript	a.rudolph@dkfz.de	280	1
277	Ingo		Runnebaum	PhD	Department of Gynecology, Jena University Hospital, Jena, Germany	contributed samples and data, edited manuscript	INGO.RUNNEBAUM@med.uni-jena.de	281	1
278	Ritu		Salani	MD	Ohio State University, Columbus, OH, USA	contributed samples and data, edited manuscript	ritu.salani@osumc.edu	282	1
279	Helga	B	Salvesen	PhD	Department of Gynecology and Obstetrics, Haukeland University Hospital, Bergen, Norway; Department of Clinical Science, University of Bergen, Bergen, Norway	contributed samples and data, edited manuscript	helga.salvesen@uib.no	283	1
280	Elinor	J	Sawyer	PhD	Division of Cancer Studies, NIHR Comprehensive Biomedical Research Centre, Guy's & St. Thomas' NHS Foundation Trust in partnership with King's College London, London, UK	contributed samples and data, edited manuscript	Elinor.Sawyer@gstt.nhs.uk	284	1

Order	First	M	Last	Degree	Affiliation	Contribution	Email	CoI Form #	COI Batch
281	Joellen	M	Schildkraut	PhD	Department of Community and Family Medicine, Duke University Medical Center, Durham, NC, USA; Cancer Prevention, Detection and Control Research Program, Duke Cancer Institute, Durham, NC, USA	provided funding and contributed samples and data, edited manuscript	schil001@mc.duke.edu	285	1
282	Marjanka	K	Schmidt	PhD	Netherlands Cancer Institute, Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands	contributed samples and data, edited manuscript	mk.schmidt@nki.nl	286	1
283	Rita	K	Schmutzler	MD	Centre of Familial Breast and Ovarian Cancer, Department of Gynaecology and Obstetrics, University Hospital of Cologne, Cologne, Germany; Centre for Molecular Medicine Cologne (CMMC), University Hospital of Cologne, Cologne, Germany	contributed samples and data, edited manuscript	Rita.Schmutzler@uk-koeln.de	287	1
284	Andreas		Schneeweiss	PhD	Department of Obstetrics and Gynecology, University of Heidelberg, Heidelberg, Germany; National Center for Tumor Diseases, University of Heidelberg, Heidelberg, Germany	contributed samples and data, edited manuscript	Andreas.Schneeweiss@med.uni-heidelberg.de	288	1
285	Minouk	J	Schoemaker	PhD	Division of Genetics and Epidemiology, The Institute of Cancer Research, Sutton, Surrey, UK	contributed samples and data, edited manuscript	Minouk.schoemaker@icr.ac.uk	289	1
286	Michael	G	Schrauder	PhD	University Breast Center Franconia, Department of Gynecology and Obstetrics, University Hospital Erlangen, Erlangen, Germany	contributed samples and data, edited manuscript	michael.schrauder@uk-erlangen.de	290	1
287	Fredrick		Schumacher	PhD	Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA	contributed samples and data, edited manuscript	fschumac@usc.edu	291	1
288	Ira		Schwaab	MD	Institut für Humangenetik Wiesbaden, Wiesbaden, Germany	contributed samples and data, edited manuscript	iraschwaab@gmx.de	292	2
289	Giulietta		Scuvera	MD	Unit of Medical Genetics, Department of Preventive and Predictive Medicine, Fondazione Istituto di Ricovero e Cura a Carattere Scientifico Istituto Nazionale Tumori (INT), Milan, Italy	contributed samples and data, edited manuscript	giulietta.scuvera@istitutotumori.mi.it	293	1
290	Thomas	A	Sellers	PhD	Department of Cancer Epidemiology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA	provided funding and contributed samples and data, edited manuscript	Thomas.Sellers@moffitt.org	294	1
291	Gianluca		Severi	PhD	Centre for Epidemiology and Biostatistics, School of Population and Global Health, University of Melbourne, Melbourne, VIC, Australia; Cancer Epidemiology Centre, Cancer Council Victoria, Melbourne, VIC, Australia; Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, VIC, Australia	contributed samples and data, edited manuscript	Gianluca.severi@cancervic.org.au	295	1
292	Caroline	M	Seynaeve	PhD	Department of Medical Oncology, Erasmus MC Cancer Institute, Rotterdam, The Netherlands	contributed samples and data, edited manuscript	c.seynaeve@erasmusmc.nl	296	1
293	Mitul		Shah	PhD	Centre for Cancer Genetic Epidemiology, Department of Oncology, University of Cambridge, Cambridge, UK	contributed samples and data, edited manuscript	ms483@medschl.cam.ac.uk	297	1
294	Martha		Shrubsole	PhD	Division of Epidemiology, Department of Medicine, Vanderbilt Epidemiology Center, Vanderbilt-Ingram Cancer Center, Vanderbilt University School of Medicine, Nashville, TN, USA	contributed samples and data, edited manuscript	martha.shrubsole@vanderbilt.edu	298	1

Order	First	M	Last	Degree	Affiliation	Contribution	Email	CoI Form #	COI Batch
295	Nadeem		Siddiqui	PhD	Department of Gynecological Oncology, Glasgow Royal Infirmary, Glasgow, UK	contributed samples and data, edited manuscript	nadeem.siddiqui@ggc.scot.nhs.uk	299	1
296	Weiva		Sieh	PhD	Department of Health Research and Policy, Stanford University School of Medicine, Stanford, CA, USA	contributed samples and data, edited manuscript	wsieh@stanford.edu	300	1
297	Jacques		Simard	PhD	Centre Hospitalier Universitaire de Québec Research Center and Laval University, Quebec, Canada	contributed samples and data, edited manuscript	jacques.simard@crchul.ulaval.ca	301	1
298	Christian	F	Singer	MD	Department of Obstetrics and Gynecology, Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria	contributed samples and data, edited manuscript	christian.singer@meduniwien.ac.at	302	2
299	Olga	M	Sinilnikova	PhD	INSERM U1052, CNRS UMR5286, Université Lyon 1, Centre de Recherche en Cancérologie de Lyon, Lyon, France; Unité Mixte de Génétique Constitutionnelle des Cancers Fréquents, Hospices Civils de Lyon, Centre Léon Bérard, Lyon, France	contributed samples and data, edited manuscript	sylvie.mazoyer@lyon.unicancer.fr	303	1
300	Dominiek		Smeets	PhD	Laboratory for Translational Genetics, Department of Oncology, University of Leuven, Belgium; Vesalius Research Center (VRC), VIB, Leuven, Belgium	contributed samples and data, edited manuscript	Dominiek.Smeets@vib-kuleuven.be	304	1
301	Christof		Sohn	PhD	Department of Obstetrics and Gynecology, University of Heidelberg, Heidelberg, Germany	contributed samples and data, edited manuscript	Christof.Sohn@med.uni-heidelberg.de	305	1
302	Maria		Soller	MD	Department of Clinical Genetics, University and Regional Laboratories, Lund University Hospital, Lund, Sweden	contributed samples and data, edited manuscript	maria.soller@med.lu.se	306	1
303	Honglin		Song	PhD	Centre for Cancer Genetic Epidemiology, Department of Oncology, University of Cambridge, Cambridge, UK	contributed samples and data, edited manuscript	hs310@medschl.cam.ac.uk	307	1
304	Penny		Soucy	PhD	Centre Hospitalier Universitaire de Québec Research Center and Laval University, Quebec, Canada	contributed samples and data, edited manuscript	penny.soucy@crchul.ulaval.ca	308	1
305	Melissa	C	Southey	PhD	Genetic Epidemiology Laboratory, Department of Pathology, The University of Melbourne, Melbourne, Australia	contributed samples and data, edited manuscript	msouthey@unimelb.edu.au	309	1
306	Christa		Stegmaier	PhD	Saarland Cancer Registry, Saarbrücken, Germany	contributed samples and data, edited manuscript	krebsregister@gbe-ekr.saarland.de	310	1
307	Dominique		Stoppa-Lyonnet	MD	Institut Curie, Department of Tumour Biology, Paris, France; Institut Curie, INSERM U830, Paris, France; Université Paris Descartes, Sorbonne Paris Cité, France	contributed samples and data, edited manuscript	dominique.stoppa-lyonnet@curie.net	311	3
308	Lara		Sucheston	PhD	Department of Cancer Prevention and Control, Roswell Park Cancer Institute, Buffalo, NY, USA	contributed samples and data, edited manuscript	Lara.Sucheston@roswellpark.org	312	1
309			SWE-BRCA		Department of Oncology, Lund University, Lund, Sweden	contributed samples and data, edited manuscript	ake.borg@med.lu.se	313	1
310	Anthony		Swerdlow	PhD	Division of Genetics and Epidemiology, The Institute of Cancer Research, Sutton, Surrey, UK; Division of Breast Cancer Research, The Institute of Cancer Research, Sutton, Surrey, UK	contributed samples and data, edited manuscript	Anthony.Swerdlow@icr.ac.uk	314	1
311	Ingvild	L	Tangen	MD	Department of Gynecology and Obstetrics, Haukeland University Hospital, Bergen, Norway; Department of Clinical Science, University of Bergen, Bergen, Norway	contributed samples and data, edited manuscript	Ingvild.Tangen@k2.uib.no	316	1

Order	First	M	Last	Degree	Affiliation	Contribution	Email	CoI Form #	COI Batch
312	Muy-Kheng		Tea	MD	Department of Obstetrics and Gynecology, Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria	contributed samples and data, edited manuscript	muy-kheng.tea@meduniwien.ac.at	317	1
313	Manuel	R	Teixeira	MD	Department of Genetics, Portuguese Oncology Institute, Porto, Portugal; Biomedical Sciences Institute (ICBAS), Porto University, Porto, Portugal	contributed samples and data, edited manuscript	manuel.teixeira@ipoporto.min-saude.pt	318	1
314	Kathryn	L	Terry	PhD	Obstetrics and Gynecology Epidemiology Center, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA; Department of Epidemiology, Harvard School of Public Health, Boston, MA, USA	contributed samples and data, edited manuscript	kterry@partners.org	319	1
315	Mary Beth		Terry	PhD	Department of Epidemiology, Columbia University, New York, NY, USA	contributed samples and data, edited manuscript	mt146@columbia.edu	320	1
316	Mads		Thomassen	PhD	Department of Clinical Genetics, Odense University Hospital, Odense, Denmark	contributed samples and data, edited manuscript	mads.thomassen@rsyd.dk	321	1
317	Pamela	J	Thompson	PhD	Samuel Oschin Comprehensive Cancer Institute, Cedars Sinai Medical Center, Los Angeles, CA, USA	contributed samples and data, edited manuscript	Pamela.Thompson@cshs.org	322	1
318	Laima		Tihomirova	PhD	Latvian Biomedical Research and Study Centre, Riga, Latvia	contributed samples and data, edited manuscript	laima@biomed.lu.lv	323	1
319	Marc		Tischkowitz	MD	Program in Cancer Genetics, Departments of Human Genetics and Oncology, McGill University, Montreal, Quebec, Canada	contributed samples and data, edited manuscript	mdt33@medschl.cam.ac.uk	324	1
320	Amanda	Ewart	Toland	PhD	Divison of Human Cancer Genetics, Departments of Internal Medicine and Molecular Virology, Immunology and Medical Genetics, Comprehensive Cancer Center, The Ohio State University, Columbus, OH, USA	contributed samples and data, edited manuscript	amanda.toland@osumc.edu	325	1
321	Rob	A E M	Tollenaar	PhD	Department of Surgical Oncology, Leiden University Medical Center, Leiden, The Netherlands	contributed samples and data, edited manuscript	r.a.e.m.tollenaar@lumc.nl	326	1
322	Ian		Tomlinson	PhD	Welcome Trust Centre for Human Genetics, University of Oxford, UK; Oxford Biomedical Research Centre, University of Oxford, UK	contributed samples and data, edited manuscript	iant@well.ox.ac.uk	327	1
323	Diana		Torres	PhD	Molecular Genetics of Breast Cancer, German Cancer Research Center (DKFZ), Heidelberg, Germany	contributed samples and data, edited manuscript	dianatlopez@yahoo.com	328	1
324	Thérèse		Truong	PhD	INSERM U1018, CESP (Center for Research in Epidemiology and Population Health), Environmental Epidemiology of Cancer, Villejuif, France; University Paris-Sud, UMRS 1018, Villejuif, France	contributed samples and data, edited manuscript	therese.truong@inserm.fr	329	1
325	Helen		Tsimiklis	PhD	Genetic Epidemiology Laboratory, Department of Pathology, The University of Melbourne, Melbourne, Australia	contributed samples and data, edited manuscript	htsi@unimelb.edu.au	330	1
326	Nadine		Tung	MD	Department of Medical Oncology, Beth Israel Deaconess Medical Center, Boston, MA, USA	contributed samples and data, edited manuscript	ntung@bidmc.harvard.edu	331	1
327	Shelley	S	Tworoger	PhD	Department of Epidemiology, Harvard School of Public Health, Boston, MA, USA; Channing Division of Network Medicine, Harvard Medical School and Brigham and Women's Hospital, Boston, MA, USA	contributed samples and data, edited manuscript	nhsst@channing.harvard.edu	332	1
328	Jonathan	P	Tyrer	PhD	Centre for Cancer Genetic Epidemiology, Department of Oncology, University of Cambridge, Cambridge, UK	contributed samples and data, edited manuscript	jpt34@medschl.cam.ac.uk	333	1

Order	First	M	Last	Degree	Affiliation	Contribution	Email	CoI Form #	COI Batch
329	Celine	M	Vachon	PhD	Department of Health Sciences Research, Division of Epidemiology, Mayo Clinic, Rochester, MN, USA	contributed samples and data, edited manuscript	vachon.celine@mayo.edu	334	1
330	Laura	J	Van 't Veer	PhD	Netherlands Cancer Institute, Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands	contributed samples and data, edited manuscript	l.vt.veer@nki.nl	335	1
331	Anne	M	van Altena	PhD	Department of Gynecology, Radboud University Medical Centre, Nijmegen, Netherlands	contributed samples and data, edited manuscript	annevana@hotmail.com	336	1
332	C	J	Van Asperen	PhD	Department of Clinical Genetics, Leiden University Medical Center, Leiden, The Netherlands	contributed samples and data, edited manuscript	c.j.van_Asperen@lumc.nl	337	1
333	David		van den Berg	PhD	Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA	contributed samples and data, edited manuscript	dvandenb@usc.edu	338	1
334	Ans	M W	van den Ouweland	PhD	Department of Clinical Genetics, Erasmus University Medical Center, Rotterdam, The Netherlands	contributed samples and data, edited manuscript	a.vandenouweland@erasmusmc.nl	339	1
335	Helena	C	van Doorn	PhD	Department of Gynecology, Erasmus MC Cancer Institute, Rotterdam, The Netherlands	contributed samples and data, edited manuscript	h.vandoorn@erasmusmc.nl	340	1
336	Els		Van Nieuwenhuysen	PhD	Division of Gynecologic Oncology , Department of Obstetrics and Gynaecology, University Hospitals Leuven, Leuven, Belgium; Leuven Cancer Institute, University Hospitals Leuven, Leuven, Belgium	contributed samples and data, edited manuscript	Els.Vannieuwenhuysen@uzleuven.be	341	1
337	Elizabeth	J	van Rensburg	PhD	Department of Genetics, University of Pretoria, Pretoria, South Africa	contributed samples and data, edited manuscript	Lizette.vanrensburg@up.ac.za	342	1
338	Ignace		Vergote	PhD	Division of Gynecologic Oncology , Department of Obstetrics and Gynaecology, University Hospitals Leuven, Leuven, Belgium; Leuven Cancer Institute, University Hospitals Leuven, Leuven, Belgium	contributed samples and data, edited manuscript	Ignace.vergote@uzleuven.be	343	1
339	Senno		Verhoef	PhD	Netherlands Cancer Institute, Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands	contributed samples and data, edited manuscript	s.verhoef@nki.nl	344	1
340	Robert	A	Vierkant	MS	Department of Health Sciences Research, Division of Biomedical Statistics and Informatics, Mayo Clinic, Rochester, MN, USA	contributed samples and data, edited manuscript	vierkant.robert@mayo.edu	345	1
341	Joseph		Vijai	PhD	Clinical Genetics Research Laboratory, Memorial Sloan-Kettering Cancer Center, New York, NY, USA	contributed samples and data, edited manuscript	josephv@mskcc.org	346	1
342	Allison	F	Vitonis	PhD	Obstetrics and Gynecology Epidemiology Center, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA	contributed samples and data, edited manuscript	avitonis@partners.org	347	1
343	Anna		von Wachenfeldt	MD	Department of Oncology, Karolinska University Hospital, Stockholm, Sweden	contributed samples and data, edited manuscript	annavwachenfeldt@hotmail.com	348	4
344	Christine		Walsh	MD	Women's Cancer Program, Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, CA, USA	contributed samples and data, edited manuscript	christine.walsh@cshs.org	349	1
345	Qin		Wang	PhD	Centre for Cancer Genetic Epidemiology, Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK	contributed samples and data, edited manuscript	qw232@medschl.cam.ac.uk	350	1
346	Shan		Wang-Gohrke	PhD	Department of Obstetrics and Gynecology, University of Ulm, Ulm, Germany	contributed samples and data, edited manuscript	shan.wang-gohrke@uniklinik-ulm.de	352	1

Order	First	M	Last	Degree	Affiliation	Contribution	Email	CoI Form #	COI Batch
347	Barbara		Wappenschmidt	PhD	Centre of Familial Breast and Ovarian Cancer, Department of Gynaecology and Obstetrics, University Hospital of Cologne, Cologne, Germany; Centre for Molecular Medicine Cologne (CMMC), University Hospital of Cologne, Cologne, Germany	contributed samples and data, edited manuscript	Barbara.Wappenschmidt@uk-koeln.de	353	1
348	Maren		Weischer	PhD	Copenhagen General Population Study, Herlev Hospital, Copenhagen University Hospital, University of Copenhagen, Copenhagen, Denmark; Department of Clinical Biochemistry, Herlev Hospital, Copenhagen University Hospital, University of Copenhagen, Copenhagen, Denmark	contributed samples and data, edited manuscript	maren.weischer@regionh.dk	354	2
349	Jeffrey	N	Weitzel	MD	Clinical Cancer Genetics, City of Hope, Duarte, CA, USA	contributed samples and data, edited manuscript	jweitzel@coh.org	355	1
350	Caroline		Weltens	PhD	Multidisciplinary Breast Center, University Hospital Leuven, University of Leuven, Belgium	contributed samples and data, edited manuscript	Caroline.Weltens@uzleuven.be	356	1
351	Nicolas		Wentzensen	PhD	Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD, USA	contributed samples and data, edited manuscript	wentzenn@mail.nih.gov	357	1
352	Alice	S	Whittemore	PhD	Department of Health Research and Policy, Stanford University School of Medicine, Stanford, CA, USA	contributed samples and data, edited manuscript	alicesw@stanford.edu	358	1
353	Lynne	R	Wilkens	PhD	Cancer Epidemiology Program, University of Hawaii Cancer Center, Honolulu, HI, USA	contributed samples and data, edited manuscript	lynne@cc.hawaii.edu	359	1
354	Robert		Winqvist	PhD	Laboratory of Cancer Genetics and Tumor Biology, Department of Clinical Genetics, University of Oulu, Oulu University Hospital, Oulu, Finland; Biocenter Oulu, University of Oulu, Oulu, Finland	contributed samples and data, edited manuscript	robert.winqvist@oulu.fi	360	1
355	Anna	H	Wu	PhD	Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA	contributed samples and data, edited manuscript	Anna.Wu@med.usc.edu	361	1
356	Xifeng		Wu	PhD	Department of Epidemiology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA	contributed samples and data, edited manuscript	xwu@mdanderson.org	362	1
357	Hannah	P	Yang	PhD	Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD, USA	contributed samples and data, edited manuscript	yanghan@mail.nih.gov	363	1
358	Daniela		Zaffaroni	PhD	Unit of Medical Genetics, Department of Preventive and Predictive Medicine, Fondazione Istituto di Ricovero e Cura a Carattere Scientifico Istituto Nazionale Tumori (INT), Milan, Italy	contributed samples and data, edited manuscript	daniela.zaffaroni@istitutotumori.mi.it	364	1
359	M Pilar		Zamora	PhD	Servicio de Oncología Médica, Hospital Universitario La Paz, Madrid, Spain	contributed samples and data, edited manuscript	zamorapilar@gmail.com	365	1
360	Wei		Zheng	PhD	Division of Epidemiology, Department of Medicine, Vanderbilt Epidemiology Center, Vanderbilt-Ingram Cancer Center, Vanderbilt University School of Medicine, Nashville, TN, USA	contributed samples and data, edited manuscript	wei.zheng@Vanderbilt.Edu	366	1
361	Argyrios		Ziogas	PhD	Department of Epidemiology, Center for Cancer Genetics Research and Prevention, School of Medicine, University of California Irvine, Irvine, CA, USA	contributed samples and data, edited manuscript	aziogas@uci.edu	367	1

Order	First	M	Last	Degree	Affiliation	Contribution	Email	CoI Form #	COI Batch
362	Georgia		Chenevix-Trench	PhD	Department of Genetics, QIMR Berghofer Medical Research Institute, Brisbane, Australia	conducted analysis, provided funding, and contributed samples and data, edited manuscript	Georgia.Trench@qimr.edu.au	368	1
363	Paul	D P	Pharoah	MD, PhD	Centre for Cancer Genetic Epidemiology, Department of Oncology, University of Cambridge, Cambridge, UK	wrote the initial manuscript, conducted analysis, provided funding, and contributed samples and data	pp10001@medschl.cam.ac.uk	369	1
364	Matti	A	Rookus	PhD	Division of Molecular Pathology, Netherlands Cancer Institute, Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands	wrote the initial manuscript and contributed samples and data	m.rookus@nki.nl	370	1
365	Maartje	J	Hooning	PhD	Department of Medical Oncology, Erasmus MC Cancer Institute, Rotterdam, The Netherlands	wrote the initial manuscript, conducted analysis and contributed samples and data	m.hooning@erasmusmc.nl	371	1
366	Ellen	L	Goode	PhD	Department of Health Sciences Research, Division of Epidemiology, Mayo Clinic, Rochester, MN, USA	wrote the initial manuscript, provided funding, and contributed samples and data	egoode@mayo.edu	372	1

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Ellen L. Goode, Ph.D., M.P.H.
Department of
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April 13, 2015

Gynecologic Oncology
3251 Riverport Lane
Maryland Heights, MN 63043

Ms. No.: GYN-15-262
Title: No Clinical Utility of KRAS Variant rs61764370 for Ovarian or Breast Cancer
Corresponding Author: Dr. Andrew Berchuck

Dear Editors,

Thank you for taking the time to review our manuscript. We are pleased to provide a revised version of the manuscript entitled, "No Clinical Utility of KRAS Variant rs61764370 for Ovarian or Breast Cancer". In preparing the revision, we have addressed each question or concern as follows:

Reviewer #1:

The author list is extremely long. Other than contributing patients, did all authors directly participate in this manuscript? Can the list be restricted to only those with direct roles in the work.

> *All of the authors from the three research consortia made contributions to the manuscript that warrant authorship on the paper. We believe it would be reasonable, as suggested by the editors, to list the three consortia (Ovarian Cancer Association Consortium, Breast Cancer Association Consortium and Consortium of Investigators of Modifiers of BRCA1 and BRCA2) as the authors in the title of the paper when it is published in the journal. The full list of authors would be included in an appendix to the paper. All authors would be included in the PubMed citation and the article would be able to be identified by searching on any of their names. This is how many of the TCGA papers that have large numbers of authors have dealt with this issue.*

On line 633, there is a typo - a comma is needed between OCAC samples, BCAC samples

> *This has been corrected.*

Line 761 - references multiple "confirmed" susceptibility alleles for breast and ovarian cancer. I feel the use of the word confirmed could be an overstatement, "suspected" or something less definitive seems more appropriate given that all are common alleles. Or the authors should define what a "confirmed" susceptibility allele is (magnitude of risk, how strong the association is, etc).

A threshold for confirming a significant genome wide significant genetic association has been established at 5 x 10^{-8}. This threshold is widely accepted and was achieved for the common SNP variants that our consortia have identified. We have added this threshold to the Discussion.

Overall, this is an important negative study that should be published.

No response required.

Reviewer #2:

This is clearly an important and timely study. The authors should be applauded for the effort to evaluate the role of the rs1764370 inherited variant. The authors provided a detailed introduction regarding the place of this variant in the clinical genetic setting. The study seems to be well-designed to deal with its defined objectives. Because of the large scale evaluation and the merging of study populations from three consortiums, I recommend further review of the methods by a professional statistician. The presentation of the Results is clear and precise. Apparently, the authors used relevant figures to support the detailed text of the Results section, which indicate the negative associations. The manuscript is well written and the Discussion covers the relevant subjects appropriately, with pertinent, updated references. A major strength of this study is that the authors evaluated a large, well-defined cohort of women including patients and controls with relatively long-term median follow-up. The limitations of the retrospective analysis are well noted in the manuscript. This important, timely study contributes valuable information about the clinical meaningful of this specific inherited variant. Based on the results of this study it seems that genotyping this variant has no clinical utility related to the prediction or management of breast and ovarian cancers. The results demonstrate the power of large consortia to refute false-associations and highlight the danger of commercially promoting genetic tests without appropriate data base. The results are important and worth publishing.

*No response required***.**

Editor

The author list needs to be revised as previous discussed in a prior email.

*See response to the first comment by Reviewer #1***.**

Thank you for the timely review of this paper. Please do not hesitate to contact me or Andrew Berchuck if further discussion is needed related to the issue of acknowledgement of the long list of authors.

Sincerely,

Ellen L. Goode, Ph.D., M.P.H.
Professor of Epidemiology

***2. Conflict of Interest Forms**

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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 was 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 7,904 *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.

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 8,669 cases, 10,012 controls, and 2,682 *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.

METHODS

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 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: 2,332 affected and 12,433 unaffected *BRCA1* carriers, 599 affected and 7,305 unaffected *BRCA2* carriers; for breast cancer analyses: 7,543 affected and 7,222 unaffected *BRCA1* carriers, 4,138 affected and 3,766 unaffected *BRCA2* carriers). For OCAC, overall and progression-free survival data were available for 3,096 patients from 13 studies. Overall survival data were available for 28,471 patients from 26 BCAC studies and for 2,623 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.

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 1,056 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 1,001 variants genotyped and imputed for CIMBA, including rs61764370 (Supplementary Tables S5, S6, and S7).

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, 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, 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 >1cm) and of post-menopausal patients (age at diagnosis >52 years). Survival analysis of BCAC patients used Cox

683 proportional hazard models estimating HRs and 95% CIs considering overall and breast cancer-
684 specific survival following breast cancer diagnosis. Models were adjusted for age at diagnosis,
685 tumor size, nodal status, grade, adjuvant hormonal and/or chemotherapy, and stratified by study,
686 left-truncating at the date of study entry and right censoring at ten years. In addition, we performed
687 subgroup analysis on ER-positive and ER-negative patients. For CIMBA breast cancer patients
688 associations between genotype and overall survival were evaluated using Cox proportional hazard
689 models estimating HRs and 95% CIs. Models were adjusted for age at diagnosis, tumor size, nodal
690 status, grade, adjuvant hormonal and/or chemotherapy, and preventive bilateral oophorectomy and
691 stratified by study, left-truncating at the date of study entry and right censoring at twenty years.
692 Analyses were performed using STATA version 12.0 (StataCorp, Texas, USA).
693
694 **RESULTS**
695 The results of the overall analysis as well as the subgroup analyses investigating the
696 association between the minor allele at rs61764370 and ovarian cancer risk, breast cancer risk,
697 and ovarian and breast cancer risks in *BRCA1* and *BRCA2* mutation carriers are shown in Table 1.
698 Associations with clinical outcomes in and ovarian and breast cancer patients including *BRCA1*
699 and *BRCA2* mutation carriers are shown in Table 2 and Supplementary Table S4.
700 We found no evidence for association between the rs61764370 G allele and ovarian or
701 breast cancer risk. The most statistically significant association was observed for risk of low-grade
702 serous ovarian cancer (n=485; OR 0.76, 95% CI 0.59-0.97, p=0.031), but this finding was not
703 significant after Bonferroni correction for multiple testing. We also evaluated the association for
704 additional specific subgroups in which an association with rs61764370 had been reported
705 previously [3-6]. Ovarian cancer subgroups considered *BRCA1* mutation carriers as well as
706 *BRCA1* and *BRCA2* screened-negative patients with first degree family histories of breast or
707 ovarian cancer and patients who had been diagnosed with breast cancer before their ovarian
708 cancer diagnoses. For breast cancer these included, amongst others, *BRCA1* mutation carriers,
709 patients diagnosed with ER- and PR-negative tumors, and patients diagnosed with triple negative
710 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 1,001 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 (Figure 1).

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 (Figure 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 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 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. 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.

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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.

REFERENCES

[1] Esquela-Kerscher A, Slack FJ. Oncomirs - microRNAs with a role in cancer. Nat Rev Cancer Apr 2006;6(4):259-69.

[2] Salzman DW, Weidhaas JB. SNPing cancer in the bud: microRNA and microRNA-target site polymorphisms as diagnostic and prognostic biomarkers in cancer. Pharmacol Ther Jan 2013;137(1):55-63.

[3] Ratner E, Lu L, Boeke M, Barnett R, Nallur S, Chin LJ, et al. A KRAS-variant in ovarian cancer acts as a genetic marker of cancer risk. Cancer Res Aug 15 2010;70(16):6509-15.

[4] Pilarski R, Patel DA, Weitzel J, McVeigh T, Dorairaj JJ, Heneghan HM, et al. The KRAS variant is associated with risk of developing double primary breast and ovarian cancer. PloS ONE 2012;7(5):e37891.

[5] Hollestelle A, Pelletier C, Hooning M, Crepin E, Schutte M, Look M, et al. Prevalence of the variant allele rs61764370 T>G in the 3'UTR of KRAS among Dutch BRCA1, BRCA2 and non-BRCA1/BRCA2 breast cancer families. Breast Cancer Res Treat Jul 2011;128(1):79-84.

[6] Paranjape T, Heneghan H, Lindner R, Keane FK, Hoffman A, Hollestelle A, et al. A 3'-untranslated region KRAS variant and triple-negative breast cancer: a case-control and genetic analysis. Lancet Oncol Apr 2011;12(4):377-86.

[7] Chin LJ, Ratner E, Leng S, Zhai R, Nallur S, Babar I, et al. A SNP in a let-7 microRNA complementary site in the KRAS 3' untranslated region increases non-small cell lung cancer risk. Cancer Res Oct 15 2008;68(20):8535-40.

[8] Grechukhina O, Petracco R, Popkhadze S, Massasa E, Paranjape T, Chan E, et al. A polymorphism in a let-7 microRNA binding site of KRAS in women with endometriosis. EMBO Mol Med Mar 2012;4(3):206-17.

[9] Pharoah PD, Palmieri RT, Ramus SJ, Gayther SA, Andrulis IL, Anton-Culver H, et al. The role of KRAS rs61764370 in invasive epithelial ovarian cancer: implications for clinical testing. Clin Cancer Res Jun 1 2011;17(11):3742-50.

[10] Nelson HH, Christensen BC, Plaza SL, Wiencke JK, Marsit CJ, Kelsey KT. KRAS mutation, KRAS-LCS6 polymorphism, and non-small cell lung cancer. Lung Cancer Jul 2010;69(1):51-3.

[11] Luong HT, Nyholt DR, Painter JN, Chapman B, Kennedy S, Treloar SA, et al. No evidence for genetic association with the let-7 microRNA-binding site or other common KRAS variants in risk of endometriosis. Hum Reprod Dec 2012;27(12):3616-21.

[12] Weidhaas JB, Slack FJ. KRAS rs61764370 in epithelial ovarian cancer-Letter. Clin Cancer Res Oct 15 2011;17(20):6600.

[13] Risch HA, Berchuck A, Paul DP. KRAS rs61764370 in epithelial ovarian cancer-Response. Clin Cancer Res Oct 15 2011;17(20):6601.

[14] Ratner ES, Keane FK, Lindner R, Tassi RA, Paranjape T, Glasgow M, et al. A KRAS variant is a biomarker of poor outcome, platinum chemotherapy resistance and a potential target for therapy in ovarian cancer. Oncogene Dec 5 2011;31(42):4559-4566.

[15] Caiola E, Rulli E, Fruscio R, Buda A, Broggini M, Marabese M. KRas-LCS6 polymorphism does not impact on outcomes in ovarian cancer. Am J Cancer Res 2012;2(3):298-308.

[16] Pharoah P, Antoniou A, Berchuck A, Chenevix-Trench G, Gayther S, Goode E, et al. Association between KRAS rs61764370 and triple-negative breast cancer - a false positive? Lancet Oncol 2011;12(8):723-724.

[17] Weidhaas J, Slack F, Miller N, Harris L, Tuck D, Zhu Y, et al. Association between KRAS rs61764370 and triple-negative breast cancer - a false positive? Authors' reply. Lancet Oncol 2011;12(8):724.

[18] Cerne JZ, Stegel V, Gersak K, Novakovic S. KRAS rs61764370 is associated with HER2-overexpressed and poorly-differentiated breast cancer in hormone replacement therapy users: a case control study. BMC Cancer 2012;12(105.

[19] Kivimaki M, Batty GD, Kawachi I, Virtanen M, Singh-Manoux A, Brunner EJ. Don'T let the truth get in the way of a good story: an illustration of citation bias in epidemiologic research. Am J Epidemiol Aug 15 2014;180(4):446-8.

[20] Peto R. Current misconception 3: that subgroup-specific trial mortality results often provide a good basis for individualising patient care. British journal of cancer Mar 29 2011;104(7):1057-8.

[21] http://www.miradx.com.

[22] Pharoah PD, Tsai YY, Ramus SJ, Phelan CM, Goode EL, Lawrenson K, et al. GWAS meta-analysis and replication identifies three new susceptibility loci for ovarian cancer. Nat Genet Apr 2013;45(4):362-70.

[23] Michailidou K, Hall P, Gonzalez-Neira A, Ghoussaini M, Dennis J, Milne RL, et al. Large-scale genotyping identifies 41 new loci associated with breast cancer risk. Nat Genet 2013;45(4):353-361.

[24] Couch FJ, Wang X, McGuffog L, Lee A, Olswold C, Kuchenbaecker KB, et al. Genome-wide association study in BRCA1 mutation carriers identifies novel loci associated with breast and ovarian cancer risk. PLoS Genet 2013;9(3):e1003212.

[25] Gaudet MM, Kuchenbaecker KB, Vijai J, Klein RJ, Kirchhoff T, McGuffog L, et al. Identification of a BRCA2-specific modifier locus at 6p24 related to breast cancer risk. PLoS Genet 2013;9(3):e1003173.

[26] White KL, Vierkant RA, Fogarty ZC, Charbonneau B, Block MS, Pharoah PD, et al. Analysis of over 10,000 cases finds no association between previously reported candidate polymorphisms and ovarian cancer outcome. Cancer Epidemiol Biomarkers Prev May 2013;22(5):987-92.

[27] Weischer M, Nordestgaard BG, Pharoah P, Bolla MK, Nevanlinna H, Van't Veer LJ, et al. CHEK2*1100delC heterozygosity in women with breast cancer associated with early death, breast cancer-specific death, and increased risk of a second breast cancer. J Clin Oncol Dec 10 2012;30(35):4308-16.

[28] Goode EL, Chenevix-Trench G, Song H, Ramus SJ, Notaridou M, Lawrenson K, et al. A genome-wide association study identifies susceptibility loci for ovarian cancer at 2q31 and 8q24. Nat Genet Oct 2010;42(10):874-9.

[29] Price AL, Patterson NJ, Plenge RM, Weinblatt ME, Shadick NA, Reich D. Principal components analysis corrects for stratification in genome-wide association studies. Nat Genet Aug 2006;38(8):904-9.

[30] Project G. An integrated map of genetic variation from 1,092 human genomes. Nature 2012;491(7422):56-65.

[31] Delaneau O, Marchini J, Zagury JF. A linear complexity phasing method for thousands of genomes. Nature Methods Feb 2012;9(2):179-81.

[32] Howie BN, Donnelly P, Marchini J. A flexible and accurate genotype imputation method for the next generation of genome-wide association studies. PLoS genetics Jun 2009;5(6):e1000529.

[33] Howie B, Fuchsberger C, Stephens M, Marchini J, Abecasis GR. Fast and accurate genotype imputation in genome-wide association studies through pre-phasing. Nat Genet Aug 2012;44(8):955-9.

[34] Antoniou AC, Goldgar DE, Andrieu N, Chang-Claude J, Brohet R, Rookus MA, et al. A weighted cohort approach for analysing factors modifying disease risks in carriers of high-risk susceptibility genes. Genet Epidemiol Jul 2005;29(1):1-11.

[35] Boos DD. On generalised score tests. Am Stat 1992;46(327-333.

[36] Rustin GJ, Vergote I, Eisenhauer E, Pujade-Lauraine E, Quinn M, Thigpen T, et al. Definitions for response and progression in ovarian cancer clinical trials incorporating RECIST 1.1 and CA 125 agreed by the Gynecological Cancer Intergroup (GCIG). Int J Gynecol Cancer Feb 2011;21(2):419-23.

[37] Kuchenbaecker KB, Ramus SJ, Tyrer J, Lee A, Shen HC, Beesley J, et al. Identification of six new susceptibility loci for invasive epithelial ovarian cancer. Nat Genet Feb 2015;47(2):164-71.

[38] Chowdhury S, Dent T, Pashayan N, Hall A, Lyratzopoulos G, Hallowell N, et al. Incorporating genomics into breast and prostate cancer screening: assessing the implications. Genet Med Jun 2013;15(6):423-32.

[39] Pashayan N, Duffy SW, Chowdhury S, Dent T, Burton H, Neal DE, et al. Polygenic susceptibility to prostate and breast cancer: implications for personalised screening. Br J Cancer May 10 2011;104(10):1656-63.

[40] Eeles RA, Olama AA, Benlloch S, Saunders EJ, Leongamornlert DA, Tymrakiewicz M, et al. Identification of 23 new prostate cancer susceptibility loci using the iCOGS custom genotyping array. Nat Genet Apr 2013;45(4):385-91.

TABLE LEGENDS

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.

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.

FIGURE LEGENDS

Figure 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.

Figure 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.

No Clinical Utility of *KRAS* Variant rs61764370 for Ovarian or Breast Cancer

Ovarian Cancer Association Consortium, Breast Cancer Association Consortium, and Consortium of Modifiers of *BRCA1* and *BRCA2*

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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 was 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 7,904 *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.

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 8,669 cases, 10,012 controls, and 2,682 *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.

METHODS

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 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: 2,332 affected and 12,433 unaffected *BRCA1* carriers, 599 affected and 7,305 unaffected *BRCA2* carriers; for breast cancer analyses: 7,543 affected and 7,222 unaffected *BRCA1* carriers, 4,138 affected and 3,766 unaffected *BRCA2* carriers). For OCAC, overall and progression-free survival data were available for 3,096 patients from 13 studies. Overall survival data were available for 28,471 patients from 26 BCAC studies and for 2,623 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.

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 1,056 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 1,001 variants genotyped and imputed for CIMBA, including rs61764370 (Supplementary Tables S5, S6, and S7).

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, 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, 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 >1cm) 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).

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, amongst 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 1,001 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 (Figure 1).

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.

744 Our study has notable strengths. The vast majority (*i.e.* >95%) of the samples were
745 genotyped using the same genotyping platform and employing a common approach to genotype
746 calling and quality control; additional samples used denser arrays and nearly identical procedures.
747 The very large sample sizes for all the major phenotypes of interest provide substantial statistical
748 power to exclude any clinically relevant associated risks for the major phenotypes of interest
749 (Figure 2). The null results found here are thus not due to lack of statistical power, and this
750 analysis also had greater than 80% power to detect association for most of the subgroups,
751 although for some subgroups it was not possible to exclude modest risks. In contrast to the current
752 findings, other genetic association analyses using the same genotyping platform and the same
753 studies as included here have identified more than 90 common germline variants associated with
754 ovarian or breast cancer risk at $p< 5 \times 10^{-8}$ [22, 23, 37]. While critiques on a previous null *KRAS*
755 report have suggested that inclusion of male controls, use of "prevalent" cases, and reliance on a
756 surrogate genetic variant may have led to falsely negative conclusions, these are not issues in the
757 present data set. Rather, we demonstrate the importance of international collaboration to identify
758 true associations as well as to refute false associations, an equally important objective.
759 The rise of individualized medicine including the use of panels of common variants to
760 predict cancer risk more accurately than using family history alone holds great promise [38]. For
761 example, the 31 prostate cancer susceptibility alleles confirmed as of 2011 (at $p<5\times10^{-8}$) can be
762 combined to identify men in the top one percent of the risk distribution having a 3.2-fold increased
763 risk [39]. Prediction has since then improved with now over 70 prostate cancer susceptibility alleles
764 [40] and the utility of these genetic tests is currently under clinical evaluation. Similar clinical
765 examination in ovarian and breast cancer is not far behind, with now over 18 and 77 confirmed
766 susceptibility alleles, respectively, for these cancers [22, 23]. The genotype at rs61764370,
767 however, does not predict ovarian or breast cancer risk, even among particular subgroups of
768 women or for particular subtypes of disease, nor is it a marker of differential outcome following
769 diagnosis with these cancers. Therefore, genetic test results for rs61764370 should not be used to
770 counsel women about their ovarian or breast cancer risks or outcome. Our results highlight the
771 dangers of developing clinical tests without appropriate data from carefully conducted, large-scale
772 studies to establish clinical validity.

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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.

REFERENCES

[1] Esquela-Kerscher A, Slack FJ. Oncomirs - microRNAs with a role in cancer. Nat Rev Cancer Apr 2006;6(4):259-69.

[2] Salzman DW, Weidhaas JB. SNPing cancer in the bud: microRNA and microRNA-target site polymorphisms as diagnostic and prognostic biomarkers in cancer. Pharmacol Ther Jan 2013;137(1):55-63.

[3] Ratner E, Lu L, Boeke M, Barnett R, Nallur S, Chin LJ, et al. A KRAS-variant in ovarian cancer acts as a genetic marker of cancer risk. Cancer Res Aug 15 2010;70(16):6509-15.

[4] Pilarski R, Patel DA, Weitzel J, McVeigh T, Dorairaj JJ, Heneghan HM, et al. The KRAS variant is associated with risk of developing double primary breast and ovarian cancer. PloS ONE 2012;7(5):e37891.

[5] Hollestelle A, Pelletier C, Hooning M, Crepin E, Schutte M, Look M, et al. Prevalence of the variant allele rs61764370 T>G in the 3'UTR of KRAS among Dutch BRCA1, BRCA2 and non-BRCA1/BRCA2 breast cancer families. Breast Cancer Res Treat Jul 2011;128(1):79-84.

[6] Paranjape T, Heneghan H, Lindner R, Keane FK, Hoffman A, Hollestelle A, et al. A 3'-untranslated region KRAS variant and triple-negative breast cancer: a case-control and genetic analysis. Lancet Oncol Apr 2011;12(4):377-86.

[7] Chin LJ, Ratner E, Leng S, Zhai R, Nallur S, Babar I, et al. A SNP in a let-7 microRNA complementary site in the KRAS 3' untranslated region increases non-small cell lung cancer risk. Cancer Res Oct 15 2008;68(20):8535-40.

[8] Grechukhina O, Petracco R, Popkhadze S, Massasa E, Paranjape T, Chan E, et al. A polymorphism in a let-7 microRNA binding site of KRAS in women with endometriosis. EMBO Mol Med Mar 2012;4(3):206-17.

[9] Pharoah PD, Palmieri RT, Ramus SJ, Gayther SA, Andrulis IL, Anton-Culver H, et al. The role of KRAS rs61764370 in invasive epithelial ovarian cancer: implications for clinical testing. Clin Cancer Res Jun 1 2011;17(11):3742-50.

[10] Nelson HH, Christensen BC, Plaza SL, Wiencke JK, Marsit CJ, Kelsey KT. KRAS mutation, KRAS-LCS6 polymorphism, and non-small cell lung cancer. Lung Cancer Jul 2010;69(1):51-3.

[11] Luong HT, Nyholt DR, Painter JN, Chapman B, Kennedy S, Treloar SA, et al. No evidence for genetic association with the let-7 microRNA-binding site or other common KRAS variants in risk of endometriosis. Hum Reprod Dec 2012;27(12):3616-21.

[12] Weidhaas JB, Slack FJ. KRAS rs61764370 in epithelial ovarian cancer-Letter. Clin Cancer Res Oct 15 2011;17(20):6600.

[13] Risch HA, Berchuck A, Paul DP. KRAS rs61764370 in epithelial ovarian cancer-Response. Clin Cancer Res Oct 15 2011;17(20):6601.

[14] Ratner ES, Keane FK, Lindner R, Tassi RA, Paranjape T, Glasgow M, et al. A KRAS variant is a biomarker of poor outcome, platinum chemotherapy resistance and a potential target for therapy in ovarian cancer. Oncogene Dec 5 2011;31(42):4559-4566.

[15] Caiola E, Rulli E, Fruscio R, Buda A, Broggini M, Marabese M. KRas-LCS6 polymorphism does not impact on outcomes in ovarian cancer. Am J Cancer Res 2012;2(3):298-308.

[16] Pharoah P, Antoniou A, Berchuck A, Chenevix-Trench G, Gayther S, Goode E, et al. Association between KRAS rs61764370 and triple-negative breast cancer - a false positive? Lancet Oncol 2011;12(8):723-724.

[17] Weidhaas J, Slack F, Miller N, Harris L, Tuck D, Zhu Y, et al. Association between KRAS rs61764370 and triple-negative breast cancer - a false positive? Authors' reply. Lancet Oncol 2011;12(8):724.

[18] Cerne JZ, Stegel V, Gersak K, Novakovic S. KRAS rs61764370 is associated with HER2-overexpressed and poorly-differentiated breast cancer in hormone replacement therapy users: a case control study. BMC Cancer 2012;12(105.

[19] Kivimaki M, Batty GD, Kawachi I, Virtanen M, Singh-Manoux A, Brunner EJ. Don'T let the truth get in the way of a good story: an illustration of citation bias in epidemiologic research. Am J Epidemiol Aug 15 2014;180(4):446-8.

[20] Peto R. Current misconception 3: that subgroup-specific trial mortality results often provide a good basis for individualising patient care. British journal of cancer Mar 29 2011;104(7):1057-8.

[21] http://www.miradx.com.

[22] Pharoah PD, Tsai YY, Ramus SJ, Phelan CM, Goode EL, Lawrenson K, et al. GWAS meta-analysis and replication identifies three new susceptibility loci for ovarian cancer. Nat Genet Apr 2013;45(4):362-70.

[23] Michailidou K, Hall P, Gonzalez-Neira A, Ghoussaini M, Dennis J, Milne RL, et al. Large-scale genotyping identifies 41 new loci associated with breast cancer risk. Nat Genet 2013;45(4):353-361.

[24] Couch FJ, Wang X, McGuffog L, Lee A, Olswold C, Kuchenbaecker KB, et al. Genome-wide association study in BRCA1 mutation carriers identifies novel loci associated with breast and ovarian cancer risk. PLoS Genet 2013;9(3):e1003212.

[25] Gaudet MM, Kuchenbaecker KB, Vijai J, Klein RJ, Kirchhoff T, McGuffog L, et al. Identification of a BRCA2-specific modifier locus at 6p24 related to breast cancer risk. PLoS Genet 2013;9(3):e1003173.

[26] White KL, Vierkant RA, Fogarty ZC, Charbonneau B, Block MS, Pharoah PD, et al. Analysis of over 10,000 cases finds no association between previously reported candidate polymorphisms and ovarian cancer outcome. Cancer Epidemiol Biomarkers Prev May 2013;22(5):987-92.

[27] Weischer M, Nordestgaard BG, Pharoah P, Bolla MK, Nevanlinna H, Van't Veer LJ, et al. CHEK2*1100delC heterozygosity in women with breast cancer associated with early death, breast cancer-specific death, and increased risk of a second breast cancer. J Clin Oncol Dec 10 2012;30(35):4308-16.

[28] Goode EL, Chenevix-Trench G, Song H, Ramus SJ, Notaridou M, Lawrenson K, et al. A genome-wide association study identifies susceptibility loci for ovarian cancer at 2q31 and 8q24. Nat Genet Oct 2010;42(10):874-9.

[29] Price AL, Patterson NJ, Plenge RM, Weinblatt ME, Shadick NA, Reich D. Principal components analysis corrects for stratification in genome-wide association studies. Nat Genet Aug 2006;38(8):904-9.

[30] Project G. An integrated map of genetic variation from 1,092 human genomes. Nature 2012;491(7422):56-65.

[31] Delaneau O, Marchini J, Zagury JF. A linear complexity phasing method for thousands of genomes. Nature Methods Feb 2012;9(2):179-81.

[32] Howie BN, Donnelly P, Marchini J. A flexible and accurate genotype imputation method for the next generation of genome-wide association studies. PLoS genetics Jun 2009;5(6):e1000529.

[33] Howie B, Fuchsberger C, Stephens M, Marchini J, Abecasis GR. Fast and accurate genotype imputation in genome-wide association studies through pre-phasing. Nat Genet Aug 2012;44(8):955-9.

[34] Antoniou AC, Goldgar DE, Andrieu N, Chang-Claude J, Brohet R, Rookus MA, et al. A weighted cohort approach for analysing factors modifying disease risks in carriers of high-risk susceptibility genes. Genet Epidemiol Jul 2005;29(1):1-11.

[35] Boos DD. On generalised score tests. Am Stat 1992;46(327-333.

[36] Rustin GJ, Vergote I, Eisenhauer E, Pujade-Lauraine E, Quinn M, Thigpen T, et al. Definitions for response and progression in ovarian cancer clinical trials incorporating RECIST 1.1 and CA 125 agreed by the Gynecological Cancer Intergroup (GCIG). Int J Gynecol Cancer Feb 2011;21(2):419-23.

[37] Kuchenbaecker KB, Ramus SJ, Tyrer J, Lee A, Shen HC, Beesley J, et al. Identification of six new susceptibility loci for invasive epithelial ovarian cancer. Nat Genet Feb 2015;47(2):164-71.

[38] Chowdhury S, Dent T, Pashayan N, Hall A, Lyratzopoulos G, Hallowell N, et al. Incorporating genomics into breast and prostate cancer screening: assessing the implications. Genet Med Jun 2013;15(6):423-32.

[39] Pashayan N, Duffy SW, Chowdhury S, Dent T, Burton H, Neal DE, et al. Polygenic susceptibility to prostate and breast cancer: implications for personalised screening. Br J Cancer May 10 2011;104(10):1656-63.

[40] Eeles RA, Olama AA, Benlloch S, Saunders EJ, Leongamornlert DA, Tymrakiewicz M, et al. Identification of 23 new prostate cancer susceptibility loci using the iCOGS custom genotyping array. Nat Genet Apr 2013;45(4):385-91.

TABLE LEGENDS

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.

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.

FIGURE LEGENDS

Figure 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.

Figure 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.

No Clinical Utility of *KRAS* Variant rs61764370 for Ovarian or Breast Cancer

Ovarian Cancer Association Consortium, Breast Cancer Association Consortium, and Consortium of Modifiers of *BRCA1* and *BRCA2*

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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 was 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 7,904 *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.

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 8,669 cases, 10,012 controls, and 2,682 *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.

METHODS

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 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: 2,332 affected and 12,433 unaffected *BRCA1* carriers, 599 affected and 7,305 unaffected *BRCA2* carriers; for breast cancer analyses: 7,543 affected and 7,222 unaffected *BRCA1* carriers, 4,138 affected and 3,766 unaffected *BRCA2* carriers). For OCAC, overall and progression-free survival data were available for 3,096 patients from 13 studies. Overall survival data were available for 28,471 patients from 26 BCAC studies and for 2,623 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.

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 1,056 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 1,001 variants genotyped and imputed for CIMBA, including rs61764370 (Supplementary Tables S5, S6, and S7).

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, 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, 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 >1cm) 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).

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, amongst 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 1,001 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 (Figure 1).

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 (Figure 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 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 $p<5x10^{-8}$) 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. Similar clinical examination in ovarian and breast cancer is not far behind, with now over 18 and 77 confirmed susceptibility alleles (at $p<5x10^{-8}$), 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.

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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.

REFERENCES

[1] Esquela-Kerscher A, Slack FJ. Oncomirs - microRNAs with a role in cancer. Nat Rev Cancer Apr 2006;6(4):259-69.

[2] Salzman DW, Weidhaas JB. SNPing cancer in the bud: microRNA and microRNA-target site polymorphisms as diagnostic and prognostic biomarkers in cancer. Pharmacol Ther Jan 2013;137(1):55-63.

[3] Ratner E, Lu L, Boeke M, Barnett R, Nallur S, Chin LJ, et al. A KRAS-variant in ovarian cancer acts as a genetic marker of cancer risk. Cancer Res Aug 15 2010;70(16):6509-15.

[4] Pilarski R, Patel DA, Weitzel J, McVeigh T, Dorairaj JJ, Heneghan HM, et al. The KRAS variant is associated with risk of developing double primary breast and ovarian cancer. PloS ONE 2012;7(5):e37891.

[5] Hollestelle A, Pelletier C, Hooning M, Crepin E, Schutte M, Look M, et al. Prevalence of the variant allele rs61764370 T>G in the 3'UTR of KRAS among Dutch BRCA1, BRCA2 and non-BRCA1/BRCA2 breast cancer families. Breast Cancer Res Treat Jul 2011;128(1):79-84.

[6] Paranjape T, Heneghan H, Lindner R, Keane FK, Hoffman A, Hollestelle A, et al. A 3'-untranslated region KRAS variant and triple-negative breast cancer: a case-control and genetic analysis. Lancet Oncol Apr 2011;12(4):377-86.

[7] Chin LJ, Ratner E, Leng S, Zhai R, Nallur S, Babar I, et al. A SNP in a let-7 microRNA complementary site in the KRAS 3' untranslated region increases non-small cell lung cancer risk. Cancer Res Oct 15 2008;68(20):8535-40.

[8] Grechukhina O, Petracco R, Popkhadze S, Massasa E, Paranjape T, Chan E, et al. A polymorphism in a let-7 microRNA binding site of KRAS in women with endometriosis. EMBO Mol Med Mar 2012;4(3):206-17.

[9] Pharoah PD, Palmieri RT, Ramus SJ, Gayther SA, Andrulis IL, Anton-Culver H, et al. The role of KRAS rs61764370 in invasive epithelial ovarian cancer: implications for clinical testing. Clin Cancer Res Jun 1 2011;17(11):3742-50.

[10] Nelson HH, Christensen BC, Plaza SL, Wiencke JK, Marsit CJ, Kelsey KT. KRAS mutation, KRAS-LCS6 polymorphism, and non-small cell lung cancer. Lung Cancer Jul 2010;69(1):51-3.

[11] Luong HT, Nyholt DR, Painter JN, Chapman B, Kennedy S, Treloar SA, et al. No evidence for genetic association with the let-7 microRNA-binding site or other common KRAS variants in risk of endometriosis. Hum Reprod Dec 2012;27(12):3616-21.

[12] Weidhaas JB, Slack FJ. KRAS rs61764370 in epithelial ovarian cancer-Letter. Clin Cancer Res Oct 15 2011;17(20):6600.

[13] Risch HA, Berchuck A, Paul DP. KRAS rs61764370 in epithelial ovarian cancer-Response. Clin Cancer Res Oct 15 2011;17(20):6601.

[14] Ratner ES, Keane FK, Lindner R, Tassi RA, Paranjape T, Glasgow M, et al. A KRAS variant is a biomarker of poor outcome, platinum chemotherapy resistance and a potential target for therapy in ovarian cancer. Oncogene Dec 5 2011;31(42):4559-4566.

[15] Caiola E, Rulli E, Fruscio R, Buda A, Broggini M, Marabese M. KRas-LCS6 polymorphism does not impact on outcomes in ovarian cancer. Am J Cancer Res 2012;2(3):298-308.

[16] Pharoah P, Antoniou A, Berchuck A, Chenevix-Trench G, Gayther S, Goode E, et al. Association between KRAS rs61764370 and triple-negative breast cancer - a false positive? Lancet Oncol 2011;12(8):723-724.

[17] Weidhaas J, Slack F, Miller N, Harris L, Tuck D, Zhu Y, et al. Association between KRAS rs61764370 and triple-negative breast cancer - a false positive? Authors' reply. Lancet Oncol 2011;12(8):724.

[18] Cerne JZ, Stegel V, Gersak K, Novakovic S. KRAS rs61764370 is associated with HER2-overexpressed and poorly-differentiated breast cancer in hormone replacement therapy users: a case control study. BMC Cancer 2012;12(105.

[19] Kivimaki M, Batty GD, Kawachi I, Virtanen M, Singh-Manoux A, Brunner EJ. Don'T let the truth get in the way of a good story: an illustration of citation bias in epidemiologic research. Am J Epidemiol Aug 15 2014;180(4):446-8.

[20] Peto R. Current misconception 3: that subgroup-specific trial mortality results often provide a good basis for individualising patient care. British journal of cancer Mar 29 2011;104(7):1057-8.

[21] http://www.miradx.com.

[22] Pharoah PD, Tsai YY, Ramus SJ, Phelan CM, Goode EL, Lawrenson K, et al. GWAS meta-analysis and replication identifies three new susceptibility loci for ovarian cancer. Nat Genet Apr 2013;45(4):362-70.

[23] Michailidou K, Hall P, Gonzalez-Neira A, Ghoussaini M, Dennis J, Milne RL, et al. Large-scale genotyping identifies 41 new loci associated with breast cancer risk. Nat Genet 2013;45(4):353-361.

[24] Couch FJ, Wang X, McGuffog L, Lee A, Olswold C, Kuchenbaecker KB, et al. Genome-wide association study in BRCA1 mutation carriers identifies novel loci associated with breast and ovarian cancer risk. PLoS Genet 2013;9(3):e1003212.

[25] Gaudet MM, Kuchenbaecker KB, Vijai J, Klein RJ, Kirchhoff T, McGuffog L, et al. Identification of a BRCA2-specific modifier locus at 6p24 related to breast cancer risk. PLoS Genet 2013;9(3):e1003173.

[26] White KL, Vierkant RA, Fogarty ZC, Charbonneau B, Block MS, Pharoah PD, et al. Analysis of over 10,000 cases finds no association between previously reported candidate polymorphisms and ovarian cancer outcome. Cancer Epidemiol Biomarkers Prev May 2013;22(5):987-92.

[27] Weischer M, Nordestgaard BG, Pharoah P, Bolla MK, Nevanlinna H, Van't Veer LJ, et al. CHEK2*1100delC heterozygosity in women with breast cancer associated with early death, breast cancer-specific death, and increased risk of a second breast cancer. J Clin Oncol Dec 10 2012;30(35):4308-16.

[28] Goode EL, Chenevix-Trench G, Song H, Ramus SJ, Notaridou M, Lawrenson K, et al. A genome-wide association study identifies susceptibility loci for ovarian cancer at 2q31 and 8q24. Nat Genet Oct 2010;42(10):874-9.

[29] Price AL, Patterson NJ, Plenge RM, Weinblatt ME, Shadick NA, Reich D. Principal components analysis corrects for stratification in genome-wide association studies. Nat Genet Aug 2006;38(8):904-9.

[30] Project G. An integrated map of genetic variation from 1,092 human genomes. Nature 2012;491(7422):56-65.

[31] Delaneau O, Marchini J, Zagury JF. A linear complexity phasing method for thousands of genomes. Nature Methods Feb 2012;9(2):179-81.

[32] Howie BN, Donnelly P, Marchini J. A flexible and accurate genotype imputation method for the next generation of genome-wide association studies. PLoS genetics Jun 2009;5(6):e1000529.

[33] Howie B, Fuchsberger C, Stephens M, Marchini J, Abecasis GR. Fast and accurate genotype imputation in genome-wide association studies through pre-phasing. Nat Genet Aug 2012;44(8):955-9.

[34] Antoniou AC, Goldgar DE, Andrieu N, Chang-Claude J, Brohet R, Rookus MA, et al. A weighted cohort approach for analysing factors modifying disease risks in carriers of high-risk susceptibility genes. Genet Epidemiol Jul 2005;29(1):1-11.

[35] Boos DD. On generalised score tests. Am Stat 1992;46(327-333.

[36] Rustin GJ, Vergote I, Eisenhauer E, Pujade-Lauraine E, Quinn M, Thigpen T, et al. Definitions for response and progression in ovarian cancer clinical trials incorporating RECIST 1.1 and CA 125 agreed by the Gynecological Cancer Intergroup (GCIG). Int J Gynecol Cancer Feb 2011;21(2):419-23.

[37] Kuchenbaecker KB, Ramus SJ, Tyrer J, Lee A, Shen HC, Beesley J, et al. Identification of six new susceptibility loci for invasive epithelial ovarian cancer. Nat Genet Feb 2015;47(2):164-71.

[38] Chowdhury S, Dent T, Pashayan N, Hall A, Lyratzopoulos G, Hallowell N, et al. Incorporating genomics into breast and prostate cancer screening: assessing the implications. Genet Med Jun 2013;15(6):423-32.

[39] Pashayan N, Duffy SW, Chowdhury S, Dent T, Burton H, Neal DE, et al. Polygenic susceptibility to prostate and breast cancer: implications for personalised screening. Br J Cancer May 10 2011;104(10):1656-63.

[40] Eeles RA, Olama AA, Benlloch S, Saunders EJ, Leongamornlert DA, Tymrakiewicz M, et al. Identification of 23 new prostate cancer susceptibility loci using the iCOGS custom genotyping array. Nat Genet Apr 2013;45(4):385-91.

TABLE LEGENDS

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.

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.

FIGURE LEGENDS

Figure 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.

Figure 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.

4. Table

Click here to download 4. Table: Table1.docx

	Number		Minor allele frequency		Relative Risk	
	Cases	Controls	Cases	Controls	(95% CI)	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	6,938	30,816	0.0946	0.0949	1.04 (0.97-1.11)	0.26
Endometrioid	2,151	30,816	0.0834	0.0949	0.90 (0.80-1.00)	0.06
Clear cell	1,015	30,816	0.0994	0.0949	1.09 (0.94-1.27)	0.27
Mucinous	1,000	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	2,332	12,433	0.0954	0.0922	1.09 (0.97-1.23)	0.14
BRCA2 mutation carriers	599	7,305	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	1,095	10,802	0.0950	0.0940	1.05 (0.90-1.23)	0.52
BRCA2 mutation carriers	270	6,509	0.0907	0.0979	0.85 (0.60-1.20)	0.36
Menopausal Status						
Pre- or peri-menopausal	4,264	8,789	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-	4,009	37,043	0.0940	0.0932	1.04 (0.96-1.13)	0.36
ER-/PR-/ERBB2-	1,673	28,480	0.0885	0.0947	0.97 (0.85-1.10)	0.62
First-degree family history						
Breast cancer	4,357	1,943	0.0942	0.0954	0.96 (0.84-1.10)	0.59
Ovarian or breast cancer	4,593	2,265	0.0933	0.0949	0.96 (0.85-1.09)	0.52
Age diagnosis <52						
ER-/PR-	1,530	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	1,431	1,097	0.0853	0.0925	0.91(0.75-1.11)	0.35
BRCA1 mutation carriers	7,543	7,222	0.0935	0.0919	1.04 (0.97-1.12)	0.27
BRCA2 mutation carriers	4,138	3,766	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	2,595	5,976	0.0896	0.0924	0.95 (0.85-1.05)	0.30
BRCA2 mutation carriers	1,359	3,365	0.0960	0.0926	1.05 (0.90-1.23)	0.52
Menopausal atatus						
Pre- or peri-menopausal	7,086	8,642	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

4. Table

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	N Patients	N Events	Hazard Ratio (95% CI)	P-value
Ovarian Cancer				
Overall survival				
All patients	3,096	1,421	0.94 (0.83-1.07)	0.38
Patients who were suboptimally debulked after cytoreductive surgery	1,114	784	0.94 (0.78-1.13)	0.50
Post-menopausal patients > 52 years	2,226	1,276	0.97 (0.84-1.12)	0.70
Progression-free survival				
All patients	3,096	2,144	1.01 (0.90-1.13)	0.84
Patients who were suboptimally debulked after cytoreductive surgery	1,114	961	1.03 (0.87-1.21)	0.74
Post-menopausal patients > 52 years	2,226	1,603	1.02 (0.90-1.16)	0.76
Breast Cancer				
Overall survival				
All patients	28,471	3,013	0.96 (0.87-1.06)	0.38
ER-positive patients	20,071	1,754	0.96 (0.85-1.10)	0.58
ER-negative patients	4,778	771	0.97 (0.81-1.18)	0.78
Breast cancer-specific survival				
All patients	28,471	1,693	0.95 (0.83-1.08)	0.40
Overall survival				
BRCA1 mutation carriers	1,706	241	0.72 (0.48-1.08)	0.11
BRCA2 mutation carriers	917	162	0.98 (0.65-1.46)	0.90

5. Figure

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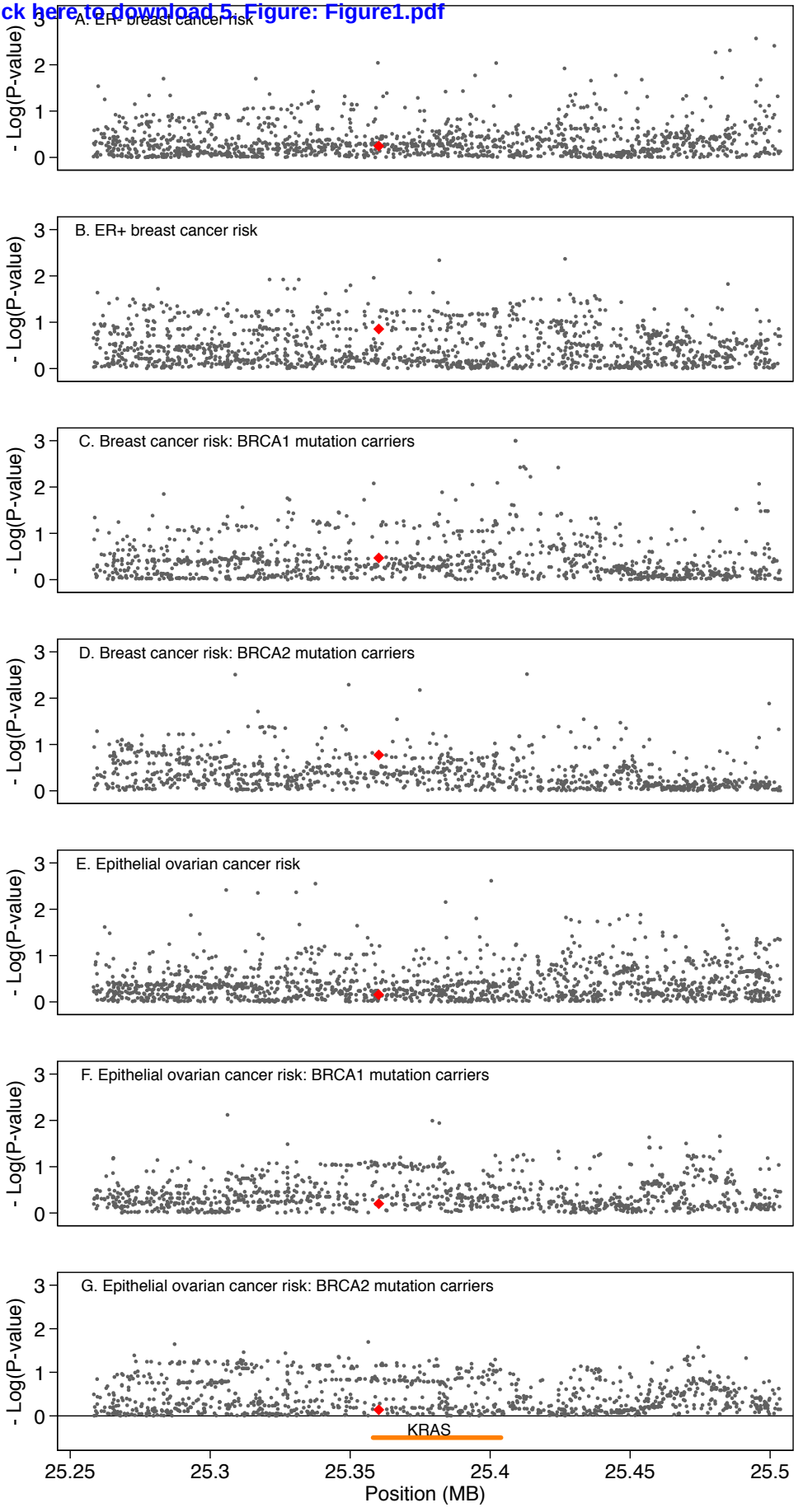

5. Figure

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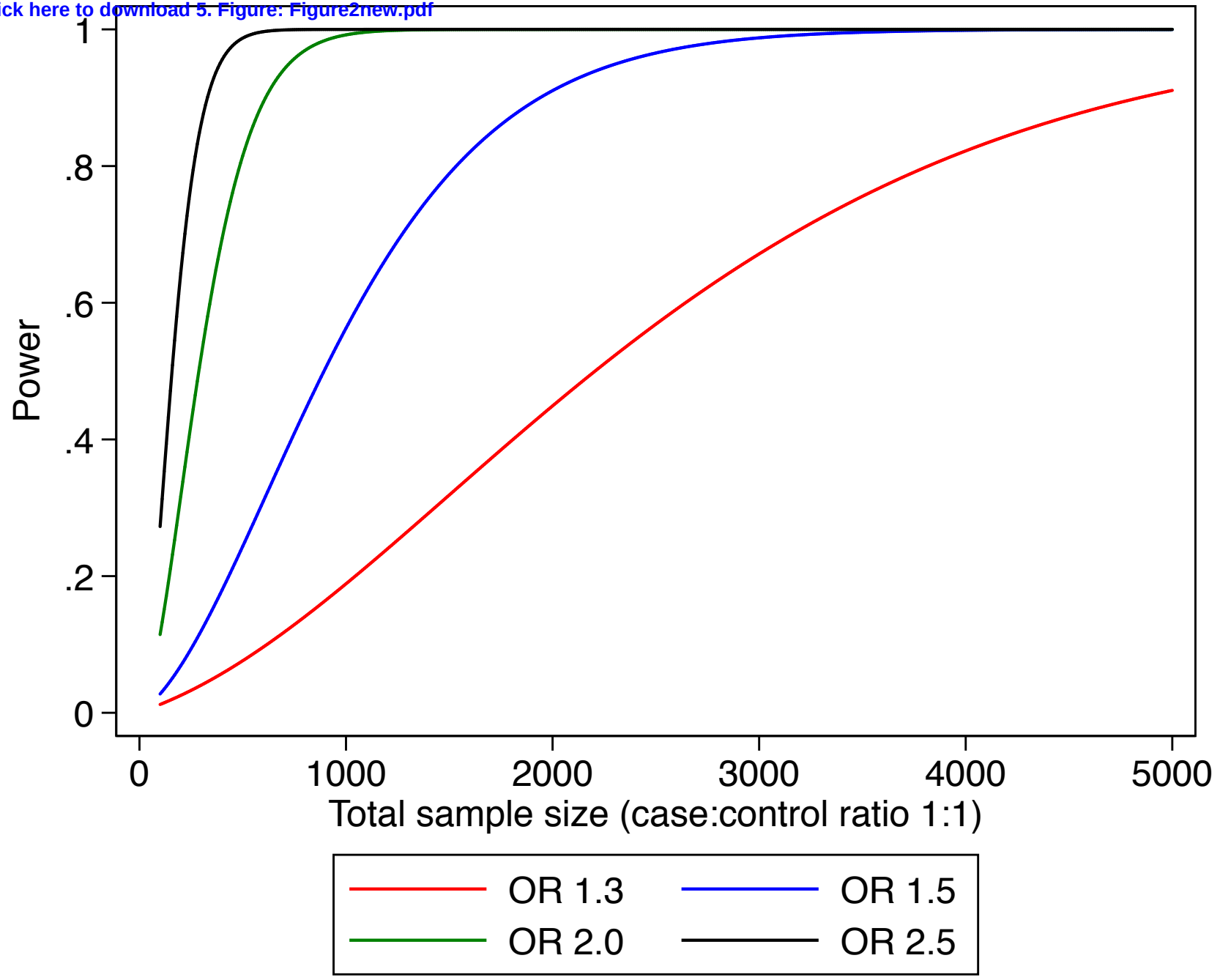

6. Supplementary Material

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Supplementary Table S1. Participating Ovarian Cancer Association Consortium (OCAC) Studies

OCAC Study Name	Abbreviation	Study Location	Study Type	Controls	Cases (with survival)
Australian Ovarian Cancer Study/Australian Cancer Study (Ovarian Cancer)	AUS	Australia	Population based/ case-control	977	880 (678)
Bavarian Ovarian Cancer Cases and Controls	BAV	Southeast Germany	Population based/ case-control	143	93 (90)
Belgian Ovarian Cancer Study	BEL	Belgium, University Hospital Leuven	Hospital based/ case-control	1,349	275 (236)
Diseases of the Ovary and their Evaluation	DOV	USA: 13 counties in western Washington state	Population based/ case-control	1,487	904 (0)
Oregon Ovarian Cancer Registry	ORE	USA: Portland, Oregon	Case only	0	55 (49)
German Ovarian Cancer Study	GER	Germany: two geographical regions in the states of Baden-Württemberg and Rhineland-Palatinate in southern Germany	Population based/ case-control	413	189 (0)
Dr. Horst Schmidt Kliniken	HSK	Germany	Case only		144 (144)
Hawaii Ovarian Cancer Case-Control Study	HAW	USA: Hawaii	Population based/ case-control	157	60 (51)
Hannover-Jena Ovarian Cancer Study	HJO	Germany	Hospital based/ case-control	273	266 (0)
Hannover-Minsk Ovarian Cancer Study	HMO	Belarus	Case-control	138	143 (0)
Helsinki Ovarian Cancer Study	HOC	Helsinki, Finland	Case-control	447	221 (0)
Novel Risk Factors and Potential Early Detection Markers for Ovarian Cancer	HOP	USA: Western PA, Northeastern Ohio, Western New York	Population based/ case-control	1,464	654 (0)
Gilda Radner Familial Ovarian Cancer Registry	GRR	USA: National	Familial cancer/ case only		132 (0)
Women's Cancer Program at the Samuel Oschin Comprehensive Cancer Institute	LAX	USA: Southern California	Case only		277 (222)
Los Angeles County Case-control studies of Ovarian Cancer-1	USC	USA: Los Angeles County, California	Population based/ case-control	1047	689 (0)
MALignant OVArian Cancer	MAL	Denmark	Population based/ case-control	828	440 (363)
Danish Pelvic Mass Study	PVD	Denmark	Case only	0	169 (152)
Mayo Clinic Ovarian Cancer Case-Control Study	MAY	USA: North Central (MN, SD, ND, IL, IA, WI)	Clinic based/ case-control	971	811 (687)
Melbourne Collaborative Cohort Study	MCC	Melbourne, Australia	Cohort/ Nested case-control	66	63 (0)
MD Anderson Ovarian Cancer Study	MDA	USA: Texas	Hospital based/ Case-control	384	373 (0)
Memorial Sloan-Kettering Cancer Center	MSK	USA: New York City	Case-control	593	467 (0)

OCAC Study Name	Abbreviation	Study Location	Study Type	Controls	Cases (with survival)
North Carolina Ovarian Cancer Study	NCO	USA: Central and eastern North Carolina (48 counties)	Population based/ case-control	826	761 (213)
New England Case Control Study	NEC	USA: New Hampshire and Eastern Massachusetts	Population based/ case-control	1,122	766 (87)
Nurses' Health Study	NHS	USA: National	Population based/ Nested case-control	455	138 (0)
New Jersey Ovarian Cancer Study	NJO	USA: New Jersey (six counties)	Case-control	181	169 (0)
University of Bergen, Haukeland University Hospital, Norway	NOR	Norway	Case-control	371	237 (0)
Nijmegen Ovarian Cancer Study	NTH	Eastern part of the Netherlands	Case-control	323	255 (0)
Ovarian Cancer in Alberta and British Columbia	OVA	Alberta and British Columbia, Canada	Case-control	748	631 (0)
Polish Ovarian Cancer Study	POC	Poland: Szczecin, Poznan, Opole, Rzeszów	Case-control	417	422 (0)
Polish Ovarian Cancer Case Control Study	POL	Poland: Warsaw, and Lodz	Population based/ case-control	741	260 (0)
Study of Epidemiology and Risk Factors in Cancer Heredity	SEA	UK: East Anglia and West Midlands	Population based/ case-control	6,024	1,385 (0)
Family Registry for Ovarian Cancer and Genetic Epidemiology of Ovarian Cancer	STA	USA: Six counties in the San Francisco Bay area	Population based/ case-control	313	251 (0)
Tampa Bay Ovarian Cancer Study	TBO	USA: Florida	Case-control	169	227 (0)
Toronto Ovarian Cancer Study	TOR	Canada: Province of Ontario	Population based	598	755 (0)
University of California Irvine Ovarian Study	UCI	USA: Southern California (Orange and San-Diego, Imperial Counties)	Population based/ case-control	367	277 (0)
United Kingdom Ovarian Cancer Population Study	UKO	UK: England, Wales and Northern Ireland	Population based/ case-control	1,104	730 (0)
Royal Marsden Hospital Ovarian Cancer Study	RMH	UK: London	Hospital based/ case only	0	154 (0)
UK Familial Ovarian Cancer Registry	UKR	UK: National	Case only/ familial register	0	47 (0)
Southampton Ovarian Cancer Study	SOC	UK: Wessex region	Case only/ hospital based	0	267 (0)
Scottish Randomised Trial in Ovarian Cancer	SRO	UK: coordinated through clinical trials unit, Glasgow UK from patients recruited world-wide	Case only/ clinical trial	0	158 (124)
Warsaw Ovarian Cancer Study	WOC	Poland: Warsaw and central Poland	Case-control	204	202 (0)
TOTAL				**30,816**	**15,397 (3,096)**

Totals represent the number of subjects passing quality control criteria included in these analyses; number in parentheses is number with survival time data.

Supplementary Table S2. Participating Breast Cancer Association Consortium (BCAC) Studies

BCAC Study Name	Abbreviation	Study Location	Study Type	Controls	Cases (with survival)
Australian Breast Cancer Family Study	ABCFS	Australia: Melbourne and Sydney	Population based/ case-control	490	720 (745)
Amsterdam Breast Cancer Study	ABCS	The Netherlands, NKI-AVL	Early onset & familial cancer/ mixed case-control	1,156	1,069 (564)
Bavarian Breast Cancer Cases and Controls	BBCC	Germany: Northern Bavaria	Mixed/ case-control	457	553 (214)
British Breast Cancer Study	BBCS	UK: England and Scotland	Mixed/ case-control	1,302	1,408 (0)
Breast Cancer in Galway Genetic Study	BIGGS	Western part of Ireland	Hospital based/ case-control	49	230 (0)
Breast Cancer Study of the University Clinic Heidelberg	BSUCH	Germany: Heidelberg and Mannheim	Hospital based/ case-control	945	799 (384)
CECILE Breast Cancer Study	CECILE	France: departments of Ille-et-Vilaine and Côte d'Or	Mixed/ case-control	991	892 (0)
Copenhagen General Population Study	CGPS	Denmark: Copenhagen	Hospital based/ case-control	3,927	2,269 (1,999)
California Teachers Study	CTS	USA: California	Cohort/ nested case-control	44	51 (0)
ESTHER Breast Cancer Study	ESTHER	Germany: Saarland	Hospital based/ case-control	500	465 (363)
Gene Environment Interaction and Breast Cancer in Germany	GENICA	Germany: greater Bonn area	Population based/ case-control	420	463 (0)
Helsinki Breast Cancer Study	HEBCS	Southern part of Finland	Mixed/ case-control	1,226	600 (1428)
Hannover-Minsk Breast Cancer Study	HMBCS	Belarus: Minsk, Gomel, Mogilev, Grodno, Brest and Vitebsk	Mixed/ case-control	130	641 (0)
Karolinska Breast Cancer Study	KARBAC	Sweden: Stockholm	Familial cancer/ mixed case-control	0	0 (402)
Kuopio Breast Cancer Project	KBCP	Finland, Kuopio University Hospital	Hospital based/ case-control	250	407 (396)
Kathleen Cuningham Foundation Consortium for Research into Familial Breast Cancer/Australian Ovarian Cancer Study	kConFab/AOCS	Australia and New Zealand	Familial cancer/ mixed case-control	867	357 (214)
Leuven Multidisciplinary Breast Centre	LMBC	Belgium: Leuven	Mixed/ case-control	1,386	2,484 (2,407)
Mammary Carcinoma Risk Factor Investigation	MARIE	Germany: Hamburg and Rhein-Neckar- Karlsruhe	Population based/ case-control	1,745	1,629 (1,577)
Milan Breast Cancer Study Group	MBCSG	Italy:Milan	Familial cancer/ mixed case-control	389	189 (152)

BCAC Study Name	Abbreviation	Study Location	Study Type	Controls	Cases (with survival)
Mayo Clinic Breast Cancer Study	MCBCS	USA: North Central (MN, SD, ND, IL, IA, WI)	Mixed/ case-control	1,917	1,532 (1,368)
Melbourne Collaborative Cohort Study	MCCS	Australia: Melbourne	Prospective cohort	506	614 (508)
Multiethnic Cohort	MEC	USA: California and Hawai	Prospective cohort	741	705 (644)
Montreal Gene-Environment Breast Cancer study	MTLGEBCS	Canada: Montreal	Mixed/ case-control	359	408 (0)
Norwegian Breast Cancer Study	NBCS	Norway: Oslo, Bergen and Tromsø	Mixed/ case-control	70	22 (0)
Nashville Breast Health Study	NBHS	USA: Nashville	Mixed/ case-control	119	122 (0)
Oulu Breast Cancer Study	OBCS	Northern part of Finland	Mixed/ case-control	410	500 (474)
Ontario Familial Breast Cancer Registry	OFBCR	Canada: Ontario	Population based/ case-control	488	820 (925)
Leiden University Medical Centre Breast Cancer Study	ORIGO	The Netherlands: South-West area	Hospital based/ case-control	0	0 (307)
Polish Breast Cancer Study	PBCS	Poland	Population based/ case-control	423	519 (436)
Karolinska Mammography Project for Risk Prediction of Breast Cancer	pKARMA	Sweden: Stockholm/Gotland area	Population based/ case-control	5,450	4,196 (4,403)
Rotterdam Breast cancer Study	RBCS	The Netherlands: Rotterdam area	Familial cancer/ mixed case-control	0	0 (541)
Singapore and Sweden Breast Cancer Study	SASBAC	Sweden	Population based/ case-control	1,268	1,150 (1,131)
Sheffield Breast Cancer Study	SBCS	UK, Sheffield	Mixed/ case-control	839	748 (674)
Study of Epidemiology and Risk Factors in Cancer Hereditary	SEARCH	Eastern part of UK	Mixed/ case-control	8,000	6,357 (6,097)
Städtisches Klinikum Karlsruhe Deutsches Krebsforschungszentrum Study	SKKDKFZS	Germany: Karlsruhe	Mixed/ case-control	0	0 (118)
Szczecin Breast Cancer Study	SZBCS	Poland: West-Pomerania	Mixed/ case-control	315	205 (0)
Breakthrough Generations Study	UKBGS	UK	Cohort/ nested case-control	461	406 (0)
TOTAL				**37,640**	**33,530 (28,471)**

Totals represent the number of subjects passing quality control criteria included in these analyses; studies with zero cases other than those with survival data were excluded from case-control comparison, but included in survival analyses; number in parentheses is number with survival time data.

Supplementary Table S3. Participating Consortium of Investigators of Modifiers of *BRCA1/2* (CIMBA) Studies

CIMBA Study Name	Abbreviation	Study Location	N Unaffected *BRCA1* carriers: BC / OC	N Affected *BRCA1* carriers: BC (with survival) / OC	N Unaffected *BRCA2* carriers: BC / OC	N Affected *BRCA2* carriers: BC (with survival) / OC
Breast Cancer Family Registry	BCFR	Australia, Canada, USA	176 / 413	285 (80) / 48	152 / 330	196 (56) / 18
Baltic Familial Breast Ovarian Cancer Consortium	BFBOCC	Lithuania	88 / 86	58 (0) / 60	0 / 0	0 (0) / 0
Beth Israel Deaconess Medical Center	BIDMC	USA	18 / 41	27 (0) / 4	5 / 9	4 (0) / 0
BRCA-gene mutations and breast cancer in South African women	BMBSA	South Africa	23 / 48	38 (0) / 13	53 / 132	93 (0) / 14
Beckman Research Institute of the City of Hope	BRICOH	USA	114 / 154	62 (0) / 22	80 / 120	48 (0) / 8
Copenhagen Breast Cancer Study	CBCS	Denmark	175 / 237	121 (0) / 59	49 / 86	45 (0) / 8
Spanish National Cancer Centre Breast Cancer Study	CNIO	Spain	53 / 97	61 (0) / 17	113 / 211	113 (0) / 15
City of Hope Cancer Center	COH	USA	86 / 202	139 (0) / 23	42 / 107	65 (0) / 0
CONsortio Studi ITaliani sui Tumori Ereditari Alla Mammella	CONSIT TEAM	Italy	220 / 348	247 (0) / 119	65 / 163	117 (0) / 19
National Center for Scientific Research “Demokritos”	DEMOKRITOS	Greece	73 / 142	121 (0) / 52	0 / 0	0 (0) / 0
Dana Farber Cancer Institute	DFCI	USA	79 / 138	77 (0) / 18	79 / 130	55 (0) / 4
German Cancer Research Center	DKFZ	Germany	18 / 58	41 (0) / 1	11 / 22	14 (0) / 3
Epidemiological study of BRCA1 & BRCA2 mutation carriers	EMBRACE	UK	726 / 1,249	724 (544) / 201	545 / 946	475 (311) / 74
Fox Chase Cancer Center	FCCC	USA	68 / 93	47 (0) / 22	35 / 45	19 (0) / 9
German Consortium of Hereditary Breast and Ovarian Cancer	GC-HBOC	Germany	334 / 828	645 (0) / 151	185 / 492	348 (0) / 41
Genetic modifiers of Cancer Risk in BRCA1/2 Mutation Carriers	GEMO	France	576 / 1,099	790 (0) / 267	204 / 653	502 (0) / 53
Georgetown Hospital	GEORGETOWN	USA	6 / 16	10 (0) / 0	0 / 0	0 (0) / 0
Ghent University Hospital	G-FAST	Belgium	121 / 237	149 (0) / 33	0 / 0	0 (0) / 0
Gynecologic Oncology Group	GOG	USA	172 / 344	172 (0) / 0	159 / 306	147 (0) / 0
Hospital Clinico San Carlos	HCSC	Spain	74 / 106	56 (0) / 24	54 / 104	59 (0) / 9
Helsinki Breast Cancer Study	HEBCS	Finland	42 / 75	55 (50) / 22	55 / 110	66 (58) / 11
Hereditary Breast and Ovarian Cancer	HEBON	Netherlands	687 / 1,113	564 (153) / 138	491 / 700	260 (45) / 51

CIMBA Study Name	Abbreviation	Study Location	N Unaffected *BRCA1* carriers: BC / OC	N Affected *BRCA1* carriers: BC (with survival) / OC	N Unaffected *BRCA2* carriers: BC / OC	N Affected *BRCA2* carriers: BC (with survival) / OC
Research Group Netherlands						
Molecular Genetic Studies of Breast and Ovarian Cancer in Hungary	HUNBOCS	Hungary	60 / 120	83 (0) / 23	0 / 0	0 (0) / 0
University Hospital Vall d'Hebron	HVH	Spain	25 / 48	33 (0) / 10	25 / 55	34 (0) / 4
Institut Català d'Oncologica	ICO	Spain	113 / 170	99 (0) / 42	102 / 199	121 (0) / 24
International Hereditary Cancer Centre	IHCC	Poland	392 / 652	311 (0) / 51	0 / 0	0 (0) / 0
Iceland Landspitali-University Hospital	ILUH	Iceland	0 / 0	0 (0) / 0	25 / 122	101 (52) / 4
Interdisciplinary Health Research International Team Breast Cancer susceptibility	INHERIT	Canada	54 / 83	42 (0) / 13	23 / 47	26 (0) / 2
Istituto Oncologico Veneto	IOVHBOCS	Italy	59 / 75	72 (0) / 56	36 / 107	90 (0) / 19
Portuguese Oncology Institute-Porto Breast Cancer Study	IPOBCS	Portugal	60 / 77	35 (0) / 18	0 / 0	0 (0) / 0
Kathleen Cuningham Consortium for Research into Familial Breast Cancer	KCONFAB	Australia	312 / 654	418 (336) / 76	175 / 402	250 (192) / 23
Modifiers and Genetics in Cancer	MAGIC	USA	16 / 18	8 (0) / 6	21 / 26	8 (0) / 3
Mayo Clinic	MAYO	USA	138 / 243	138 (63) / 33	61 / 130	80 (0) / 11
McGill University	MCGILL	Canada	30 / 50	24 (0) / 4	15 / 26	12 (0) / 1
Modifier Study of Quantitative Effects on Disease	MODSQUAD	Czech Republic	67 / 132	107 (0) / 42	0 / 0	0 (0) / 0
Memorial Sloan-Kettering Cancer Center	MSKCC	USA	137 / 311	201 (0) / 27	97 / 195	121 (0) / 23
General Hospital Vienna	MUV	Austria	222 / 380	224 (184) / 66	77 / 187	123 (88) / 13
Women's College Research Institute	NAROD	Canada	100 / 125	46 (0) / 21	0 / 0	0 (0) / 0
National Cancer Institute	NCI	USA	113 / 145	44 (0) / 12	59 / 74	21 (0) / 6
National Israeli Cancer Control Center	NICCC	Israel	0 / 0	0 (0) / 0	108 / 162	61 (0) / 7
N.N. Petrov Institute of Oncology	NNPIO	Russia	17 / 36	34 (0) / 15	0 / 0	0 (0) / 0
Ontario Cancer Genetics Network	OCGN	Canada	139 / 170	74 (0) / 43	112 / 156	65 (0) / 21
The Ohio State University Comprehensive Cancer Center	OSUCCG	USA	33 / 77	53 (0) / 9	28 / 52	33 (0) / 9
Odense University Hospital	OUH	Denmark	225 / 304	141 (121) / 62	116 / 189	88 (53) / 15
Università di Pisa	PBCS	Italy	35 / 57	45 (0) / 23	0 / 0	0 (0) / 0

CIMBA Study Name	Abbreviation	Study Location	N Unaffected *BRCA1* carriers: BC / OC	N Affected *BRCA1* carriers: BC (with survival) / OC	N Unaffected *BRCA2* carriers: BC / OC	N Affected *BRCA2* carriers: BC (with survival) / OC
Sheba Medical Centre	SMC	Israel	156 / 222	107 (0) / 41	57 / 94	47 (0) / 10
Swedish Breast Cancer Study	SWE-BRCA	Sweden	266 / 372	220 (37) / 114	31 / 46	23 (0) / 8
The University of Chicago Center for Clinical Cancer Genetics and Global Health	UCHICAGO	USA	35 / 56	25 (0) / 4	12 / 33	25 (0) / 4
University of California Los Angeles	UCLA	USA	0 / 0	0 (0) / 0	25 / 38	15 (0) / 2
University of California San Francisco	UCSF	USA	59 / 75	44 (0) / 28	11 / 23	16 (0) / 4
United Kingdom Familial Ovarian Cancer Registries	UKGRFOCR	UK	42 / 25	18 (0) / 35	13 / 6	4 (0) / 11
University of Pennsylvania	UPENN	USA	172 / 344	242 (138) / 70	104 / 215	131 (62) / 20
University of Texas M.D. Anderson Cancer Center	UTMDACC	USA	44 / 97	71 (0) / 18	0 / 0	0 (0) / 0
Victorian Familial Cancer Trials Group	VFCTG	Australia	14 / 37	40 (0) / 17	0 / 0	0 (0) / 0
Women's Cancer Program	WCP	USA	158 / 154	55 (0) / 59	56 / 55	17 (0) / 18
TOTAL			**7,222 / 12,433**	**7,543 (1,706) / 2,332**	**3,766 / 7,305**	**4,138 (917) / 599**

Totals represent the number of subjects passing quality control criteria included in these analyses. BC = breast cancer, OC = ovarian cancer; number in parentheses is number with survival time data

Supplementary Table S4. Association between *KRAS* rs61764370 and Risk of ERBB2-positive and High Grade Breast Cancer in Hormone Replacement Therapy Users

	TT	TG	GG	N Cases	MAF	OR (95% CI)	P-value
HRT users							
ERBB2 status							
Negative	1,213	240	13	1,466	0.0907		
Positive	224	55	2	281	0.1050	1.13 (0.84-1.54)	0.42
Grade							
1 or 2	1,638	331	14	1,983	0.9052		
3	461	107	9	577	0.1083	1.12 (0.96-1.49)	0.11
Postmenopausal HRT users							
ERBB2 status							
Negative	1,084	221	12	1,317	0.0930		
Positive	190	50	2	242	0.1116	1.20 (0.87-1.65)	0.27
Grade							
1 or 2	1,477	307	14	1,798	0.0932		
3	414	100	8	522	0.1111	1.20 (0.95-1.51)	0.12

Breast cancer analyses used BCAC data adjusted for study, age, and the first seven principal components.
HRT, hormone replacement therapy; N, number; MAF, minor allele frequency; OR, odds ratio; CI, confidence interval

Supplementary Table S5. Results of OCAC Analyses of Genotype

1000G Name	Chromosomal Position (Build 37)	Reference Allele
rs17327547	25258458	G
chr12:25258574:I	25258574	GA
rs142258134	25259157	C
chr12:25259356:D	25259356	T
chr12:25259581:D	25259581	T
chr12:25259628:D	25259628	T
chr12:25259676:I	25259676	AT
rs17386824	25259750	A
rs113123645	25260675	G
rs11047837	25261165	G
rs73081704	25262127	C
chr12:25262348:D	25262348	T
rs77156774	25263310	G
rs75700820	25263397	T
rs7134616	25263890	C
rs4963848	25263951	T
rs17387019	25264259	A
rs76474389	25265248	G
rs7297103	25265295	T
rs56009712	25265339	G
rs138327616	25265409	C
rs140262765	25265442	G
rs6487454	25265604	T
rs6487455	25265654	A
rs73081707	25265795	C
rs11047842	25265837	A
rs10842469	25266165	C
rs10842470	25266203	T
rs149734680	25266436	G
rs11047843	25266794	T
chr12:25266885:I	25266885	TG
rs11047845	25266983	A
chr12:25267104:I	25267104	CCTCA
rs74426171	25267557	T
rs10842471	25267940	A
rs11047846	25267999	T
chr12:25268475:I	25268475	CAAA
chr12:25268476:I	25268476	AAAG

HIGHLIGHTS

- A clinical genetic test for *KRAS* rs61764370 is marketed to US women at increased ovarian or breast cancer risk.
- The genotype of *KRAS* rs61764370 has no clinical utility related to the prediction or management of ovarian or breast cancers.
- The results of this study demonstrate the necessity of carefully conducted, large-scale studies to establish clinical validity for genetic tests.